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Abstracts of Symposia, Free Communications and Posters

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Presidential Symposium
NEURO-ONCOLOGY
Chairman: J. G. Hildebrand

PROSPECTS IN GLIOMA THERAPY

J. G. Hildebrand

Gliomas represent approximately 50% of all primary malignant brain tumours. Glioblastoma is the most common and the most malignant form with a median survival of less than one year. Most new therapeutic approaches are tested in this tumour. Before considering the prospects in glioblastoma treatment, it is essential to understand why we have largely failed in the past. The main reasons are :

The intrinsic resistance of glioblastoma to conventional chemotherapy and radiation therapy.

The presence of distant neoplastic foci which limit the efficacy of all local treatments. In addition, these small foci are protected by the blood brain barrier which limits drug access.

Tumour heterogeneity which is probably the most crucial problem. Unlike some experimental tumours, human gliomas are morphologically, biologically, and genetically heterogeneous. Also, the chemosensitivity of different clones forming the tumour differs considerably. New therapeutic approaches, including gene therapy, will have to overcome these obstacles.

Basically, gene therapy consists in a modification of cell genoma in order to affect tumour growth. The theoretical possibilities of gene therapy are almost infinite. They will be illustrated by four examples taken from works presented at previous ENS-meetings.

1. TRANSFER OF A "SUICIDE" GENE

This methodology consists in transfecting tumour cells with thymidine-kinase viral gene, a suicide gene that makes the tumour cell sensitive to drugs like gancyclovir. The therapeutic power of this system is increased by the fact that not all neoplastic cells need to be transfected to become sensitive to gancyclovir, a phenomenon called bystander effect. This system is widely known as it has been experimented in several animal models and tested in clinical trials as well. Its efficacy is limited by the low rate of transfection in vivo and the necessity of cell to cell contact for the bystander effect.

2. TRANSDUCTION WITH A TUMOUR SUPPRESSOR GENE

This approach which aims to restore cell mechanisms opposing neoplastic transformation is illustrated by transfection with wilde P53. The tumour suppressor activity of P53 in humans is strongly suggested by the observation that the protein is mutated in about half of sporadic cancers including brain glioma. In addition, families with Li-Fraumeni syndrome – where P53 abnormality is transmitted by germline cells – have an unusually high incidence of systemic cancers and brain tumours.

3. INHIBITION OF GROWTH FACTORS

Expression or over-expression of growth factors or of their receptors may modify tumour environment and stimulates cell proliferation in an autocrine fashion. Inhibition of growth factors should decrease cancer growth. This therapeutic modality will be illustrated by experiences performed by Troyan et al. using antisense insuline-like growth factor. In this model however, genetic manipulation has elicited an intense immune reaction. In fact, this type of gene therapy represents a form of immunotherapy triggered by genetic manipulation of tumour cell phenotype.

4. ANTI-ANGIOGENESIS

Increase of tumour size requires the ingrowth of vessels originating from surrounding tissues. This neo-angiogenesis is a complex process stimulated by growth factors like VEGF produced by neoplastic cells including malignant gliomas. Inhibition of neo-angiogenesis would limit malignant tumours to microscopic nodules and possibly interfere with their vascular dissemination. The advantage of this approach is that it tackles a general and fundamental cancer property overcoming tumour heterogeneity and that endothelial cells are genetically much more stable than gliomas which are a constantly changing biological target.

We all believe that a better understanding of tumour biology will eventually result in cancer cure. However we must not forget that, so far, many progress have been achieved through clinical trials. This also applies to the treatment of malignant gliomas where it has been shown that survival correlates with the extend of tumour resection, that standard external irradiation increases the survival by 50 to 100%, and that about 20 to 30% of patients will respond to chemotherapy at recurrence. Although these achievements are far beyond our expectations, there is no reason why their benefit should not be offered to every patient bearing a malignant glioma.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN IMMUNOCOMPETENT PATIENTS

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Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's lymphoma that arises within and is restricted to the CNS. It usually presents as a brain tumor, but the leptomeninges, eyes and spinal cord may also be affected. The vast majority of PCNSLs (80-90%) are classified as diffuse large B-cell lymphomas (REAL classification). Although PCNSL is a rare neoplasm, this tumor is of special concern, as an important increase in incidence has been observed during the past two decades. Immunocompromised patients such as AIDS patients and transplant recipients are specially at risk. However, the reason for the rising incidence observed in the immunocompetent population is unknown. In the general population, the peak frequency corresponds to the sixth and seventh decades. The common presenting symptoms of PCNSL include focal symptoms, raised intracranial pressure symptoms, or diffuse encephalopathy. Seizures are uncommon because of the frequently deep location of the tumor. Ocular involvement in the form of uveitis is present at diagnosis in 10-20% of cases. A complete ophtalmologic evaluation with slit lamp examination is essential in the work-up, since the uveitis is asymptomatic in half of cases. The diagnosis of PCNSL may be suggested by several radiographic findings. Tumors are usually supratentorial, are typically periventricular, enhance homogeneously with contrast administration and exhibit little surrounding edema giving their size. Multiple lesions are seen in one third of cases. But the final diagnosis requires histological or cytological confirmation of lymphoma. This can be obtained by stereotactic biopsy of the radiologic demonstrable tumor, lumbar puncture in order to detect lymphoma cells in the CSF (10-30%), or vitreous biopsy if ocular examination reveals an uveitis. As the tumor can be highly sensitive to steroïds (40% of cases), one should avoid steroïds administration as much as possible until an histological confirmation is made. Age a nd performance status at commencement of treatment are important prognostic variables. The treatment of PCNSL has changed considerably in the past decade. The limited role of whole brain radiotherapy (WBRT) alone (total dose: 30-50 Gy) has been recognized with a median survival of 12 to 18 months. The addition of chemotherapy to radiotherapy has improved the prognosis. Regimens with high dose methotrexate (MTX) seem to be the most successful with a median survival of 30-45 months. In contrast, the protocols using CHOP or CHOP like regimens in addition to WBRT do not look better than WBRT alone. However, the combined treatment associating MTX based chemotherapy and WBRT exposes the patients, specially the elderly, to the development of delayed neurotoxicity. Current protocols focus on the development of chemotherapy alone or combined treatment programs with reduced doses of WBRT in order to minimize late cognitive sequellae. Other trials such as intensive chemotherapy with autologo us stem cells transplantation and blood brain barrier disruption chemotherapy programs are currently under investigation.

PARANEOPLASIA: RECENT DEVELOPMENTS

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Paraneoplastic syndromes affecting the nervous system are unique among immune mediated disorders in that the trigger of the immune response is known: tumor expression of proteins normally restricted to neurons (or other immunopriviledged sites, such as testis) but ectopically expressed in some cancers results in an immunological response characterized by high titers of antibodies targeting the "onconeuronal" antigen. A T cell response is also elicited in some paraneoplastic syndromes and may be the cause of neuronal destruction. Several clinical syndromes are well recognized: the anti-Hu syndrome characterized by sensory neuronopathy and/or encephalomyelitis associated with small cell lung cancer, anti-Yo syndrome characterized by Purkinje cell destruction associated with ovarian and other gynecologic cancers, the anti-Ri syndrome characterized by opsoclonus/

myoclonus or other eye movement disorders associated with a variety of cancer, and the anti-Ta syndrome characterized by limbic and brainstem encephalopathy associated with testicular cancer. In each of these instances, the antigens recognized by the autoantibodies have been identified, cloned and sequenced. Some of the proteins so identified are RNA binding proteins but the specific function has not been identified. Not all paraneoplastic syndromes are characterized by identifiable autoantibodies. Even similar syndromes associated with the same cancer may be antibody positive or antibody negative. An example is paraneoplastic cerebellar degeneration associated with small cell lung cancer. Anti-Hu positive patients are more likely to have widespread neurologic signs outside the cerebellum than anti-Hu negative patients. Moreover, the prognosis is worse in the antibody positive patients. Some individuals with cancer but no paraneoplastic syndromes, low titers of antibody can be identified in the serum. Low titers of anti-Hu antibody are associated with a better prognosis of the small cell lung cancer. Experimental animals immunized against the Hu antigen are partially protected against tumors that express the Hu antigen.

Symposium 2
ADVANCES IN MANAGEMENT OF PARKINSON'S DISEASE
Chairman: E. Tolosa

HOW ACCURATELY CAN WE DIAGNOSE IDIOPATHIC PARKINSON'S DISEASE?

E. Tolosa, Barcelona, Spain.

Parkinson's disease(PD) is clinically an heterogeneous disorder that presents with numerous motor and non-motor manifestations. Clinical diagnosis is based on the identification of some combination of the cardinal motor signs of bradykinesia, rigidity, tremor and postural instability. There are no clinical markers that allow for an accurate diagnosis which needs neuropathological confirmation for its definitive diagnosis.

Accuracy of clinical diagnosis of PD has been estimated in studies of cases confirmed through autopsy findings (Rajput et al, 1991; Hughes et al, 1992) These studies have shown that diagnostic errors occurs in about 20% of cases. Another recent study involving neuropathological material from seven centers (Litvan et al, 1998) showed that the median sensitivity for the diagnosis of PD for the primary neurologists was high (93%) but the specificity only 76% and the positive predictive value at the time of the first visit was low(40%). These studies suggest that PD is overdiagnosed and that the best early features for separating PD from other disorders are asymmetrical onset parkinsonism, levodopa response and absence of pyramidal and oculomotor symptoms.

The most common diagnostic errors made when diagnosing PD are progressive supranuclear palsy and multisystem atrophy-parkinsonian type (striatonigral degeneration). Based on these studies early onset memory loss, confusional episodes, hallucinations not attributable to treatment and postural instability should be considered as red flags for the diagnosis of PD.

Laboratory and neuroimaging data are commonly used as aids in the diagnosis of PD. Some techniques, such as MRI-based volumetric measurements of subcortical structures, provide a sensitive marker to discriminate typical from atypical parkinsonism. Some neurophysiolgical studies such as the auditory startle response and studies of electrically elicited facial reflexes are also usefull for diagnostic pourposes. Information on the specificity and sensitivity of these various as well as other diagnostic techniques, generally scanty, will be reviewed in my presentation.

The absence of a completely reliable clinical marker for PD makes neuropathological confirmation essential. Classically the neuropathological features of PD are relatively straight forward, the main feature consisting of neuronal loss and Lewy bodies in the substantia nigra. The neuropathological fidings are sometimes ambiguous and conflictive, however, and the specificity adn sensitivity of individual pathological features are not knwon. In some patients Lewy bodies may be lacking. Conversely, some patients have Lewy bodies without neuronal degeneration or even clinical abnormalities. The distribution of the Lewy bodies is diverse and the importance of this distribution unclear. In my presentation currently used histopathological critera for the diagnosis of PD and their usefulness and limitations will also briefly discussed.

THE ROLE OF GLIAL CELLS IN THE NEURODEGENERATION OF PARKINSON'S DISEASE

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Parkinson's disease is characterized by a massive loss of dopaminergic neurons in the nigrostriatal pathway. Although, the gliosis in the substantia nigra of patients with Parkinson's disease is a classic neuropathological feature of the disease, it is often considered as a simple consequence of nerve cell death. Yet, glial cells may also participate in the pathophysiology of the disease as they produce putative toxic compounds. Indeed, the density of glial cells secreting cytokines such a interferon-, interleukin1- and tumor necrosis factor- is increased in the substantia nigra in Parkinson's disease. These cytokines may be involved directly or indirectly in the pathophysiology of the disease. Indirectly, they may activate the production of other toxic compounds. Indeed, in vitro experiments performed on glial cell lines show that interferon- induces the expression of CD23 a glycoprotein also known as an IgE receptor. Such an induction is even exacerbated by other cytokines. When activated by a proper stimulus, CD23 stimulates the expression of the inducible form of nitric oxide synthase and provokes a rise in nitrites production. In turn, this production of nitrites activates the synthesis of cytokines. This suggests a mutual potentiation of the pro-inflammatory reaction in glial cells by these molecules. Such biochemical events are also likely to occur in the substantia nigra of patients with Parkinson's disease, as CD23-positive glial cells are seen in this structure whereas they are undetectable in control subjects. Furthermore, the density of nitric oxide-positive glial cells is also greatly increased in the substantia nigra of patients with Parkinson's disease. Thus, the production of the cytokines may be auto-activated during the evolution of the disease. The consequences of the rise in cytokine levels in Parkinson's disease is not fully understood but may participate in the cascade of deleterious events leading to nerve cell death. Indeed, as indicated above, the cytokines are involved in the synthesis of nitric oxide that by combinaison with superoxide radicals can form peroxynitrites which are highly toxic compounds. More directly, by binding to their receptors, cytokines such as tumor necrosis factor-, can activate pro-apoptotic transduction pathways. Indeed, it has been shown on primary mesencephalic cultures of the rat mesencephalon that the activation of the sphingomyeline-dependant signalling pathway with C22-ceramide which is coupled to the TNF-receptor can induce a transient production of oxygen free radicals followed by a translocation of the transcription factor NF-B and a neuronal degeneration by apoptosis. In patients with Parkinson's disease, a translocation of NF-B has also been shown in some dopaminergic neurons which probably also degenerate by apoptosis. Taken together, these data suggest that some glial cells are likely to participate in the pathophysiology of Parkinson's disease and to induce deleterious reactions.

Anita Harding lecture: BIOCHEMICAL AND FUNCTIONAL ORGANIZATION OF THE BASAL GANGLIA

Anne Young - Biochemical and Functional Organization of the Basal Ganglia, by Anne B. Young, MD, Ph. D., Julieanne Dorn Professor of Neurology, Harvard Medical School and Chief of Neurology, Massachusetts General Hospital, Boston, MA, USA

Over the past two decades, our understanding of the functional anatomy of the basal ganglia has advanced significantly. A combination of anatomical, physiological, pharmacological and molecular biological techniques has been brought to bear on the problem and applied to both animal models of disease and to humans. The classical models are based on the notion of complementary cortico-striato-medial/pallido-thalamo-cortical loops (the direct pathway) that serve to reinforce an ongoing motor behavior and of cortico-striato-lateral/pallido-subthalamo-medial/pallido-thalamo-cortical loops (the indirect pathway) that serve to suppress unwanted or intrusive motor behaviors. These models of an direct and indirect pathway through the basal ganglia to the thalamus have received much attention. Dopamine serves to enhance activity in the direct pathway and attenuate activity in the indirect pathway. The models predict that loss of dopaminergic inputs to the striatum will lead to enhanced activity in the indirect pathway and diminished activity in the direct pathway with the cumulative effect resulting in excessive outflow from the medial globus pallidus to the thalamus. They further predict that choreic disorders will result from decreased activity in the indirect pathway. Physiological studies in primates

and humans suggest that this is the case. Furthermore, lesions of the medial globus pallidus do indeed improve parkinsonian features. Paradoxically, however, such lesions also improve the dyskinesias associated with overmedication in Parkinson's patients. The model also predicts that in the dyskinetic state, medial pallidal activity will be decreased and, in fact, that appears to be the case in recordings from dyskinetic Parkinson's patients and Huntington's patients. Curiously, medial pallidal lesions improve these clinical symptoms.

Dystonia is also difficult to explain in the context of the current models. Secondary dystonias are often associated with destruction of the putamen as seen in Wilson's disease. L-Dopa responsive dystonia occurs when dopamine levels drop to less than 20% of normal levels. Biphasic dyskinesia/dystonia in Parkinson's patients occurs when dopamine levels are present but diminished as in the period just after ingesting L-Dopa or in the period of wearing off. One possible explanation of these observations is that dystonia occurs when both the direct and indirect pathways are turned off. Since dopamine inhibits the indirect pathway and enhances the direct pathway, if the indirect pathway is more sensitive to dopamine than the direct pathway, then low levels of dopamine would turn off the indirect pathway but not turn on the direct pathway thus effectively shutting down the striatal outflow. In such a situation, the medial globus pallidus would be left to its own devises. Interestingly, lesions of the medial globus pallidus appear to improve dystonia.

More recent data provide evidence that the processing of information in the basal ganglia is not binary, i. e., 'on' or 'off' but rather reflects a complex mixture of spatial and temporal sequencing and coincidence detection. The sum of such intricate information processing is difficult to depict in a simple circuit diagram. Furthermore, the circuits provided in current models cannot reconcile the clinical observations. Current data suggest that the direct and indirect pathways play a major role in the spatial and temporal sequencing of movements and that abnormal movements result from aberrations in the extent and coincidence of inputs into the medial globus pallidus rather than the overall activity of the nucleus. Thus, no activity in the medial globus pallidus is preferable to aberrant input. In comparison to our knowledge of twenty years ago, we have come a long way but as we open new doors, it is clear we have a long way to go before we fully understand the intricacies of the basal ganglia.

THE ROLE OF SUBTHALAMIC NUCLEUS IN THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE: RECENT LESSONS FROM SURGERY

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Subthalamic nucleus (STN) stimulation is a very effective treatment for advanced Parkinson's disease. All the cardinal parkinsonian motor symptoms are alleviated and the morbidity is low. The degree of improvement is predicted by the response to levodopa before surgery and reaches the same magnitude. Therefore, antiparkinson drug doses are markedly reduced and levodopa may be stopped with a consequent reduction in dyskinesia. The increase in dyskinesia threshold can also be related to the continuous stimulation of the STN. Since high frequency stimulation mimics the effects of a lesion, it is suggested to work through an inhibitory mechanism. This would lead to a decrease in the overactivity of the STN, in keeping with the current concept of the basal ganglia functioning. In PD, it is proposed that akinesia is related to a STN overactivity. Intraoperative microrecordings corroborate this hypothesis. Therefore, STN inhibition would reverse akinesia and a further STN inhibition would induce dyskinesia. STN lesions usually induce contralateral hemiballism, which tends to abate over time. In PD patients, we reported that after acute levodopa challenge, STN stimulation reduced diphasic mobile dystonia by 50%, and peak dose choreic dyskinesia by 30%. STN stimulation suppressed off-period dystonia. In the immediate postoperative period, an acute STN stimulation carried out with increasing voltages mimicked a levodopa challenge, regarding both parkinsonism and dyskinesia: off-period dystonia was abated by low voltage stimulation whereas intermediate voltages led to diphasic dyskinesia and high voltages to peak dose dyskinesia. Therefore, different types of dyskinesia can be related to different levels of STN neuronal activities modulated by the intensity of stimulation. When stimulation is arrested many months after surgery, most parkinsonian signs revert to the preoperative baseline values except for gait and equilibrium, which remain improved.

Neuropsychological studies show that STN stimulation improves performance on some tests involving executive functions but worsens performance on other tests involving immediate control. STN stimulation may also modify mood or motivational aspects of behaviour. Although motor disability can be greatly improved, some patients exhibit a loss of initiative and aboulia. More rarely, laughter with merriment may occur.

A PET study showed that STN stimulation was associated with significant activation of the supplementary motor area, dorsolateral prefrontal cortex and anterior cingulate during movements.

All these results suggest that the STN is involved in the regulation of the sensorimotor, associative and limbic cortico-striatal loops and plays a key role in modulating the functioning of the frontal cortex and brainstem structures. More specifically, the STN function could consist in withholding unwanted or inappropriate responses in the motor, cognitive and affective domains.

Symposium 3
FUNCTIONAL IMAGING OF THE NERVOUS SYSTEM – THE ANATOMY OF COGNITION
Chairman: R. Frackowiak

THE ANATOMY OF COGNITION – "BRAIN PLASTICITY"

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Modern brain charting techniques are perfectly suited to re-test classical hypotheses about the human brain in-vivo. It is the obligation of neurologists to use these findings to improve the care of patients. Two aspects are of major importance to understand the mechanisms underlying reorganisational changes during recovery of lost function after central lesions.

Brain functions are localised either in distinct brain regions (e. g. ; visual perception of motion in V5 or MT) or in extended, connected, overlapping and highly parallel or reciprocal processing networks, the modular parts of which may substitute each other.

Localisation is not unchangeable, even the adult human brain retains a "plastic" potential.

These plastic changes represent a uniform reaction pattern of the brain and are either the result of an active learning process mediated by use or represent a passive adaptation to environmental stimuli, without any obvious teleological reason or without any improvement of function. We can differentiate between learning effects resulting in changes in the anatomical somatotopy of the primary cortices and functional effects in higher order cortices or across modalities. E. g. movement programmes for the hand can be used by the foot and can be learned by the other hand, which gradually builds up its own representation. Such transfer of movement parameters and its learning is mediated by the unimodal association cortices. The electrophysiological correlates of learning are different under normal conditions and in the lesioned brain. Associative learning under normal conditions results in repetition suppression together with a concomitant increase in effective connectivity. After a lesion, however, a temporary repetition augmentation is observed.

Recent studies showed a correlation between learning induced reorganisation and improvement of altered function in stroke. While repetitive proprioreceptive stimulation or the application of serotonin reuptake inhibitors alters motor activation patterns in normal subjects, forced-use therapy in hemiplegics or language training in aphasics influences brain organisation in the damaged brain. The future should evaluate the neurophysiological basis of neurorehabilitation and allow for individual prognostic estimation and allocation to the "ideal" rehabilitation regime.

In our opinion, there is not one single crucial component of recovery. Rather, recovery of function seems to imply the "reconnection" or perhaps better the recoordination of a network of areas, each of which may be specialised in one or more aspects of the lost function but requires the coherent support from others to reach a high level of proficiency.

PERCEPTION AND ATTENTION

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The sensory system most intensely studied is vision which uses afferent signals received through the dioptric system at the retina. Non-invasive functional neuroimaging studies in humans have localised specific neuronal stimulus-response functions known from animal electrophysiology or human psychophysical experiments. Yet, until recently, only indirect evidence for neural correlates of perceptually determined brain activity has been presented. Using functional magnetic resonance imaging of visual signal processing in the human brain, the studies presented here isolate neural correlates of perception and thus provide models of emergent instead of instructed direction of attentional resources. Our experimental approach is to maintain constant sensory input that the brain can interpret in two distinct but incompatible ways. Such perceptual ambiguity leads to a rivalry between these two percepts with one being dominant and the other suppressed. Over time, there are spontaneous fluctuations between the two percepts. Visual-motion presents such a perceptual ambiguity because it can result from object- or self-motion. We scanned subjects looking at a rotating disc with radial stripes. This object can either be perceived as such or induce circular vection, i. e. the illusory sensation of rotating around the axis of gaze while looking at a stationary object. Subjects' reports of alternation between these states enabled us to assign our data to either perception. We identified unique signatures of cerebral activity that encode object-motion and self-motion. In the occipito-temporal area corresponding to the human motion complex (V5/MT) an anterior portion responds to visual-motion irrespective of its perceived origin (object- or self-). We propose this area to be the human homologue of V5a/MST as defined in non-human primates. A similar behaviour was observed in dorsomedial cortex, extending from the cuneus to parieto-occipital cortex. Conversely, a set of areas extending from primary (V1) to both ventral occipital (V4) and temporo-occipital visual cortex (V5) responded to visual-motion across both percepts but decreased activity during perceived self-motion. These areas are thus functionally more strongly engaged by deriving "form-from-motion" than by reconstructing observer locomotion. Equally, deactivation during vection occurred in parietoinsular cortex, an area not responsive to visual-motion but previously identified as a human homologue of vestibular cortex. Finally, the cerebellar nodulus was the only structure found to activate during perceived self-motion, an effect that may relate to a slight gain increase in torsional nystagmus driven by the perceptual alternation. Together, these findings illustrate that a sensory cue such as motion yields brain activity patterns that represent not only physical stimulus properties but also the perceptual interpretation assigned to them. Thus, a motion stimulus may be processed for speed or direction in one brain area but account for activity in other areas as a function of whether it subserves seeing objects or guiding and monitoring ego-motion. In a second step, we used a perceptual ambiguity that occurs within the cognitive process of object perception to define brain structures involved in perceptual alternation between states. When looking at ambiguous figures, perceptual experience rapidly flips between two rivalling percepts. With an event-related analysis, we contrasted perceptual reversals with perceptual stability. Reversals were accompanied by transient activity surges across several "late" visual processing areas. These areas are specialised for different object attributes, e. g., spatial or categorical, and subject to strong top-down attentional modulation. Our experimental design demonstrated their concerted contribution to an integrated percept and their responsiveness to salience changes that are neither determined by the physical stimulus nor by observer instruction. Conversely, during perceptual flips a transient activity breakdown compared to perceptual stability was observed in "early" visual cortex (V1) and integrative subcortical structures (pulvinar complex). Th ese findings demonstrate functional cooperation in a distributed network that reveals its context-dependent flexible interplay as rapid activity adjustments. Together, these studies illustrate how functional neuroimaging can define neural processes occuring when the brain "goes beyond the information given". Thus, they provide a functional neuroanatomical framework within which the deficits subsequent to lesions in different visual areas, e. g., agnosia and neglect, can be understood as logical counterparts of their physiological contributions to cognition.

LANGUAGE, COMMUNICATION AND NUMERACY
J.-F. Demonet (Toulouse)

MEMORY FOR WORDS AND PLACES

Eraldo Paulescu (Milan)

Symposium 4
PROTEIN NEUROPATHOLOGY OF DEGENERATIVE DISORDERS
Chairman: A. Aguzzi

THE ROLES OF MUTANT PRESENILINS AND APP IN FAMILIAL ALZHEIMER'S DISEASE

Sangram S. Sisodia, Seong Kim, Satoshi Naruse, Gopal Thinakaran, Phil Wong, David Borchelt, and Donald Price. The University of Chicago, Chicago, IL and The Johns Hopkins University School of Medicine, Baltimore, MD.

Mutations in genes encoding the amyloid precursor protein (APP) or presenilins (PS1 and PS2) cosegregate with pedigrees with autosomal dominant, familial Alzheimer's disease (FAD). APP, an integral membrane protein, matures through the secretory pathway, and is subject to alternative proteolytic processing pathways. Proteolysis by b- and g-secretase activities liberates amyloidogenic Ab peptides. PS are polytopic membrane proteins that accumulate as endoproteolytic derivatives, in vivo. The PS1 fragments coassemble and we have proposed that stabilization of the derivatives is mediated by their association with limiting cellular components. Subcellular fractionation of membranes from cultured mammalian cells on Iodixanol gradients reveal that PS1 derivatives cofractionate with endoplasmic reticulum (ER) markers and a membrane fraction with light buoyant density that does not contain markers of the Golgi complex, COPII vesicles, ERGIC and endosomes. Remarkably, derivatives generated from FAD-linked mutant PS1 are prominent in "ER" fractions, and largely excluded from the "light" membrane fractions. Interestingly, FAD-linked PS1 variants expressed in cultured cells promote the production of highly fibrillogenic Ab42 peptides, and mutant PS1 accelerates the deposition of Ab peptides in brains of transgenic mice. We have also examined the consequence of PS1 deficiency on the trafficking and metabolism of membrane proteins. Remarkably, cells from PS1-1- mice fail to secrete Ab peptides, commensurate with the accumulation of cellular APLP1, also accumulates in from PS1-1- cells, suggesting a role for PS1 in trafficking of CTFs to cellular compartments in which g-secretase reside. Ongoing investigations are focused on the role of PS1 in facilitating g-secretase processing and Ab production and membrane protein trafficking. Supported by NIH, NIA, Adler Foundation, Alzheimer's Association and Develbiss Fund.

APP AND AMYLOID IN CELLS, SLICES AND BRAIN OF TRANSGENIC MICE

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Different strains of transgenic mice were generated with neuronal overexpression of Amyloid Precursor Protein (APP). We used the mouse thy1 gene promoter to express specifically in neurons, either wild type APP or the London, Swedish, Dutch or Flemish clinical APP mutants. Remarkably, all APP transgenic strains displayed in essence the same phenotype we described previously for the APP/RK transgenic mice (Moechars et al., 1996, EMBO J, 15:1265-1274). Major symptoms include: disturbed behavior, neophobia, agression, increased tendency for seizures, hypersensitivity to kainic acid, hypo-sensitivity to NMDA, premature death. Differences were mainly quantitative, i. e. in intensity, severity or age of onset of the symptoms which related to transgene expression levels. The exception was the occurrence of amyloid plaques in the brain of APP/london transgenic mice more than 12 months old. Occasional plaques were observed in APP/swedish transgenic mice, but not in the other transgenic strains showing at the most some diffuse amyloid deposits. Biochemical analysis of secreted and membrane-bound APP, C-terminal "stubs" and Aβ(40) and Aβ(42) peptides in brain, indicated that no single intermediate can be responsible for the complex of phenotypic dysfunctions. Aβ(42) levels were especially prominent in APP/London transgenic mice and correlated directly with the formation of amyloid plaques in older mice of this line. Their characteristics were very reminiscent of plaques in AD patients, including some immunoreactivity for hyperphosphorylated tau, however without real tau-pathology. Measured in the Morris watermaze paradigm, a cognitive deficit was most marked in the APP/london transgenic mice

even at 4 to 6 months of age, but was also observed in APP/wild type transgenic mice. This dissociates in time the early, general deficits from the late, more selective development of amyloid plaques in old APP/london and swedish mice. Wheras the ocurrence of amyloid plaques is explained by higher levels of Aβ42 peptide, they are clearly not essential for the cognitive and behavioral phenotypic traits, which appeared linked to other metabolites, i. e. Aβ40 peptide and b-cleaved C-terminal domain of APP (Moechars et al, 1999, JBC, in press). Double transgenic mice, generated by crossing the APP/london with Presenilin-1 transgenic mice develop amyloid plaques when only 6 months old, due to increased production of Aβ42 peptide. The other APP-metabolites are relatively unchanged, which is concordant with the observation that the early behavioral traits in the APP/Lo x PS1 double tg mice are not essentially different from the single APP/london tg mice, while the PS1 tg mice have essentially no pathology or phenotypic abnormalities. Since mice deficient in PS1 are not viable, we used primary neuronal embryonal cultures to demonstrate that the production of the amyloid peptides is reduced dramatically in the absence of PS-1 (De Strooper et al, Nature, 1998, 391: 387-390). PS-2 knockout mice on the other hand are viable and phenotypically normal, and the absence of PS2 does not affect amyloid peptide production in neuronal cultures. "Deletion" or "inbreeding" of other relevant genes is ongoing to determine which of the APP metabolites is causing the early signs of the phenotype described above and to induce and eventually determine the importance, if any, of the intraneuronal tangles, the other lesion essential for diagnostics of AD.

HUNTINGTON'S DISEASE AND POLYGLUTAMINE DISORDERS

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disease. Whilst onset is generally within the 4th or 5th decade, symptoms can appear at any time from early childhood until very old age with a mean duration of 15 - 20 years. Patients exhibit a diverse set of symptoms, with well recognised emotional, cognitive and motor components. Neuropathological examination shows that the majority of specific cell loss occurs in the cortex and the striatum although this can be more widespread in the juvenile disease frequently including the cerebellar Purkinje cells.

The HD gene contains 67 exons and extends across 170 kb DNA and is expressed in all tissues. The CAG repeat that is expanded on HD chromosomes lies within exon 1 and is translated into a stretch of polyglutamine (polyQ) residues in the huntingtin protein. The normal and expanded ranges are (CAG)6-39 and (CAG)36-180 respectively. The majority of adult onset cases have expansions ranging from 40-55 units, whereas expansions of 70 and above invariably result in a juvenile onset. Within the brain, huntingtin is found predominantly in neurons and is present in cell bodies and neurites but is absent from the nucleus.

In addition to HD, a polyQ expansion has been found to cause seven other late onset, inherited neurodegenerative diseases, namely: spinal and bulbar muscular atrophy (SBMA), dentatorubral pallidoluysian atrophy (DRPLA) and the spinocerebellar ataxias (SCA) 1, 2, 3, 6 and 7. These diseases bear many similarities in their genetics and molecular biology. Therefore, we would predict that these diseases operate via the same molecular pathway. However, despite the widely overlapping expression patterns of the polyQ expansion proteins, strikingly different patterns of neurodegeneration are evident (although the juvenile forms show a wider and less distinct neuropathology). The molecular event that triggers pathogenesis must correlate with the polyQ pathogenic size threshold, account for the late onset of the disorders and explain the differential selective neuronal vulnerability.

The R6 transgenic lines

The R6 lines are transgenic for a 2 kb genomic fragment that spans the 5¢ end of the human HD gene, encompassing 1 kb of control elements and which produces an N-terminal exon 1 protein corresponding to approximately 3% of huntingtin. Four lines contain expanded CAG repeats of a size larger than that generally associated with juvenile HD: R6/1, (CAG)115; R6/2 (CAG)145, R6/5 (CAG)135-156; R6/0 (CAG)142 and a further two lines: HDex6 and HDex27 contained (CAG)18 as normal repeat controls. In all cases except line R6/0 (in which the transgene is silenced by the site of integration), the transgene protein is expressed across all tissues.

A progressive neurological phenotype develops in lines R6/1 and R6/2 when hemizygous for the transgene and in line R6/5 when bred to homozygosity. On the basis of home cage behaviour, the onset ages are approximately 2 months in line R6/2 and 4-5 months in line R6/1. The phenotype includes a movement disorder and weight loss with similarities to HD. Rotarod analysis of motor function demonstrates that significant deficits can be detected in R6/2 mice as early as 5 weeks. The phenotype progresses rapidly and by 12 weeks the movement disorder is pronounced. Mice are generally studied at 4, 8 and 12 week time points and a small number of mice have been available at 16-17 weeks of age.

A detailed neuropathological analysis of R6/2 mice was initially disappointing as no evidence of selective neuronal cell death could be identified by 12 weeks. The first major differences were detected by immunocytochemistry with antibodies directed toward the N-terminus of the huntingtin protein which uncovered the presence of neuronal intranuclear inclusions (NII). These inclusions can be identified at the ultrastructural level in the absence of immunostaining as a granular and fibrillar structure devoid of a membrane. Inclusions are first present before 4 weeks in the cerebral cortex and hippocampus but can be identified in every neuron well before the end stage of the disease. In contrast, selective cell death is not seen until 14 weeks and has only been found in the frontal cortex, striatum and in cerebellar Purkinje cells. By ultrastructure these neurons appear as dark osmophillic condensing neurons which show some but not all features of apoptosis and the process has been dubbed "dark cell degeneration". These dark condensing neurons have also been identified in the parallel regions of postmortem HD brains.

The symptoms observed in the R6 lines occur after the appearance of neuronal inclusions but long before a specific cell loss can be detected. Insights into a possible cause of this neuronal dysfunction have arisen from neurotransmitter receptor binding and expression studies in line R6/2. In some cases by 4 weeks, and in all cases by 8 weeks, major alterations in the dopamine and glutamate neurotransmitter systems have been detected, both of which have importance in striatal function. Neuronal inclusions in polyglutamine disease NII have now become the pathological signature of polyQ disease and have been identified in HD, SBMA, DRPLA and SCA1, 3 and 7 postmortem brains. In all cases they are found in the nucleus, except in HD in which they have also been described as dystrophic neurites. In HD, inclusions appear to contain the N-terminus of huntingtin suggesting the requirement for a rate limiting processing step that would have been by-passed in the R6 lines.

Polyglutamine aggregation

GST-exon 1 fusion proteins generated in E. coli have shown that upon removal of the GST tag, proteins containing pathogenic polyQ repeats form ordered fibrillar structures. Congo red staining and the corresponding birefringence when observed under polarised light indicates that the fibres are amyloid-like with a cross b-sheet structure. That is consistent with the prediction that polyQ repeats could adopt this structure, termed a polar zipper, via H-bonding between main-chain and side-chain amides. The remarkable correlation between the pathogenic polyQ lengths and the ability of the exon 1 protein to form orderd fibrils strongly suggests that aggreation forms the molecular basis of the polyQ diseases.

PRIONS AND THE IMMUNE SYSTEM

Adriano Aguzzi, Institute of Neuropathology, University Hospital of Zürich, CH-8091 Zürich.

A wealth of evidence points to the identity of PrPSc with the prion, the transmissible agent causing spongiform encephalopathies (TSEs) (1-2). To address the question of CNS pathogenesis, we grafted neuroectoderm from mice which overexpress PrPC into the brain of scrapie-resistant PrP-deficient mice, and inoculated it with scrapie prions. Infected grafts developed scrapie and contained high amounts of PrPSc and infectivity, while neighbouring cells remained unaffected. The host life span was not reduced. Therefore, availability of endogenous PrPC to the infectious agent, rather than deposition of PrPSc, correlates with scrapie neurotoxicity *in vivo* (3). We then addressed the spread of prions from peripheral sites to the CNS, by transplanting neuroectoderm from overexpressing PrP to the brain of *Prn-po/o* recipients. Scrapie was not detected in grafts after intraocular (*i. o.*), intraperitoneal (*i. p.*), or subcutaneous (*s. c.*) inoculation. Immunity to PrP developed in several animals soon after grafting, but anti-PrP titers did not influence the course of the disease after *i. c.* inoculation, and no transport of i. o. infectivity was detected in animals tolerant to PrP (4). Adoptive transfer of PrP-expressing bone marrow cells restored prion replica-

tion in the spleen, but did not reconstitute neuroinvasion via i. p. route (5). These results indicate that PrPC supports infectious spread from the periphery to the CNS, and imply that neuroinvasion depends on the neuroimmune interface (6). We also showed that B-lymphocytes are crucial for neuroinvasion (7), independently of whether they express PrPC or not (8). This may indicate a target for post-exposure prophylaxis (9-10).

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Symposium 5
CONTROVERSIAL TREATMENTS IN NEUROLOGY
Chairman: J. Bogousslavsky

THE IMPLEMENTATION OF B-INTERFERON IN MULTIPLE SCLEROSIS

C Confavreux (Lyon)

THROMBOLYSIS IN ACUTE STROKE

W. Hacke

(Abstract added in proof – see page I/183)

WHAT IS THE GOAL OF SURGICAL TREATMENT IN PARKINSON'S DISEASE?

Alberto Albanese

Parkinson's disease is a degenerative condition of the nervous system associated with the loss of dopaminrgic nigrostriatal neurones. Many symptoms of the disease can be explained by the loss of dopamnergic function in the central nervous system, but non-dopaminergic symptoms are also observed. No etiologic treatment is available for Parkinson's disease; current studies are aimed to identify treatments capable to interfere with the pathophysiology of the disease. Symptomatic treatments which enhance dopaminergic function in the brain are particularly efficacious in controlling motor symptoms.

The role of surgery in Parkinson's disease is historically correlated to the efficacy of drug treatments. Stereotactic surgery has flourished in the 1950s and has progressively declined after the discovery of levodopa. Current surgical indications for Parkinson's disease address two main issues which are not currently solved by antiparkinsonian medication: (1) protective and restorative therapy can be provided by the intracerebral administration of trophic factors or by the graft of neural and non-neural cells; (2) symptomatic benefit can be provided by high frequency stimulation of the glutamatergic subthalamic nucleus.

Brain grafting has provided a revolutionary concept for the treatment of Parkinson's disease. This approach is based on the implant of dopamine neurones (or of dopamine-producing cells) into a structure originally innervated by the endogenous dopaminergic system. The degenerated nigrostriatal pathway cannot be reconstituted by grafts, which are to be placed into the neostriatum, where dopaminergic terminals are contained. Grafted neurones are expected to form synaptic connections with the host neostriatum: the resulting neuroanatomical reorganisation provides a new network, whose function can compensate for the motor deficits associated with the loss of nigrostriatal neurones. To date, more than 250 Parkinson's disease patients have received substantia nigra foetal grafts; this procedure has gained unanimous scientific acceptance, but has not become a common treatment. In few outstanding cases patients have been able to withdraw levodopa therapy following the graft. Motor improvement is highly variable and depends, in all likelihood, on the extension of graft-to-host reinnervation. About two-thirds of the patients had a partial recovery of motor function, while few patients had improvement of gait, language and balance associated with improvement of dyskinesias. Glial cell-derived neurotrophic factor (GDNF has been shown to enhance survival and function of foetal nigral dopaminergic grafts, but its potency and specificity raise the question whether it may be used as a solo therapeutic agent to restore the degenerated nigrostriatal tract in Parkinson's disease. Sertoli cells also provide a source of factors improving the survival and maturation of embryonic dopaminergic neurones; it has been shown recently that porcine Sertoli cells provide a trophic effect on human mesencephalic neurones in vitro. Other strategies are based on the use of xenografts with largely available foetal tissue from mammals, such as pigs, or the use of genetically modified cells or of stem cells.

Subthalamic nucleus (STN) stimulation has provided a new approach to the treatment of Parkinson's disease. This procedure has been developed very recently, when standard stereotactic procedures consisted in thalamic or pallidal lesions and stimulations. Thalamic surgery is capable to control tremor and dyskinesias (if the operation extends beyond the Vim nucleus). Pallidal surgery can control dyskinesias (and other parkinsonian signs to a limited extent). These two operations allow to control a limited set of parkinsonian signs, are not always safe if performed bilaterally and often require a compensatory increase of medication. STN surgery should not be ablative, due to the risk of hemiballism. STN neurostimulation allows to reduce drug medication to a very significant extent, and to stop it in some cases, as demonstrated by published and still unpublished patient series. Continuous stimulation is particularly indicated to provide continuous benefit, smoothing up daily fluctuations and allowing for adequate mobility at night. Reduction of medication further allows to prevent drug-related side effects, such as hallucinations and psychosis. The high cost of the implanted devices is balanced by the improvement of motility and of daily living activities, and by the possibility to pursue working activity.

DEALING WITH NEW DRUGS IN EPILEPSY

J. Sander (London)

(Abstract added in proof – see page I/185)

Oral Sessions

Cerebrovascular disorders – 1

1

SILENT INFARCTS IN STROKE PATIENTS: INFLUENCE ON 2-YEAR OUTCOME. F. Corea, H. Hénon, F. Pasquier, D. Leys and the Lille stroke/dementia group. Department of Neurology. Stroke and Memory Clinics. University Hospital, Lille, France.

Silent infarcts (SI) are frequent findings in stroke patients, but their clinical significance remains unclear. Only a few controversial data are available concerning the influence of SI on stroke outcome. Objective: To evaluate the prevalence of SI in consecutive stroke patients, associated factors, and influence on outcome. Methods: The study population consisted of 202 patients (97 males) with a median age of 75 years (range: 42-100), consecutively admitted for an ischemic or hemorrhagic acute stroke with clinical deficits lasting more than 24 hours. Survivors were followed-up at month-24. Patients with Rankin scores of 0 or 1 were considered as independent. Results: Of 202 patients, 53 (26. 2%) had SI on CT-scan. SI were deep hemispheric in 46 patients (86. 8%), superficial hemispheric in 5 (9. 4%) and in the posterior fossa in 7 (13. 2%). Using logistic regression analysis, factors independently associated with the presence of SI were higher leukoaraiosis scores (p=0.0003) and small-vessels occlusion as presumed cause of the index stroke (p=0.004). Conclusion: SI are present in one fourth of stroke patients and involve deep territories in most cases. Our study shows that SI is associated with leukoaraiosis and small-vessel disease, but did not influence mortality or functional outcome. F Corea received an ENS fellowship stipend to conduct this study in Lille.

2

FOLLOW-UP OF VERTEBRAL ARTERY DISSECTION USING COLOR-CODED DUPLEX-SONOGRAPHY AND ANGIOGRAPHY. [1]Maria Mosso, [3]Christof Klötzsch, [3]Johannes Noth, [2]Ulrich Sliwka. Depts. of

Neurology, [1]Universitätsspital Zürich, Switzerland, [2]FSU Jena, [3]RWTH Aachen, Germany.

Objective: To follow-up vertebral artery dissection using colour-coded duplexsonography (CCD) and digital subtraction angiography (DSA). Methods: Thirty-three patients (18 men,15 women, mean age 42+/–12 years (+/–SD) with 40 sonographically diagnosed dissections of the vertebral artery were enrolled in the study. The dissections were confirmed with DSA (n=38) or magnetic resonance angiography (MRA) (n=2). Extra- and transcranial CCD were performed using an Acuson XP128/10 device (5/7. 5-MHz- and 2/2. 5-MHz-probe). For transcranial studies and for deeply located vertebral arteries echo contrast enhancer (LevovistR, Schering, Germany) was applied. All patients were reinvestigated using extra- and transcranial CCD, while 23 patients underwent a second DSA (n=17) or MRA (n=5) after receiving anticoagulation for 6 months. Results: Dissections occurred after trauma in 14, after minor trauma in 8 and spontaneously in 18 cases. DSA showed signs of fibromuscular dysplasia in 8 patients (24%). 94% of the patients presented brainstem or cerebellar symptoms. The initial findings were irregular stenosis (n=16), occlusion (n=18) and pseudo-aneurysm (n=6). The V4-segment was involved in 22 cases, the atlas loop (V3) in 21 cases and the V0-V2-segments in 16 cases. Twenty dissections (50%) were multisegmental. CCD was able to detect all extra- and intracranial stenoses and occlusions, but failed to detect the 6 pseudoaneurysms. During a mean follow-up of 42 years (SD) 20 dissections (50%) normalised, two recanalized incompletely and 18 dissections remained unchanged. CCD demonstrated these findings in 37 (93%), but failed to detect 2 pseudoaneurysms and one intracranial stenosis. 29 patients (88%) had a good outcome. No recurrent vertebral artery dissection was seen, an internal carotid artery dissection occurred in 2 cases (6%) during follow-up. Conclusion: CCD is able to detect dissection of the extra- and intracranial segments of the vertebral artery and makes a differentiation from atherosclerotic changes possible in most cases. Recanalization of vertebral artery dissection can easily be monitored by CCD, but this method failed to detect pseudoaneurysms of the V3-segment, which in rare cases can be an embolic source.

3
THE LAUSANNE EMOTION IN STROKE STUDY. EMOTIONAL BEHAVIOR IN ACUTE STROKE. F. Ghika-Schmid, A. Berney, G. van Melle, P. Guex, J. Bogousslavsky. Lausanne University, Switzerland.

We assessed early patterns of emotional behavior in stroke and correlated them with stroke features, location and prognosis. We prospectively studied all patients with first-ever stroke during the 4 first days, with a Behavioral index form specifically designed and validated with inter-examiner fidelity on 35 patients. It included a quantified rating of reactions: overt sadness, passiveness, aggressiveness, indifference, disinhibition, denial, adaptation, abnormal sleep/feeding. Days 7 and 90 follow-up included mood scales (Hamilton), functional scores (Barthel/Rankin/ADL) and psychiatric interview. 83 patients (45 men, 38 women, age 63 ± 18 years) had stroke in the MCA territory (46) or posterior circulation (37) ; 33 right, 48 left and 2 bilateral, with acute reactions of disinhibition (68), denial (54), indifference (57), overt sadness (63), aggressiveness (58), or abnormal sleep/feeding (69). On day 7, 46 (55%) patients had adequate memory of the acute event, whereas recall was partial in 28 (34%) and impossible in 14 (17%). On the 3rd month, 41 patients (49%) were anxious (16), anxio-depressive (13), depressed (10), or sub-manic (2). Preliminary analysis suggested that behavior of denial, may be related to post-stroke depression. We conclude that early emotional behavior can be quantified in acute stroke using the Behavioral Index Form. This will allow us to delineate the best predictors of subsequent mood disorder and to perform detailed clinical-topographical correlations.

4
UPREGULATION OF IL10- AND IL12P40-MRNA AFTER FOCAL CEREBRAL ISCHEMIA IN THE RAT. G. Stoll, S. Jander, M. Schroeter. Department of Neurology, Heinrich-Heine-Universität, Düsseldorf, Germany

Focal brain ischemia triggers a strong glial and inflammatory response that is accompanied by an early and transient upregulation of the proinflammatory cytokines tumor necrosis factor (TNF)α and interleukin (IL) 1β (reviewed in Stoll et al. (1998) Prog. Neurobiol. 56:149-171). The mechanisms that consecutively downregulate proinflammatory cytokines in stroke are unknown at present. We used semiquantitative reverse transcriptase-polymerase chain reaction to assess mRNA expression of the potentially immunosuppressive cytokines IL 10 and IL12 p40 in ischemic lesions after permanent occlusion of the middle cerebral artery in rats. We found induction of IL10-mRNA and IL12p40-mRNA within 4 hours after infarction concomitant with increased IL1β and TNFα expression which peaked during the first 48 hours. IL10 and IL12p40 persisted at lower levels until day 6. Our data extent previous studies showing that cerebral ischemia induces a dramatic cytokine upregulation that precedes the inflammatory response. The cellular sources and functional roles of pro- and antiinflammatory cytokines in stroke development await further clarification. Supported by the DFG (SFB 194, B6) and the Hermann- and Lilly-Schilling-Stiftung

5
CEREBRAL ISCHEMIC STROKE AND SUBSEQUENT PREGNANCIES. Hamon JB, Lamy C, Mas JL. For the Stroke in Pregnancy French Study Group, France.

The risk of recurrence of an ischemic stroke associated with subsequent pregnancies is unknown. The aims of this study were to assess whether 1) the occurrence of an ischemic stroke affects the number and desire for subsequent pregnancies 2) subsequent pregnancies increase the risk of recurrent stroke. We identified all consecutive women aged between 15 and 45 years admitted for an ischemic stroke between January 1987 and 1997 in 8 neurologic academic centers of France. Outcome after stroke, number of subsequent pregnancies and occurrence of recurrent strokes were recorded by a written and telephone interview. Four hundred and seventy-two patients were included in the study; informations were obtained for 420 (89%). One hundred and eighty-three subsequent pregnancies occurred during the study period (8. 7 % women-year). Thirty-four percent of women were not satisfied by the number of pregnancies following stroke. The main reasons for not considering pregnancy were worry about a recurrent stroke and residual handicap. Sixteen had a recurrent stroke outside pregnancy, during a mean follow-up of 4. 7 years +/– 2 (rate of recurrence: 0. 8 percent women-year; 95% IC: 0. 5-1. 3). Two recurrent strokes were associated with pregnancy or the puerperium (rate of recurrence: 1. 9 percent women-year; 95% IC: 0. 2-6. 7). Conclusion: The rate of subsequent pregnancies after an initial ischemic stroke seems to be low and more than a third of women are not satisfied by the number of pregnancies following stroke. The risk of recurrent stroke does not appear to be much increased by subsequent pregnancies.

6
PREVALENCE OF SYMPTOMATIC INTRACRANIAL ANEURYSM AND ISCHAEMIC STROKE IN PSEUDOXANTHOMA ELASTICUM. JSP van den Berg, MD[1], M Limburg, MD[2]. [1]Department of Neurology, University Hospital Nijmegen, Nijmegen. [2]Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands.

Background Pseudoxanthoma elasticum (PXE) is a heritable connective tissue disorder with clinical manifestations of the ocular, dermal, and cardiovascular system. The purpose of this study was to investigate the prevalence of symptomatic intracranial aneurysms (IAs) and ischaemic stroke (IS) in PXE. Methods The records of 100 patients with PXE were retrieved. All patients were contacted and data on complications were collected. The literature was reviewed regarding PXE, ISs, and IAs. Findings No patient with PXE had a symptomatic IA as presenting symptom. One patient presented with an IS. During follow-up of 94 of the 100 patients (mean follow-up 17. 1 years, range from 1 to 49 years) none presented a symptomatic IA (3168 retrospective patient observation years and 1602 prospective patient observation years). A gastrointestinal haemorrhage during follow-up occurred in 18 patients, in one patient during aspirin use. One patient had IS as presenting symptom and a recurrence during follow-up, and seven patients had IS during follow-up. All were caused by small vessel disease. The relative risk of IS in PXE compared with normal population was 22 (95% confidence interval 10. 8-39. 1). Interpretation A association between symptomatic IAs and PXE s unlikely. However, the incidence of IS, due to small vessel disease, was clearly increased. Antiplatelet therapy in patients with PXE may lead to a high incidence of gastrointestinal haemorrhages.

Cerebrovascular disorders – 2

7
ENDOVASCULAR TREATMENT RESULTS OF PATIENTS WITH SEVERE SUBARACHNOID HEMORRHAGE (GRADE IV AND V)

ACCORDING TO ANEURYSM LOCALIZATION. C. Kremer, C. Groden*, H. C. Hansen, H. Zeumer*, K. Kunze. Department of Neurology, *Department of Neuroradiology, University of Hamburg, University Hospital Eppendorf, Germany

The most common cause of poor treatment outcome in patients with a aneurysmal subarachnoid hemorrhage (SAH) is cerebral vasospasm especially in cases of poor Hunt and Hess grades (grade IV and V). A further prognostic factor in surgically treated patients is aneurysm localization. Aim of this retrospective study is to compare the endovascular treatment outcome in such poor grade patients according to aneurysm localization in either the anterior (AC) or posterior (PC) circulation. Forty poor grade patients admitted between 1993 and 1998 were treated by endovascular approach within 23 days after rupture. 18 had aneurysms in the AC, 22 in PC. One patient showed multiple aneurysms. In 36 cases the aneurysm was occluded by Guglielmi detachable coils (GDC), in 4 cases by parent vessel occlusion. The incidence of a delayed neurological dysfunction (DIND) or a cerebral infarct due to vasospasm did not differ significantly between the anterior and posterior groups. At 6 months follow-up the result was good in 5 patients and poor in 13 in the AC group, good in 11 patients and poor in 11 in the PC group. Conclusions: Under comparable incidence of vasospasm in poor grade patients a better treatment outcome was achieved in patients with aneurysms in the posterior than in the anterior circulation

8
CEREBRAL BLOOD FLOW AFTER INTRAARTERIAL AMOBARBITAL INJECTION. TK Pfefferkorn, C Hundt, U Missler, J Ilmberger, S Arnold, GF Hamann, Klinikum Grosshadern, LMU Muenchen, Germany

The influence of neuronal activity on cerebral blood flow has mainly been investigated in settings with increased cerebral activity. In this study blood flow was examined after pharmacological reduction of neuronal activity. Patients and Methods: Ten patients that were considered for temporal lobe surgery (epilepsy and/or brain tumor) were examined. In all patients an intraarterial amobarbital injection in both internal carotid arteries with concommitant EEG documentation and neuropsychological testing (WADA test) was performed to decide on hemispheric dominance. Throughout the test middle cerebral artery (MCA) mean flow velocity (MFV) was monitored by continuous bilateral transcranial dopplersonography. Results: Off line analysis of MFV could not be performed in 7 of 20 measurements because of insufficient signal quality. In the remaining 13 cases ipsilateral MFV started to decline 20 seconds after injection to a minimum of 50. 4% 9. 1% of pre-injection values at 60 seconds. In the following 9 minutes MFV gradually normalized (66. 0% +/- 17. 1%, 88. 5% +/-10. 1%, and 95. 3% +/- 11. 4% after 2, 5, and 10 minutes post injection). EEG changes and the maximum of neurological deficits were consistently seen prior to MFV changes (5-10 seconds after injection). Conclusion: Our investigation demonstrates a marked secondary reduction in cerebral blood flow velocity after pharmacologically induced loss of neuronal function with a latency of about 20 seconds. This reduction is preceded by EEG changes and functional deficits.

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THE NATURAL HISTORY OF FAMILIAL CEREBRAL CAVERNOMAS. A RETROSPECTIVE MR STUDY OF 40 PATIENTS. Authors: P. Labauge* (MD), L. Brunereau** (MD), C. Lévy** (MD), S. Laberge* (MD), J-P Houtteville*** (MD). *INSERM U25, Faculté de Médecine Necker-Enfants Malades, 156 Rue de Vaugirard Paris 75730 France. **Service de Radiologie. CHU Saint-Antoine. 184 Rue du Faubourg Saint-Antoine. 75012 Paris. France. ***Service de Neurochirurgie. CHU Côte de Nacre. 14033 Caen. Cedex. France

Objective. To determine the natural history and prognosis factors of familial forms of cerebral cavernous malformations (CCM). Background. Cavernomas are one of the most frequent central nervous system vascular malformations. Familial CCM is increasingly diagnosed but little is known about the natural history. Methods. During a previous national survey, we have studied clinical and magnetic resonance (MR) imaging features of 57 French families including 173 patients. Of these patients, 40 had undergone at least two serial clinical and MR examinations. MR follow-up analysis have been retrospectively established. Occurrence of hemorrhage, new lesions appearance, change in signal intensity and size of lesions have been studied by means of comparison between first and last MRIs. Results. Mean follow-up period was 3. 2 years (range 0. 5-6. 5). A total number of 232 cavernomas were followed (mean 5. 9 lesions per patient, range 1-17). Serial MRIs demonstrated changes in 28 patients (70 %): i) bleeding occurred in 21 lesions (9. 1 %) of 14 patients (35 %). The haemorragic risk was of 2. 5 % per lesion-year. Increased risk is observed in brainstem cavernomas; ii) 23 new lesions appeared in 11 patients (27. 5 %) with an incidence of 0. 2 lesion per patient year; iii) MR signal intensity change was observed in 11 patients (27. 5 %) including 14 lesions (6 %), whereas 9 lesions (3. 9 %) in 9 patients (22. 5 %) changed significantly in size. Conclusions. Our study underlines the specific features of familial CCM, i. e. high frequency of multiple lesions and hemorrhagic risk and occurrence of new lesions.

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MATRIX METALLOPROTEINASES (MMPS) AND IL-8 CSF-LEVELS ARE CORRELATED WITH BRAIN EDEMA FOLLOWING STROKE. Braker C., Shapiro S., Lahat N., Sobel E., Honigman S., Miller A. Division of Neuroimmunology, Department of Neurology and Immunology Research Unit, lady Davis Carmel Medical Center; Haifa, Israel.

A variety of immune-mechanisms have been recently suggested to play a role in cerebral ischemia, both in experimental animal models as well as in stroke patients. Inflammatory cells (neutrophils, monocytes) and mediators (TNFa, IL-1) have been identified in cerebral infarcts. Methods: Using Elisa assays, CSF samples from 18 acute stroke patients and 12 controls, were evaluated for the extracellular matrix degrading enzymes MMP-2 and MMP-9, the chemokines IL-8, RANTES, MIP-1a and the soluble adhesion molecule sICAM-1 levels. In parallel, the number of CSF cells and protein levels as well as clinical (NIH scale) and neuroradiological characteristics (infarct size and cerebral oedema) were assessed. Results: MMP-2, MMP-9, IL-8 and ICAM-1 levels in CSF were significantly higher in patients with moderate or severe peri-infarct oedema, compared to patients with mild oedema or controls. In contrast, RANTES and MIP-1a levels were not detected either in controls or in stroke patients. Conclusions: These results provide further support for the role of immune-reactivity in the pathogenesis of hypoxic brain injury and implicates specific chemokine-antagonists and MMPs inhibitors as potential therapeutic strategies for stroke.

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VASCULAR APHASIAS IN ACUTE STROKE UNITS: CHARACTERISTICS AND OUTCOME. 0 Godefroy, C Dubois, B Debachy, A Kreisler, I Declerc and D Leys, France.

Although aphasia is mainly caused by stroke and influences its prognosis, aphasia characteristics at the acute stage of stroke and its outcome remain poorly documented . The study population consisted of 308 consecutive stroke patients (mean age: 62. 5) examined using a standardised aphasia battery. Language disorders have resolved in 50 patients, dysarthria or non-aphasic cognitive disorders was observed in 35 patients, and aphasia in 207. Global and non-classified aphasias were observed in 107 patients and classical syndromes, in 100 patients only. General factors (age: p=0. 6, sex: $p < -0.8$) did not influence aphasia type whereas previous stroke was more frequent in non-classified aphasia (p=0.04). Among the 207 contacted patients, aphasia outcome was assessable in only 72 patients who were younger (mean age: 56. 5) (p=0.0001). Oral communicatiòn (Functional Communication Measures) was severely impaired in 3 patients, moderately impaired in 28 and allowed independent communication for daily activities in 38 patients. Predictors of aphasia outcome were the initial syndrome (p=0.01), age (p=0.0001), initial severity (p=0.003), and intensity of speech therapy (p=0.0001). This study showed that (1) global and non-classified aphasias are the most frequent syndromes at the acute stage of stroke whereas classical aphasias are less frequent; (2) outcome remains poor even in this younger E subgroup of patents, and (3) that it depends mainly on age, initial severity and treatment.

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CLINICAL CHARACTERISTICS AND PREDICTORS OF DISABILITY OF STROKE IN THE OLD. M. Lamassa, A. Di Carlo, AM. Basile, G. Pracucci, P. Vanni, S. Spolveri, MC. Baruffi, D. Inzitari on Behalf of EC Biomed Stroke Project.

Data on characteristics of diseases in different age groups are relevant for health care planning and for resources allocation. The objective of the present work was to analyze differences in risk factors, clinical presentation, resource use and 3-month outcome in stroke patients aged 80 years and over compared to patients in the younger age group. In a context of EC

Biomed Stroke Project the patients hospitalized in seven European Countries were evaluated. Data collected were risk factors, clinical presentation, resource use and 3-month disability as assessed by the Barthel Index. Were studied 4499 patients (50. 2 % females; mean age 71. 812. 6 years) of whom 3141 were 80 years and 1358 were 80. Old patients were more often females, institutionalized prior to stroke, with atrial fibrillation, previous transient ischemic attacks, previous stroke and had also a worse pre-stroke Rankin Score. During hospitalization old patients were more frequently comatose and with paralysis, aphasia, swallowing problems and urinary incontinence. The use of diagnostic tools was by far less frequent in this age group. At logistic regression analysis, controlling for age and sex, independent predictors of 3-month disability in patients 80 were paralysis (OR,3. 58; 95%CI,2. 28-5. 63), swallowing problems (OR,2. 02; 95%CI,1. 16-3. 53), urinary incontinence (OR,3. 97; 95%CI,2. 49-6. 30), and pre-stroke institutionalization (OR,2. 31; 95%CI,1. 20-4. 47). The information on stroke patterns and outcome in the old may improve the quality and cost-effectiveness of stroke care in Europe.

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EAAT1 AND EAAT2 IMMUNOREACTIVITY IN THE SPINAL CORD IN AMYOTROPHIC LATERAL SCLEROSIS - S. Sasaki, M. Iwata. Department of Neurology, Neurological Institute, Tokyo Women's Medical University, Tokyo, Japan

We immunohistochemically investigated the spinal cord of 20 patients with amyotrophic lateral sclerosis (ALS), 5 patients with lower motor neuron disease (LMND) and, as controls, 20 patients without any neurological disease, using anti-human excitatory amino acid transporter 1 (EAAT1) and EAAT2 antibodies. In controls, spinal cord grey matter was densely immunostained with antibodies, whereas the white matter was generally not immunostained. In motor neuron disease patients, EAAT1 immunoreactivity was relatively well-preserved in the grey matter, while EAAT2 immunoreactivity in anterior horns correlated with the degree of neuronal loss: anterior horns were densely immunostained in the patients with mild neuronal depletion, but much less immunostained in those with severe neuronal loss. Degenerated anterior horn cells frequently showed a much denser EAAT1 and EAAT2 immunoreactivity than normal-appearing neurons did. These findings suggest that in the early stage of ALS, the function of astroglial glutamate transporters is preserved in the astrocytic foot directly attached to normal-appearing neurons,'whereas in that directly attached to degenerated anterior horn neurons levels of EAAT1 and EAAT2 protein rather increase probably to reduce the elevated glutamate level; that in the later stage, EAAT2 protein levels diminish as a secondary effect of neuronal loss, which in turn, causes further neurotoxicity in the anterior horn cells, resulting in an acceleration of motor neuron degeneration.

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EARLY PROGNOSTIC FACTORS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): AN INCIDENT-BASED PROSPECTIVE SURVEY. Anna A Terreni, for the Piemonte and Valle d'Aosta ALS Register, Turin, Italy

ALS prognostic factors have been usually determined in retrospective studies, often based on series referring to a single specialized center or to areas with a small population. We have investigated early prognostic factors in an incident cohort of ALS patients resident in Piemonte and Valle d'Aosta regions, Italy (population: 4,418,503), diagnosed during 1995-1996, and prospectively followed-up. Cases were identified through the Piemonte and Valle d'Aosta ALS Register. Disease progression was determined by means of manual muscle testing, bulbar scale, Norris scale and spirometry. For each parameter, mean monthly progression rate was established as mean number of points lost each month from the first visit to the 6-month follow-up visit. Of the 193 incident cases (mean annual crude incidence rate, 2. 17/100.000 [c. i. 1. 88-2. 50]), 6 were lost to follow-up. In univariate analysis, factors significantly related to outcome were age, bulbar onset, and progression rate of bulbar, lower limbs, and respiratory symptoms. Cox's multivariate model retained rate of progression of bulbar, lower limbs and respiratory symptoms; age; and percutaneous endoscopic gastrostomy. The results of this prospective population-based study indicate that the rate of progression of symptoms during the first 6 months of follow-up may reveal, with good reliability, the future outcome of ALS.

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STUDY OF THE CORTICO-SPINAL TRACT DEGENERATION IN AMYOTROPHIC LATERAL SCLEROSIS: CORRELATION OF NEUROPHYSIOLOGICAL AND MRI FINDINGS. Girlanda P., Quartarone A., Longo M., Ricciardi G., Battaglia F., Majorana G., Musumeci O. and Messina C. (Messina – Italy)

Objective: to assess the pyramidal tract involvement in ALS correlating the findings of MRI with clinical, and neurophysiological data. Methods: We studied ten consecutive ALS patients (6 men and 4 woman) with a mean age of 53. 8 9. 6 years (range 41-65). The diagnosis was made on the basis of the new El-Escorial criteria. The duration of illness was of 23. 3 8 months (range 17-36). All the patients underwent a complete neurological examination and were scored with the ALS functional rating scale. Motor evoked potentials after transcranial magnetic stimulation were recorded from FDI in all patients. The parameters that we took into account were the threshold, the silent period duration and the central conduction time (CCT). The MRI protocol included the conventional spin-echo technique and the FIRMS technique. Results: Eight out of ten patients with ALS, studied by MRI, demonstrated well defined round lesions, hyperintense on T2-weigthed images, along the CST that were best seen at the level of middle or lower internal capsule. Low signals intensity were detected within the motor cortex. The motor evoked potentials revealed alterations in 7 out of the 8 patients diagnosed by the mean of MRI. The alterations included changing in the threshold, reduction of the silent period and increase of the CCT.

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INTRAFAMILIAL PHENOTYPIC VARIABILITY IN MOTOR NEURON DISEASES: COEXISTENCE OF AMYOTROPHIC LATERAL SCLEROSIS AND INFANTILE SPINAL AMYOTROPHY IN 4 FAMILIES. P Corcia, J Khoris, P Couratier, B de Toffoll, C Hommet', A Autret', W Camu-1 CHU Bretonneau, Tours, France-2 CHU Guy de Chauliac, Montpellier, France-3 CHU Dupuyten, Limoges, France

The most frequently motor neuron diseases are amyotrophic lateral sclerosis (ALS) and infantile spinal atrophy (ISA). Incidence is 1 to 51100 000 inhabitants and 1/10 000 births, respectively. 10% of ALS cases are familial, in which 10% carry a mutation on the SODI gene. In 98% of the ISA cases, there is a homozygous deletion in the SMN I gene (telomeric part of the SMN gene). We report on 4 families where ISA and ALS coexist. It concerns 3 times a grand-parent with ALS and little-child with ISA, an association rarely described in the literature. The fourth family associates 3 ALS (2 siblings and a cousin) and 2 ISA cases : a cousin suffered from ISA type III and a nephew had type 1. Coincidental association can't be formally excluded especially in the families where 1 ALS and 1 ISA coexist. On the other hand, this seems highly improbable in the fourth family. Genetic analysis is under way. Mutation on SOD 1 gene and deletion in the SMN 1 gene have already been ruled out in the ALS cases.

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MOTONEURONAL DEATH INDUCED BY POLYGLUTAMINE TRACT ELONGATION IN ANDROGEN RECEPTOR DOES NOT CORRELATE WITH INTRACELLULAR AGGREGATE FORMATION. A Poletti, S Simeoni, L Martini. Istituto di Endocrinologia, via Balzaretti 9, Milano.

Spinal and Bulbar Muscular Atrophy (SBMA) is linked to an expansion of the CAG repeats in androgen receptor (AR) gene. These repeats give a polyglutamine (polyGln) stretch larger than 40 Gln in AR-SBMA. Eight different proteins containing expanded polyGln tracts have also been linked to neurodegenerative disordes, and elongation correlates with intracellular aggregates formation. To determine whether inclusions induce neuronal death, we have transfected immortalized motoneurons (NSC34 cells) with mutated forms of AR (without, with normal, or with elongated polyGln tracts giving NSC. QO, NSC. Q23, or NSC. Q46, respectively). We have tested A) cell survival B) aggregate formation and C) cell morphology. A) Cell viability is reduced in NSC. Q46 cells, but testosterone treatment partially counteracts the adverse effect. B) Transfection of NSC34 with AR. Q48 fused to green fluorescent protein indicates that aggregates are formed only after AR activation by androgens: no inclusions detectable in untreated cells, but several cytoplasmic aggregates formed after testosterone addition. C) Co-transfections of AR. Q(n) with EGFP-N1 produces dystrophic neurites in NSC. Q46/EGFP cells, suggesting abnormal neurite function in presence of polyGln of abnormal length. These observations indicate that neuronal degeneration in SBMA might be sec-

ondary to AR gene mutation causing axonal/dendritic insults independently from the aggregate formation. Grants funding TeleThon-Italy (A. 096) is gratefully acknowledged (IR 10,98 01326).

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QUALITY OF LIFE IN MOTOR NEURON DISEASE: A FOCUS ON THE INDIVIDUAL. Anne Hickey*, Ciaran O'Boyle*, Sarah Clarke*, Orla Hardiman - *Department of Psychology, Royal College of Surgeons in Ireland; Department of Neurology, Beaumont Hospital, Dublin.

This study examines the reliability and validity of an individualised quality of life measure (SEIQoL: Schedule for the Evaluation of Individual Quality of Life) in assessing the impact of Motor Neuron3Disease (MND) and disease progression on patient quality of life (QoL). The study sample comprised patients on the Irish Register for MND agreeing to participate following written invitation. Measures included the ALS-FRS (assesses disease status); HADS (assesses psychological distress); SEIQoL (QoL assessment). Of the first ten patients included in the study, illness duration ranged from 4 months to 6 years, severity scores from 14 to 36 (based on ALS-SS). Eight patients completed SEIQoL. Global SEIQoL scores ranged from 2 to 78. 1, with a mean of 42. 9. Mean SEIQoL outcome of the MND group was not statistically different from that of a group of palliative care patients with terminal cancer, but was significantly poorer than other patient groups (surgical patients: $p < 0.05$; peptic ulcer disease patients: $p < 0.05$). Reliability and validity of the SEIQoL were high (0. 82 in both cases), indicating the feasibility of using this measure in the context of MND. In conclusion, assessment of disease severity indicated respondents at various stages of MND, ranging from mildly to severely affected. SEIQoL was feasible in a majority of cases and yielded scores with high reliability and validity.

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HUMAN SPINAL CORD DEVELOPMENT IN ABSENCE OF SUPRASPINAL INFLUENCES (ANENCEPHALY). Vincenzo Silani, Massimiliano Braga, Andrea Ciammola, Antonio Pizzuti, Guglielmo Scarlato. The Institute of Neurology of the University of Milan Medical School - IRCCS Ospedale Maggiore, Milano, Italy

Anencephaly is characterized by a profound disorganization of the spinal cord anatomy due mainly to the absence of the supraspinal pathways. In three anencephalics at postconception week 15.0-16.2 the lumbar spinal cord demonstrated a significant volume reduction (about 65% compared to control) with both total cell and motor neuron (MN) loss (over 70%). Membrane ($Ganglioside_{GM1}$) and cytoplasm (Microtubule Associate Protein 1, 2, and Glial Fibrillary Acidic Protein) markers of neuronal and glial cells revealed the features of profound changes in the anatomical structure. Neurotrophin low ($p_{75\text{-}NGFR}$) and high (trkB) affinity receptor immunoreactivity were increased in the anterior column where developing MNs are located, suggesting a disconnection from the muscle target in presence of a normal innervation. β-Nerve growth factor (NGF) mRNA expression was detected in both the anencephalic cord and neuronal enriched cultures, demonstrating that NGF is locally synthesised and ruling out its deficiency as pathogenic in anencephaly. Anencephaly provides the demonstration of the capability of human MNs to innervate skeletal muscle independently from supraspinal influences. With some logical limitations related to the model, anencephaly represents an invaluable tool in gaining crucial information on supraspinal and segmental influences on MN development, survival, and muscle innervation in humans with possible implications for diseases characterized by MN loss such as Amyotrophic Lateral Sclerosis.

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AMYOTROPHIC LATERAL SCLEROSIS CASES WITH SOD1 MUTATIONS DO NOT FULFILL EL ESCORIAL CRITERIA FOR ALS: NOSOLOGIC CONSEQUENCES. Camu W, Khoris J, Portet F, Montpellier, France. Rouleau GA, Montreal, Canada. Salachas f, Meininger V, Paris, France. And the French study group on ALS.

In about 10 % of the amyotrophic lateral sclerosis (ALS) cases, the disease is inherited. In those familial cases, 10 % of the patients carry a mutation in the Cu/Zn superoxide dismutase gene (SOD1). A few families have been presented clinically, but recently it has been described that ALS patients carrying the A4V mutation never exhibit upper motor neuron signs (UMNS) and, at pathology, the corticospinal tract is not involved. Goals and methods. We analyzed the clinical profile of the 15 French patients with a SOD1 mutation, regarding El Escorial criteria. Medical reports of all the family members with ALS were also studied. Results. Several points are to be noted: 1) Atypical clinical signs such as paresthesia, severe pain or urgency micturition are frequent (1/3 of the families). 2) In more than 50 % of the families there is at least one member that never exhibited UMNS. 3) Within a family, the clinical presentation can be as variable as some members were considered as having Charcot-Marie Tooth disease, Friedreich's ataxia or multiple sclerosis. Conclusion: The clinical profile of ALS patients with SOD1 mutations is highly variable even within a family. It frequently does not meet the El Escorial criteria of "probable" or "definite" and is also atypical. More pathological presentations of these patients are warranted to better analyze the precise link that exist between ALS and motor degeneration linked to SOD1 mutations. We thank the Association Française pour la Recherche sur la SLA and the Association Française contre les Myopathies.

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THE RNA OF THE GLUTAMATE TRANSPORTER EAAT2 IS VARIABLY SPLICED IN AMYOTROPHIC LATERAL SCLEROSIS AND NORMAL INDIVIDUALS. Thomas Meyer, Andrea Fromm, Christoph Münch, Birgit Schwalenstöcker, Anne E. Fray, (1), Paul G. Ince, (2), Stefan Stamm, (3), Pamela J. Shaw, (1), and Albert C. Ludolph. Department of Neurology, University of Ulm, Federal Republic of Germany. (1) Department of Neurology, (2) Department of Neuropathology, University of Newcastle, United Kingdom; (3) Max Planck Institute of Neurobiology, Martinsried, Federal Republic of Germany.

An impaired re-uptake of synaptic glutamate, a substantial reduction of the glial glutamate carrier EAAT2, and abnormal splicing of the EAAT2 RNA has been reported in the motor cortex and spinal cord of ALS patients. Two of several novel EAAT2 transcripts have been reported to be specifically associated with ALS and to account for the loss of the EAAT2 protein in this disease. We studied the presence of five distinct splice forms of the EAAT2 RNA in the motor cortex of 17 ALS cases and 11 controls using reverse transcription and PCR. One transcript resulting from the retention of intronic sequences showed a more frequent expression of 59% in ALS cases as compared to 36% of controls suggesting that an altered expression of this transcript may be related to the disease process. Four other EAAT2 RNA resulting from the deletion of complete and partial exon sequences were equally amplified in diseased and normal tissue. We conclude that the presence of variably spliced EAAT2 RNA is not ALS-specific and more complex than previously recognized.

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BULBAR ONSET IN A SERIE OF 106 ALS PATIENTS. J. Pascual Calvet, A. Rodriguez Campello, A. Pou Serradell Servei de Neurologia. Hospital del Mar Universitat Autonoma de Barcelona.

Objective: to describe clinical, neurophysiological and neuroimaging characteristics, and prognosis in 30 patients with ALS of bulbar onset in order to find those features that differenciate this subgroup of patients.

Patients and methods: we review a series of 106 patients with ALS seen during the years 1988-1998, and select 30 with onset as progressive bulbar palsy (PBP). We analysed age, sex, age at onset, risk factors, follow-up, death and clinical features. We also describe the neurophysiological findings, functional respiratory pattern and MRI imaging of these patients. Eighth patients had peculiar oculomotor manifestations. Results: in a total of 30 patients, 20 were women and 10 men. The mean age was 68.6 in women and 60.8 in men. The mean duration of illness until death was 26.3 months. Pyramidal and bulbar signs appeared in 93.4 and 90.0% respectively; pseudobulbar symptoms were less frequents (76.7%). Oculomotor manifestations were present in 23.3% of patients (7 patients). They were characterized by palpebral apraxia and supranuclear vertical gaze palsy. Conclusions: 1) there was a higher proportion of women (66.6%), 2) tbe age of onset appeared to be later than in other forms of ALS, 3) supranuclear oculomotor features were associated signs in PBP (7 patients), 4) these patients had a shorter time evolution (mean 26.3 months). These features differentiate this subgroup from other clinical forms of ALS.

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RELIABILITY OF THE EL ESCORIAL CRITERIA FOR THE DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS (ALS). M. Poloni,

L. Manfredi, C. Balzarini, E. Beghi, A. Micheli, R. Riva, G. Logroscino and G. Filippini for the Italian ALS Study Group Bari, Como, Gussago, Milano, Monza, Piancavallo, Veruno, Italy

Diagnostic criteria for ALS have been recently devised for use in clinical studies and therapeutic trials (El Escorial WFN criteria for the diagnosis of ALS. J Neurol Sci 1994, 124 (suppl):96-107) The clinical features required for the diagnosis are the topographical location of upper (UMN) and lower motor neuron (LMN) signs in four CNS regions, the progression of these signs, and the absence of other diseases. The diagnosis is made on clinical grounds and the degree of diagnostic certainty (definite, probable, possible, suspected, no ALS) is based on the combinations of UMN and LMN signs. The reliability of the El Escorial criteria has been assessed in 39 patients with ALS (20) or diseases considered in the differential diagnosis (19). For each patient, the caring physician recorded the relevant clinical and laboratory features in an abstract form. Two experienced neurologists examined the forms and classified the patients according to the five El Escorial categories. Their agreement was tested at different diagnostic levels (1. definite vs others; 2. definite + probable vs others; 3. definite + probable+possible vs others; 4. no ALS vs others). The overall agreement was slight (kappa 0.11). The agreement was 77% (kappa 0.29) at the first level, 72% (kappa 0.40) at the second level, 64% (kappa 0.30) at the third level, and 64% (kappa 0.16) at the fourth level. The inter-rather agreement on the El Escorial criteria is at best modest even when the different diagnostic levels are combined.

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^{11}C-FLUMAZENIL PET STUDY OF FUNCTIONAL AND STRUCTURAL CORTICAL CHANGES IN AMYOTROPHIC LATERAL SCLEROSIS. Bonnaud I., Spelle L., Salachas F., Chiras J., Samson Y., Meininger V., Orsay and Paris, France

Amyotrophic Lateral Sclerosis (ALS) is characterized by degeneration of lower motors neurons. It may be associated with retrograde degeneration of cortical pyramidal motor neurons. ^{11}C-Flumazenil (CFLU) PET studies allow to quantify BZR loss which may reflect cortical structural changes. Thus, this method may be useful to map cortical structural changes and their evolution in ALS. Objective: To study functional and structural cortical abnormalies in ALS. Methods: Nine patients with ALS were compared to ten controls using CFLU PET. BZR loss was assessed on Bmax-dependant images, and rCBF abnormalities on early PET images. Both group and individual analysis were performed. Results: BZR loss was detected (p. 001) in the right frontal (area 10) and parietal (area 3) cortex and in the left frontal (area 45) and parietal (area 40) cortex. Decreased rCBF (p. 001) was detected within the same regions, and within the bilateral precentral gyrus (areas 6 and 4). Individual analysis depicted abnormalities in all patients. Conclusions: CFLU PET detects in ALS both rCBF abnormalities and BZR loss. BZR loss may reflect structural cortical changes such as neuronal loss, while rCBF decreases may reflect functional abnormalities. Thus, CFLU PET can be used to monitor in vivo cortical neuronal degeneration in ALS and may become a standardized evaluation tool for pharmacological studies.

Infectious disorders of the nervous system

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REACTIVE OXYGEN SPECIES (ROS) PRODUCTION OF CEREBROSPINAL FLUID (CSF) PHAGOCYTES IN THE EARLY PHASE OF BACTERIAL MENINGITIS *- Böttcher[1], R. Nau[2], R. Benecke[1], U. K. Zettl[1]. [1]Dept. of Neurol., University of Rostock, and [2]Dept. of Neurol., University of Göttingen, Germany

The outcome of infectious diseases of the central nervous system depends essentially on the functional capacity, activation and lifespan of phagocytes. An important criterion of the functional activity of these cells is the production of ROS by the respiratory burst. The time course of phagocyte-mediated ROS production was studied in five rabbits which were intracisternically infected with Streptococcus pneumoniae and treated with antibiotics at 16h, 18h, 21h and 24h after infection. Before the first and after every subsequent application of the antibiotics ROS production was measured in CSF cell subpopulations by flow cytometry using rhodamine 123 (RH) technique. ROS production by CSF granulocytes showed a peak before antibiotic treatment. Its subsequent decline (mean fluorescence channels of RH representing the ROS production: 100.1 at 16h after infection vs. 30.5 at 26 h) was strongly negatively correlated (r = -0.87) to the total CSF cell count (1010 Mpt/l vs. 8654 Mpt/l). CSF monocytes showed the same time course of ROS production (mean fluorescence channels of RH: 22.4 at 16h vs. 4.8 at 26h; r = -0.93). We conclude that phagocyte ROS production is important for further investigation of the pathophysiology of bacterial meningitis. As a cell specific functional parameter it is particularly useful for experimental studies and may have prognostic relevance in long term follow up of human meningitis cases. *Supported by the Deutsche Akademie der Naturforscher Leopoldina*

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MATRIX METALLOPROTEINASES (MMPS), IL-8 AND SICAM-1 IN BACTERIAL AND VIRAL MENINGITIS. Shapiro S., Lerner A., Lahat N., Sobel E. & Miller A. Center for Multiple Sclerosis, Immunology Research Unit, & Pediatric Department, Lady Davis Carmel Medical Center, and Technion-Israel Institute of Technology; Haifa, Israel.

Matrix Metalloproteinases (MMPs) have been implicated in blood brain barrier (BBB) eruption and in the pathogenesis of inflammatory CNS disorders. Although previous reports have shown the involvement of inflammatory cytokines (TNFa, IL-1 and IL-6) in meningoencephalitis, the role of MMPs in these processes has not yet been elucidated. In the present study we examined, by zymography and ELIZA, the CSF of children with clinical and PCR-positive (n=39) viral or culture-positive bacterial (n. =5) meningitis, as well as control CSF (n=32) samples, for the presence and activity of MMPs. ELISA was used to evaluate also CSF levels of the neutrophil recruiting chemokine Interleukin-8 (IL-8) and the soluble adhesion molecule ICAM-1 (sICAM-1). High levels of MMP2 (72kDa) and MMP9 (92kDa) gelatinase activity and protein levels, as well as IL-8 levels were observed in both viral and bacterial meningitis samples compared to controls. sICAM-1 levels were significantly higher in bacterial in comparison to viral, but not observed in controls. These findings provide further insight into the role of inflammatory-mediators in the mechanism(s) of BBB eruption and brain oedema associated with either viral or bacterial meningitis as well as other immune-mediated CNS processes.

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SELECTIVE UPREGULATION OF MATRIX METALLOPROTEINASES IN EXPERIMENTAL MENINGITIS. B. C. Kieseier[1], R. Paul[2], U. Koedel[2], J. Clements[3], A. Gearing[3], H.-W. Pfister[2], H.-P. Hartung[1]. [1]Department of Neurology, Karl-Franzens-Universität, Graz, Austria; [2]Department of Neurology, Ludwig-Maximilians-Universität, München, Germany; [3]British Biotech Pharmaceuticals Limited, Oxford, UK.

Matrix metalloproteinases (MMPs) are implicated in the pathogenesis of various inflammatory diseases of the central nervous system. Evidence is increasing that gelatinase B might be involved in the pathogenesis of meningitis, however, the role of various other MMPs in the inflammatory process of this disease has not been investigated so far. In the present study, the mRNA expression pattern of gelatinase B and 6 other MMPs was studied in experimental meningococcal meningitis in rats. Increased mRNA levels for gelatinase B, collagenase-3, and stromelysin-1 were found in animals injected with meningococci. Elevated gelatinase B mRNA expression was accompanied by enhanced proteolytic activity, as evidenced by gelatin zymography, and positive immunoreactivity. In contrast, mRNA levels for gelatinase A, matrilysin, stromelysin-2, and -3 remained unchanged throughout the entire course of the disease. Our data indicate that gelatinase B, collagenase-3, and stromelysin-1 are selectively upregulated in bacterial meningitis and suggest that they may contribute to the pathogenesis of this infectious disease of the central nervous system.

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POTENTIAL ROLE OF THE CHEMOKINE IP-10 IN LEUKOCYTE RECRUITMENT INTO THE SUBARACHNOID SPACE DURING LYME NEUROBORRELIOSIS. B. Muehlberger*, U. Koedel*, V. Fingerle*, B. Wilske*, A. Fontana and H.-W. Pfister*. *Ludwig-Maximilians-University of Munich, Germany; University of Zurich, Switzerland

In this study we investigated (1) chemokine levels and (2) chemotactic activity of cerebrospinal fluid (CSF) samples from 29 patients with acute neuroborreliosis (NB). CSF-samples of patients with noninflammatory neurological disorders (n=30) served as controls. MCP-1 (monocyte chemotactic protein-1), MIP1- (macrophage inflammatory protein-1 alpha), RANTES (regulated upon activation, normal T cell expressed and secreted), IP-10 (interferon- inducible protein), and IL-8 (interleukin-8) were measured by ELISA. The IP-10 mean values of CSF-samples of patients with NB (2216.2 ± 1597.1 pg/ml; mean ± SDV) were significantly

elevated compared to controls (82.8 ± 59.5 pg/ml). The CSF MCP-1 and IL-8 mean values did not significantly differ between patients with NB and controls. However, CSF MCP-1 and IL-8-levels were above the normal range in 9 of 24 patients and 6 of 13 patients with active NB, respectively. MIP1- and RANTES were not detectable in the CSF of all patients investigated. Whereas IP-10 may contribute to chemotactic activity on activated T-cells, MCP-1 and IL-8 may be involved in recruitment of mononuclear cells and neutrophils. Indeed, the concentrations of the latter two chemokines and the extent of CSF pleocytosis correlated with chemotactic activity of CSF-samples. Collectively expression of chemokines in the CNS may guide the migration of mononuclear cells from blood into the subarachnoid space in Lyme neuroborreliosis.

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POLY (ADP-RIBOSE) POLYMERASE (PARP) – A KEY ENZYME IN THE PATHOPHYSIOLOGY OF PNEUMOCOCCAL MENINGITIS. U. Koedel*, R. Paul, B. Sporer, H.-W. Pfister. Department of Neurology, University of Munich, Germany

Rationale: Reactive oxygen and reactive nitrogen intermediates - central mediators of meningitis-associated brain injury – are potent triggers of DNA single strand breakage, resulting in PARP activation. Activation of PARP triggers a futile energy-consuming cycle, resulting in massive depletion of cellular NAD^+ and ATP, and eventually induces cell death. Methods: This study assessed the effects of the PARP inhibitor 3-aminobenzamide (3-AB) (1) on clinical symptoms and intracranial complications in experimental pneumococcal meningitis in the rat, and (2) on pneumococci-induced endothelial cell injury *in vitro*. Results: Treatment with 3-AB significantly improved the clinical status of infected rats. This beneficial effect was correlated with a significant reduction of the increase in intracranial pressure (ICP), blood-brain barrier permeability, and CSF pleocytosis, compared to untreated, infected rats (e. g. ICP: 11.01.6 vs 16.12.0 mm Hg in infected rats). In addition, 3-AB prevented the impairment of cerebral autoregulation and CO_2 reactivity. This endothelial dysfunction may be due to PARP-induced endothelial energy depletion, as observed in our cell culture system. Treatment with 3-AB significantly attenuated the reduction of mitochondrial respiration, NAD content, and cytotoxicity, as observed in endothelial cells, co-cultured with macrophages and stimulated with pneumococci (e. g. NAD content [expressed as percentage of change related to controls, defined as 100%]: 81.95.8 vs 49.91.6 % in untreated endothelial cells). Conclusion: Our data suggest a crucial role of PARP activation in the development of intracranial complications during experimental pneumococcal meningitis.

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ROLE OF PEROXYNITRITE AS A MEDIATOR OF PATHOPYSIOLOGICAL ALTERATIONS IN EXPERIMENTAL PNEUMOCOCCAL MENINGITIS. S. Kastenbauer, U. Koedel, R. Paul, H.-W. Pfister. Department of Neurology, Klinikum Großhadern, Ludwig-Maximilians-University, Munich, Germany.

Reactive oxygen species (ROS) and nitric oxide (NO), well-characterized mediators in bacterial meningitis, can react to form peroxynitrite. The aim of our study was to determine the role of this strong oxidant in the pathophysiology of bacterial meningitis. Methods: Male Wistar rats were injected intracisternally with phosphate-buffered saline (PBS, controls) or live pneumococci. Infected rats were either left untreated or pre-treated with 300 mg/kg uric acid, a scavenger of peroxynitrite. 24 hours after infection, cerebrospinal fluid white blood cell count (CSF-WBC) and intracranial pressure (ICP) were determined. Brain slices were stained immunohistochemically with an anti-nitrotyrosine antibody to identify protein nitration products of peroxynitrite. Blood-brain barrier disruption was demonstrated by the Evans-Blue extravasation (EBE) method. Results: A substantial increase in ICP, CSF-WBC and EBE was seen in infected animals vs controls (meanSD: 21.6 ± 9.3 mmHg, 5,776 ± 1,790 cells/µl and 9.7 ± 6.4 µg/ml vs 1.4 ± 0.9 mmHg, 150 ± 178 cells/µl and 0.00 µg/ml). ICP, CSF-WBC and EBE were significantly reduced by uric acid treatment (7.2 ± 1.6 mmHg, 2,004 ± 904 cells/µl and 1.11 µg/ml). In infected untreated rats, a positive nitrotyrosine staining was found in the leptomeninges colocalized with Evans-Blue extravasation. Nitrotyrosine-immunoreactivity was abolished in uric acid treated animals, while it was still detectable in infected, neutrophil-depleted rats, implying additional sources of ROS and NO. Conclusion: Our study suggests an important role of peroxynitrite in the pathophysiology of bacterial meningitis.

Multiple Sclerosis – 1

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IMMUNOMONITORING OF PATIENTS WITH RR MS UNDER THERAPY WITH INTERFERON BETA-1B (INFβ-1B): INFLUENCE OF INFβ-1B ON SOLUBLE, BIOACTIVE FORMS OF VCAM-1, ICAM-1 AND ICAM-3 - PRELIMINARY RESULTS. B. S. Kühne[1], P. Oschmann[1], E. Sindern[2], J. Tofighi[1], L. M. Ossege[2], J. Kraus[1], C. Laske[1], B. Engelhardt[3], W. Dorndorf[1]. 1: Dep. of Neurology, Clinical Research Group MS, University of Gießen. 2: Dep. of Neurology, University of Bochum; 3: Dep. of Molecular Cell biology, Max-Planck-Institute Bad Nauheim, Germany

Objective: To investigate whether the levels of the soluble forms of VCAM-1, ICAM-1 and/or ICAM-3 in the blood of MS patients treated with IFNβ-1b are suitable surrogate markers for the evaluation of disease activity and consequently for the effectiveness of therapy. Methods: In this open, non randomized study 60 patients (VCAM-1: 70 patients) are observed for a period of two years. In the therapy group (T) 30 patients (VCAM-1: 40 patients) are treated with IFNβ-1b (Betaferon); in the control group (C) 30 patients are not receiving any immunomodulatory treatment. sVCAM-1, sICAM-1 and sICAM-3 values are determined in all patients every three months. In 10 patients VCAM-1 was determined on day 1, 5, 15 and 6 weeks after begin of treatment. All values were assessed by ELISA. Results: The comparison of the control group (n=27) and the therapy group (n=30) yielded a significant increase of sVCAM-1 levels (ng/mL) in the first three months after the start of treatment (T (d0, n=30): =775; T (3 months, n=30): =1133). After three months sVCAM-1 levels tended to decrease but remained higher in the therapy group than in the control group. sVCAM-1 levels correlated to disease activity. It was shown that after six months the control group had a constant level for the inactive group (no relapse) (d0: =731; 6 months: =713), whereas the active group (1 relapse) showed an increase of the sVCAM-1 level (d0: =769; 6 months: =828). In contrast, an increase of sVCAM-1 levels was observed within the active (d0: =756; 6 weeks: =1389 ($p < 0,05$)) and inactive group (d0: =820; 3 months: =1219 ($p < 0,05$)) of the therapy group as well. However, further follow ups (9 month) demonstrated solely persisting elevated sVCAM-1 levels in the active patients under treatment. ICAM-1 levels were slightly increased in INFβ-1b treated patients whereas ICAM-3 levels were not. Conclusion: The preliminary results of this study show a limited potential of the adhesion molecules as surrogate markers for therapeutic efficacy of IFNβ-1b. However, the ongoing increase of sVCAM-1 in IFNβ-1b treated patients with active MS has to be further investigated.

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AGE RELATED DIFFERENCES IN THE RATE OF REMYELINATION IN RODENT CENTRAL NERVOUS SYSTEM. Shields, S. A., Comspton D. A. S., Blakemore W. F. and Franklin, R. J. M., Cambridge, U. K.

In experimental models and human disease, remyelination of axons follows central nervous system demyelination. Pathological examination of chronic plaques in multiple sclerosis reveals that this response is incomplete. Evidence that remyelination occurs more readily in children comes from the recovery of normal visual evoked potential latency after childhood optic neuritis. In animal models, older age is associated with reduced remyelination in lysolecithin-demyelinated rat spinal cord, but no difference in mouse brain after cuprizone-induced demyelination. One explanation for these apparently conflicting observations is that remyelination was allowed to proceed for longer in the latter study, suggesting that the pace of oligodendrocyte remyelination may be reduced in older animals rather than its final extent. To test this, the caudal cerebellar peduncles (c. c. p.) of thirteen young (8 week) and ten old (9-12 month) female Sprague-Dawley rats were demyelinated by stereotaxic injection of ethidium bromide. Four and nine weeks later animals were killed and the proportion of demyelinated and remyelinated axons estimated on toluidine blue stained resin sections. Four weeks after injection, significantly more oligodendrocyte remyelination was seen in young rats than old. By nine weeks there had been an increase in both oligodendrocyte and Schwann cell remyelination in old rats such that remyelination was not significantly different in old and young animals. These results demonstrate a reduction in pace rather than extent of remyelination with increasing age.

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IMMORTALISED CELLS OF ADULT HUMAN OLIGODENDROCYTE LINEAGE: BIOLOGY, BEHAVIOUR AND MYELINATING

POTENTIAL. HC Wilson[1], SC Barnett[2], NS Scolding[1]. [1]Cambridge and [2]Glasgow, UK.

Oligodendrocytes are the cells responsible for producing and maintaining myelin in the CNS. Oligodendrocyte progenitor cells (OPCs) have been characterised and are present in cultures of normal adult human brain. They can be identified in tissue sections of normal brain and within the lesions of multiple sclerosis (MS). These cells may be responsible for the limited remyelination seen in MS and an understanding of the factors which encourage their proliferation, differentiation and myelinating capacity is important for the development of strategies attempting to augment intrinsic remyelination in MS. Further study of adult human OPCs is hampered by low yields of cells from scarce supplies of human brain tissue and incomplete knowledge of their proliferative signals. We have begun to produce immortalised adult human cell lines by techniques well established in the rodent. Antibiotic-selectable retroviral vectors were used to introduce a panel of oncogenes into primary cultures of normal adult human brain, enriched for cells of oligodendrocyte lineage. One cell line (produced by infection with a temperature sensitive mutant of SV40 large T antigen) has an immunophenotype corresponding to cells of early oligodendrocyte lineage, exhibiting positive staining for surface gangliosides recognised by the A2B5 monoclonal antibody and O4. Further characterisation of this cell line should provide important insights into the cell biology of the human adult OPC.

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VARIABILITY OF IL-1 RECEPTOR ANTAGONIST INDUCTION BY INTERFERON-BETA$_{1B}$: IMPLICATIONS FOR THE THERAPY OF MULTIPLE SCLEROSIS. Francesca L. Sciacca, Cinzia Ferri, Elena Brambilla, Lucia Moiola, Giancarlo Comi, Nicola Canal, Luigi M. E. Grimaldi. Department of Neuroscience, San Raffaele Scientific Institute, Milan, Italy.

Interferon (IFN)β_{1b} is currently used for the treatment of patients with multiple sclerosis (MS), but its therapeutic efficacy is varies from patient to patient and the mechanisms underlying its clinical effects are still partially unknown. Previous observations have reported that serum levels of the antiinflammatory cytokine interleukin (IL) -1 receptor antagonist (IL-1ra) were increased after IFNβ treatment in MS patients. In this study we report that IFNβ_{1b} induced IL-1ra at both mRNA and protein levels in different experimental systems and in longitudinally evaluated MS patients. Myelomonocytic cell lines treated with several stimuli (LPS, IL-1β, IFNγ, IL-4, dexamethasone and IFNβ_{1b}) revealed that IFN$\beta_{1b}$was consistently the best inducer of IL-1ra. *Ex vivo* experiments confirmed that IFNβ_{1b} treated peripheral blood mononuclear cells (PBMC) responded by inducing IL-1ra mRNA and soluble protein. Finally, in MS patients treated with IFNβ over an 18 months period, serum levels of IL-1ra increased after the beginning of treatment. In all these systems we observed a high variability in the IL-1ra basal and IFNβ_{1b}-induced levels. We are currently evaluating whether genetically-determined intersubject differences of induction of IL-1ra could, at least partially, account for the variability of the IFNβ_{1b} therapeutic action in patients with MS.

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ASSOCIATION STUDY OF TWO APOE POLYMORPHISMS IN ITALIAN MS PATIENTS. C. Ferri; F. L. Sciacca, F. Veglia, F. Martinelli, G Comi, N. Canal and L. M. E. Grimaldi. Department of Neuroscience, San Raffaele Scientific Institute, Milan, Italy.

Apolipoprotein E (APOE)-dependent uptake of lipoproteins plays an important role in myelin degradation. A role for APOE has been proposed in multiple sclerosis (MS), a demyelinating disease characterized by destruction of myelin and marked alteration of myelin cholesterol and lipid metabolism. Apart from the well known polymorphism in the coding region (ε alleles), APOE gene is polymorphic in promoter region (-491). We studied the two APOE polymorphisms (ε and -491) in 161 relapsing-remitting MS patients (108 females, 53 males; mean age 40.9 $\pm$ 11.3 years) and in 153 unrelated healthy controls (HC) (49 females, 104 males; mean age 56.2 $\pm$ 5.3 years). We found no statistically significant difference in APOE ε or APOE -491 allele and genotype frequencies when comparing HC and MS patients. Among MS patients, APOE -491 allele and genotype frequencies were not significantly different after stratification for different types of disease (benign and non benign; relapsing-remitting or chronic progressive). We conclude that, at least in our cohort, APOE ε and -491 polymorphisms do not seem to influence occurrence and clinical variability of MS.

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LINKAGE DISEQUILIBIRUM BETWEEN THE DR3-DR4 SARDINIAN SUSCEPTIBILITY HAPLOTYPES AND THE 101 AND 121 BP ALLELES OF THE TNF-a MARKER IN 95 SARDINIAN NIS SIMPLEX FAMILIES. F. Coraddu[1-2], S. Sawcer', M. Lai[2], M. Pugliatti[3], S. Broadley', M. G. Marrosu[2] and D. A. S. Compston'. 'Neurology Unit, University of Cambridge . [2]Department of Neuroscience, University of Cagliari . [3]Clinic of Neurology, University of Sassari.In our United Kingdom families we have previously shown that multiple sclerosis is associated with the 121base pair (bp) allele of the TNFa marker and that this allele is in linkage disequilibrium with the HLA haplotype "DR 15" (DRBI*1501-DQAI*0102-DQBI*0602) known to be associated to multiple sclerosis in Northern Europeans. Since the HLA associated haplotypes are quite distinct in Sardinian multiple sclerosis, we investigated the TNFa marker in 95 Sardinian families in order to establish which if any of the TNFa alleles were associated with multiple sclerosis and/or in linkage disequilibrium (LD) with the Sardinian risk HLA haplotypes, "DR4" (DRB I *0405-DQAI *0501 DQB 1 *0301) and "DRY (DRB I *0301-DQA I *0501-DQB 1 *0201). Although none of the TNFa alleles showed statistically significant association with multiple sclerosis, there was evidence that the common 101 bp allele was in LD with the DR3 haplotype, and that the 119 bp allele was in LID with the DR4 haplotype; both these alleles showed excess transmission. We also typed the TNFd marker. As with TNFa, none of the TNFd alleles showed statistically significant association with multiple sclerosis, although the 233 bp allele was in LD with both the DR3 and the DR4 haplotypes. These haplotypes both include the DQA 1 *0501 allele, which as would be excepted shows the strongest transmission distortion of any of the HLA alleles considered alone. These data support the suggestion that LD extends from the class II genes out to the TNF genes but suggest that the causative mutation in multiple sclerosis is more likely to be in class 11 than in the region of the TNF genes.

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RESULTS OF THE 3-YEAR, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF INTERFERON BETA-1A (REBIF) IN SECONDARY-PROGRESSIVE MS. D. W. Paty on behalf of the SPIMS (Secondary Progressive Interferon beta-1a MS) Study Group.

Immunology – 1

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EFFECTS OF CORTICOSTEROIDS ON THE MRNA-EXPRESSION OF TNF AND ITS 55 KDA-RECEPTOR IN BLOOD MONONUCLEAR CELLS OF PATIENTS WITH MULTIPLE SCLEROSIS. L. M. Ossege, E. Sindern, J.-P. Malin. Institute of Neurology, Ruhr-University of Bochum, BG Klinikum Bergmannsheil, Bochum, FRG

The treatment of an acute relapse in multiple sclerosis (MS) with corticosteroids is well established. There is evidence that the antiinflammatory effects of corticosteroids are mediated by inhibition of the synthesis and release of immunoregulatory molecules like TGF-1, IL-2 and IFN by activated T-cells, which promote the expansion of antigen-specific helper or suppressor T-cell clones as well as natural killer cells. Tumor-necrosis-factor-alpha (TNF) is a proinflammatory cytokine. Its association with disease activity in MS has been demonstrated. The 55-kDa-TNF-receptor (TNF-R) may antagonise and inhibit effects of TNF. We investigated the expression of TNF- and TNF-R-mRNA in blood mononuclear cells (MNC) of patients with acute relapse in multiple sclerosis (MS) during the treatment with corticosteroids. Ten patients were investigated. They all were treated with 500 mg prednisolone daily over 5 days. Blood samples

were taken before onset of therapy and at day 3-5 and 8-10 after onset of treatment. The mRNA-expression was investigated by the method of non-radioactive in situ hybridization. In all patients a significant decrease of TNF-mRNA was detectable at day 3-5 ($p < 0.01$, Wilcoxon-rank-sum test), but not at day 8-10. The expression of TNF-R-mRNA increased significantly at day 3-5- and day 8-10 ($p < 0.01$, Wilcoxon-rank-sum test) with a maximum at day 3-5.These data show that corticosteroids reduce the mRNA-expression of TNF and induce that of TNF-R in blood MNC of MS patients in vivo. These might be further mechanisms by which corticosteroids mediate its antiinflammatory effect in the treatment of acute exacerbations in MS.

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AUTOIMMUNE RESPONSE TO MOG IN MS: CROSS REACTING ANTIBODIES TO MOG AND BUTYROPHILIN. C. G. Haase, R. Hohlfeld, C. Linington. Martinsried, Germany

In multiple sclerosis (MS) enhanced T and B cell autoreactivity to myelin oligodendrocyte glycoprotein (MOG) suggests that MOG may act as a target autoantigen. A milk protein, butyrophilin (BTN), shares substantial amino acid (a. a.) sequence identity with MOG, and can induce an autoreactive response to MOG as a consequence of molecular mimicry between the proteins. We tested the serum of 22 patients with MS and 21 healthy donors (HD) for the prevalence of autoantibodies to epitopes represented by nine overlapping peptides of the extracellular Ig-like domains of MOG and BTN. Results: Anti-BTN antibodies were found against all peptides in 60% of MS and 76% of HD, the immunodominant epitope being a. a. 14-50. Antibodies recognizing homologous sequences of both antigens were equally found in MS and HD. However, homologous epitopes with a. a. 1-26 and a. a. 101-125 were exclusively recognized by patients with MS. Conclusions: Epidemiological studies indicate an association between diet and MS, in particular the consumption of dairy products and the prevalence of MS. Our data are consistent with peripheral triggering of an anti-MOG antibody response directed against particular epitopes via contact with BTN in milk.

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MICROGLIA FAIL TO INITIATE A MIXED LYMPHOCYTE RESPONSE BUT RECALL ANTIGEN PRESENTATION BY GAMMA INTERFERON-ACTIVATED MICROGLIA RESULTS IN T CELL PROLIFERATION, CYTOKINE RELEASE AND PROPAGATION OF THE IMMUNE RESPONSE. Gillian L. Hall, John Girdlestone, D. Alastair S. Compston,and Mark G. Wing. UK.

The interaction between microglia and T cells is important in the development of central nervous system inflammation. The exact nature of this interaction remains controversial. This may result in full T cell activation, a partial state of activation, anergy or apoptosis of the 'responding' T cell. We have demonstrated that neonatal rodent microglia not only fail to initiate a mixed lymphocyte reaction (MLR), but suppress background T cell proliferation. Even after activation with γ-IFN or following phagocytosis, microglia remain unable to support a MLR. By contrast, γ-IFN-activated microglia are able to activate memory T cells in a recall assay resulting in T cell proliferation and cytokine (γ-IFN) release. Supernatants from the recall assay stimulate γ-IFN-dependent activation of a STAT (signal transducer and activator of transcription) factor within resting microglia. This demonstrates that memory T cells not only receive sufficient stimulation from the γ-IFN-activated microglia to proliferate and produce cytokines, but that there is also a reciprocal stimulation of resting microglia. This provides evidence that microglia could be able to propagate immune responses in the central nervous system.

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CD45RA+ ICAM-3+ LYMPHOCYTES IN CEREBROSPINAL FLUID AND BLOOD AS DIAGNOSTIC AND ACTIVITY MARKERS IN MULTIPLE SCLEROSIS. J. Kraus*, P. Oschmann*, B. Engelhardt°, S. Kuehne*, J. Tofighi*, N. Chatzimanolis*, C. Laske*, A. Kern*, W. Dorndorf*. Justus-Liebig-Universität Gießen/Germany, Department of Neurology, Clinical Research Group for Multiple Sclerosis*; Max Planck/W. G. Kerckhoff-Institut Bad Nauheim/Germany, Department of molecular cell biology°;

Autoreactive T cells targeted against antigens of the myelin sheath are suggested to play a predominant role in the pathogenesis of MS. Naive (CD45RA+) T cells were suggested to be important for the development of the immunological process and correlate with clinical activity of the disease. Intercellular adhesion molecule-3 (ICAM-3), a member of the Ig supergene family, also seems to be a marker for resting T-lymphocytes. This study was performed to investigate whether the coincidence of both antigens on lymphocytes in cerebrospinal fluid (CSF) and blood can be used as diagnostic and activity markers in multiple sclerosis (MS). Materials and Methods: Paired blood and CSF samples were drawn from 30 patients (18 women and 12 men, mean age 33.5 years) with relapsing remitting multiple sclerosis. 22 of the 30 MS patients were suffering from acute relapses whereas 8 of them had been in remission over more than four weeks. The control group consisted of 12 healthy persons. The relative number of CD45RA+ ICAM-3+ within the lymphocyte population was evaluated by two-colour FACS analysis. Results: The CSF of MS patients with relapses showed a significant increase of the relative number of CD45RA+ ICAM-3+ cells in comparison to patients in remission (M= 14.8% versus M= 9.8%; p 0.05). In blood the values of CD45RA+ ICAM-3+ cells from both MS groups were at the same levels (M= 68.5% versus M= 64.9%; p= 0,96). But there were significant differences for individuals from the control group (M= 74.3%) to both patient groups (p 0.05,p 0.10). Conclusion: Our data suggest that the relative number of CD45RA+ ICAM-3 lymphocytes in CSF could act as a activity marker. In contrast to this our results from the blood must be further investigated whether they are useful as diagnostic tools in MS.

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EFFECTS OF INTRAVENOUS IMMUNOGLOBULINS ON OLIGODENDROCYTES *IN VITRO*. M. Stangel, D. A. S. Compston, N. J. Scolding, MRC Centre for Brain Repair, Cambridge, U. K.

Intravenous immunoglobulins (IVIg) have been used successfully in multiple sclerosis for reduction of the relapse rate. Experimental evidence also indicates that they promote remyelination. To study the mechanism of how augmented remyelination may be achieved, we first studied the effect of IVIg on rat oligodendrocyte progenitor cell functions *in vitro*. Using a BrdU incorporation assay, IVIg had no effect on the proliferation of $A2B5^+$ progenitor cells. Similarly, the mitogenic effect of neither PDGF nor FGF2 was modulated. Furthermore, differentiation of oligodendrocytes in vitro was not affected by the presence of IVIg, neither was their migratory capacity. Investigating other potential mechanisms of IVIg, the influence on complement mediated injury was assessed using the oligodendroglial cell line CG4. Direct complement mediated injury was not affected by IVIg. However, antibody-mediated complement toxicity was inhibited by IVIg, but not by albumin. These results argue against a direct effect of IVIg on oligodendrocyte progenitor functions as a mechanism for enhanced remyelination in demyelinated lesions, but are in favour of a protective mechanism on immunological oligodendrocyte injury.

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IMMUNOLOGICAL PROFILE OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS: A DIFFERENT MECHANISM? E. Martínez-Cáceres, I. Durán, J. Río, N. Barberà, I. Sáez-Torres, M. Tintoré, X. Montalban. Barcelona. Spain.

Primary progressive multiple sclerosis (PPMS) differs clinically and radiologically from relapsing forms of the disease (RFMS) [relapsing-remitting (RRMS) or secondary progressive (SPMS)]. The aim of this study was to analyse if these differences account for distinct immunological mechanisms. Patients/Methods: Soluble serum levels of L-selectin, ICAM-1, VCAM-1 and ICAM-3 were measured by ELISA in 25 PPMS, 50 RFMS (25 RRMS, and 25 SPMS) and 30 healthy controls (HC); Membrane leukocyte expression of ICAM-1, LFA-1, VLA-4, L-selectin and ICAM-3 was measured by flow-cytometry in 29 PPMS, 30 RFMS (15 RRMS, and 15 SPMS) and 16 HC; The percentage of IL-10, IL-12, TNF- and IFN-γ producing cells was measured by flow-cytometry in 14 PPMS, 14 RFMS (7 RRMS, and 7 SPMS) and 14 HC. Results: Soluble serum levels of L-selectin and ICAM-1 were significantly increased in MS patients (mainly due to the RFMS). A significant decrease of surface expression of these molecules plus VLA-4 was found in RFMS, whereas no differences were found in PPMS compared to HC, except for L-selectin (increased in PPMS). An increase of IFN- producing cells (p=0.03) was observed in RFMS whereas no differences in cytokines were observed between PPMS and HC. Conclusions: The differences observed in adhesion molecules expression and percentage of IFN-γ producing cells, suggest different immunological mechanisms between PPMS and RFMS

Immunology – 2

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T-CELL INTERFERON-γ BINDING IN MYASTHENIC PATIENTS. P Bongioanni, R Ricciardi, MR Romano, B Boccardi, C Baldini, D Lucchesi, S Nuti, B Rossi, Pisa, Italy

Myasthenia gravis (MG) is a T-cell-dependent and antibody-mediated autoimmune disease of the neuromuscular junction, in which the cytokine network may be deranged. Specific binding sites for interferon (IFN)-γ, a neuroimmune cytokine, have been found on human lymphocytes. The aim of the present study was to assay IFN-γ binding on peripheral blood T cells from MG patients (mean (± SD) age: 50.2 ± 17.6 years), assigned to I, II A, and II B groups according to the Osserman's criteria. Ten patients were in treatment with pyridostigmine alone, 18 with pyridostigmine and corticosteroids; 8 subjects were *de novo*. We found that T lymphocytes have significantly fewer IFN-γ receptors in MG patients than in age- and sex-matched controls (B_{max}: 483 ± 14 vs 734 ± 13 (mean ± SEM) receptors/cell). The reduced T-cell IFN-γ binding is due to a decreased number of IFN-γ receptors on T-helper lymphocytes. Ligand-receptor affinity values were similar in patients and healthy subjects. These results are discussed in terms of MG immunopathogenesis, since it has been reported that activated T cells have decreased amounts of IFN-γ receptors.

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ORGAN-SPECIFIC AND NON ORGAN-SPECIFIC AUTOANTIBODIES (AUTOAB) AND NEUTRALIZING ANTI-INTERFERON AB(NAB) DURING INTERFERON BETA(IFNB) TREATMENT OF MULTIPLE SCLEROSIS(MS). L. Durelli, A. Ricci, Torino, E. Simeoni, P. Di Marco, Rome, & G. Antonelli, Pisa, and the Betaferon Safety Trial group, Italy.

NAB are autoAb that may counteract IFN clinical effects and their frequency may increase in patients with autoimmune abnormalities. We prospectively followed up 156 MS patients treated with IFNb for 1-year in 18 MS centers. Liver and thyroid function, anti-thyroid(AT) (detected by IRMA), and anti-tissular (anti-nuclear, -smooth-muscle, -parietal cell, -microsomal, -mitochondrial) autoAb (detected by indirect immunofluorescence) were monitored. NAB were tested by the neutralisation of IFNb antiviral activity on Sindbis virus cytopathic effect. AutoAb were present at baseline in 35 patients(22%; AT Ab, 15%; anti-tissular Ab, 8%), and de novo during treatment in 12 patients(8%). Hepatic enzymes increased in 54 patients(35%) with antitissutal autoAb in 20%. Thyroid disorder was observed in 24 patients(16%) (in 12 already present at baseline) with AT Ab in 45%. NAB occurred in 38 patients(32%), repeatedly confirmed in 20 (17%). Twelve NAB positive patients(32%) had also autoAb, 14(37%) had liver function alteration, 5(13%) thyroid disorder. Liver function alteration peaked during first months of treatment disappearing thereafter. Thyroid disorder appeared after 3-6 months of treatment being persistent in most patients. NAB occurred after 6-12 months persisting in half patients. NAB occurrence was not significantly associated with autoAb, liver or thyroid dysfunction during treatment or at baseline. MS patients with an associated autoimmune disorder (either present before or occurring during IFNB treatment) do not have an increased risk of NAB development.

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IN VIVO EFFECTS OF TREATMENT WITH INTERFERON ?-1B ON THE EXPRESSION OF VLA-4 ON T LYMPHOCYTE SUBSETS OF MULTIPLE SCLEROSIS PATIENTS. P. A. Muraro*‡, T. Leist *, B. Bielekova*, D. Gambi‡, and H. F. McFarland*. * Neuroimmunology Branch, NIH, Bethesda, MD 20892-1400 USA. ‡ Department of Oncology and Neuroscience, University "G. D'Annunzio", Chieti 66013 Italy

The mode of action of interferon β (IFN-β) in multiple sclerosis (MS) may involve an effect on adhesion molecules on blood-brain barrier endothelial cells and/or immune cells. Methods. We have prospectively analyzed by three-color flow cytometry the expression of the adhesion molecules CD49d (VLA-4) and CD11a (LFA-1) on T lymphocyte subsets and monocytes from 5 MS patients before and after treatment with IFN- β1b and from 3 healthy control subjects. Results. The expression of CD49d on CD3+ lymphocytes was decreased after IFN- β treatment (P=0.034, paired t-test). This was due in part to a relative reduction of CD8+ (P=0.024) and increase of CD4+ T cells (P=0.036). In fact, CD8+ cells had higher CD49d levels than CD4+ cells (P=0.001). In addition, CD49d expression was downregulated after treatment on the CD8+ (P 0.01) and on the CD4+/CD45RO+ T cell subset (P = 0.033). The levels of CD49d on monocytes and of CD11a on either T cells or monocytes did not change significantly. Conclusions. The reduced expression of VLA-4 on T cells from MS patients after IFN- β1b treatment depends on decreased proportions of CD8+ T cells and on downregulation of CD49d on the CD8+ and CD4+/CD45RO+ subsets.

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DEMYELINATION AND AXONAL DAMAGE IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS INDUCED IN *CALLITRIX JACCHUS*. Mancardi GL,Roccatagliata L,Capello E,BroK H*,Bontrop R*, Massacesi L**,'t Hart B*,Uccelli A. Genova, Department of Neurological Sciences, University of Genova, Italy- *Rijswijk, Biomedical Primate Research Center, The Netherlands-**Firenze, Department of Neurological Sciences, Italy

Demyelination with relative sparing of axons is considered the neuropathologic hallmark of multiple sclerosis (MS). However, axonal damage and axonal loss have been recently emphasized by histopathological and magnetic resonance imaging techniques. We carried out a MRI and neuropathologic study in EAE induced in non human primate *Callitrix jacchus* (*CJ*), mainly focusing our attention on the degree, topography and timing of demyelination and axonal damage. EAE was induced in 4 monkeys by immunization with whole human myelin (WHM), omitting *Bordetella pertussis* injection. Clinical disease course was scored daily and MRI was carried out before and after sacrifice. On T2 weighted images, areas of hyperintensity were easily observed in the white matter of the cerebral hemispheres, especially around the ventricles. At neuropathologic examination large demyelinated areas with inflammation were observed. Axonal damage was detected using mabs anti phosphorylated and non phosphorylated neurofilaments (SMI32) and mabs anti amyloid precursor protein (APP). A morphometric quantitative study revealed that in early active lesions the number of SMI32 and APP positive axons was higher than in late active lesions. EAE induced in *CJ* is characterized by plaques of demyelination and by signs of early axonal damage, similarly to the pathological picture of MS.

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EARLY AND LASTING DECREASE OF PERIPHERAL B LYMPHOCYTES IN MULTIPLE SCLEROSIS (MS) PATIENTS TREATED BY MITOXANTRONE. E. Lepage, N. Genetet, J. Y. Bransart, M. Coustans, O. De Marco, G. Edan. Rennes, France.

As part of our controlled trial (JNNP 1997; 62: 112-118), we assessed the effect of mitoxantrone on the immune system by measuring the absolute number of B (CD20) and T (CD3, CD4, CD8) lymphocytes and the cytokines production (TNF alpha, IL10, INF gamma) in MS patients. We compared, monthly before the next injection, these values observed in 5 patients of the MX treated group (combination of MX 20 mg IV / month and methylprednisolone (MP) 1g IV/month) with those in 4 patients of the control group (MP 1g IV/month). Comparison was performed, month after month, using Man and Withney test. From month 1 to Month 5 there was a significant decrease of B lymphocytes ($p < 0.05$) in the MX treated group. Concerning the number of T lymphocytes (CD3, CD4, CD8), similar significant decrease was observed later, only at month 4. Cytokines production from peripheral white cells were low in both groups. In conclusion, this study suggests that 1-this rapid and lasting effect on peripheral B lymphocytes observed every month after MX injection might account for the strong and rapid clinical efficacy we had with MX, contrasting with the modest short term clinical efficacy observed with T cell immunomodulating drugs 2- B lymphocyte count in peripheral blood might be a marker of MX efficacy.

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CASPASE-1 IS CRITICALLY INVOLVED IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS. R Furlan, F Galbiati, PL Poliani, S Smiroldo, A Bergami, G. Desina, MS Su, R Flavell, G Comi, L Adorini, G Martino, Milan and San Giovanni Rotondo (FG), Italy; Cambridge and New Haven, USA

Caspase-1 has been shown to play a crucial role in the proteolytic activation and release of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-1α, IL-6, tumor necrosis factor (TNF)α and interferon (IFN)γ. We studied the role of caspase-1 in the induction and effector phase of experimental autoimmune encephalomyelitis (EAE) in mice. We found that its levels are strongly elevated (eight-fold increase) and associated with clinical course and with the transcription rate of other pro-inflammatory cy-

tokine genes such as IL-1 β, IL-6, TNF α, IFN γ, as determined by semi-quantitative RT-PCR. We then studied the susceptibility of caspase-$1^{-/-}$ mice to myelin oligodendrocyte glycoprotein (MOG)-induced EAE and found that disease incidence is dependent on amount and immunogenicity of the antigen used: caspase-$1^{-/-}$ mice are resistant to EAE induction by low doses of MOG40-55 compared to wild type C57BL/6 which are fully susceptible to the same immunization protocol. We also found that caspase-$1^{-/-}$ T-cells are able to respond normally to encephalitogenic antigens in an antigen-specific proliferation assay but produce less IFN γ then T-cells from control strains. We then studied pharmacological inhibition of caspase-1 by implanting intraperitoneal osmotic pump releasing Z-Val-Ala-Dl-Asp-FMK, a caspase-1 specific inhibitor, for about 10 days. EAE was dramatically reduced (60% disease-free animals) when the osmotic pumps were implanted one day before immunization. We found no difference between caspase-1 inhibitor treated mice and controls when implanting the osmotic pumps on day seven post-immunization. Neuropathological examination revealed decreased myelin and axonal damage and a reduced number of infiltrating macrophages. We therefore conclude that caspase-1 plays a crucial role in the induction phase of EAE and might represent a suitable therapeutic target in autoimmune demyelination.

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THE ASSOCIATION OF POLYMORPHISMS AT THE IL-1 GENE CLUSTER; TNF; APOE; AND GST WITH PROGNOSIS IN A COHORT OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS PATIENTS. [1]CLA. Mann, VL. [2]Stevenson, [2]SM. Leary, [1]SJM. Weatherby, [1]AA. Fryer, [1]RC. Strange, [2]AJ. Thompson, [1]C. P. Hawkins; [1]Keele Multiple Sclerosis Research Group, Royal Infirmary, Stoke on Trent, [2]Institute of Neurology, London, England.

We examined the association of polymorphisms in the IL-1 gene cluster, Tumour Necrosis Factor (TNF), Apolipoprotein E (APOE), and Glutathione S-transferase M3 gene (GST). The pro-inflammatory cytokines interleukin-1 (IL-1) and TNF have been associated with blood brain barrier breakdown in experimental models. An allelic variant of the ApoE gene has been shown to influence Alzheimers disease. There are associations between GST alleles and CNS pathology. 67 Primary (n=55) and (n=12) transitional progressive MS patients were scored by the Kurtzke Expanded Disability Status Scale (EDSS). Genotyping was performed by standard PCR. Results were corrected by logistic regression for independent confounding factors; gender, disease duration and age of onset. There were no associations found between TNF-308, APOE & GSTM3 genotypes and EDSS. Homozygosity for allele 2 of the IL-1 beta–511 polymorphism was more frequent with severe disease (EDSS 6-10) (n=67, p=0.14, OR=2.42, 95%CI=0.74-7.87). Allele 2 of The IL-1RN VNTR was less frequent in patients with severe disability (EDSS 6-10) (n=67, p=0.11, OR=2.40, 95%CI=0.81-7.10). This trend although not significant in this small population corresponds with the previously reported significant association of these alleles in a larger cohort (400) of relapsing and secondary progressive patients. This further supports the hypothesis that the IL-1 genotype may influence prognosis in MS.

Muscle Disorders – 1

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CREATINE MONOHYDRATE IN MUSCULAR DYSTROPHIES – A DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL STUDY. M. C. Walter, MD, H. Lochmüller, MD, M. Hartart, MD, P. Reilich, MD, D. Pongratz, MD, W. Müller-Felber, MD, Munich, Germany.

Muscular dystrophies (MD) are a heterogeneous group of inherited muscle diseases. Creatine monohydrate (Cr) is a derivative of amino acids in the body. Cr is responsible for ATP resynthesis in skeletal muscle and is used by athletes as a food supplement. In this trial, effects of Cr supplementation in MD patients on strength and daily-life activities were assessed. Thirty-six patients with MD were included in the study. Thirty-two patients, mean age 26.47 ± 16.98 years (21 adults, mean age 35.05 ± 14.63; 11 children, mean age 10.09 ± 3.7) were treated for the full study period. They were randomized by a double-blind, placebo-controlled, crossover design using Creapure^{R} (adults 10g, children 5g per day) or placebo (microcrystalline cellulose) for 8 weeks each. Before crossing-over there was a wash-out period of 3 weeks. Response to treatment was evaluated using MRC scales, Quantitative Strength Measurement (QSM), Neuromuscular Symptom Score (NSS), Hammersmith Motor Ability Score (HMAS), Task Time Test (TTT), Vignos Functional Classification Test (VFC) and patients own assessment of improvement. Throughout treatment no severe side-effects were found. We found mild but significant improvement using MRC, QSM, NSS, TTT, and patients own assessment comparing verum to placebo administration ($p < 0.05$). Therapy with Cr may be effective in the symptomatic treatment of MD. Short-term Cr supplementation is safe and does not cause muscle damage. Long-term studies are needed to further evaluate the benefit from Cr treatment in MD.

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IMMUNOLOCALISATION OF FAS AND FAS-LIGAND (FAS-L) IN INFLAMMATORY MYOPATHIES J. De Bleecker, V. Meire, S. Pappens; Gent, Belgium.

Fas/Fas-L interaction can induce apoptosis or act in costimulation or as a mechanism by which cytotoxic T cells produce target cell lysis. Fas+ muscle fibers and inflammatory cells, and Fas-L+ T cells, have been described in polymyositis (PM) and sporadic inclusion body myositis (IBM), but others failed to confirm this. These myopathies are characterized by a CD8 T cell mediated cytotoxic reaction against an unknown muscle fiber antigen. By contrast, in dermatomyositis (DM), an antibody or immune-complex mediated immune response is directed against a vascular component. Methods: We used commercially available antibodies in dual color immunofluorescence to study Fas and Fas-L expression in PM, 113M, DM, normal and disease controls. Results: A strong Fas signal occurred on the sarcolemma, and to a lesser extent in the sarcoplasin of NCAM+ regenerating muscle fibers in all myopathies and of injured fibers with abortive regenerative activity. Groups of atrophic fibers in IBM were strongly Fas+. Actively invading CD8 T cells in PM, 113M and some dystrophies had Fas upregulation. We found no Fas-L antibody that consistently labeled the positive control tissue (testis). Conclusions: Regenerating muscle fibers represent the main site of Fas activity in myopathies. Commercially available Fas-L antibodies fail to produce reliable results. Pending the unequivocal demonstration of upregulated Fas-L on target structures, the conclusio by others of a prominent role of Fas/Fas-L interaction in the pathogenesis of inflammatory myopathies seems premature. Our data are in line with observations Lhat apoptosis has no major role in inflammatory myopathies. The upregulated Fas on invading CD8 T cells may represent costimulation.

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UP-REGULATION OF DYSTROPHIN BRAIN AND PURKINJE-CELL ISOFORM IN SKELETAL MUSCLE OF BMD AND DMD PATIENTS. M. Sironi*, A. Bardoni*, M. Robotti*, G. Felisari*, GP Comi^, N. Bresolin^. * IRCCS E. Medea, Associazione La Nostra Famiglia. Bosisio Parini (LC) – ^ Centro Dino Ferrari, Istituto di Clinica Neurologica, Università di Milano, IRCCS Ospedale Maggiore Policlinico, Milan, Italy

Numerous dystrophin isoforms driven by various promoters have been described. The muscle, brain and Purkinje-cell transcripts are tissue-specific and give origin to a full-length dystrophin protein. Up-regulation of the dystrophin brain and Purkinje-cell isoforms in skeletal muscle has been reported in Becker muscular dystrophy patients (BMD) but not in Duchenne muscular dystrophy patients (DMD) so far. We analysed the pattern of dystrophin transcription in skeletal muscle of 11 BMD and 11 DMD patients in order to determine whether up-regulation of the brain and Purkinje-cell isoforms is a common event with a functional significance. Detection of full-length dystrophin isoforms was performed by radiolabeled PCR amplification of the unique first exon of each isoform. The muscle isoform was detectable in all samples. Neither the brain nor the Purkinje-cell isoforms were expressed in BMD patients, while four DMD patients presented an up-regulation of the non-muscle isoforms. Ectopic expression of the two isoforms did not correlate with clinical phenotype, age and immunohistochemical findings (percentage of revertant fibres). We present the first evidence that muscle expression of dystrophin brain and Purkinje-cell isoforms also occurs in DMD patients. Despite the clinical etherogeneity, no up-regulation was detected in BMD patients. Thus, it seems difficult to speculate that the clinical features of the course of dystrophinopathies could be modulated by the compensatory activation of non-muscle promoters, as previously suggested.

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TRANSFORMING GROWTH FACTOR-β1 SERUM LEVEL IN MUSCULAR DYSTROPHIES. P. Bernasconi, M. Mora, L. Morandi, F. Baggi, P. Confalonieri, C. Antozzi, O. Simoncini, F. Cornelio, R. Mantegazza. Istituto Nazionale Neurologico "Carlo Besta", Milan, Italy.

Increase of connective tissue in the endomysium of muscle tissue is a crucial feature of muscular dystrophies. Accumulation of collagen types I to V, laminin, and fibronectin has been detected in dystrophic muscles; however, the mechanisms by which fibrosis develops are not yet clearly understood. TGF- β, a key element in collagen synthesis and accumulation, stimulates matrix formation, and inhibits matrix degradation. Since TGF-β1 mRNA has been demonstrated to be highly expressed in DMD muscle tissues and to correlate with the progression of fibrosis, we decided to determine whether monitoring TGF- β1 serum levels in dystrophic patients could be useful for assessing the extent and progression of fibrosis. We studied 39 DMD (6 months to 13 yrs), 27 Becker muscular dystrophy (BMD) (2 to 64 yrs), 8 CMD patients (4 months to 39 yrs), 15 LGMD patients (3 months to 68 yrs) and 33 healthy controls by ELISA. All dystrophic patients had a significantly higher TGF- β1 serum levels than healthy controls ($P < 0.0001$). Stratification of patients by age revealed a progressive increase of TGF- β1 levels in DMD patients, whereas in BMD a peak was observed at age 2-10, which declined thereafter. Each TGF-β1serum level has been correlated with the extent of fibrosis, detected by morphometric analysis. These data suggest that TGF- β1 serum detection may be used as non-invasive marker for fibrosis evaluation.

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NOVEL PARAMYOTONIA CONGENITA MUTATIONS WITH SPECIAL FEATURES. Jurkat-Rott K, Meola G, Moog U, Scherr S, Lehmann-Horn F. Dept. of Applied Physiology, Ulm, Germany

Hallmarks of paramyotonia congenita are (i) paradoxical myotonia, defined as myotonia evoked and aggravated by exercise, (ii) worsening of the exercise-induced myotonia by cold, (iii) weakness after prolonged exercise and exposure to cold, and (iv) a predilection of the myotonia for the face, neck, and distal upper extremity muscles. Many paramyotonia patients also exhibit the lid lag phenomenon such as an African female and her daughter we studied, who also presented with intermittent diplopia, a phenomenon otherwise frequently observed in patients with chloride channel myotonia congenita. Screening for mutations in the gene encoding the alpha subunit of the skeletal muscle sodium channel SCN4A revealed a novel I1455T mutation. In another family presenting with painful contractions lasting for hours after provocation of muscle stiffness by cold, another novel mutation, V1458F, was detected. Both mutations have in common that they are located in the voltage-sensing segment S4 in domain four of the channel. While the first mutation induces paramyotonia already upon very slight muscle movement leading to glance-induced diplopia, the second mutation generates long-lasting depolarizations which surprizingly remain *under* the threshold values for the sodium channel corresponding to muscle contractures for hours instead of the normally observed transition of paramyotonia into flaccid weakness. The broad spectrum of symptoms associated with paramyotonia should not discourage mutation screening within the SCN4A gene, whereby the S4 segment of domain 4 remains a decisive hot spot for the localization of disease-causing mutations.

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LIPID PEROXIDATION, FREE RADICALS AND ANTIOXIDANTS IN PATIENTS WITH MYOTONIC DYSTROPHY. Toscano A., Annesi G., Campo G., Musumeci O., Rodolico C., Spadafora P., Pasqua A., Annesi F., Caputi A., Vita G. Messina, Cosenza. - Italy

Myotonic Dystrophy (MD) is the most common form of muscular dystrophy affecting adults. The genetic basis of MD includes a mutational expansion of a repetitive trinucleotide sequence (CTG). The number of expansions in terms of number of triplets divides individuals in 5 categories related to the severity of the molecular changes (E0, E1,E2, E3,E4). It is also well known that, in MD, the severity of the clinical presentation is well correlated to the molecular changes. Few years ago, in a preliminary study, Japanese authors observed increased levels of free radicals and lipid peroxides in six MD patients. We have investigated 31 patients of 17 families with MD from the clinical, biochemical and molecular point of view. Biochemical analysis detected blood levels of superoxide dismutase (SOD), malonilaldehyde (MDA), vitamin E (VE), hydroxyl radicals (HO) before and after using the "spin trap" technique and total antioxidant system (TAS). The patients examined were compared to age-matched controls and other types of myotonic disorders. The clinical-molecular classification of subjects showed 2 E0, 7 E1, 9 E2, 11 E3 and 2 E4. Biochemical results revealed that MDA was increased in about 1/3 of patients as well as SOD was in more than 50% of patients. VE levels were augmented in the majority of patients. Production of HO before and after stimulation by salicylate (spin trap) was slightly altered in pts with MD. These results suggest that: 1) lipid peroxides and free radicals may play a role in the pathogenesis of DM although the antioxidant systems are quite active; 2) biochemical changes are not always present in MD pts with clinical and molecular alterations.

Muscle Disorders – 2

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EXPRESSION OF MATRIX METALLOPROTEINASES IN MYOSITIS. B. C. Kieseier[1], C. Schneider[2], J. Clements[3], A. Gearing[3], R. Gold[2], H.-P. Hartung[1], K. V. Toyka[2]. [1]Department of Neurology, Karl-Franzens-Universität, Graz Austria; [2]Department of Neurology, Julius-Maximilians-Universität, Würzburg, Germany; [3]British Biotech Pharmaceuticals Limited, Oxford, UK.

The matrix metalloproteinases (MMPs) belong to a large group of proteolytic enzymes that are implicated in the pathogenesis of several inflammatory diseases. The expression pattern of MMPs in muscular disorders has not been studied to date. Using a competitive polymerase chain reaction assay the mRNA expression pattern of interstitial collagenase, gelatinase A and B, matrilysin, stromelysin-1, -2, and -3, as well as the tissue inhibitors of metalloproteinases (TIMP) -1, -2, and -3 were investigated in muscle biopsies from patients with polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), and different forms of muscular dystrophy (MD). mRNA and protein levels, as demonstrated by zymography and Western blot, for interstitial collagenase and gelatinase B were found to be selectively upregulated in the myositis cases, with highest levels in the PM biopsies, and a moderate increase in the IBM cases. Using immunohistochemistry gelatinase B could be localized to invading mononuclear cells, most likely T cells, as demonstrated on serial sections. Positive staining for interstitial collagenase was found along fibroblasts and the sarcolemma of diseased muscle fibers. Our findings indicate that gelatinase B and interstitial collagenase are selectively upregulated in myositis and raise the possibility that they contribute to the pathogenesis of these inflammatory disorders.

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MACROPHAGIC MYOFASCIITIS: A REACTION TO INTRAMUSCULAR INJECTIONS OF ALUMINUM-CONTAINING VACCINES. Gherardi Rk, Coquet M, Belec L, Chariot P, Moretto P, Figarella-Branger D, Cherin P, Authier Fj. For The Germmad (Groupe d'Etude et de Recherche sur les Maladies Musculaires Acquises Dysimmunitaires), AFM, France.

OBJECTIVE: To determine the cause of the recently emerged condition known as macrophagic myofasciitis (MMF) (Gherardi et al, Lancet 1998;352:347-52). BACKGROUND We documented 38 MMF cases from 1993 to 1998. MMF was detected by deltoid muscle biopsy in adult patients with diffuse myalgias, and by quadriceps muscle biopsy in young children. In some patients, MMF was associated with an autoimmune disorder (multiple sclerosis: 6, dermatomyositis: 3, inclusion body myositis: 3). MMF is characterized by stereotypical epi-, peri- and endomysial accumulations of densely packed macrophages containing intracytoplasmic osmiophilic crystal inclusions of an unknown nature, and sparse CD8 T-cell infiltrates. DESIGN/METHODS: 3 muscle biopsy samples were evaluated with a nuclear microprobe and by X-ray microanalysis to determine the chemical nature of macrophage inclusions. Then, aluminum levels were determined in muscle samples from 4 other patients with MMF (3 including the lesion, 4 remote from the lesion) and 14 normal controls, and in serum of 12 MMF patients. RESULTS: Microanalysis showed that MMF inclusions were composed of aluminum phosphate. Aluminum muscle levels were in the range of 77-1428 mg/g in samples including macrophages, 5-431 mg/g remote from macrophage infiltrates (584±735 *vs* 137±199, $p < 0.04$), and 1-58 mg/g in controls (584±735 *vs* 10±17, $p < 0.0001$). All MMF patients, except one, had normal to slightly elevated circulating aluminum levels (0.1-0.9 mM, N0.4). The data suggested focal aluminum accumulation rather than systemic intoxication. Aluminum is used as an adjuvant of vaccines against HAV and HBV infections, and these are admininstered intramuscularly into deltoid or quadriceps muscles. All 13 MMF patients had circulating anti-HAV (10/13) and/or HBV (8/13) antibodies. The proportion of positive anti-HAV testing was much higher than in general french population, and positive anti-HBV testing was due to previous vaccination in 7 of 8 patients as assessed by isolated positivity of anti-HBs antibodies. CONCLUSION: MMF likely represents an unusual reaction to intramuscular injections of aluminum-containing vaccines.

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MITOCHONDRIAL DISEASE WITHOUT CENTRAL NERVOUS SYSTEM INVOLVEMENT: A MAGNETIC RESONANCE SPECTROSCOPY-BRAIN ACTIVATION STUDY. Mario Rango, Marco Bozzali, Alberto Castelli, Alessandro Prelle, Nereo Bresolin, and Guglielmo Scarlato, Milano, Italy

We sought to evaluate lactate and high energy phosphates (HEP) content in the brain of patients with mitochondrial disease without CNS involvement (MDW) at rest and during functional activation. We utilized a 1 H/31 P Magnetic Resonance Spectroscopy (MRS) combined approach to monitor changes of Lac and HEP in the visual cortex at rest, during and following visual activation in five MDW patients and in five normal volunteers (NV). A 1.5 T system was utilized. Spectra were collected during three 7-minute periods (at rest, during activation and during recovery). The 31 P MRS technique and visual stimulation method have been fully described (Rango et al. Proc Int Soc Mag Res Med 1996; 1235:2; Rango et al. MRM 38:878-883 (1997). Proton spectra were obtained using a PRESS sequence (TR=1500, TE=272 msec). The HEP content was expressed as Phosphocreatine + bATP (PCr + bATP). T test and variance analysis (ANOVA) were used. Mean Lac at rest was higher in MDW patients than in NV ($p < 0.01$). In NV mean Lac increased during activation ($p < 0.025$) and returned towards rest values during recovery. In MDW patients mean Lac decreased during the activation/recovery period ($p < 0.01$). Mean PCr + bATP did not differ between NV and MDW patients at rest and during activation. During recovery mean PCr + bATP increased in NV and decreased in MDW patients. ($p < 0.01$). We conclude that in MDW patients the brain HEP content is kept normal at rest by an increase of anaerobic glycolysis. Unlike in normal subjects anaerobic glycolysis is down-regulated by activation in MDW patients this leading eventually to brain energy failure. Lac is not a reliable index of impairment of oxidative metabolism in the activated brain.

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INCREASED EXPRESSION OF β-CHEMOKINES IN INFLAMMATORY MYOPATHY MUSCLES. P. Confalonieri, P. Bernasconi, F. Cornelio, R. Mantegazza. Istituto Nazionale Neurologico "C. Besta", Milan, Italy.

Idiopathic inflammatory myopathies (IIM), such as polymyositis (PM), inclusion body myositis (IBM) and dermatomyositis (DM), are a group of autoimmune muscle diseases characterized by a mononuclear cell infiltrate in muscle tissue. $CD8^+$ T and B cells play a primary role in mediating muscle damage, but the mechanisms by which the autoimmune process is triggered and maintained are still unknown. Recent studies on cell homing have demonstrated that the accumulation of mononuclear cells at site of inflammation is mediated by chemokines. Thus,we evaluated the espression of two β-chemokines, monocyte chemotactic protein 1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1 α), by PCR and immunohistochemistry in muscles of patients affected by PM, DM and IBM, correlating the expression to myofiber necrosis, inflammatory cells, extracellular matrix and angiopathy. MCP-1 and MIP-1α mRNA were detected in all patients but not in controls. The protein colocalized with mononuclear cells and endomysial extracellular matrix which surrounds the infiltrate, while in normal muscles a very faint positivity was detected only in relation to blood vessels. These data suggest that chemokine storage in the extracellular matrix could be a crucial element for the amplification of lymphocyte attraction, activation and migration into inflamed tissue, and finally for the automaintenance of the autoimmune attack in IIM.

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EXPANDED CD8+ T CELL CLONES IN MUSCLE AND PERIPHERAL BLOOD OF POLYMYOSITIS: CORRELATION OF CDR3 SPECTRATYPING AND SINGLE CELL PCR. *+N. Goebels, +S. Wiesener, A. Roers°, H. Babbe°, #D. Pongratz, +H. Wekerle, *+R. Hohlfeld. *Dept. of Neurology, Klinikum Großhadern; #Friedrich-Baur-Institute, Munich,; +Dept. of Neuroimmunology, MPI of Neurobiology, Martinsried, ° Institute for Genetics, Cologne, Germany.

Polymyositis (PM) is considered to be an autoimmune disease caused by CD8+T lymphocytes which destroy HLA class I expressing skeletal muscle fibers. Recently we identified identical clonally expanded T cell populations both in the inflamed muscle tissue and in the peripheral blood of untreated PM patients. We employed a new PCR-based method to identify and characterize clonally expanded T cell populations. The method ("CDR3 spectratyping") relies on the natural length variation of the third hypervariable region (CDR3) of the rearranged T cell receptor gene: whereas a polyclonal T cell population shows a random, Gauss-distributed length variation of the CDR3, a clonally expanded population has a uniform CDR3 length, which can be identified as a single band on a sequencing gel. We analysed matched pairs of cDNA from muscle biopsies and peripheral blood lymphocytes (PBL) of PM patients and repeatedly detected identical clonally expanded T cell populations both in the inflamed muscle tissue and in the peripheral blood of untreated PM patients. Additionally we now analysed individual T cells which we micromanipulated from polymyositis tissue sections by single cell PCR. Using this technique we could confirm the expansion of T cell clones we had identified by CDR3 spectratyping *in situ*. In conclusion CDR3 spectratyping may be useful for the systematic identification of clonally expanded T cell clones and their monitoring during the course of disease and treatment. In combination with single cell PCR we eventually hope to be able to determine the disease relevance and antigen specificity of these expanded T cell clones.

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ROLE OF THE D4/S4 SEGMENT IN SLOW INACTIVATION OF SODIUM CHANNELS. [1,2]N. Mitrovic and [2]R. Horn [1]Departments of Neurology and Applied Physiology, University of Ulm, 89069 Ulm, Germany and [2]Department of Physiology, Thomas Jefferson University, Philadelphia, PA 19107, USA

Hyperkalemic periodic paralysis is caused by point mutations in the gene encoding the human skeletal muscle sodium channel. The electrophysiological studies in vitro showed that these mutations impair both fast and slow sodium channel inactivation. Little is known about mechanisms of slow inactivation. To learn more about the voltage dependence of slow inactivation we studied a mutation that substitutes a cysteine for positively charged arginine in the S4 segment of the fourth domain (D4:R3C). Covalent modification of this cysteine with a negatively charged thiol reagent (MTSES) causes a -25 mV shift of steady-state slow inactivation. Fast trains of depolarizations (2, 5 and 20 Hz) cause a reduction of the peak current of mutant channels modified by MTSES in the manner of use-dependent block. In addition, two mutations in the same S4 segment, located close to D4:R3C, also show a use-dependent block after chemical modification with MTSES. Two-pulse protocol experiments show that D4:R3C channels modified by MTSES readily enter, and reluctantly leave, a slow inactivated state. Our data suggest that the D4/S4 segment plays an important role in slow inactivation.

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SINGLE-VOXEL BRAIN 1H MR SPECTROSCOPY IN MITOCHONDRIAL DISEASES: DIAGNOSTIC AND PREDICTIVE ROLE. G. Siciliano, M. Mancuso, M. Renna, V. Lombardi, ML. Manca, M. Tosetti, C. Bianchi, L. Murri. Neuroscience Department, Neurological Institute, University of Pisa, Italy.

Mitochondrial encephalomyopathies (ME) are a wide group of diseases characterised by impairment of oxidative energetic production. Diagnosis of ME is established on clinical grounds in association with the presence of a typical histochemical findings, namely the presence of ragged red and COX negative fibers, and mitochondrial DNA mutations at muscle biopsy. To evaluate if neuroimaging, and in particular 1H Magnetic Resonance Spectroscopy (1H-MRS), can improve the diagnostic criteria for ME, we performed conventional brain MR imaging and single-voxel 1H MRS in 15 patients affected by different types of ME. Spectroscopic studies revealed a significant N-Acetyl-Aspartate and Choline 1H spectroscopy peak reduction, these data possibly being explained by neuronal rarefaction or dysfunction and decrease of phospholipids membrane turn-over due to cellular metabolic rate reduction. Lactate was never found, but a 0.9 ppm resonance signal corresponding to resonance frequency of branched-chain amino acids (BCAA) was found in some patients, indicating an increased BCAA cytyoplasmatic concentration as a likely result of insufficient mitochondrial oxidative decarboxylation. These data suggest a possible usefulness of brain 1H-MRS in detecting cerebral metabolism alterations in patients affected by ME.

Multiple Sclerosis – 2

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COGNITIVE DYSFUNCTION IN MULTIPLE SCLEROSIS (MS). Marié RM, Defer GL. . CHU de Caen, France.

Standardized and specific cognitive tools are recently used in MS. In summary, in previous studies, global efficiency and language are preserved whereas executive functions and memory are altered. Moreover we observe a large heterogeneity of the population studied and of the cognitive tools. We focused our study on executive and mnesic processes. 21 patients were included (41.6 ± 9 years). The following tasks were performed: Mattis dementia rating scale, the language Montréal-Toulouse task, the California Verbal Learning Task, the working memory Brown-Peterson paradigm, the mirror reading procedural learning task, the Wisconsin and the verbal fluency tasks. The performances were compared to control subjects matched for age and educational level using T test. Finally motor deficit was assessed by EDSS. Global efficiency and language are preserved; episodic, procedural and working memory as well as most of the executive processes are altered ($p < .001$). Patients with progressive forms seems to have lower performances especially for mnesic processes. We found no correlation between motor deficit and cognitive performance. Our battery shows wellknown cognitive results but also some new facts will be discussed as the alteration of procedural capacities and the caracteristics of the encoding processes in MS.

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GENDER SPECIFIC DIFFERENCES IN THE PROCESS OF COPING IN FAMILIES WITH MULTIPLE SCLEROSIS (MS). B Steck, F. Amsler, L. Kappos, D. Bürgin, Switzerland.

Objective: To analyze how the process of coping with MS of the patient and his or her partner is affected by such variables as the gender of the patient, the degree of disability or an associated elevated depression score and how it influences the process of coping in offsprings. Methods: Semi-structured interviews with 52 parents (26 female, 26 male patients) and 84 offsprings 3-26 years old were videotaped and rated to obtain an overall evaluation of the coping process. The neurological status (including EDSS) and questionnaires (including the Beck Depression Inventory) were recorded and statistical methods applied. Results: There was a significant inverse correlation between the degree of disability and the efficiency of the process of coping in the female patients, not in the male patients. As the degree of disability increases in the male patient, the better is the process of coping in the female partner. Female patients with a an elevated depression score influence negatively the coping process of their partners, in whom a depression score is also measured. There are significant correlations between the coping process of the offspring and his parents. Conclusions: This suggests that female healthy partners tend to cope better with the disease than healthy male partners. The interaction of the coping process with MS and other variables like for instance cognitive impairment should be further investigated.

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T1 HYPOINTENSELESION LOAD MEASUREMENTS IN A DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF INTERFERON BETA-1B IN SECONDARY PROGRESSIVE MS. PA Brex, PD Molyneux, C Middleditch, S Lewis, S Gregory, C Fogg, DG MacManus, GJ Barker, IF Moseley, DH Miller & The European Study Group on Interferon β-1b in Secondary Progressive MS

A proportion of high signal lesions seen on T2-weighted MRI appear as hypointense areas when viewed on T1-weighted images. A small histopathological study suggested that this subgroup of lesions represents those with more severe axonal loss. Hypointense lesions have been shown to have a better correlation with disability than T2 lesion load. Methods: 125 patients from 7 European sites, who had been randomised into either placebo or treatment groups, underwent T1-weighted MRI following an intravenous bolus of gadolinium at 6 monthly intervals for the first 2 years of the trial. The outlines of hypointense lesions were marked on hard copies of the T1-weighted images, with reference to the T2-weighted images, by a single blinded observer. The hypointense lesions load was then quantified using a semi-automated local thresholding technique. Results: After 2 years, the volume in the placebo group increased by a mean of 10.6% with reference to baseline, ($p=0.16$). In contrast, in the treated group there was a mean decrease of 16.5% ($p=0.007$). A significant difference was found between the treated and placebo groups ($p=0.0001$). Conclusion: Treatment with Interferon beta-1b resulted in a significant decrease in T1 lesion load. This reduction suggests a reversible element to hypointense lesion loads on enhanced images.

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MEASUREMENT OF BRAIN ATROPHY IN EARLY MULTIPLE SCLEROSIS. R Jenkins [1], PA Brex [2], N Fox [1], W Crum [1], DH Miller [2,1] Dementia Research Group & [2] NMR Research Group, Institute of Neurology, London, UK.

Brain atrophy is known to occur in established multiple sclerosis (MS). Atrophy is likely to be due to the loss of myelin and/or axons and correlates well with clinical progression in MS. The timing of onset of atrophy is however not known. To investigate this we studied patients presenting with clinically isolated syndromes suggestive of MS. Methods: T1-weighted 2D axial images were acquired at presentation and after 1 year. Retrospectively 9 patients who had developed MS during the year were selected (group 1), along with 8 age and sex matched patients who had normal imaging to act as controls (group 2). All image data was analysed on Sun workstations using MIDAS software. Whole brain regions were obtained using semi-automated iterative morphological techniques and ventricular regions using a threshold technique. Each subject's pair of scans were registered to allow accurate comparison of equivalent slices. Results: At baseline there were no significant differences between median brain volume or ventricular volumes. After 1 year the median ventricular volumes were significantly larger in the MS group (group 1= 5.05cm^3, group 2= 3.25cm^3; $p=0.034$). Conclusion: This preliminary study suggests that subtle tissue loss in the brain occurs early in the course of MS. The role of brain atrophy measurements as a predictive factor of prognosis in patients presenting with isolated syndromes will need to be further explored.

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SEVERITY AND SUSCEPTIBILITY OF MULTIPLE SCLEROSIS RELATED TO POLYMORPHISMS OF APOLIPOPROTEIN E. S. J. M. Weatherby[1], D. Carthy$_2$, C. Mann[1], M. Davies[1], J. Aldersea[1], M. Boggild$_3$, C. Young$_3$, A. Fryer[1], W. Ollier$_2$, R. Strange[1], C. P. Hawkins[1]. [1]Keele Multiple Sclerosis Research Group, Stoke-on-Trent; $_2$Manchester University; $_3$Walton Centre, Liverpool, U.K.

Apolipoprotein E (ApoE) is produced and secreted in the central nervous system. Allelic variants of the ApoE gene are known to influence Alzheimers disease. There is evidence that the cerebrospinal fluid concentration and intrathecal synthesis of ApoE is decreased in multiple sclerosis (MS). This may impair neuronal remodelling. A study of 85 patients has suggested 4 allele is associated with more aggressive disease in MS. We have therefore further investigated the hypothesis that variation in the ApoE gene influences disease course in MS. 371 patients with clinically definite MS and 158 healthy controls were studied. Genotyping was performed by standard polymerase chain reaction methods. There was no significant difference in ApoE allele frequency or genotype between patients and controls, between disease subtypes or between the sexes. Three measures of severity were assessed -1) expanded disability status scale (EDSS) of 0-5.5 and 6-10 at 10 years; 2) "benign" disease (EDSS 0-3 at 15 years); and 3) a progression index (EDSS /disease duration at 10 years). No significant relationship between genotype and severity was found. This study suggests that polymorphisms of apolipoprotein E may not be associated with severity or susceptibility in multiple sclerosis.

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LONGITUDINAL STUDY OF MOTOR ACTIVATION FMRI IN PATIENTS WITH MULTIPLE SCLEROSIS (MS). D. Ibarrola[1], JP. Ranjeva[1], C. Mekiies$_2$, K. Boulanouar$_3$, C. Manelfe[1], I. Berry[1], M. Clanet$_2$. 1 - Neuroradiology, 2 - Neurology, 3 - INSERM U455, Toulouse, FRANCE

The aim of this study is to contribute to the evaluation of the interest of motor FMRI in MS follow up. Methods 5 patients with a motor deficit of at least one hand (2 with a relapsing-remitting form (R-R) and 3) with a progressive form of MS) entered the study. _3 monthly clinical evaluation (Nine Hole Peg Test (NHPT) and BMRC motor testing) and FMRI examinations were performed at 1. 5T during one year, with a motor task activation (fist grasping), followed by a spectroscopy located in the precentral white matter and an imaging of the brain and cervical spine. Results and Conclusion No activation was observed in the controlateral precentral motor cortex when 2 of the 3 patients with a progressive form attempted to move their most affected hand. For the hand with the less severe deficit, large activation was observed in the ipsilateral cortex in one patient. During the relapse, one patient with a R-R form showed a large asymetry in activated areas of the motor controlateral regions between the 2 hands which was in good accordance with a decreased left motor efficiency on the NHPT. NAA/Creatine and Choline/Creatine ratios showed significant differences between the 2 forms of MS. These results suggest different patterns of motor cortex reorganization following a motor impairment secondary to demyelinative lesions.

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MAGNETIZATION TRANSFER IMAGING HISTOGRAM PARAMETERS IN MULTIPLE SCLEROSIS;CORRELATION WITH CLINICAL COURSE AND DISABILITY N. F. Kalkers[1], R. Q. Hintzen[2], J. H. T. M. van Waesberghe[3], R. H. C. Lazeron[3], R. A. van Schijndel[4],C. H. Polman[1] and F. Barkhof[3]. [1]Dept. of Neurology; [2]Dept. of Neurology, Leiden University Medical Center, Leiden; [3]Dept. of Radiology; [4]Dept. of Clinical Physics and Informatics, [1, 3,4]Free University Hospital Amsterdam, Amsterdam. The Netherlands.

Introduction Magnetization transfer (MT) imaging is an MRI technique that is based on the exchange of magnetization between water protons and protons bound to macromolecules. It reflects the histologic heterogeneity of multiple sclerosis (MS) lesions, and it might be senstitive to more subtle and diffuse abnormalities in the normal-appearing white matter (NAWM) in MS patients. Methods We analyzed 26 primary progressive (PP)-, 30 secondary progressive (SP)- and 34 relapsing-remitting (RR) MS patients and 14 healthy individuals. The correlation of MTR parameters as derived from histogram analysis with the EDSS as a measure of disability and the Paced Auditory Serial Addition Test (PASAT) as a measure of neuropsychological functioning (cognition) was studied. Results Various MTR parameters are significantly lower in MS patients compared with healthy individuals. The amount of pixels with signal-intensity 0 (amount of CSF) is significantly higher in RR and SPMS patients. There is a significant negative correlation in PPMS patients between PASAT and pixels with intensity 0 (R=-0.46). The PASAT is significantly correlated with the absolute peak height (aHp) in RR (R=0.56) and SPMS (R=0.52). In the RR group there is a significant correlation between the EDSS and the aHp (R=-0.44). Conclusion These preliminary data indicate that MTR histogram parameters show differences between various forms of MS (RR, PP and SP) and are also significantly correlated to clinically meaningful phenomena in MS (disability, cognition) and therefore could provide a tool to monitor objectively the evolution of the disease.

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A MAGNETIZATION TRANSFER HISTOGRAM STUDY OF NORMAL APPEARING CEREBRAL TISSUE IN MULTIPLE SCLEROSIS. C. Tortorella, B. Viti, M. Bozzali, M. P. Sormani, V. Martinelli*, G. Comi*, M. Filippi. Neuroimaging Research And *Clinical Trials Units, Dept Of Neuroscience, H San Raffaele, Milan, Italy.

We evaluated a) the ability of magnetization transfer ratio (MTR) histogram analysis in detecting the extent of the changes occurring outside multiple sclerosis (MS) lesions seen on conventional scans, b) whether such changes are different in the different MS clinical phenotypes, c) whether they are associated with the extent and severity of the macroscopic disease burden and d) their contribution to brain atrophy. Dual-echo, T1-weighted and MT scans of the brain were obtained from 77 patients with varying MS courses and 20 age- and sex-matched controls. To create MT histograms of the normal-appearing cerebral tissue, MS lesions were segmented from dual-echo scans and superimposed automatically and nulled out from the co-registered and scalp-stripped MTR maps. The following MTR histogram-derived measures were considered: average MTR, peak height and peak position. T2 and T1 lesion loads, average lesion MTR and brain volume were also measured. Average histogram MTR and peak position from patients with relapsing-remitting (RR) or primary progressive (PP) MS were significantly lower than those from controls. Patients with PPMS had also lower histogram peak height (p=0.01). Patients with secondary progressive MS had lower peak height (p= 0.05) than those with RRMS. Average lesion MTR ($p < 0.0001$) was the best predictor of the histogram MTR. Average histogram MTR ($p < 0.0001$) and T2 lesion load ($p = 0.001$) were the best predictors of brain volume. The amount of microscopic changes account for an important fraction of the disease burden in MS. They may contribute to the development of brain atrophy and tend to be more evident in patients in the more advanced and disabling phases of the disease.

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COMPARISON OF THREE MR SEQUENCES FOR THE DETECTION OF CERVICAL CORD LESIONS IN PATIENTS WITH MULTIPLE SCLEROSIS. M. A. Rocca, G. Mastronardo, G. Iannucci, [1]B. Colombo, [1]L. Moiola, [1]G. Comi, M. Filippi. Neuroimaging Research and [1]Clinical Trials Units, Dept of Neuroscience, H San Raffaele, Milan, Italy.

Aim of this study was to compare rapid acquisition with relaxation enhancement (RARE) with magnetization transfer-prepared gradient-echo (MT-GE) and fast short-tau inversion recovery (fast-STIR) magnetic resonance (MR) images to determine which sequence was best for imaging cervical cord lesions in patients with multiple sclerosis (MS). RARE, MT-GE and fast-STIR MR images were obtained from 56 MS patients and 10 healthy controls, using a 1.5 T MR system with a phased array coil. Spinal cord lesions seen using each sequence were counted by agreement by two observers in two stages (stage 1: random review of complete sets of scans from each technique; stage 2: side-by-side review with a 'retrospective' count of lesions). No abnormalities were seen in the controls. At the end of stage 1, a mean of 1.16 cord lesions per patient were seen on RARE scans, 1.57 on MT-GE (35% more than RARE) and 1.92 (66% more than RARE) on fast-STIR scans (p=0.005). Two or more cervical cord lesions were found on 16 RARE (29%), 23 MT-GE (46%) and 30 fast-STIR (54%) scans (p=0.02). Differences were reduced after stage 2: MT-GE detected 22% more and fast-STIR 36% more lesions than RARE. This was mainly due to the higher number of 'false negative' lesions seen on the RARE and MT-GE MR images (p=0.006). Considering the three sequences together, 113 cervical cord lesions were seen in 50 patients (89%). Both MT-GE and fast-STIR sequences show more cervical cord MS lesions than RARE, with fast-STIR having the best sensitivity. Fast-STIR MR images may be useful in the diagnostic workout of patients with suspected MS and for improving our understanding of MS evolution.

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CEREBRAL ATROPHY AND DISABILITY IN MULTIPLE SCLEROSIS: A FOUR-YEAR SERIAL MRI STUDY. BP Turner, G Calmon, N Roberts and LD Blumhardt - Universities of Nottingam and Liverpool, UK.

Cerebral atrophy has long been recognised as a feature of late multiple sclerosis (MS). Recent studies suggest that axonal loss accounts for both the atrophy and at least a proportion of the fixed neurological disability of early MS. *Aim:* To investigate the relationship between cerebral volume changes and disability at different stages of the disease course over a four-year period. *Methods:* We measured disability (EDSS) and 3D-MRI at baseline and up to 48 months in 20 patients with relapsing-remitting (RRMS) and 18 with secondary progressive (SPMS). Volumes for total brain (TBV) and lateral ventricles were obtained using a semi-automatic method. *Results* Over 48 months the total cohort had a median 0.6% decrease in TBV (median -7.49cm_3; $p < 0.002$) and an 14.0% increase in ventricular volume (median 2.91cm_3; $p < 0.0001$). Increases in ventricular volumes were similar for RR and SPMS, but the median TBV was significantly reduced only in RR patients (median reduction: RR, -12.77cm_3, $p < 0.006$; SP, -4.05, p=0.119). Significant (>95% CI) TBV, but not ventricular changes, were more frequent in RR patients (7 vs. 1, p=0.045). For the total cohort, EDSS change correlated with ventricular (rho= -0.46, p=0.004) and TBV (rho= -0.37, p=0.022) changes. *Conclusions:* These results suggest that cerebral atrophy is occurring faster in RR than SPMS, but the rate of ventricular enlargement, which correlates with clinical disability, appears to be similar at different stages of the disease.

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DEMYELINATING DISEASE AND HEPATITIS B VACCINE. RESULTS OF A SURVEY FROM 735 PATIENTS SEEN AT THE MULTIPLE SCLEROSIS CLINIC. M. Coustans, P. Brunet, O. De Marco, E. Le Page, J. Yaouanq, J. Chaperon, G. Edan. Rennes, France.

From February 1997 to August 1998, we set up a survey in order to study possible relationship between multiple sclerosis (MS) and hepatitis B (HB) vaccine. During that period, the 735 patients who were referred to our MS Clinic were systematically asked if they had been vaccinated against HB. Ninety two patients answered positively. Forty four of them were included in this study. Twenty four patients had a clinicaly definite MS disease, diagnosed before the HB vaccine. Their mean annual relapse rate was 0,62 within the 24 months before vaccination and 0,50 after vaccination (Wilcoxon test, NS). A group of twenty other patients had a first episode of a central nervous system demyelinating disease less than two months after vaccination. Their clinical status and their demographic data at the time of their first neurological manifestation were compared with those of the non-vaccinated patients. The only significative difference was that the vaccinated patients were younger than the non-vaccinated patients (24 vs 28 at onset). This last difference was the only argument we found favoring the hypothesis that HB vaccination might precipitate MS disease in genetically predisposed patients.

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3D BRAIN MR IMAGING OF MULTIPLE SCLEROSIS LESIONS S. Miron, M. Faibel, S. Gicquel, M. Masseneau, A. Achiron. Neuroimmunlgy Unit, Sheba Medical Center, Tel Hashomer, Israel, IOTEC, Paris, France.

Magnetic resonance imaging (MRI) is an advantageous tool for the diagnosis and follow-up of multiple sclerosis (MS) patients. Despite its widespread use inaccurancies in measuring lesion load on conventional T2-weighted images are well known. 3-D volumetric quantification can attribute to the true scope of disease burden. The aim of the present study was to construct an identification module of MS demyelinating lesions and reproduce 3-D images for accurate lesions quantification. MRI digital images of MS patients were transferred from the MRI device (Prestige 2T Elscint, Haifa, Israel) to a Macintosh workstation (IOTEC 3.0, Paris, France) specialized in (dicom 3.0) medical image archiving and processing. MRI images of 3 mm slice thickness (no gap) were acquired. T1, T2, Gd enhanced and fast FLAIR techniques were used. Restoration stage identified lesions, CSF, gray and white matter brain tissue. Using an algorithm the intensity distribution (segmentation) of each MRI modality was computed. Then, the information contained in the segmented slices was used by the algorithm to perform the 3-D reconstitution step. Finally, on screen, the user is presented with a lesion volume list together with a 3-D map of all the lesions in spatial relation to the ventricles. The 3-D method provides information about lesions localization in the X, Y, and Z axis, and enables precise, fastand non-biased volumetric 3-D quantification of MS disease burden. Results: Accuracy of 3-D volumetric measurement by the software was evaluated by scanning at 3mm contiguous axial slices a phantom of a known volume (550 cm3). Brain MRI scans of 12 patients with clinically definite MS were evaluated by both a neuroradiologist and the automated 3-D module. MRI assessments of T2 images showed moderate computer-observer agreements. 15-30% of lesions identified by the computer were not identified by the neuroradiologist. Measurments by the software were faster and accuracy increased by 14-22%. Gd enhanced lesions had a better agreement with only 2% of lesions not identified by the neuroradiologist.

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ANTICIPATION OF MULTIPLE SCLEROSIS (MS) ONSET IN CHILDREN OF PARENT/CHILD PAIRS FROM ITALIAN MS MULTIPLEX FAMILIES. M. Trojano, M. Liguori, *M. G. Marrosu, *M. Lai, *E. Cocco, °M. Pugliatti, F. De Robertis, Avolio C., F. Giuliani, D. Paolicelli, Livrea P; Universities of Bari - *Cagliari - °Sassari - Italy

A comparative analysis of clinical (EDSS, disease course and functional systems involved at onset - FSs) and demographic (sex, age, age at onset, year of onset) features was performed between 114 affected pairs (92 sibling and 22 parent/child) from 98 MS Multiplex families (no. 43 from continental Italy and no. 55 from Sardinia). Both the sib and the parent/child pairs differed ($p < 0.0001$) for ages and calendar year of onset and resulted significantly concordant for dates of birth ($p < 0.0001$) and years of onset ($p= 0.015$). The sib pairs were only concordant for the ages at onset ($p= 0.05$), whereas parent/child pairs significantly differed for ages at onset; particularly, parents developed MS at an age 17.02 ± 11.5 yrs. older than their children ($p= 0.0008$). A significant concordance for EDSS ($p= 0.02$), and brainstem and pyramidal FSs involvement at onset ($k= 0.3$ and 0.35) was found in siblings, and for cerebellar and sensitive FSs involvement at onset ($k= 0.39$ and 0.37) in parent/child pairs. These data confirm previous results obtained on a smaller population (J. Neurol. Sci., *in press*) showing an anticipation of MS onset in children of parent/child pairs and the presence of clinical phenotypes that cluster within MS multiplex families.

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HIGH RESOLUTION DIFFUSION MRI USING STANDARD GRADIENT EQUIPMENT. R. Bammer[1, 2], M. Augustin[1, 2], R. Stollberger[1], J. Simbrunner[1], F. Ebner[1], H. P. Hartung[2], F. Fazekas[1,2]. [1]Magnetic Resonance Institute and [2]Department of Neurology, University of Graz, Austria

Purpose: To demonstrate the technical feasibility and precision of a novel high-resolution dual-echo diffusion weighted imaging (DWI) method with interleaved echoplanar imaging (IEPI) and phase navigation, and to test its diagnostic sensitivity for ischemic stroke. Material and Methods: Measurements of the apparent diffusion coefficient (ADC) in phantoms (water and acetone) and healthy adult volunteers were performed with a MR scanner equipped with conventional gradient hardware. DWI maps and lesion rADC values (ipsi- to contralateral ratio) were determined in 34 consecutive stroke patients to evaluate the sensitivity and reliability of the proposed DWI-IEPI technique for ischemic brain damage as well as for the temporal evolution of the ADC in stroke. Results: Studies in phantoms and volunteers yielded ADC-values which were in excellent agreement with published data. IEPI allowed the rapid acquisition of high quality images of the entire brain without any significant artifacts and all patient studies were of diagnostic quality. Within the first week the sensitivity of DWI-IEPI for acute infarction was 90% of first examinations and was independent of lesion location. Conclusions: Phase navigated dual-echo DWI-IEPI in conjunction with cardiac triggering to correct for pulsatile brain motion is a robust, reliable and fast technique for DWI. With its high sensitivity for early ischemic infarction DWI-IEPI promises to be a useful tool for evaluating stroke patients using MR equipment with conventional gradient systems. It also allows to recognize acute but clinically silent associated ischemic lesions which promises to provide important information in regard to the pathophysiology of stroke.

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CLINICAL COURSE AFTER PERCUTANEOUS CLOSURE OF PATENT FORAMEN OVALE (PFO) IN 100 PATIENTS WITH UNEXPLAINED STROKE USING FIVE DIFFERENT TECHNIQUES. FOLLOW-UP OF MORE THAN 170 PATIENT-YEARS. Sascha Rux, Patrick Keppeler, Dorothea Krüger, Jürgen Dirks, Ulrike Krumsdorf, Horst Sievert, Rainer Schräder. Cardiovascular Center Bethanien, CCB, Frankfurt, Germany

Non-surgical closure of patent foramen ovale (PFO) has been proposed to prevent recurrence of presumed paradoxical embolism in patients with unexplained stroke. Over the past years, several devices for transcatheter PFO-occlusion have been developed. Patients: Between 08/94 and 01/99 transcatheter closure was attempted in 100 patients aged 17 - 77 years (mean SD: 46 14). The PFOs were suspected to have caused between one and four paradoxical embolic events. The incidence of cerebral (arterial) embolism was 3.6% per year before PFO-closure. In all cases, right-to-left-shunt through the PFO was proven by transoesophageal contrast echocardiography. Other causes for cerebral ischemia or embolic sources were excluded. Results: PFO-closure was successfully performed in 23/26 patients with SIDERIS-Buttoned-Devices, in 11/11 patients with the ASDOS-double-umbrella, in 20/20 patients with ANGEL-WINGS-device, in 20/20 patients with the Cardio-Seal-occluder and in 23/23 with the PFO-star. The primary overall success rate was 97%. Seven weeks after the intervention one SIDERIS-Device was surgically explanted because of partial unbuttoning. During the follow-up period of total 172 patient-years only two patients, treated with the SIDERIS-Buttoned-Device, suffered a recurrent embolic event. The risk of stroke-recurrence was therefore 1.2% per year after the intervention. Conclusion: All systems are suitable for transcatheter PFO-occlusion. In comparison to operative or medical treatment percutaneous defect-closure seems to be an appropriate and reliable method in preventing recurrent embolism.

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STROKE AND ATRIAL FIBRILLATION : WAS STROKE PREVENTION APPROPRIATE BEFOREHAND ? D. Deplanque, F. Corea, C. Arquizan,L. Parnetti, JL. Mas, V. Gallai, D. Leys and the SAFE study investigators. University of Perugia, Italy . Paris Sainte Anne and Lille University hospitals, France.

Randomized trials have shown that anticoagulation and aspirin respectively lead to a two-thirds and a 42% risk reduction of stroke in patients with atrial fibrillation. The aim of the study was to determine the proportion of patients with atrial fibrillation who were not under antithrombotic therapy before stroke onset and their characteristics. SAFE was conducted in 213 patients with atrial fibrillation consecutively admitted in 1997 in 3 European centers for an acute stroke or transient ischemic attacks. We determined whether they were under antithrombotic therapy beforehand. Atrial fibrillation was previously known in 148 patients (69.5 %). Of 213 patients, 34 (16.0%) were under anticoagulation before stroke, 65 (30.5 %) were under antiplatelet therapy and 3 (1.4 %) were under both. Of 137 eligible patients for oral anticoagulation, 108 (78.8 %) did not received it. Of 142 eligible patients for any antithrombotic therapy, 62 (43.7 %) were not treated. The logistic regression analysis assuming anticoagulation as dependent variable found digoxin therapy, absence of arterial hypertension, mitral stenosis and cardioversion as independent factors. Assuming

any antithrombotic therapy as dependent variable, we found atrial fibrillation being previously known, lower age, being non-smoker and absence of arterial hypertension as independent factors. More than half patients with atrial fibrillation admitted for acute stroke or TIA were not under any antithrombotic therapy before stroke. New onset atrial fibrillation and contraindications account for a minority of non-prescriptions. Thus, other reasons should be identified to improve stroke prevention in the community.

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CEREBRAL INFARCTION IN HIV - PATHOLOGY WITH CLINICAL CORRELATION. M. D. Connor, A. Lammie, J. E. Bell, P. A. G. Sandercock. Department Of Clinical Neurosciences, Western General Hospital, Edinburgh, Scotland.

Cerebral infarction in HIV positive patients is said to occur in 0.5 to 10% of patients, either in isolation or secondary to opportunistic infections or neoplasia. HIV vasculitis is often considered causative. The clinical relevance of cerebral infarcts in this setting, is unclear. Aims: 1. To establish pathological evidence of pure ischaemic lesions in autopsied patients from the Edinburgh HIV Cohort Study, and 2. To correlate these findings with relevant clinical features. Methods: Selection of cases: 1. Prospectively selected pathological slides exhibiting ischaemic changes in cerebral tissue, 2. Review of all remaining autopsy reports. If a report did not clearly document normality of the brain tissue or an exclusion criteria, the slides were reviewed. Inclusion Criteria: All patients with brain lesions that appeared ischaemic. Exclusion Criteria: Evidence of non-HIV related cerebral infection, cerebral malignancy, haemorrhage, traumatic injury. All brain histology and clinical records were reviewed. Results: 10/183 (5%) patients fulfilled all criteria. All demonstrated similar hypoxic-ischaemic lesions. Small vessel thickening was seen in 9 patients, but vasculitis was not found. Clinically, one patient had a history of previous TIAs. Conclusion: Pure hypoxic-ischaemic cerebral lesions in the autopsy cohort were rare. These were not due to vasculitis. The pathological findings did not correlate with clinical features. In HIV positive patients presenting with clinical features of a cerebral infarct, potentially treatable causes should be sought.

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GIANT LACUNES: DIFFERENT FROM OTHER LACUNES? Isabel L Henriques, José Correia*, António L Leitão. Neurology and Internal Medicine* Departments. Hospital Espírito Santo, Èvora, Portugal

Lacunar infarction (LI) definition is limited to a diameter up to 1.5mm by imagiologic methods, but in clinical practice bigger round lesions in the distribution of the perfurators from anterior and posterior circulation do occur. We studied the hypothesis that the lesion size could be associated with different etiologies. Methods: We studied all patients with first ever stroke(October 1997- October 1998), according to a protocol that includes at least one CTscan or MRI, preclinical, clinical and diagnostic data. Previous cardiac disease was defined as any potential cardioembolic disease known before stroke. We considered large lacunar infarction (LLI) any LI with a diameter over 1.5 mm on CT or MRI. Clinical correlation with symptoms was necessary for the diagnosis of LI. Results: From 44 patients with LI, 10 were considered LLI. Major differences between the two groups (LLI *vs* LI) were found regarding previous cardiac disease (20% *vs* 3%), smoking habits (10% *vs* 33%), sex (60% male *vs* 79%) and territory infarction (anterior circulation 90% *vs* 50%). No differences were found concerning hypertension, diabetes, dyslipidemia or previous TIA. Conclusion: In comparison to lacunar infarction, large lacunar infarction may be related to different a etiology. In our patients, previous cardiac disease and territorial distribution had a different prevalence in the two groups. This might be related to embolism. Further research is needed to clarify the role of small vessel disease and potential embolism in the etiology of large lacunar infarction.

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SUPERIOR SAGITTAL SINUS THROMBOSIS TREATED WITH DIRECT UROKINASE THROMBOLYSIS: ANALYSIS OF 25 PATIENTS. Mohammad Wasay MD, George Bobustuc MD, Rohit Bakshi MD, Suleman Kojan MD, Neeraj Dubey MD, Saadat Kamran MD

Objective: To evaluate safety and efficacy of direct urokinase thrombolysis for superior sagittal sinus thrombosis (SSST). Methods: At three centers (Southwestern University, Dallas, TX; University of Texas, Houston; State University of New York at Buffalo) 78 consecutive dural sinus thrombosis patients were reviewed to identify urokinase treated SSST patients. Twenty-five such patients received a local catheter-infused urokinase bolus into the SSS (50,000-250,000 units) followed by continuous urokinase infusion (10,000-80,000 u/hr) for 16-84 hours (mean 52 hr). The primary outcome measure, neurologic deficit, was rated at baseline (pretreatment) and discharge (postreatment) on a four point neuroscore scale: 0=normal; 1=mild (patient able to ambulate and communicate); 2=moderate (unable to ambulate but able to communicate); 3=severe (patient unable to ambulate and communicate). Results: Age range was 4-61 yr (mean 34 yr; 11 males; 14 females). Eight patients had venous infarctions on CT/MRI (hemorrhagic: n=5, non-hemorrhagic: n=3). Angiogram showed SSST alone (n=4), SSST + transverse sinus thrombosis (n=10), or SSST + 2 or more thrombosed sinuses (n=11). Patency of SSS was achieved in all cases. Complications did not require invasive treatment [retroperitoneal hemorrhage (n=1); subdural hematoma (n=1)]. Initial neuroscore deficit was normal (n=7), mild (n=8), moderate (n=6), or severe (n=4). Discharge neuroscore deficit was normal (n=19), mild (n=5), moderate (n=1), or severe (n=0). Differences between pretreatment and postreatment neuroscores were highly significant (p=0.0002; Mann-Whitney U Test). Only 1 patient had recurrent SSST, which responded to repeat local urokinase. There were no deaths. Conclusion: Local urokinase thrombolysis therapy significantly promotes neurologic recovery in patients with SSST and this therapy appears to be well tolerated. Prospective trials comparing urokinase to conservative therapies of SSST are warranted.

General Neurology – 1

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PROGNOSIS OF INFECTIVE ENDOCARTIDIS REVEALED BY NEUROLOGICAL COMPLICATIONS. M. Pages, A. Lebourg, C. Tannier, JM. Blard. Service De Neurologie, CHU Gui De Chauliac, Montpellier, France

Neurological complications are observed in 20 to 40% patients with infective endocarditis. They occur as the first manifestation of the disease in increasing percentages of cases. Methods and results : we reviewed clinical, radiological and laboratory data in 14 cases of infective endocarditis revealed by neurological complications. Eleven patients were male and 3 female, aged 35 to 79 years ; 7 had a predisposing cardiac disease and streptococcus was the most causative organism (9 cases). There were 8 ischaemic strokes : 1 transient ischaemic attack ; 1 regressing stroke ; 6 completed strokes (5 in the middle cerebral artery and one in the posterior cerebral artery distribution). 3 patients died from infective complications and 3 had hemiplegic sequelea. Haemorrhages were observed in 2 cases. One patient had ruptured mycotic aneurysm and recovered after neurosurgical treatment. The other one partially recovered but had a second stroke due to cerebellar and brain stem infarction. Two elderly patients presented with confusional state and behavioral disorders. Diagnosis was delayed and both of them died from stroke. One patient had a septic meningitis and died from embolic and cardiac complications. In the last case, who recovered without sequelae, endocarditis was diagnosed after a grand mal seizure. Conclusion : our study confirm the bad prognosis of neurological complications as primary presenting manifestation of infective endocarditis.

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HERPES ENCEPHALITIS - LESIONAL PATTERN ON MRI. Simbrunner J, MD (1), Feichtinger M, MD (2), Kleinert R., MD (3), Fazekas F, MD (1, 2), Ebner F, MD (1) MR-Institute (1), Department of Neurology (2), Department of Pathology (3), Karl-Franzens University, Graz, Austria.

Purpose – Herpes simplex virus (HSV) type I encephalitis has a special affinity for the limbic brain, but the pattern of affected regions differs in various patients. We analyzed the MR images of patients with proven HSV encephalitis with respect to the following questions: 1) Are there common findings in all patients? 2) Can the lesional pattern be explained on anatomical basis? 3)Is there a relationship with clinical symptomatology and outcome? Methods – Five patients with the clinical diagnosis HSV encephalitis were included in the study. In all of them HSV DNA genomes by sensitive PCR-hybridization method were detected in CSF taken from the acute stage. T2W and T1W MR images pre and post gadolinium were acquired in the axial and coronal plane. The affected areas, which showed high signal on T2W images and partially enhanced, were analyzed on a macroanatomical basis. Results – In all patients the uncus, hippocampus, parahippocampal gyrus, perirhinal and insular cortices were affected, whereas the temporal pole, the frontobasal cortex, the ante-

rior part of the cingulate gyrus, the septal region and the basal forebrain were variously included. The extent of the involved brain regions did not correspond with the clinical disease state and outcome. Conclusion – There seems to be a special affinity of the HSV type I for the temporomedial limbic cortices. Lesional spread can be explained on basis of the known intrinsic and extrinsic axonal connections of the temporomedial lobe.

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FRUCTOSAMINE LEVELS AND THE RISK OF DEMENTIA. THE ROTTERDAM STUDY. S Kalmijn, A Ott, AH Bootsma, A Hofman, HAP Pols, MMB Breteler. Rotterdam, the Netherlands.

Several studies have shown that persons with diabetes mellitus have an increased risk of dementia. This association did not seem to result from macrovascular disease, which is more prevalent among diabetic subjects. A possible explanation may be a direct effect of chronically increased or recurrently decreased glucose concentrations. Fructosamine offers a reliable estimate of glycemic control over the past four weeks. Therefore, we examined the association between fructosamine levels and the risk of dementia among 4970 participants, aged 55 years and over, from the population-based prospective Rotterdam Study. Multiple logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). After an average duration of follow-up of 2.1 years 115 persons became demented. Among non-diabetics, after adjustment for age, sex, and education, the risk of dementia increased with decreasing fructosamine levels (OR 1_{st} (281 mol/l) vs 4_{th} (335 mol/l) quartile = 1.9, 95%CI: 1.0-3.8, p-linear trend=0.03). Among diabetics, the association appeared to be U-shaped (p-quadratic term=0.08) since the risk was increased in the 1_{st} fructosamine quartile (315 mol/l, RR=2.8, 95%CI: 0.7-11.3) and in the 4_{th} quartile (411 mol/l, RR=4.7, 95%CI: 1.2-18.8) as compared to the 2_{nd} quartile. This study suggested that high fructosamine levels, which were mainly present among diabetics and may reflect worse glycemic control, increase the risk of dementia. A low fructosamine level was also associated with an increased risk of dementia, regardless of the presence of diabetes.

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NEUROIMAGING FEATURES OF LISTERIA MONOCYTOGENES RHOMBENCEPHALITIS. D. Annesley-Williams, P. Brennan, O. Hardiman, S. Murphy. Department of Neuroradiology/Neurology, Beaumont Hospital, Dublin, Ireland

Aim: To describe the appearances of Listeria Monocytogenes Rhombencephalitis on computed tomography (CT) and magnetic resonance imaging (MRI) and to evaluate the role of neuroimaging in establishing the diagnosis. Materials/Methods: Neuroimaging findings in three patients who presented to this centre over the last year were assessed independently by two experienced neuroradiologists. The cohort included two men and one woman with an age range from 26-68 years. Results: Findings at CT showed distortion of the left lateral aspect of the fourth ventricle with a low attenuation, non-enhancing mass in the left middle cerebellar peduncle in one case. The two other CT examinations were normal. MR imaging in two patients revealed areas of high signal on T2 weighted sequences in the pontomedullary region. Patchy enhancement of the lesions following contrast administration was seen in one patient. Discussion: Infection with Listeria Monocytogenes may cause a rhombencephalitis manifested by progressive cranial nerve dysfunction in combination with cerebellar signs following a prodromal illness. The elderly, the very young and the immunocopromised are particularly susceptible. Overall mortality associated with this pathogen may exceed 50%; therefore prompt therapy with the appropriate antibiotic is of paramount importance. Conclusion: Familiarity with neuroimaging appearances in this condition may be crucial to the early diagnosis of the disease leading to a reduction in mortality and permanent neurological sequelae.

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RECURRENT ACUTE DISSEMINATED ENCEPALOMYELITIS (ADEM). Oren Cohen, Bettina Steiner-Birmanns, Iftah Biran, Sylvia Honigman*, Dov Sofer**, Oded Abramsky, Israel Steiner. Department of Neurology and **Pathology, Hadassah University Hospital, Jerusalem, and *Carmel, Haifa, Israel.

Objectives: To describe characteristics of recurrent ADEM. Background: ADEM is an acute demyelinating disorder of the CNS. The disease is considered monophasic and most patients with recurrent episodes are eventually diagnosed as having multiple sclerosis (MS). Recurrent ADEM cases can therefor be overlooked. Methods:During the years 1983-1998 ADEM was diagnosed in 20 patients at the Hadassah University Hospital, based on the clinical context, laboratory and imaging findings and brain biopsy (when available). The medical records of these patients were reviewed. Recurrence was defined as appearance of new symptoms and signs at least 2 months after previous episode. Results: Four out of 20 ADEM patients (20%) developed recurrent disease episodes. These patients were 2 men and 2 women, aged 30-77, and in all, the diagnosis was confirmed by brain biopsy. One patient had four disease episodes and the other two. Presentation consisted of acute onset of headache, confusion, fever and focal neurological signs. Recurrence appeared 2-30 months after previous episode, and involved different brain territory in 3/6 recurrences. Brain biopsy was available in 3/6 recurrences and in all it was compatible with ADEM. In 2 patients neuropsychiatric signs were evident during recurrence. Three patients responded to immunosuppressive therapy at the initial episode and two responded at relapses. Conclusions: Recurrent ADEM may be more prevalent than previously regarded and the disease may have a polyphasic course. Neuropsychiatric signs may be part of the relapse and some patients may respond to treatment at recurrent episodes.

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ANTI-NEURONAL ANTIBODIES IN NEUROLOGICAL DISORDERS. Giometto B, Nicolao P, Scaravilli T, Vianello M, Keir G, Scaravilli F, Tavolato B. Department of Neurology, University of Padova (Italy) and Institute of Neurology, University of London (United Kingdom)

The characterisation of anti-neuronal antibodies extended the variety of immunologically related neurological disorders. However, to date, studies have investigated them in well defined groups of disorders. Our aim is to identify the range of disorders expressing antineuronal antibodies, evaluate the different patterns of reactivity and analyse the contribution of these procedures to the identification of subgroups of patients. Material and methods: 862 patients with known neurological disorders (from the discharge summary) and controls with tumours and autoimmune disorders were reviewed. The patients were divided into 4 groups according to the suspected diagnosis and their serum and CSF were tested for antineuronal antibodies. Antibodies were detected by immunohistochemistry, Western Blot of gradient separated neuronal proteins and RIA. Results: Cerebellar Degeneration was the commonest neurological disorder associated with detection of PND-related anti-neuronal antibodies. These included atypical antibodies: anti-GAD in 3 and atypical in other 3 patients. Atypical antibodies were also detected in patients with peripheral neuropathy, most of them associated with sensory and sensory-motor neuropathy. Few patients with Stiff-Person syndrome, Temporal Lobe Epilepsy and Myoclonus harboured anti-GAD, and atypical antibodies where rarely detected in patients with Dementia, MND and MSA. No antibodies were detected in patients with neurological complications of collagen disorders other than Sjogren syndrome, nor in other conditions. Conclusions: The spectrum of neurological disorders associated with anti-neuronal antibodies is extending. These procedures could allow the identification of subgroups of patients in whom strategies directed to modify the immunological derangement could be of some benefit.

Peripheral neuropathy – 1

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LONG-TERM OUTCOME OF GUILLAIN-BARRÉ SYNDROME (GBS): A PROSPECTIVE, POPULATION-BASED STUDY. Adriano Chiò, for the Piemonte and Valle d'Aosta GBS Register, Turin, Italy

The few studies devoted to the analysis of prognostic factors in GBS are based on hospital series, with a possible selection bias. Therefore, we have investigated long term outcome of GBS evaluating early prognostic factors in an incident cohort of patients resident in Piemonte and Valle d'Aosta regions, Italy (population: 4,418,503), diagnosed during 1995-1996, and prospectively followed-up. Cases were identified through the Piemonte and Valle d'Aosta GBS Register. Diagnosis of GBS followed NINCDS criteria. A total of 108 patients were identified (mean crude incidence rate, 1.22/100,000/year). The patients were prospectively followed-up for two years after dismissal; clinical status was evaluated according to Hughes' scale. Factors related to poor recovery (Hughes' grades 2) at 2 years were analyzed with a forward stepwise multivariate logistic regression. Five patients were lost to follow-up and 7 deceased within 1 month after GBS onset. At the end of the 2-years period, 82 patients (85.4%) had a good recovery (Hughes' grades 1). The factors significantly related to

poor recovery in univariate analysis were: Hughes' grade at nadir 3, respiratory impairment, age 50 years, axonal damage, infective antecedents, and autonomic involvement. The multivariate model retained only Hughes' grade and age. Therefore, most of GBS patients had a good recovery and Hughes' grade at nadir and age resulted significantly related to the outcome. No difference of recovery was found when comparing main treatments (plasma exchange vs. IV immunoglobulins).

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T CELL RECOGNITION OF NON PROTEIN ANTIGENS IN GUILLAIN BARRE SYNDROME. JC Cooper, S Hughes, A Ben-Smith, COS Savage, JB Winer. Divisions of Medical Sciences and Neurosciences, University of Birmingham, UK.

Campylobacter jejuni is the major antecedent infection associated with acute inflammatory demyelinating polyneuropathy (AIDP) and other subtypes of the Guillain-Barré Syndrome. Antibody cross-reactivity between the lipopolysaccharide of *C. jejuni* and peripheral nerve ganglioside has been demonstrated suggesting a possible mechanism for the pathogenesis of the syndrome. T cell recognition of non-protein antigens, however, has so far received little attention as a factor in disease pathogenesis. We have found that two patients with AIDP associated with preceding *C. jejuni* infection had significant T cell proliferation in the peripheral blood *to C. jejuni* antigens (SI 105 and 23). Treatment of the antigen with proteases did not prevent substantial T cell proliferation (SI 53 and 7) suggesting that these cells were responding to non-protein antigens. The phenotype of these cells in one of these patients was $CD4^{-}CD8^{-}\alpha\beta$ TCR^{+}. Such double negative T cells have a T cell receptor capable of recognising non-protein antigens and may be CD1 restricted. γδ T cells are similar in having the potential to recognise non-protein antigens and we have further shown that we can identify γδ T cells in 6 out of 11 (55%) sural nerve biopsy specimens from patients with AIDP by immunohistochemistry. Our results support a role for non-protein recognition by T cells in the pathogenesis of GBS.

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IGG FC RECEPTOR POLYMORPHISMS IN INFLAMMATORY NEUROPATHY. C. A. Vedeler, K-M. Myhr, G. Raknes, B. Kluge, H. Nyland. Department of Neurology, University of Bergen, Norway

Both cellular and humoral immune mechanisms are involved in the pathogenesis of acute and chronic inflammatory demyelinating polyneuropathy (AIDP, CIDP). The IgG Fc receptors (FcγRs) link cellular and humoral immunity by serving as a bridge between antibody specificity and effector cell function. The Fcγ RIIA and Fcγ RIIIB subclasses have different affinity for IgG subclasses which influence the efficacy of effector functions such as phagocytosis and cytotoxicity. We studied genotype frequencies of these two Fcγ Rs in 62 AIDP patients, 24 CIDP patients and 96 healthy controls from Norway. The Fcγ RIIA H/H, H/R, R/R and Fcγ RIIIB NA1/NA1, NA1/NA2, NA2/NA2 frequencies of the AIDP and CIDP patients did not differ significantly from the controls. AIDP patients homozygous for Fcγ RIIIB NA1 had less disease severity than patients heterozygous or homozygous for Fcγ RIIIB NA2 (p=0.04). The results indicate that the Fcγ RIIA and Fcγ RIIIB genes are not significantly associated with AIDP or CIDP. However, Fcγ RIIIB may be a disease modifying gene in AIDP.

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INTERFERON-β DECREASES TRANSMIGRATION OF LYMPHOCYTES FROM PATIENTS WITH GUILLAIN-BARRÉ SYNDROME (GBS). Créange A, Sharshar T, Plonquet A, Poron F, Farcet J-P, Raphaël J-C, Gherardi RK Créteil and Garches, France

OBJECTIVE: To Evaluate The Effect Of Interferon-β (IFN-β) on lymphocyte transmigration in GBS. BACKGROUND: GBS is characterized by an early neural infiltration of activated lymphocytes and monocytes. IFN-β can modulate the course of experimental allergic neuritis and has been recently proposed in GBS. METHODS: Lymphocytes from nine patients with GBS and six healthy subjects were collected. Motor deficit was assessed using the London severity scale. Lymphocyte transmigration rate (LTR) was investigated ex vivo using a modified Boyden chamber assay (coated with fibronectin) without or with IFN-β1a (Rebif®). The number of transmigrating cells was determined after 24 hours. Lymphocytic populations were characterized by flow cytometry. RESULTS: LTR was 13.3±12% in GBS, and 6.07±3.5% in controls ($p < 0.0003$). IFN-β decreased LTR from 13.3±12 to 9±6.3% ($p < 0.03$) in GBS. IFN-β -induced decrease of transmigration was more pronounced in the less severe cases (-58% stage 2-3; -25% stage 4; -15% stage 5). Similar lymphocyte populations were observed in the upper and lower compartments of the chamber. CONCLUSION: Lymphocyte transmigration capacities are increased in GBS and decrease in the presence of IFN-β according to the severity of the disease, suggesting a potential interest of IFN-β in the treatment of GBS.

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REVERSIBLE, COMBINED, PRE- AND POSTSYNAPTIC BLOCKADE OF NEUROMUSCULAR TRANSMISSION BY ANTI-GQ1B ANTIBODIES FROM PATIENTS WITH MILLER FISHER SYNDROME (MFS). B. Buchwald, J. Bufler*, M. Carpo', E. Nobile-Orazio', K. V. Toyka; Departments of Neurology, Universities Würzburg, *Munich, Germany; 'Milano, Italy.

Background: Neuromuscular blocking antibodies have been demonstrated in sera of patients with Miller Fisher syndrome (MFS), but their mode of action differs depending on different physiological techniques. Materials and Methodes: We have investigated the in vitro effects of serum, IgG and purified anti-GQ1b antibodies from additional patients with typical MFS (n=9) and after recovery from acute disease (n=3). Endplate currents were recorded by means of a perfused macro-patch-clamp electrode in mouse hemidiaphragms and outside-out patch-clamp measurements were performed on mouse myotubes. Results: All MFS-sera depressed evoked quantal release and reduced the amplitude of postsynaptic currents. Purified anti-GQ1b antibodies were as effective as whole serum. No blockade could be induced by sera obtained after recovery from MFS. Five sera additionally examined by outside-out patch-clamp analysis caused a concentration dependent and reversible decrease in acetylcholine induced currents; channel gating was not affected. Conclusion: Our study confirms and extends our previous study that in MFS circulating antibodies induce both pre- and postsynaptic blockade and suggests that these are of pathogenic relevance in causing muscle weakness during acute stage of disease. In MFS, GQ1b may be the principal but not exclusive antigen to which the humoral immune response is directed.

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OUTCOME IN GUILLAIN-BARRE SYNDROME (GBS) PATIENTS IN TRIAL VERSUS NON-TRIAL CENTRES. Van Koningsveld R. [1], van Doorn P. A. [1], Schmitz P. I. M. [1], van der Meché F. G. A. [1]. Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands.

Problem: After publication of the results of a trial, comparing plasma-exchange with intravenous immunoglobulin (IVIg), IVIg became the treatment of choice in patients with GBS in the Netherlands. This resulted in a change in referral pattern because IVIg is easy applicable and therefore more patients stayed in smaller centres. The course of GBS is unpredictable and autonomic dysfunction may occur. Therefore one must consider whether it is advisable to transfer all patients to larger centres. We studied the outcome in patients admitted in centres participating in GBS trials versus non-participating hospitals. Methods: All GBS patients admitted in the Southwest of the Netherlands between 1987 and 1996 were reviewed. Records of 331 GBS patients unable to walk unaided (functional grading score [f-score] at nadir 3) were selected for this analysis. Results: There was no difference in percentage of patients able to walk at 8 weeks and 6 months between the trial and non-trial centres. Furthermore no difference was found in mortality rate. Complications were more frequently found in trial centres. Multivariate analysis showed that this could be explained by the admission of relatively worse patients (f-score 4 or 5 at nadir) in the trial centres. Conclusion: Studying outcome parameters in patients admitted in trial versus non-trial centres did not reveal data supporting thoughts that all GBS patients are per se better of in larger centres.

Peripheral neuropathy – 2

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EFFECT OF HIGH-DOSE INTRAVENOUS IMMUNOGLOBULINS (IVIg) ON ANTI-GLYCOLIPID REACTIVITY IN MULTIFOCAL MOTOR NEUROPATHY (MMN). Meucci N., Terenghi F., Carpo M., Allaria S., Scarlato G., Nobile-Orazio E., Milan, Italy.

To clarify the possible mechanism of action of IVIg on anti-glycolipid reactivity in MMN we studied the effect *in vivo* and *in vitro* of IVIg in 5 MMN patients improving after IVIg and not receiving other immune ther-

apies. Patients' sera were tested by ELISA for GM1, asialoGM1, GM2, GD1a reactivity before and after IVIg infusions. Pre-treatment sera and purified anti-glycolipid antibodies from positive sera, were also tested for anti-glycolipid reactivity after pre-incubation with increasing IVIg concentration, to evaluate the effect *in vitro* of IVIg on anti-glycolipid antibodies. Three patients had high serum anti-glycolipid IgM antibodies including one with selective anti-GM2 reactivity and two with antibodies to both GM1 and GM2. Even if IgM antibody titers did not change after treatment in any patient, in two of them the optical density of anti-GM2 reactivity at the highest positive dilution decreased after IVIg infusions. Preincubation with IVIg did not inhibit anti-glycolipid antibodies even if all reactivities tended to decrease at the highest IVIg concentrations and the same results were observed after pre-incubation of purified antibodies. In our patients with MMN and high anti-glycolipid IgM responding to IVIg, antibody reactivity was only marginally affected both *in vivo* and *in vitro* by IVIg, indicating that other mechanisms than anti-idiotypic neutralization of anti-glycolipid antibodies may be involved in the improvement of MMN due to IVIg.

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EPIDERMAL INNERVATION IN HEALTHY SUBJECTS AND IN SENSORY NEUROPATHY. G. Lauria, D. Pareyson, JC McArthur*, JW Griffin*, A. Sghirlanzoni. Milan, Italy; * Baltimore, USA.

Skin biopsy allows assessment of unmyelinated C and small-myelinated A nerve fibers, by immunoreactivity to the pan-axonal marker PGP9.5. In this study we addressed: 1) the degree of variation in intra-epidermal nerve fiber (IENF) density and morphology with respect to lower limb rostral:caudal orientation in healthy controls; 2) the effect of age, and 3) the morphological changes, including branching, in patients with small fiber sensory neuropathies. Ten healthy subjects (5 aged 23-45 years and 5 aged 70-75 years) and 6 sensory neuropathy patients (4 with idiopathic and 2 with diabetic sensory neuropathies) were submitted to skin biopsies at the distal leg, proximal calf, distal thigh, proximal thigh and trunk. Linear density quantitation of IENF was assessed at each site. "Branching ratio" (no. epidermal fibers/ branch points) was compared between healthy controls and neuropathy cases. Spearman's correlation coefficients gave significant intra- and inter-observer agreements. We observed that IENF density shows a rostral:caudal gradient, without significant age-related changes. We also classified the branching patterns of IENF into four groups in normal controls. Sensory neuropathy patients had a significant decrease of IENF density at distal sites, while branching ratio was significantly increased at proximal sites where density was still within normal values. Increased branching is likely to represent an early pre-degenerative change in length-dependent sensory neuropathies. Skin biopsy is a reliable tool for the study and follow-up of sensory neuropathies.

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CLINICAL FEATURES AND RESPONSE TO TREATMENT IN GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH ANTIBODIES TO THE MINOR GANGLIOSIDE GM1B. N. Yuki,[1] C. W. Ang,[2] M. Koga,[1] B. C. Jacobs,[2] P. A van Doorn,[2] K. Hirata,[1] - F. G. A. van der Meché[2]. [1]Department of Neurology, Dokkyo University School of Medecine, Japan; [2]Department of Neurology, Erasmus Medical Centre Rotterdam, The Netherlands

GM1b is a minor ganglioside present in human peripheral nerve. Serum anti-GM1b antibodies are found specifically in patients with Guillain-Barré syndrome (GBS). In this collaborative study, we investigated the clinical features and response to treatment in GBS patients with anti-GM1b antibodies. Out of 132 GBS patients who participated in the Dutch GBS trial, 25 (19%) patients had anti-GM1b antibodies. IgM antibodies were found in 14 of the 25 patients, IgG antibodies in 15, and both isotypes in 4 patients. The 25 patients with anti-GM1b antibodies had a distinctive clinical pattern compared to the other 107 GBS patients. They more frequently had experienced an episode of gastro-intestinal illness (p0.001) and were more frequently found to have a serological evidence for an infection with *Campylobacter jejuni* ($p < 0.001$). The anti-GM1b-positive subgroup was marked by a more rapidly progressive (p=0.004), more severe ($p < 0.001$), and predominantly distal weakness (p=0.001). Cranial nerve involvement ($p < 0.001$) and sensory deficits (p=0.003) were less common in patients with anti-GM1b antibodies. The subgroup of GBS patients with anti-GM1b antibodies responded well to treatment with immunoglobulins but not with plasmapheresis. These distinctive clinical features of patients with anti-GM1b antibodies demonstrate that the acute motor neuropathy represents a specific subgroup within GBS and recognizing these patients may have consequences for the choice of therapy.

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METALLOPROTEINASES MMP-9 AND MMP-2 IN SURAL NERVE BIOPSIES OF INFLAMMATORY AND NON-INFLAMMATORY POLYNEUROPATHIES. Huber S, Leppert D, Erne B, Fuhr P, Said G, Lacroix C, Steck AJ

Introduction: Matrix Metalloproteinases are a family of zinc containing enzymes that play an important role in inflammation and tissue degradation. MMP-9 and MMP-2 are gelatinases that have been implicated in the degradation of the blood-brain or blood-nerve barrier. We present an immunohistochemical study on sural nerve biopsies of inflammatory and non inflammtory polyneuropathies. Methods: Tissue sections of 11 sural nerve biopsies were stained for MMP-2 and MMP-2.5 were vasculitic neuropathies, 4 chronic inflammatory demyelinating polyneuropathies (CIDP) and 2 non-inflammatory polyneuropathies (1 alcohol induced, 1 drug toxicity). Results: Perineurium and endothelium were positive for MMP-2 in all tissue sections. MMP-9 positive cells could be detected in vessel walls, infiltrates, epineurium and endoneurium of vasculitic neuropathies. In CIDP MMP-9 positive cells were prominent in vessel walls. In noninflammatory controls we could only detect a few MMP-9 positive cells in circulation and adhering to vessel walls. Double staining with CD3/DC68 indicates that the infiltrating cells are T-cells and macrophages. Conclusion: MMP-9 seems to play an important role in inflammatory peripheral neuropathy probably as a means for inflammatory cell invasion.

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CROSS-REACTIVE ANTIBODIES AGAINST GANGLIOSIDE GM2 AND CYTOMEGALOVIRUS IN PATIENTS WITH GUILLAIN-BARRÉ SYNDROME. CW Ang, BC Jacobs, AF Brandenburg, JD Laman, ADME Osterhaus, MA De Klerk, FGA Van Der Meché, PA Van Doorn. Erasmus University Medical Centre Rotterdam, The Netherlands

Guillain-Barré syndrome (GBS) patients with an antecedent infection with cytomegalovirus (CMV) frequently have antibodies to the ganglioside GM2. In the present study, we used an inhibition ELISA method to investigate the hypothesis that anti-GM2 antibodies arise through molecular mimicry between GM2 and CMV. Incubation of three anti-GM2 containing serum samples with CMV-infected fibroblasts resulted in a dose dependent inhibition of anti-GM2 reactivity (47-79%). This effect was observed not only with a CMV strain isolated from a GBS patient but also with a CMV reference strain. Uninfected fibroblasts and fibroblasts that were infected with varicella zoster virus and herpes simplex virus type I had no or only a slight effect on anti-GM2 reactivity. Incubation of anti-GQ1b containing serum samples with CMV-infected fibroblasts did not reduce anti-GQ1b reactivity. In conclusion, we found that CMV-antigens cross-react with anti-GM2 antibodies in GBS patients. These findings indicate that molecular mimicry may play a role in the induction of anti-GM2 antibodies in CMV-associated GBS.

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PERINEURIUM MEDIATES AXONAL DAMAGE IN ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY (AIDP). Berciano J, García A, Figols J, Muñoz R, Berciano MT, Lafarga M, Santander, Spain.

Background. Increase of endoneurial fluid pressure (EFP) in nerve trunks possessing epi-perineurium may be an outstanding mechanism of axonal damage in AIDP. Objective. To describe a clinicopathological study supporting such a pathogenetic hypothesis. Case report. A male aged 79 suffered a 2-day history of ascending paralysis and acroparesthesiae culminating in quadriplegia, areflexia, bilateral facial palsy and mechanical ventilation. Five intravenous immunoglobulin cycles were given without response. He died day 60. Three electrophysiological exams (days 2, 15 and 48) showed initially normal motor conduction velocities with further slowing, severe and progressive attenuation of compound muscle action potentials, and profuse denervation. Pathological material, methods and results. Samples of peripheral nervous system included preforaminal anterior and posterior L3 and L5 spinal roots, third lumbar nerve and its posterior branch, fifth lumbar nerve and lumbosacral trunk, and femoral and sural nerves. Conventional staining, immunostaining, thin sections, fibre teasing and morphometry were performed. Density of myelinated fibres was preserved in preforaminal spinal roots and reduced in the other nerves. The main lesion was inflammatory demyelination with variable degree of wallerian degeneration. Both in lumbar nerves and their branches there were centrofascicular or wedge-shape lesions with marked loss of myelinated fibres, those remaining being remyelinated. Conclusion. Appearance of

epi-perineurium determines a drastic change of pathology with superimposed ischemic lesions and axonal loss indicating that EFP increase is a pathogenetically relevant mechanism for axonal damage in AIDP. *Supported by Fundación La Caixa (Barcelona, Spain)*

Neurogenetics – 1

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AN ASSESSMENT OF REVERSE TRANSCRIPTION – POLYMERASE CHAIN REACTION (RT-PCR) AND PROTEIN TRUNCATION TEST (PTT) IN THE DETECTION OF DYSTROPHIN POINT MUTATIONS IN DUCHENNE MUSCULAR DYSTROPHY. John Nixon, David Cockburn, Janina Hopkin and Susan Huson. Departments of Neurology and Medical Genetics, Radcliffe Hospital, Oxford, UK.

Duchenne muscular dystrophy (DMD) results from mutations in the dystrophin gene. The identification of mutations is important for accurate carrier testing and prenatal diagnosis in DMD families. Two thirds of the mutations are detectable by routine laboratory methods. The remaining cases are due to point mutations which are not easily detected. Families with point mutations are analysed by linkage which is less accurate than mutation specific analysis. We present the results of a study of the use of RT-PCR and PTT in a service laboratory. We analysed samples from twelve affected males, and from five carrier females from families where there was no surviving male to analyse. Point mutations were found in six of the affected males but in none of the five carrier females. These results suggest that RT-PCR and PTT are technically feasible, but may not be useful for the detection of mutations directly in females. A mathematical analysis indicated that the use of point mutation analysis can prevent the termination of unaffected male fetuses which would have been terminated after prenatal diagnosis by linkage analysis. We recommend the introduction of routine point mutation analysis for DMD.

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PHENOTYPES OF AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS. Alexandra Dürr, Agnes Camuzat, Giovanni Stevanin, Isabelle Evrard, Géraldine Cancel, Imed Feki, Alexis Brice; Paris, France

Five genes, SCA1, SCA2, SCA3 or MJD, SCA6 and SCA7, with expanded CAG repeats responsible for autosomal dominant cerebellar ataxias (ADCA) have been identified. We analyzed 313 families with ADCA of various geographical origin. In this sample 11% were SCA1, 16% SCA2, 27% SCA3, 9% SCA7 and only 2% SCA6. We compared the phenotypes among groups, including 88 SCA1, 94 SCA2, 137 SCA3 and 69 SCA7 patients and characterized the influence of the normal and pathological CAG repeat within genotypes. The clinical presentation varied according to disease duration and was predominantly cerebellar at onset. Once the full picture reached, the major features were: pyramidal signs in SCA1, abolished reflexes and neuropathy, fasciculations and slow ocular saccades in SCA2, neuropathy and gaze-evoked nystagmus in SCA3, gaze-evoked nystagmus in SCA6 and visual loss, pyramidal signs with slow ocular saccades in SCA7. The frequency of clinical signs in a single patient depended on the locus, the disease duration and the size of the CAG repeat on the normal and the expanded allele. Instability of the CAG repeat, which is reflected by the anticipation of age at onset and severity of the disease varies according to the locus. There was no correlation between the size of the CAG expansion and instability, except for SCA7 where the instability increases with the length of the repeat.

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GENETIC BACKGROUND OF APPARENTLY IDIOPATHIC SPORADIC CEREBELLAR ATAXIA. Schöls L[1], Peters S[1], Krüger R[1], Przuntek H[1], Epplen C[2], Riess O[2-1]Department of Neurology, St. Josef Hospital, Ruhr-University, D-44791 Bochum; [2]Molecular Human Genetics, Ruhr-University, D-44780 Bochum, Germany

Disease-causing mutations have been identified in autosomal dominant cerebellar ataxia and Friedreich's ataxia (FA). However, no molecular pathogenic factors are known for idiopathic sporadic cerebellar ataxia (ISCA). We investigated the CAG trinucleotide repeat expansions causing spinocerebellar ataxia (SCA) type 1, 2, 3, 6 and 7, as well as the GAA repeat expansion causing FA in 84 patients with ISCA including 26 patients with the clinical diagnosis of multiple system atrophy (MSA). We excluded patients with a positive family history of gait disturbance, a symptomatic form of ataxia, or a phenotype compatible with the clinical diagnostic criteria of FA. Genetic analysis dissolved the FA mutation in 11 patients with an age at onset between 13 and 36 years. We found a SCA2 mutation in one patient with onset at 28 years and a de novo mutation from a paternal intermediate allele. The SCA6 mutation was present in 10 patients with onset between 47 and 68 years of age. Dominant inheritance may be missed in SCA6 patients due to uninformative family history in which parents died before manifestation of the disease. We did not find the SCA1, SCA3 or SCA7 mutation in ISCA patients. No mutation was found in the MSA subgroup. Investigation of the SCA6 mutation is recommended in so called late onset cerebellar cortical atrophy, whereas the FA mutation should be searched for in ataxia patients with onset before age 40, even with phenotypes untypical for FA.

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IMPLICATION OF 1-ANTICHYMOTRYPSIN POLYMORPHISM IN FAMILIAL ALZHEIMER'S DISEASE. B. Nacmias, A. Tedde, A. Orlacchio, S. Latorraca, P. Forleo, S. Piacentini and S. Sorbi. Department of Neurological and Psychiatric Sciences, University of Florence, Viale Morgagni 85, 50134 Florence, Italy; Neurologic Clinic, University of Perugia, Perugia, Italy.

A polymorphism in the 1-antichymotrypsin (ACT) gene has been shown to modify the Apolipoprotein E (ApoE) 4-associated Alzheimer's disease (AD) risk. We analized the segregation of the ACT and ApoE polymorphisms in 59 mutated subjects belonging to seven early onset AD families carrying pathogenetic mutations: 28 subjects with the PS-1 Met146Leu mutation, 11 subjects with the PS-2 Met239Val mutation, 20 subjects carrying the APP 717 ValIle mutation. Moreover 49 patients belonging to 42 autopsy-proven AD families without mutations in the APP, PS-1 and PS-2 genes have been analysed. With regard to the distribution of the three ACT genotypes, no statistically significant differences were found in any of the disease groups compared to controls. In the APP group the ACT/A allele showed the highest frequency compared to the control group (67.5% versus 50.4%; p=0.072). In 6 of the 28 late onset familial AD patients we found the combination of the ACT/AA and ApoE 4/4 genotypes. Our data suggest that ACT does not represent an additional risk factor for APP, PS-1 and PS-2 mutated families. However, our results suggest that ACT may interact with ApoE and play a role in late onset familial AD. *Supported by Italian National Research Council (CNR) Targeted Project on Aging. SS was also supported by Telethon Italia (grant no E. 482).*

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A WIDE RANGE OF MUTATIONS IN THE PARKIN GENE IS RESPONSIBLE FOR AUTOSOMAL RECESSIVE PARKINSONISM IN EUROPE C. B. Lücking[1], N. Abbas[1], A. Dürr[1], S. Ricard[2], V. Bonifati[3], G. de Michele[4], N. W. Wood[5], T. Gasser[6], B. S. Harhangi[7], B. A. Oostra[7], A. Filla[4], G. Meco[3], P. Denefle[2], Y. Agid[1], A. Brice[1], French Parkinson's Disease Genetics Study Group and European Consortium on Genetic Susceptibility in Parkinson's Disease. [1]Paris, France, [2]Evry, France, [3]Rome, Italy, [4]Naples, Italy, [5]London, UK, [6]Munich, Germany, [7]Rotterdam, The Netherlands.

Autosomal recessive juvenile parkinsonism (AR-JP) was initially described in Japan and is typically characterized by onset before age 40, marked response to levodopa and levodopa induced dyskinesias. Recently, the responsible gene, *parkin,* was identified. To determine the frequency, the nature and the phenotype of mutations in this gene in European patients with autosomal recessive parkinsonism, we have analyzed 38 families by PCR based direct sequencing. Homozygous exon deletions were detected in four families. In addition, eight previously undescribed point mutations were identified in eight families (4 truncating and 4 missense mutations). The missense mutations resulted in the same phenotype as truncating mutations or homozygous exon deletions, indicating the high functional importance of the amino acids implicated. Mean age at onset was 38±12 years (ranging from 7 to 58). In conclusion, a wide range of different mutations in the *parkin* gene is a common cause for autosomal recessive parkinsonism in Europe. In addition, mutations in the *parkin* gene are not invariably associated with early onset parkinsonism and the phenotype can be indistinguishable from idiopathic Parkinson's Disease.

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AUTOSOMAL DOMINANT CEREBELLAR ATAXIA TYPE III: LINKAGE OF A LARGE BRITISH FAMILY TO A 7.6CM REGION (SCA 11) ON CHROMOSOME 15Q14-21.3. P. F. Worth, P. Giunti, C.

Gardner-Thorpe, P. H. Dixon, M. B Davis and N. W. Wood. Institute of Neurology, London, UK.

Autosomal dominant cerebellar ataxia type III is a relatively benign, late-onset, slowly progressive neurological disorder characterized by an uncomplicated cerebellar syndrome. Three genetic loci have been identified: a moderately expanded CAG trinucleotide repeat in the SCA 6 gene, the SCA 5 locus on chromosome 11 and a third locus on chromosome 22 (SCA 10). We have identified 2 British families in which affected individuals do not have the SCA 6 expansion, and in which the disease is not linked to the SCA 5 or SCA 10 loci. Both families exhibit the typical phenotype of ADCA III. Using a genome-wide searching strategy in one of these families, we have linked the disease phenotype to the marker D15S1039. Construction of haplotypes has defined an interval of 7.6 centiMorgans between the flanking markers D15S146 and D15S1016, thereby assigning a further ADCA III locus to the proximal long arm of chromosome 15 (SCA 11). We excluded linkage of the disease phenotype in the second family to this region. These results indicate the presence of two additional ADCA III loci, and more clearly define the genetic heterogeneity of ADCA III.

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CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY: IDENTIFICATION OF THREE NOVEL MUTATIONS. Thomas Wieser, Marcus Deschauer, Thomas Herrmann*, Stephan Zierz - Martin-Luther-Universität Halle/Wittenberg, Halle/S., Germany; *Institute de Biologie Molèclulaire et Cellulaire, Straßbourg, France

Carnitine-palmitoyltransferase II (CPT II) deficiency is an inherited disorder of lipid metabolism affecting skeletal muscle. The gene was identified in 1990 and several disease causing mutations are described so far. 16 clinically and biochemically well defined patients were investigated. In a second step we tried a prediction of the protein structure by identifying homologous regions. Seven patients were homozygous and seven were heterozygous for the main mutation S113L. Of the other known mutations only the P50H mutation was present in our patient sample. By direct sequencing of the entire coding region three novel mutations were identified. (M214T, P448F and Y479F). Further we identified a domain that shares 50% identical residues to a membrane-located helix of a mitochondrial ATPase. It is proposed to be a membrane anchor consisting of two parallel packed helices forming a helix-turn-helix motif spanning one layer of the lipid membrane. It seems apparent that the marked clinical heterogeneity of this disease corresponds to a as marked genetic heterogeneity. The membrane anchor leads to the partial insertion of CPT II into the membrane, in line with findings of a relatively loose association of this protein with the inner mitochondrial membrane. Two of the newly identified mutations are located within this structure and we assume that disease pathology in these cases results through a altered membrane association of the protein.

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SEGMENTAL/MOSAIC NEUROFIBROMATOSIS TYPE 1 (NF1). A CLINICAL STUDY. Martino Ruggieri (1), Celia Moss (2), Meena Upadhyaya (3) & Susan M Huson (1). Departments of. Clinical Genetics, Oxford, (2) Paediatric Dermatology, Birmingham (3), Medical Genetics, Cardiff, UK

Patients with the signs of Nf1 limited to one or more body segments are usually referred to as having segmental Nf1. This condition is most likely due to somatic mutations of the Nf1 gene. Objectives: To study the phenotype, natural history and prevalence of segmental Nf1 and to determine the risk to off-springs. Methods: Ninety patients (48 M, 42 F; age 4-72 years) ascertained through the Oxford neurofibromatosis clinic (ONC), geneticists, dermatologists and neurologists in the UK followed-up during years 1995-1998. Results: We found: 1) pigmentation anomalies only (n= 52); 2) neurofibromas (dermal and/or nodular) only (n=15); 3) combination of pigmentation lesions and neurofibromas (n=9); and 4) plexiform neurofibromas only (n=14). Age at onset of Nf1 manifestations varied according to the presence of pigmentation anomalies (birth-2 years of age) or neurofibromas only (puberty- young adulthood). In cases with pigmentation changes, alone or in combination, the whole segment of affected skin had a darker background. In some patients the segment involved seemed to be more severely affected that would be expected in generalised Nf1. We found Lisch nodules in one case. Cases with pigmentation anomalies alone were the only ones with associate Nf1 complication (frequency 11%). In 11 families a parent with segmental Nf1 had a child affected either by full-blown Nf1 (n=9) or segmental Nf1 (n=2). Prevalence was 1 in 70,000-80,000 or 0.014%. Conclusions: Mosaic/segmental Nf1 is more common than expected. There is no specific management. Patients need to be advised they: 1) do not have generalised Nf1; 2) are at a low risk of developing any disease associated complications; 3) have a small but definite risk of having a child with generalised Nf1.

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PROXIMAL MYOTONIC MYOPATHY (PROMM) FIVE-YEAR FOLLOW-UP STUDY. A RELATIVELY BENIGN DISORDER? G. Meola*, V. Sansone*, LJ Ptacek**, R Krahe*** - *Dept. Neurology, Univ. Milan, San Donato Hospital, San Donato Milanese, Milan - Italy; **Dept. Neurology and Human Genetics, Univ. UTAH, Salt Lake City - USA; ***Div Human Cancer Genetics, OHIO State University, Columbus, OHIO - USA.

Background: Only a few patients with PROMM, compared to patients with the similar disorder myotonic dystrophy, have been reported to have cardiac or respiratory abnormalities. Linkage to chromosome 3 has been found in some of these families. Objective: The aim of our study is to provide data on the natural history of PROMM and to see whether cardiac involvement is more typically present in chromosome 3-linked families with PROMM. Materials and Methods: We studied 30 patients from 5 unrelated PROMM families having proximal weakness, myotonia, cataracts and a normal (CTG)n expansion. Linkage to chromosome 3 was excluded. EKG, echocardiograms and 24-hour Holter monitoring were performed every 6 months over a 5-year period as well as manual muscle testing of strength in 18 muscles. Results: Our results demonstrate a very slow progression of weakness, especially in the lower limbs. None of our patients developed symptoms or signs related to cardiac involvement. Conclusions: Our data suggest that cardiac involvement may be present in chromosome-3 linked families with PROMM and that unlinked families like ours show a more benign course. Further genetic and follow-up studies will confirm or refute this hypothesis.

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COGNITIVE IMPAIRMENT AND DELETION OF Dp140 REGULATORY REGION IN DYSTROPHINOPATHIES A Bardoni*, M Sironi*, G Felisari*, M Lai*, GP Comi^, N Bresolin^. * IRCCS E. Medea, Associazione La Nostra Famiglia. Bosisio Parini (LC), Italy - ^ Centro Dino Ferrari, Istituto di Clinica Neurologica, Università di Milano, IRCCS Ospedale Maggiore Policlinico, Milan, Italy

Mental retardation (MR) is a clinical feature present in both Duchenne and Becker muscular dystrophy patients and its pathogenesis is still unknown. Dp140 is a brain specific dystrophin isoform with a mainly fetal expression. Its promoter and first exon lie in the large intron between exon 44 and 45, a region that is commonly deleted in dystrophic patients. PCR amplification was performed to screen eleven DMD and twenty-three BMD patients carrying deletions in this critical region in order to find a possible association between the Dp140 transcription unit loss and mental retardation. Intelligence Scales scoring Full IQ (FIQ) were administered to all patients. Statistical analysis was performed by chi-square test. Eleven patients were mentally retarded (FIQ75; mean score 61.8). Twenty-three patients had normal or borderline IQ level (mean FIQ 95.5). All patients with FIQ 75 presented no deletions in the Dp140 promoter region or first exon. In the subset of patients with FIQ 75, five had no deletions in the region; seven had a deletion including Dp140 first exon and promoter. Correlation between the absence of Dp140 promoter and first exon and mental retardation is statistically significant ($p < 0.001$). Although the role of dystrophin gene products in brain development is currently unknown, our study reveals that impairment of cognitive abilities in some DMD and BMD cases may be related to dysfunction of Dp140.

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FREQUENCY OF SPECIFIC CLINICAL FEATURES AND LABORATORY ALTERATIONS IN MITOCHONDRIAL DNA DISORDERS: A 207 PATIENT SURVEY. Sciacco M., Napoli L., Prelle A., Comi G., Chiveri L., Fagiolari G., Bordoni A., Scarlato G., Moggio M., Milan, Italy

Mitochondrial disorders are clinically heterogeneous human genetic diseases associated with several mtDNA and nDNA mutations. A strict clinical-genetic correlation is made difficult by the extreme variability of both

clinical and laboratory findings even among members of the same family. We evaluated 207 patients affected with genetically different mitochondrial diseases and combined clinical and laboratory data obtained from their observation. We selected the following laboratory-instrumental criteria and accordingly examined most patients: serum CK and basal lactate levels, EEG, EMG and cardiac studies, neuroradiologic evaluation. In our series of patients, abnormal serum CK levels best correlate with either CPEO and ptosis or limb weakness, and EMG myopathic patterns exceed the number of patients with clinically evident limb weakness, though no pure myopathic patterns are seen in the A8344G point mutation. Abnormal EEG patterns are more frequently associated with mtDNA point mutations, and cardiac abnormalities are rarer among multiple deleted patients. High serum basal lactate levels are found in about 80% A3243G and A8344G point mutations, even in clinically oligo-presymptomatic patients. Pathologic head neuroimaging almost invariably correlates with encephalopathies. We therefore conclude that, despite their phenotypical heterogeneity, correlating clinical features and laboratory findings in mitochondrial disorders may give important clues to the genetic studies and therefore allow quicker and less expensive diagnosis.

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PRIMARY CARNITINE DEFICIENCY (PCD) AS A NOVEL CAUSE OF EXERCISE-INDUCED RECURRENT MYOGLOBINURIA. Invernizzi F., Garavaglia B., Confalonieri P., Antozzi C., and Taroni F. ; Milan, Italy.

Common metabolic causes of paroxysmal myoglobinuria include enzyme defects of glycogen metabolism as well as defects of mitochondrial enzymes (most commonly CPT2) of long-chain fatty-acid oxidation. Although carnitine is an essential cofactor for long-chain fatty-acid oxidation, PCD has never been associated with pure recurrent myoglobinuria. Usually, it is a life-threatening disorder characterized by progressive cardiomyopathy and skeletal myopathy and/or hypoketotic hypoglycaemia and liver failure. We describe two new patients with exercise-induced myoglobinuria, no glycogen or lipid accumulation in skeletal muscle, normal activities of CPT2 and glycolytic enzymes, and normal profiles of urinary organic acids and plasma free fatty acids. Both patients had low carnitine levels in plasma and muscle. Patient 1 is a 22-year-old woman who manifested recurrent episodes of paroxysmal myoglobinuria and muscle weakness since the age of 15y. There was no sign of cardiomyopathy, as documented by echocardiography. Plasma total carnitine was 10.5 µmol/l (n. v. 45±3). Carnitine uptake in fibroblasts was reduced to 25% of the control mean. Patient 2 is a 16-year-old boy who has frequently suffered of muscle pain after mild exercise since the age of 10y. At the age of 11y an episode of myoglobinuria was documented. Carnitine levels in plasma and muscle were 10 µmol/l (n. v. 45±3) and 8.2 µmol/g (n. v. 24±4), respectively. After a few months of daily administration (3-6 g) of L-carnitine, treatment appears to be beneficial in both patients. In conclusion, our findings indicate that PCD should always be considered as a cause of recurrent myoglobinuria even in the absence of lipid accumulation in muscle. Molecular analysis of the recently discovered PCD gene is in progress, in order to clarify the molecular defect which underlies this unusual phenotype. (Partly supported by a Telethon-Italia grant to FT)

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COMPARISON OF THE EFFECTS OF E2F-1 AND P53 PROTEINS IN THE APOPTOSIS OF GLIOMAS: RELEVANCE FOR GENE THERAPY STRATEGIES. C. Gomez-Manzano, J. Fueyo, P. Mitlianga, A. P. Kyritsis, V. A. Levin, W. K. A. Yung. Houston, TX, USA.

Understanding the cell growth and apoptosis pathways in glioma cells may provide insights into the mechanism regulating gliomas. As a result of previous studies, a clinical trial using an adenovirus vector to transfer p53 to gliomas is in progress at M. D. Anderson Cancer Center. In the future, other genes may be added to p53 in the search for a treatment for gliomas. Here, we use adenoviral vectors able to express the tumor suppressor genes: p53, p16, Rb, or E2F-1, and the cell-cycle regulatory molecules p21, E2F-2, and E2F-4, to glioma cells. The expression of the proteins was studied by immunohistochemistry and western blot assays. Cell cycle analyses were performing by flow cytometric measurements of the DNA content. Cell death studies included optic and electronic microscopy, trypan blue viability assay, and flow cytometry analyses of the sub-G1 area, and TUNEL assay. Results: E2F-1-mediated apoptosis is started 2-4 days after E2F-1 transfer, however p53 starts earlier (1-2 days). E2F-1-programmed death is independent of the status of p16, p21, p53 or Rb proteins. However, several modifiers of the cell cycle including the endogenous p53, p21 and Rb modulate negatively the effect of p53. The transfer of p53 is able to induce bax expression. The E2F-1 effect is independent of bax. p53 does not induce apoptosis in cells expressing wild-type p53 protein, such normal fibroblasts, E2F-1 is able to induce apoptosis in normal cells. Other members of the E2F family including E2F-2 and E2F-4 upregulated genes (like Rb, p107, cyclin D1 and E), and induced entry of cells into S phase, but did not induce cell death, demonstrating that the apoptotic-effect of E2F-1 is specific. Conclusions: E2F-1 is more powerful than p53 in the induction of apoptosis in glioma cells since the spectrum of cells sensitive to its apoptotic effect is wider. In future clinical trials of gene therapy for gliomas, with more genetic tools avalaible, it will be necessary to select for every patient the best strategy to induce apoptosis.

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TRAIL ACTIVATES CASPASE 3 AND INDUCES APOPTOSIS IN GLIOMAS INDEPENDENT OF P53 STATUS. AUTHORS: V. K. Puduvalli, Houston, USA, R. Xu, Houston, USA, and A. P. Kyritsis Houston, USA.

Death receptors of the TNF family interact with their respective ligands to directly activate the apoptotic machinery via caspases in susceptible cells. The TRAIL ligand and its family of death and decoy receptors including DR4, DR5, DcR1 and DcR2 are recently described members of this family and are expressed in a variety of tissues. Unlike Fas and TNF receptors, they appear unique in their ability to selectively induce apoptosis in malignant cells which sparing normal cells based on selective death or decoy receptor expression. We studied the effect of TRAIL treatment on gliomas and its relation to p53 status by exposing three cell lines, D54 (wt p53), U251 (mutant p53) and U87MG (wt p53), derived from malignant gliomas. A His-tagged construct of the extracellular portion of TRAIL ligand was purified using the expression vector, pET15B-TRAIL. The D54 cell line was most susceptible to TRAIL treatment and showed a dose dependent growth inhibition by MTT assay (LD_{50}=1g/ml). U87 cells were resistant to the effect of TRAIL while U251 showed an intermediate degree of sensitivity. Flowcytometric analysis showed no changes in cell cycle kinetics but demonstrated the appearance of a sub G-1 population indicating apoptosis in D54 and U251 but not U87 cells. Western blot analysis showed activation of cpp32 and cleavage of PARP in D54 and U251 cells within 6 h of TRAIL treatment. Our results indicate that TRAIL can potently induce apoptosis in gliomas and that the effect is independent of p53 status. The findings that TRAIL selectively affects malignant cells and the results of the present study suggest that this pathway may be potentially exploited in the development of novel therapies against gliomas.

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SYSTEMIC DELIVERY OF AN ANGIOSTATIN DERIVATIVE SUPPRESSES INTRACEREBRAL GLIOMA GROWTH. PI Meneses, LE Abrey, KA Hajjar, SH Gultekin, RM Duvoisin, KI Berns, MR Rosenfeld, New York, NY, USA.

Angiogenesis plays a role in the growth of many tumors and may be particularly important in gliomas. Angiostatin is an endogenous inhibitor of tumor neovascularization that acts by inhibiting the proliferation of endothelial cells. We have cloned, expressed, and purified a recombinant human angiostatin derivative, K1-3, using a mammalian expression system. The presence of a secretory signal and a polyhistidine sequence tag allows K1-3 to be purified from post-culture medium by simple nickel column chromatography. Recombinant K1-3 retains its physiologic conformation as evidenced by its ability to bind to lysine-Sepharose. *In vitro,* K1-3 significantly suppressed endothelial cell proliferation in a dose dependent manner with an IC_{50} of 50 nM. Using an animal model of intracranial brain tumors in immune competent rats, subcutaneous administration of purified recombinant K1-3 resulted in up to 85% suppression of tumor growth (P=0.011). Growth suppression was accompanied by a 32% decrease (P=0.01) in tumor neovascularization. This study demonstrates that a recombinant angiostatin derivative is easily produced in mammalian cells and may have therapeutic value in the treatment of malignant glial tumors.

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DISPUTABLE DIAGNOSIS OF "GLIOBLASTOMA MULTIFORME" IN PATIENTS WITH LONG SURVIVAL TIME Jürgen A. Kraus[1], Guido Reifenberger[2], Andreas von Deimling[3], Matthias Schmidt[2], Uwe Schlegel[1] Departments of Neurology[1] and Neuropathology[2], University of Bonn Medical Center, Germany; Department of Neuropathology[3], Free University of Berlin Medical Center, Germany

The prognosis for patients with glioblastoma multiforme (WHO grade IV, GBM) is poor. However, there are remarkable interindividual differences with respect to survival. The objective of this study was to neuropathologically reevaluate GBM specimens of patients with an unusual long survival. Materials and Methods: 106 primary GBM patients were selected for "short-term" time to tumor progression (TTP) (6 months) or "long-term" TTP (> 12 months). The histological specimens were reevaluated by two neuropathologists blinded with regard to clinical course. In case of a diagnosis other than GBM at reevaluation, the specimens were reviewed again by another neuropathologist with knowledge of clinical outcome. Results: Among the patients with "short-term" survival (n=54; mean age at operation: 51 years), one diagnosis (1.9%) was revised as anaplastic oligoastrocytoma (WHO grade III). Among the patients with "long-term" survival (n=52; mean age at operation: 53 years), 13 diagnoses were discrepant compared to the initial diagnosis (25%): Seven anaplastic oligodendrogliomas (WHO grade III), 3 anaplastic astrocytomas (WHO grade III), 2 anaplastic oligoastrocytoma and 1 anaplastic pilocytic astrocytoma (WHO grade III). Among the "long-term" survivors, 29 patients lived longer than 24 months. Among these 29 cases, 11 discrepant diagnoses were found (38%): 4 anaplastic oligodendrogliomas, 3 anaplastic astrocytomas, 1 anaplastic oligoastrocytoma. Conclusions: The group of GBMs with "long-term" survival shows a considerable contamination with gliomas of lower grade. The majority of such misdiagnosed GBMs shows evidence of oligodendroglial differentiation. This offers therapeutic options because these tumors may respond to chemotherapy with procarbazine, CCNU and vincristin (PCV).

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MALIGNANT PROGRESSION ON RECURRENCE OF LOW-GRADE OLIGODENDROGLIAL TUMORS. R. Rudà, *F. Benech, D. Schiffer, R. Soffietti, Dept. of Neurosciences, Division of Neurology and *Neurosurgery, University of Torino, Italy

Unlike in astrocytomas, the risk of malignant transformation in oligodendroglial tumors is not well known. Objective: to define the rate of biopsy proven malignant transformation in a single Institution series of oligodendroglial tumors. Patients and Methods: we rewiewed 20 patients with an histological diagnosis of oligodendroglioma (14) and oligoastrocytoma (6) grade II WHO at first surgery, which were reoperated for recurrence (median time to recurrence: 36 months). At the time of first diagnosis, CT or MR contrast enhancement was absent in 10/20, mild in 9/20 and intense in one case. Treatment after first surgery was radiotherapy (5) or chemotherapy (7),whereas 8 patients were observed with serial MR. Results: at reoperation 9/20 cases (45%) were histologically unchanged (grade II) and 11/20 (55%) were malignant (grade III). Two tumors showed a glioblastomatous component and other two a sarcomatous component. Malignant transformation was observed in 7/14 pure oligodendrogliomas and 4/6 oligoastrocytomas. Among tumors which were histologically unchanged, the degree of contrast enhancement was unmodified in 8/9, while it was increased in 1/9. All tumors, which were histologically malignant at recurrence, displayed an increased contrast enhancement. Conclusions: malignant trasformation is not an infrequent event among oligodendroglial tumors. The modification of contrast enhancement during the follow-up is useful in predicting malignant transformation.

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ACCELERATION OF V-SRC CARCINOGENESIS BY RETROVIRAL INSERTIONAL MUTAGENESIS. M. G. D'Angelo, T. Afanasieva, V. Pekaric, A. Aguzzi. Milano, Zurich

The generation of a transgenic mouse model for astrocytoma by expressing the v-src kinase under control of the glial fibrillary acidic protein (GFAP) gene regulatory element in astrocytes offered an useful research tool in neurocarcinogenesis. GFAP positive cells in v-src mice can undergo neoplastic transformation, however the relative late and infrequent appearance of tumours implies that even a potent oncogene such as v-src requires other co-operating genetic alteration. Here, we show that Moloney Murine Leukemia virus (Mo-MuLV) can infect neuroectodermal cells obtained from GFAP-v-src embryos mice. We established clonal cell lines exibiting immunocytochemical positivity for both GFAP and envelope protein after more than 120 days in culture (uninfected cells showed a life span ranging from 40 to 70 days). FACS analysis (83A25 antibody for detection of envelope protein) showed a viral infection efficiency ranging from 25% to 70% from clone to clone. Proliferative advantage has been demonstrated, in all the selected clones, by the appearence of multiple transformed foci after 14-20 days in culture. Anchorage-indipendent growth on semisolid media has been showed only in 5 cell lines. Injections in nude mice resulted in the formation of solid GFAP-envelope positive tumors. Our data demonstrate that preneoplastic astrocytes can be infected by Mo-MuLV and will progress to malignant transformation. This in vitro study is a preliminary model to identify co-operating retroviral hits in the progression from low grade astrocytoma to anaplastic astrocytoma and eventually to glioblastoma in GFAP-v-src mice.

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TUMOR-SELECTIVE ADENOVIRUS FOR BRAIN TUMOR TREATMENT: AN *IN VIVO* STUDY. J. Fueyo, C. Gomez-Manzano, R. Alemany, PSY. Lee, W. K. A. Yung, V. A. Levin, and A. P. Kyritsis. Houston, Texas. U. S. A.

The p16/E2F-1 pathway is abnormal in the majority of gliomas. We reported previously the construction of an adenovirus (Δ 24) able to replicate selectively in cancer cells. Here, we demonstrate the strong and selective anti-cancer effect of the adenovirus Δ 24 *in vivo*. Electronic microscopy showed the increase in the number of virus after 4 days of the infection. U-251 MG, D-54 MG, and U-373 MG cells treated with doses of 5 to 10 viral particles resulted in cytolysis within 5-7 days. These results were confirmed by optical microscopy and crystal violet staining of the viable cells. The ? 24 and another tumor-selective adenovirus dl1520 (Bischoff et al. Science 1996) showed similar potency in mutant p53 cells. However, D24 was more efficient in wild-type-p53 glioma cells. The ability of the adenovirus to lyse arrested cells expressing wild-type Rb, was tested by restoring the Rb function to Rb-null cells. We observed a reduction of cell death (80%) up to 10 days after the infection of the Rb positive cells, indicating that normal brain cells may be resistant to the effect of the Δ 24. The anti-cancer effect of the virus was then examined *in vivo*. In an animal model that use subcutanous tumors, a single intratumoral injection of 10e7 viruses was enough to inhibit the growth of glioma and medulloblastoma tumors ($p < 0.02$). In addition, in two animals we observed regression of the tumor, a fact not observed with the multiple-dose-transfer of powerful pro-apoptotic tumor suppressor genes like E2F-1 (Fueyo et al. Nature Med 1998). Therefore, the tumor selective adenovirus Δ 24 is more potent than replication deficient adenoviruses carrying exogenous genes. This mutant adenovirus is critical to address the delivery problem in the gene therapy of brain tumors. These results should propel the development of a future clinical trial.

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DETECTION OF 14-3-3 PROTEIN IN THE CEREBROSPINAL FLUID (CSF) OF PATIENTS WITH PARANEOPLASTIC NEUROLOGIC DISORDERS (PND). Saiz, J. Dalmau[1], A. Pifarré, C. Marín, E. Tolosa, F. Graus. Hospital Clínic, Barcelona, Spain. Memorial Sloan-Kettering Cancer, New York[1], USA.

The 14-3-3 protein is a useful CSF marker for diagnosis of Creutzfeldt-Jakob disease (CJD). False-positive results are seen in disorders with acute neuronal damage. We analyzed the frequency of 14-3-3 protein in the CSF of patients with PND whose presenting symptoms may mimic those of sporadic CJD. Methods: The 14-3-3 protein was evaluated by immunoblot in the CSF of 80 patients with PND; 53 patients with definite or probable CJD; and 55 patients with other neurologic disorders (non-CJD) considered in the differential diagnosis. Results: The 14-3-3 protein was positive in 10 of the 80 PND patients (12.5%), one patient with limbic encephalitis and Hu antibodies, and 9 with paraneoplastic cerebellar degeneration (six with Yo antibodies), in all but five CJD patients (all 5 associated with the D178N mutation), and in 6/55 patients with non-CJD. Among the positive patients, the 14-3-3 protein was detected as a single band in 47 of 48 CJD patients and as a double band in one. This double band pattern was observed in 9 of 10 PND patients and in 3 of 6 non-CJD patients. The double band pattern predicted the possibility of a "false-positive" diagnosis rather than a true diagnosis of CJD ($p < 0.0001$). Conclusions: The 14-3-3 protein assay may be positive in the CSF of patients with PND that can be initially misdiagnosed as CJD. However, the immunoblot pattern distinguish the majority of PND samples from those of CJD.

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ULIP PROTEINS ARE PERIPHERAL NERVE ANTIGENS RECOGNIZED BY ANTI-CV2 ANTIBODIES IN PATIENTS WITH PARANE-

OPLASTIC PERIPHERAL NEUROPATHY. JC Antoine, JF Mosnier, L Absi, J Hormorat, V Rougemont, D Michel. Saint-Etienne, Lyon. France.

Paraneoplastic anti-CV2 antibodies react with a family of 4 nematode Unc-33-like phosphoproteins (ULIPs) possibly involved in axonal growth and guidance. To test the hypothesis that ULIPs are the target of the immune process in the peripheral nervous system (PNS) in some patients with paraneoplastic neuropathies (PN), we reviewed 10 patients with anti-CV2 antibodies and PN. We also tested the expression of ULIPs in mammalian PNS. The neuropathy was usually sensory-motor and associated with central nervous system involvement. Electrophysiology indicated an axonal/neuronal pattern in 8 and a mixed axonal and demyelinating pattern in 2. Pathology showed axonal and demyelinating lesions. The serum of these patients tested with the 4 recombinant ULIPs reacted with ULIP 3 or 4. Four/ten patients also had anti-Hu antibodies. In one of them, autopsy showed inflammatory demyelination and ganglionitis. RT PCR using specific primers showed that mRNA of the 4 ULIPs were present in mammalian peripheral nerve. By immunohistochemistry with an antibody raised against ULIPs (antiP3), the developing PNS was immunolabeled in rat embryo. In adults, Schwann cells and axons were immunoreactive. Anti-P3 and anti-CV2 antibodies reacted with a similar band of 66 kd in western-immunoblots of an endoneurial preparation. These data indicate that ULIPs are expressed in peripheral nerve and that an anti-ULIP autoimmune reaction may explain PN in patients with anti-CV2 antibodies.

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SEARCH INTERNATIONAL CASE-CONTROL STUDY OF CHILDHOOD BRAIN TUMOURS: PARENTS' AND CHILD'S EXPOSURE TO SMOKING. Graziella Filippini,[1] Patrick Maisonneuve,[1] Margaret McCredie,[2] Raphael Peris-Bonet, [3] Elizabeth A. Holly,[4] Susan Preston-Martin,[5] NW Choi,[6] Sylvaine Cordier,[7] Baruch Modan,[8] Beth Mueller,[9] Julian Little,[10] Annie Arslan,[11] and Peter Boyle.[1] - [1]Milan, Italy; [2]Otago, New Zealand; [3]Valencia, Spain; [4]SanFrancisco, USA; [5]Los Angeles, USA; [6]Winnipeg, Canada; [7]INSERM, Villejuif, France; [8]Tel-Hashomer,Israel; [9]Seattle, USA;[10]Aberdeen, Scotland; [11]Lyon, France.

A series of coordinated population-based case-control studies of childhood brain tumours (CBT) was undertaken under the auspices of the Surveillance Environmental Aspect Related to Cancer in Human (SEARCH) program of International Agency for Research on Cancer (IARC) to evaluate, *inter alia*, the risk in relation to parents' and child's exposure to smoking. Subjects comprised 1,218 cases aged 0-19 years and 2,223 population controls. By means of a structured interview, information was sought on the mother's smoking pattern before and during the pregnancy, on the father's smoking pattern up until the pregnancy, on the mother's regular exposure during the pregnancy to passive smoke by the father, by other household members, or at work and on the child's passive exposure to tobacco smoke during the first year of life. Risk estimates were calculated by unconditional logistic regression, adjusted for age, sex and centre, for all types of CBT combined as well as for four groups defined by histopathology and for five age groups. Neither active smoking by the child's mother or father before and/or during the pregnancy, nor regular passive exposure to tobacco smoke by the mother during the pregnancy or by the child in the first year of life were associated with an increase risk of brain tumour in the child.

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IDENTIFICATION AND MOLECULAR CLONING OF A NEW AUTOANTIGEN ASSOCIATED WITH PARANEOPLASTIC ENCEPHALOGANGLIONEURITIS AND BRONCHIAL SMALL CELL LUNG CANCER (SCLC). I. Andreou[1,2], S. Rauer[1], G. Neuhaus[2], R. Kaiser[1] - [1]Department of Neurology, Albert Ludwig University of Freiburg, Germany; [2]Department of Cellbiology, Albert Ludwig University of Freiburg, Germany

Paraneoplastic neurologic syndromes (PNS) are rare disorders of the nervous system that cannot be ascribed to metastases or to destruction of vital systemic organs by the tumor or its treatment. In certain PNS specific autoantibodies initially directed against tumor antigens also recognize neuronal proteins. We studied an autoantibody detected in the serum of a patient with paraneoplastic encephalitis and bronchial carcinoma (SCLC). In immunoblotting, the serum did not react with Hu, Yo, or Ri antigens, but with a 55 kDa antigen, found in a cerebral and a cerebellar protein extract. In immunofluorescent staining the antibody binds on Purkinje-cells and on Plexus myentericus. We isolated a complementary DNA-clone by screening of a human cerebellar gene expression library with the patients serum. Although the sequence of this clone has been found in the Genebank, the function of this protein still remains unclear. There are homologies between this DNA sequence and proteins involved in the intracellular transport and the organisation of the cytoskeleton. Binding of the autoantibody to these proteins might impair the function of the cytoskeleton thus interfering with the intraneuronal transport.

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PARANEOPLASTIC CEREBELLAR DEGENERATION(PCD) AND HODGKIN'S DISEASE(HD) WITH ANTI-Tr ANTIBODIES(Tr-Ab): IMMUNOLOGICAL AND CLINICAL DESCRIPTION OF 11 PATIENTS. R. Sánchez-Valle, MD[1]; J. Dalmau, MD[2]; R. Reñé, MD[3]; A. Saiz, MD[1]; J. Baiges, MD[4]; J. Foronda, MD[5]; J. M. Girón, MD[6]; J. Peltola, MD[7]; Ch Vecht, MD[8]; M. J. Vila, MD[6]; F. Graus, MD[1]. Hospital Clínic[1] and CSU Bellvitge[3] Barcelona, Verge de la Cinta[4], Tortosa, Hospital de Jaen[5], Hospital de Jerez[6], Spain, Sloan-Kettering Cancer Center[2], New York, USA, University of Tampere[7], Finland, and Daniel den Hoed Cancer Center[8], Rotterdam, The Netherlands.

Tr-Ab are described as markers of PCD and HD, if all antineuronal antibodies reported in this clinical setting are Tr-Ab is unknown. We studied 11 HD patients with PCD. Tr-Ab were defined by the immunoreactivity of the Purkinje cells and the characteristic dotted labeling in the molecular layer of the rat cerebellum. None of the patients presented any immunoreactivity other than Tr-Ab on human or rat cerebellum. Nine patients had Tr-Ab in their sera and CSF(available in 6 patients) and 2 presented Tr-Ab only in the CSF. Nine patients were men with a median age of 60 years(range:14-75). PCD antedated the diagnosis of HD in10 patients and the HD relapse in one. Two patients died from treatment complications shortly after the diagnosis of HD, 9 are in remission from the HD and the PCD improved in only two although Tr-Ab disappeared after treatment of HD in all the 5 patients that could be tested. We conclude that, unlike other antineuronal antibodies, Tr-Ab may be detected only in the CSF and the titers drop shortly after effective treatment of the HD. Although PCD is described after the diagnosis of HD, the presence of Tr-Ab usually antedates the diagnosis of the HD.

Higher functions disorders

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INFLUENCE OF APOLIPOPROTEIN E GENOTYPE ON CLINICAL COURSE IN ITALIAN ALZHEIMER'S DISEASE PATIENTS. Forleo P., Nacmias B., Orlacchio A., Tedde A., Latorraca S., Bracco L., Guarnieri B. M., Piacentini S. and Sorbi S. Department of Neurological and Psychiatric Sciences, University of Florence, Viale Morgagni 85, 50134 Florence, Italy; Casa di Cura Villa Serena, Pescara, Italy;Neurologic Clinic, University of Perugia, Perugia, Italy.

Contrasting results have been published on the rate of decline in Alzheimer's disease (AD) as a function of Apolipoprotein E (ApoE) genotype. The aim of the study is to correlate the role of ApoE genotype on the rate of decline in AD using different clinical parameters of disease progression Ninety-three AD patients (mean age of onset 63.22 ± DS 8.37) were clinically assessed and ApoE genotyped. Patients were followed up for three years. We applied the Kaplan-Meier statistical method to evaluate the time required to reach three specific end-points: very severe cognitive impairment (untestability), sphinteric incontinence and death. No statistical differences in age of onset compared to sex, ApoE and 4/dose were found. ApoE4 is not statistically significant related to any of the clinical parameter assessed. Kaplan-Meier analysis shows for 2/carriers a longer disease duration and a virtual absence of sphinteric incontinence. Furthermore, over 60% of 2/carriers evidenced only a slight cognitive impairment after 6 years of disease . Our data do not suggest a role of the 4/allele on the rate of decline of AD providing evidence for a possible role of 2/allele on the course of the disease. *Supported by Telethon Italia grant n. E. 482*

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EXPRESSION OF -D-MANNOSIDASE IN AMYOTROPHIC LATERAL SCLEROSIS AND ALZHEIMER'S DISEASE. [1]An. Orlacchio, [2]S. Sorbi, [2]S. Latorraca, [2]G. Mazzotta, [3]L. Parnetti, [3]V. Gallai, [4]C. Emiliani. 1 Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada; 2 Dipartimento di Scienze Neurologiche e Psichiatriche, Università di Firenze, Italy; 3 Clinica Neurologica, Università di Perugia, Italy; 4 Dipartimento di Biologia Cellulare e Molecolare, Università di Perugia, Italy.

-D-Mannosidases, a complex enzyme system involved in the biosynthesis and catabolism of the N-linked glycans, were estimated in serum and in fibroblasts of patients affected by Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's Disease (AD). All -D-mannosidase forms, previously characterized as either acidic or lysosomal origin -D-mannosidase (pH optimum of 4.0-4.5), Golgi compartment -D-mannosidase (pH optimum of 5.5-6.0) and endoplasmic reticulum membrane associated -D-mannosidase (neutral optimum pH), were taken into account. Levels of all forms decreased significantly in serum and in cell extracts (fibroblasts) of ALS and AD patients: the most important decrease was in the Golgi -D-mannosidase (total activity in control subjects: 0.260.04 mU/ml of serum; in ALS and AD patients the activity ranged from 0.09 to 0.19 mU/ml of serum). In addition, altered biochemical properties of -D-mannosidases (i. e., Km, thermal stability) were found. Separation of isoenzymes by ionic exchange chromatography confirmed the anomalous expression of the enzyme in both diseases. All these data support the involvement of the Golgi apparatus in ALS and AD and suggest that an accurate analysis of this enzyme system could be informative about events occurring in different cell compartments in these diseases. *We thank [1]Prof. P. St. George-Hyslop for helpful advice and C. N. R., Italy, for funding (An. O.).*

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APOE -491 REGULATORY REGION POLYMORPHISM AND THE RISK OF ALZHEIMER'S DISEASE IN ITALY. V. M. Casadei, C. Ferri; F. Veglia, A. Gavazzi, G. Salani, M. Cattaneo, S. Sorbi, G. Annoni, F. Licastro, C. Mariani, M. Franceschi and L. M. E. Grimaldi. Milan, Bologna, Florence, Italy.

The carriage of the apolipoprotein (APO) E ε4 allele increases the risk for Alzheimer's disease (AD). Recently, a new polymorphism located within the transcriptional regulatory region of ApoE (A to T variation at -491 bp: APO E -491), has been associated with an APOE ε4-independent increased risk for AD in two groups of patients from Spain and North America. In order to sought confirmation for this association in a different population, we carried out a case-control study comparing 358 patients with clinically probable AD and 367 non demented age-matched controls from Northern Italy. A moderate increase in the frequency of the AA genotype was found only in AD patients with an age at disease onset ≥ 65 years ($p = 0.016$). The AA genotype in this age group increased the relative risk for AD provided by ε4 alone from 6.76 to 8.89. We conclude that, at least in Italians, the contribution of APOE -491 polymorphism to the occurrence of AD is restricted to patients with a late onset of disease.

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THE ROLE OF THE TAU GENE IN EARLY-ONSET ALZHEIMER DEMENTIA.. G. Roks*[1], M. Cruts[2], P. Heutink[3], B. Dermaut[2], C. Van Broeckhoven[2], C. M. Van Duijn[1]. 1 Department of Epidemiology & Biostatistics, Erasmus University Medical School, Rotterdam The Netherlands. 2 Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, Born-Bunge Foundation, University of Antwerp (UIA), Antwerp Belgium. 3 Department of Clinical Genetics, Erasmus University Medical School, Rotterdam The Netherlands.

Mutations in the tau gene on chromosome 17 have been found as a cause of frontal lobe dementia and several neuro-degenerative disorders. One study showed an association of tau polymorphisms with Alzheimer dementia (AD). Because aggregation of tau in neurofibrillary tangles is one of the pathological characteristics of AD we studied it as a candidate gene for early onset AD (EOAD). We screened exons 9 to 13 of the tau gene, in which mutations were identified, for new mutations in a sample of 100 EOAD patients and 113 controls, ascertained from four regions in the Netherlands in the period of 1980-1987. No mutations were found in the 5 exons using SSCP analysis. However, we identified 3 polymorphisms: 2 bi-allelic markers in exon 9 and 1 in exon 11. We analyzed 1 of the exon 9 polymorphisms and a CA repeat in intron 9 in the EOAD sample and controls. Because these two polymorphisms were in tight linkage disequilibrium, we only used the bi-allelic polymorphism in the further analysis. Association was studied with a logistic regression model with age, gender, and APOE genotype as covariates. Survival was studied using Kaplan-Meier analysis. Genotype frequencies (11-12-22) in patients (4%-35.6%-60.4%) were similar to that in controls (6%-33.6%-60.3%, p= 0.77). Allele frequencies (1-2) were similar in patients (21.8%-78.2%) and controls (22.8%-77.2%, p=0.81). We found no evidence for interaction of this polymorphism with APOE genotype. Survival analysis showed similar survival times for the three genotypes. In conclusion, the tau gene does not seem to be a major player in the pathogeneses of EOAD.

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POTENTIAL IN VIVO VISUALISATION OF THE -AMYLOID PROTEIN OF ALZHEIMER'S DISEASE WITH $_{99M}$TC-MAMA-CHRYSMINE G. N. Dezutter, T. de Groot, G. Bormans, A. Verbruggen, R. Dom. University Hospital, Leuven, Belgium

We developed a ^{99m}Tc complex of chrysamine G (CG), a lipophilic analogue of Congo red with affinity for -amyloid protein *in vitro*, as a possible in vivo probe for beta-amyloid deposition in Alzheimer's disease (AD). Methods. A conjugate of CG was synthesised by coupling CG via an acetylamino spacer with a bis-S-trityl protected monoamide-monoaminedithiol tetraligand (MAMA-Tr_2), a chelating system used to incorporate ^{99m}Tc. The conjugate was deprotected and labelled efficiently with ^{99m}Tc resulting in ^{99m}Tc-MAMA-CG (^{99m}Tc-1). Tissue distribution was studied in NMRI mice. In vitro autoradiography was performed on brain sections of an Alzheimer patient and a control. Results. In mice, ^{99m}Tc-1 was mainly cleared by the hepatobiliary system resulting in fast blood clearance, but net brain uptake was low (0.3 % ID/g, 2' p. i.). Coinjection with the blood pool tracer $_{125}$I-HSA demonstrated a brain/blood ratio of ^{99m}Tc-1 that was significantly higher than for $_{125}$I-HSA ($p < 0.005$) indicating that ^{99m}Tc-1 crosses the blood-brain barrier. Autoradiography studies demonstrated pronounced binding of ^{99m}Tc-1 to beta-amyloid deposits in sections of AD parieto-occipital cortex compared to control. The binding of ^{99m}Tc-1 was displaced by adding 10 μM Congo red during incubation. Congo red staining and autoradiography images of the same sections identified the same lesions. Conclusions. ^{99m}Tc-1 seems to bind selectively to beta-amyloid deposition in human brain parenchyma and blood vessels *in vitro*.

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REM SLEEP BEHAVIOR DISORDER INDUCED BY ANTICHOLINESTERASIC TREATMENT IN ALZHEIMER'S DISEASE PATIENTS. Touchon J[1, 2], Portet F[1, 2], Nicolas A[2]. (1) UNC CHU Gui de Chauliac (2) INSERM CJF 97-02 Montpellier France

REM sleep behavior disorders (RBD) is a recently described parasomnia (Shenck et al, Sleep; 1986: 293-308). While RBD may occur at any age, it is far more frequent in elderly persons, specially those with neurodegenerative disorders. Abnormal mouvements or vocalization (abrupt, spectacular, or violent behavior, sometimes dangerous for patient or spouse) manifest during REM sleep. RBD is usually explained by the lack of normal atonia permitting dream-related behaviors. Aims of the study : To describe RBD in Alzheimer's disease patients receiving cholinergic treatment. Results : 4 patients with a history of probable Alzheimer's disease (NINCDS-ADRA) presented typical RBD after introduction of anticholinesterasic treatment: rivastigmine (9mg/day) in one case, donepezil (10mg/day) in one case and tacrine (160mg/day) in two cases. Treatment withdrawal led to disappearence of RBD in 3 cases, diminution of its frequency in 1 case. One of these cases has been extensively documented with polysomnography before, during and after the treatment. Conclusion : The polysomnographic study allowed us to confirm the diagnosis of RBD and the possible role of the anticholinesterasic treatment. A dopaminergic-cholinergic imbalance may play a prominent role in generating RBD.

Prion disease and dementia

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CREUTZFELDT-JAKOB DISEASE: CORRELATION WITH SPINAL FLUID NSE AND 14-3-3 PROTEINS. A. J. Aksamit, M. D., H. A. Homburger, M. D., C. M. Preissner, Mayo Clinic, Rochester, MN, U. S. A.

A study was performed to prospectively evaluate patients with rapid-onset dementia or other clinical symptoms suggestive of Creutzfeldt-Jakob disease (CJD) and correlating spinal fluid results for assay of neuron-specific enolase (NSE) and 14-3-3 protein. One hundred fifty-three patients were studied prospectively between 1996 and 1998. All had spinal fluid analysis for NSE and 14-3-3 protein. Clinical correlation was made prospectively from the medical record. The patients were characterized as Creutzfeldt-Jakob disease with subtypes of definite, probable, and possible. Neuron-specific enolase was performed quantitatively on spinal fluid by immunochemiluminometric assay. Seventeen patients were identified with neuron-specific enolase values greater than 35 ng/mL and 14-3-3 proteins greater than 10 ng/mL, and all had possible, probable, or definite CJD. One hundred twelve patients were identified with NSE values less than 30 and 14-3-3 values less than 10. Among these 112 patients, only 1 patient with possible familial Creutzfeldt-Jakob disease was identified.

NSE values greater than 35 and 14-3-3 protein values greater than 10 correlate with a diagnosis of Creutzfeldt-Jakob disease. NSE values less than 30 and 14-3-3 values less than 10 were helpful in excluding the diagnosis of Creutzfeldt-Jakob disease. Intermediate values were of indeterminate significance, and correlated with patients with CJD and other causes of dementia.

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PHENOTYPIC CHARACTERISTICS IN JUVENILE SPORADIC CREUTZFELDT-JAKOB DISEASE Zerr, Inga*, Henkel, K*, Tschampa, H*, Schröter, A*, Bodemer, M*, Windl, O°, Schulz-Schaeffer, W°, Kretzschmar, HA°, Poser, S* *Department of Neurology and °Neuropathology, University of Göttingen, Germany.

Creutzfeldt-Jakob disease (CJD) is a rare dementing disorder with a short duration of several months typically affecting patients at the age of 65 years. Here were report the clinical features of young CJD patients seen in the German CJD surveillance. Each notified case was seen by a physician visiting the hospital and underwent a detailed examination. The final diagnosis was done after autopsy. Since June 1993 10 males and 13 females with disease onset less than 50 years were diagnosed to have sporadic CJD, the youngest patient was 24 years (median 44). The mean disease duration was 14 months (range 3-31). Psychiatric conditions were often diagnosed initially. 16 patients presented with progressive dementia and 7 with ataxia, followed by various neurological signs. Only 5 patients developed typical pattern in the EEG. The clinical diagnosis of CJD was corroborated by the detection of 14-3-3 protein in the cerebrospinal fluid (CSF) in all cases with this analysis (n=21) and typical high signals in basal ganglia were seen in MRI in most cases. All but one were either homozygous for methionine (n=12) or valine (n=10) at the codon 129 of the prion protein encoding gene, revealing a higher proportion of valine homozygous cases in this subgroup than seen in sporadic CJD in general. Patients with sporadic CJD may show atypical phenotype especially in younger age groups, therefore increased awareness for this differential diagnosis in patients with dementia is required.

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VALUE OF MRI IN DIAGNOSIS OF CREUTZFELDT-JAKOB DISEASE. M. Grisoli, Mg Bruzzone, G. Giaccone, F. Tagliavini, M. Savoiardo, O. Bugiani. Milano (Italy)

We retrospectively reviewed the MRI findings of 31 patients with CJD to determine the distribution and frequency of MRI signal abnormalities and to establish whether patients with probable CJD have the same MRI pattern found in proven cases. CJD was neuropathologically proven in 8 cases and by DNA analysis in 7. In 16 cases the diagnosis met the standard clinical criteria and was considered probable. MRI investigation was carried out with a 1.5T equipment including sagittal SE T1-w. i., axial and coronal SE proton density (PD) and T2-w. i. In 18 out of 31 cases a FLAIR sequence was obtained. In definite CJD, all patients presented symmetric bilateral hyperintense signal changes in the putamina and heads of the caudate nuclei in PD and T2-w. i. Hyperintensity in the globus pallidus was present in 3 patients, asymmetrical in 1. In 13 patients signal hyperintensity in the posterior and medial part of the thalami was found. Three patients presented mild hyperintensity of the cerebellar cortex, 2 in the hippocampal formations. In 5 patients studied with FLAIR sequences, hyperintensity was demonstrated in the cerebral cortex. In 3 cases a T1 hyperintensity in the pallidum was seen. In patients with probable CJD the distribution of findings was nearly identical; hyperintensity of the neostriatum was constantly present, and thalami, cerebral and cerebellar cortex were similarly involved. Accordingly, MRI can be regarded as a useful tool to support the diagnosis of probable CJD.

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EXPERIMENTAL PRION PROTEIN DISEASE : COMPARISON OF NEUROPATHOLOGY WITH MAGNETIC RESONANCE IMAGING (MRI). MG Bruzzone,B. Canciani,L. Farina,T. Awan,M. Cova,G. Poli,G. Giaccone,O. Bugiani,M. Savoiardo,F. Tagliavini - Milano (Italy)

Prion-related encephalopaties are transmissible degenerative diseases characterized by the accumulation of an abnormal form of the prion protein (PrP) in the brain leading to spongiosis, gliosis and neuronal loss. In Creutzfeldt-Jakob disease MRI demonstrates hyperintense signal changes mainly in the neostriatum and thalami on proton density (PD) and T2-weighted images. To investigate the neuropathological basis of these signal abnormalities, we carried out a comparative neuroradiological and neuropathological study in an animal model. A 1.5T MRI protocol including T1 and T2-weighted sequences was used to examine forty hamsters, injected intracerebrally with 263K scrapie-infected brain homogenate. Every 10 days four animals were submitted to MRI and sacrificed for histological and immuno-histochemical investigations. Signal hyperintensity in T2 images in the thalamus was observed at day 50, before the onset of clinical symptoms, and increased with the progression of the disease. In later stages the hyperintensity extended to the hypothalamus, striatum and septum correlating with the sites of remarkable gliosis. A T1 thalamic hyperintensiy corresponding to a striking accumulation of PrP was observed at day 50 and became undetectable at day 70 when PrP spread across the entire brain. These data suggest that astrogliosis is probably the structural basis for T2 signal alterations while PrP accumulation could be responsible for the rarely observed T1 hyperintensity in human. The value of MRI in the early diagnosis of prion diseases is confirmed.

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DEMENTIA WITH LEWY BODIES: A MULTICENTRE CLINICO-PATHOLOGICAL STUDY OF 21 CASES GK Wenning[1], G Ransmayr[1], K Ray Chauduri[2], A McKee[3], M Verny[4], RKB Pearce[2], S Bösch[1], K Jellinger[5], W Poewe[1], I Litvan[6] - [1]Innsbruck, Austria; [2]London, UK; [3]Boston, USA; [4]Paris, France; [5]Vienna, Austria; [6]Bethesda, USA

The clinical evolution of dementia with Lewy bodies (DLB) has not been studied systemically in postmortem verified cases. Further natural history data are required to improve suboptimal diagnostic accuracy during early stages. We therefore retrospectively analyzed the clinical records of 21 well documented and pathologically proven cases of DLB derived from 5 international brain banks. There were 10 male and 11 female subjects. Average age at disease onset was 6612 years and average disease duration was 87 years. First and last neurological visits took place on average 4 and 7 years after disease onset. Frequent clinical features (>50% of cases) present at the first neurological visit included gait disturbance (62%), bradykinesia (57%), limb rigidity (52%) and dementia (52%). During follow-up a range of additional features emerged in the majority of patients including fluctuating cognition (76%), dysarthria (71%), delusions (67%), hallucinations (62%), axial rigidity (62%) and falls (57%). Our data show that many DLB patients appear to be demented and parkinsonian at the time of first neurological evaluation. Characteristic red flags such as fluctuating cognition and psychotic events emerged later during follow-up, perhaps accounting for the poor diagnostic accuracy reported earlier by our group.

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FAMILIAL CREUTZFELDT-JAKOB DISEASE IN A PATIENT CARRYING BOTH A PRESENILIN 1 MISSENSE MUTATION AND A PRION PROTEIN GENE INSERTION. B. Dermaut[1], M. Cruts[1], H. Backhovens[1], U Lübke[3], B. Van Everbroeck[2], R. Sciot[4], MD, R. Dom[4], J.-J. Martin[3],C. Van Broeckhoven[1], P. Cras[2] - [1]Department of Molecular Genetics, Laboratory of Neurogenetics, Flanders Interuniversity Institute of Biotechnology (VIB), Born Bunge Foundation (BBS), University of Antwerp (UIA), Department of Biochemistry, Universiteitsplein 1, B-2610 Antwerpen, Belgium, [2]Laboratory of Neurobiology and [3]Neuropathology, Born Bunge Foundation (BBS), University of Antwerp (UIA), Department of Medicine, Universiteitsplein 1, B-2610 Antwerpen, Belgium, [4]Laboratory of Neuropathology, Catholic University of Leuven (KUL), Faculty of Medicine, Herestraat 49, B-3000 Leuven, Belgium.

We report a case of familial inherited dementia with an age at onset of 35 years who died at the age of 42 years. This individual was clinically diagnosed with familial early-onset Alzheimer disease (AD) and a Glu318Gly mutation in presenilin 1 (PSEN1) was detected. Surprisingly, neuropathological examination failed to show AD pathology and, in contrast, numerous cerebellar prion protein deposits, compatible with Creutzfeldt-Jakob disease (CJD), were demonstrated. Molecular genetic analysis further revealed an insertion of 7 octapeptide coding repeats in the prion protein gene (PRNP). Clinico-pathological and molecular genetic analysis showed that the observed CJD phenotype in this family is fully explained by the PRNP insertion. This observation is consistent with our previous finding that PSEN1 Glu318Gly is not causally related to AD.

Multiple sclerosis – 4

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ANALYSIS OF DISABILITY ENDPOINTS IN PLACEBO COHORTS FROM RELAPSING-REMITTING MULTIPLE SCLEROSIS TREATMENT TRIALS. Clarence Liu and Lance D. Blumhardt, University of Nottingham, U. K.

The behaviour of placebo groups and the outcome measures employed in relapsing-remitting multiple sclerosis (RRMS) treatment trials may have considerable influence on the apparent efficacies of different putative therapies. *Methods-* EDSS data from the placebo-treated subjects (n=313) of the multi-centre glatiramer acetate (*Copaxone®*) and interferon -1a (*Rebif®*) trials, with similar demographic characteristics, were combined and masked. Endpoints measuring disability change ('two-year EDSS difference' and 'area under EDSS/time curve' (AUC)), and disease progression ('confirmed EDSS progression' and 'in-trial EDSS trend'), were examined systematically both in the overall cohort and in two subgroups with baseline EDSS3.5 and >3.5.*Results-* For the entire cohort, the median 'two-year EDSS difference' was +0.5 (IQR=1.5); the 'AUC change' was +0.34 EDSS-years (IQR=1.57) for scheduled assessments and +0.47 EDSS-years (IQR=1.66) for combined scheduled and relapse data. Increasingly more stringent 'confirmed progression' definitions (increase of 1.0-EDSS point at 3 months, 1.0-point at 6 months, 2.0-point at 3 months and 2.0-point at 6 months) resulted in 32%, 21%, 12% and 9% of patients respectively reaching these endpoints. 'In-trial EDSS trend' evaluations demonstrated that 26%, 59% and 15% of subjects followed 'stable', 'relapsing-remitting' and 'progressive' courses, respectively. Patients with baseline EDSS>3.5 had significantly worse 'two-year EDSS difference' (p=0.023), and were more likely to experience 'confirmed progression' and 'progressive' EDSS trend (p=0.020) than their EDSS3.5 counterparts. *Conclusions-* 'Conventional' and 'alternative' techniques for analysing 'disability change' and 'disease progression' were verified using EDSS data from the placebo-treated arms of two large RRMS trials. Subjects with baseline EDSS3.5 often recovered after prolonged periods of worsening while more patients with entry EDSS>3.5 maintained in-trial progression.

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APOE GENOTYPE OF MS PATIENTS AFFECTS THE SEVERITY OF TISSUE DESTRUCTION AS SEEN ON MRI. F. Fazekas, C. Enzinger, S. Strasser-Fuchs, H. Schmidt, A. Lechner, S. Ropele, E. Flooh, R. Schmidt, and H. P. Hartung. Department of Neurology, MR Institute and Institute of Medical Biochemistry, Karl-Franzens University Graz, Austria

Clinical data suggest a modifying effect of the ApoE genotype on the course of MS. As this might translate into morphologic differences we used MRI to obtain further confirmation for such an impact. Methods: We analysed the MR scans of 89 patients (mean age 36+/-9.7 yrs.) who participated in a cross-sectional study on genotype patterns in MS. The total lesion load (LL) was measured on conventional proton-density weighted (T2-LL) and T1-weighted (T1-LL) scans and we recorded the presence of contrast enhanced lesions (0.1mmol Gd-DTPA). To determine the proportion of more severe tissue destruction we also calculated a "black-hole ratio" (BHR) as follows: [(T1-LL/T2-LL) x 100]. Results: Patients with the ApoE-3/4 genotype (n=19) showed a greater T2-LL (16.0+/-14.0; p=0.06) than patients with the 2/3 (n=11; 13.3+/-9.5) or the 3/3 genotype (n=53; 9.3+/-9.3). Both the T1-LL (2.6+/-3.4 vs. 1.6+/-2.4 and 1.2+/-3.0; p=0.018) and the BHR (14+/-12 vs. 7+/-9 and 8+/-13; p=0.014) were significantly higher in 3/4 patients. In contrast, the proportion of active scans was lower in patients with the 3/4 genotype (5% vs. 27% and 27%, p=0.048). Conclusions: These data confirm the clinical evidence for a more rapidly progressive course of MS in patients with the 4 allele. The mechanisms involved may relate not so much to higher disease activity but rather to a more destructive type of lesions.

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IN-VIVO DIFFUSION WEIGHTED MRI OF THE HUMAN SPINE . R. Bammer[1,2], M. Augustin[1,2], J. Simbrunner[2], F. Ebner[2], R. Stollberger[2], H. P. Hartung[1], F. Fazekas[1,2] - 1 Department of Neurology and 2 Magnetic Resonance Institute, University of Graz, Austria

Purpose: To show the feasibility of rapid diffusion-weighted (DW) MRI in the human spinal cord using a novel phase–navigated SE DW interleaved echoplanar imaging (IEPI) sequence. Methods: All studies were performed on a 1.5T whole body unit. Two DW IEPI sequences with and without fat-sat were used. The b-values used were 0 and 709 s/mm^2. DW measurements were performed for each principal axis. Six young healthy volunteers as well as five patients (glioma: 1, myelitis: 1, syringomyelia: 1, anterior spinal arterery syndrome: 2) were imaged and high resolution DW spine images were obtained. Results: The apparent diffusion coefficients (ADC) found in the volunteers correspond well (57832 x 10^{-6} mm^2/s perpendicular to fiber tracts; 185043x10^{-6} mm^2/s parallel to fiber tracts) with values measured in the human brain. As in the brain, acute ischemic lesions were rapidly visible on DW images of the spinal cord. Hyperintensity from decreased ADC was also seen in the myelitis patient. Discussion: Frequently used single-shot DW EPI might be critically impaired by large susceptibility gradients as well as limited spatial resolution in the human spine. Conventional SE-based sequences are too tedious for practical use. Using the newly devised DWI sequence, the human spinal cord was well visualized in volunteers and patients, respectively. The chosen EPI-factor (7-13) provides a good tradeoff between EPI-induced artifacts and acquisition time. CSF suppression techniques might be helpful since partial volume effects may become an issue. The proposed method sets the basis for further evaluation of the diagnostic contribution of DW imaging in the human spine.

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SERIAL ANALYSIS OF CYTOKINE MRNA PROFILES IN WHOLE BLOOD SAMPLES FROM PATIENTS WITH EARLY MULTIPLE SCLEROSIS. K. G. Kahl, N. Kruse, K. V. Toyka, and P. Rieckmann. Department of Neurology, Clinical Research Unit for Multiple Sclerosis and Neuroimmunology, Julius-Maximilians University, Würzburg, Germany

Several lines of evidence support a crucial role of cytokines in the pathogenesis of multiple sclerosis. Of special interest is whether there is a shift towards a Th1 cytokine phenotype during an acute relapse. Method: We determined the cytokine messenger RNA (mRNA) expression pattern in whole blood samples from 12 patients with early multiple sclerosis (MS) using a sensitive quantitative polymerase chain reaction (PCR) method. All patients had laboratory-supported definite MS and none received long-term immunomodulatory therapy. Results: We found significantly higher levels of tumor necrosis factor α (TNFα), interferon-gamma (IFN-γ) and interleukin-10 (IL-10) mRNA in MS patients during a relapse compared to age and sex matched healthy controls while interleukin-4 (IL-4) mRNA levels were significantly higher in the control group. After treatment with methylprednisolone (MP) IFN-γ and TNF-α mRNA expression declined significantly. On follow up 3-6 months and 1 year later none of the patients sustained a clinical relapse and IL-10 levels were still higher in MS patients compared to controls. No correlation was found between the cytokine mRNA detected and the total number of leucocytes, lymphocytes or monocytes present in the blood. Conclusion: As several indications point to a direct involvement of cytokine dysregulation in the pathogenesis of MS, the serial analysis of the cytokine mRNA profiles in whole blood samples may be a useful immunological parameter in future therapeutic studies to monitor disease activity in MS.

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DIFFUSE INCREASE IN BLOOD-BRAIN BARRIER PERMEABILITY ASSOCIATED WITH PROGRESSIVE MS. NC Silver, PS Tofts, MR Symms, AJ Thompson, DH Miller. NMR Research Unit, Institute of Neurology, University College London, UK.

In multiple sclerosis(MS), focal gadolinium (Gd-DTPA) enhancing lesions are indicative of blood-brain barrier (BBB) breakdown with associated inflammation. Disease progression may however occur in their absence, especially in primary progressive (PP) MS. We have investigated whether subtle BBB leakage occurs in MS within regions of "normal-appearing white matter (NAWM) or "apparent non-enhancing" lesions (ANEL. We studied 33 MS patients (5 benign, 12 relapsing-remitting (RR), 9 secondary progressive(SP) and 7 PP) and 5 matched controls. Quantitative evaluation of signal intensity (SI) change at 7, 20 and 40 minutes following 0.3mmol/kg Gd-DTPA was carried out in 1846 regions of MS NAWM (vs. 425 comparable healthy control regions) and 1238 ANEL (vs. matched contralateral MS NAWM control regions). Fixed radiofrequency gains and spatial registration of images allowed accurate measurement of SI change. In controls, SI increased maximally 7 minutes following Gd-DTPA (median=1.8%, $p < 0.0005$) suggesting the presence of intravascular Gd-DTPA. In MS NAWM, significantly greater increases were seen at 20 (1.0% vs 0.1%, $p < 0.0005$) and 40 minutes (0.4% vs -0.3%, $p < 0.005$). The greatest increases were seen in progressive MS, especially those with PP disease. Such changes in RR NAWM were not significant. In ANEL, significantly greater SI increase was observed for all

3 timepoints (5 minutes=3.2%, 20 minutes=2.5%, 40 minutes=1.8%, $p < 0.0005$). Such changes were apparent in all MS subgroups. These findings suggest the presence of widespread low-grade and possibly chronic BBB leakage in NAWM and ANEL that may contribute to disease progression in MS.

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THE PATHOGENESIS OF RELAPSING REMITTING MULTIPLE SCLEROSIS [MS]; DESIGN OF A LARGE LONGITUDINAL STUDY. CMB Griffin, DH Miller, AJ Thompson. NMR Research Unit, Institute of Neurology, University College London, UK.

We report the design of a unique serial multi parameter study aimed at examining the temporal relationship between inflammation,demyelination and axonal loss in early MS. At least fifty patients will be recruited with relapsing remitting disease of less than 3 years duration with an EDSS < 3. Follow up will be over at least 3 years as follows; M. R. I. Triple dose gadolinium enhanced images of brain and cord[inflammation]. Magnetisation transfer imaging[demyelination]. Proton spectroscopic imaging[axonal loss]. Hypointense lesion load[axonal loss]. Diffusion tensor imaging[white matter fibre tract integrity] 3D volume imaging of the brain and cord [to quantify atrophy;a marker of axonal loss and demyelination] T1 relaxation measurements [possibly correlating with gliosis]. Clinical: Kurtzke expanded disability status scale, U. S. National M. S. society task-force composite scale; visual analogue of fatigue, modified fatigue impact scale, short form 36, Queen Square Disease Impact Scale. These will elucidate the relationship between evolving pathology and functional impact. Immunological: Blood; C reactive protein,soluble adhesion molecules,soluble T. N. F. alpha,nitric oxide metabolites. Urine; neopterin and free light chains. This study will elucidate the mechanisms of irreversible tissue damage [especially axonal loss] which is likely to result in clinical progression.

Multiple sclerosis – 5

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ERAZIMUS: EARLY AZATHIOPRINE VERSUS BETA-INTERFERON TREATMENT IN MULTIPLE SCLEROSIS. RESULTS OF PILOT SAFETY STUDY. Moreau T, Blanc S, Riche G, Confavreux C (Department of Neurology, Hôpital de l'Antiquaille and Hôpital de la Croix-Rousse, Lyon, France)

As single therapies, both recombinant interferon beta and azathioprine have shown proven efficacy in patients with relapsing-remitting Multiple Sclerosis (MS). The current single-center open pilot study is designed to evaluate the safety and tolerance of interferon beta-1a (AVONEX™) in combination with azathioprine (IMUREL™) for the treatment of relapsing-remitting MS. Thirty patients already receiving azathioprine treatment for at least 6 months for relapsing-remitting MS have been enrolled. Three different dose groups of 10 subjects each have been made up: 50 mg, 100 mg or 150 mg daily. After enrollment, the patients received the first intramuscular injection of interferon beta-1a (6 MIU) followed by a weekly injection for 4 months. The safety profile of the combination was evaluated through hematology and biochemistry laboratory parameters and clinical tolerance performed at specific time points throughout the study. A secondary objective is to produce information on the effects of the combination about residual concentrations of neopterin and 6-thioguanine nucleotide levels. Our results confirm the biological and clinical safety and tolerance of the combination of interferon beta-1a and azathioprine.

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ORAL FUMARIC ACID ESTER (FAE) IN RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS). A SHORT TERM, OPEN, CLINICAL, IMMUNOLOGICAL AND MAGNETIC RESONANCE IMAGING (MRI) CONTROLLED PHASE II TRIAL. Schimrigk S, Meier D, Brune N, Krane M, Hellwig K, Hoffmann V, Rieks M*, Pöhlau D*, Przuntek H. Department of Neurology, St Josef Hospital, 44791 Bochum, Ruhr University Bochum, Germany; * Sauerlandklinik Hachen, Germany

FAE (Fumaderm®) initially proven to be effective in the treatment of psoriasis also showed a semi-selective immuno-modulating influence on T-cells. FAE seem to be very effective in up-regulating TH_2-type cytokines especially IL-4, IL-10 and TGF-. According to the hypothesis that MS is caused by autoreactive T-cells, triggered by the dysbalance of TH_1- and TH_2-type cytokines, we investigated peripheral blood lymphocytes (PBLs) from patients with RRMS under FAE treatment. Methods and subjects: FAE therapy was investigated in regards to effectiveness and safety in a small explorative group of 10 patients over six months. Intracellular TH_1- and TH_2- type cytokines (IL-2, IL-4, IL-10, TNF-α, TGF-β, IFN-γ) of PBLs from patients with RRMS were detected. Serial T1 weighted MRI with triple dose Gd-DTPA during the study phase were performed regulary. Primary outcome parameter of the study was the reduction of active Gd enhancing lesions in T1 weighted MRI. Results: FAE decrease significantly the amount of active lesions and lesion load of Gd-enhancing lesions in T1 weighted MRI. The cytokine balance changed significantly in favor of the TH_2-type cytokines. Clinically 7/10 patients remained stable or improved under FAE therapy during the study. One drop out because of stomach disturbances and two not drug related drop outs. Conclusion: In our small group of patients with RRMS oral FAE therapy was effective most probable due to the selective immunomodulation of TH_2-type cytokines. The influence on serial T1 weighted MRI is striking. The clinical use of oral fumaric acid ester as a possible relevant drug for the treatment of multiple sclerosis is now conceivable.

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EFFECTS OF GLATIRAMER ACETATE ON MRI MEASURED DISEASE ACTIVITY: RESULTS OF A RANDOMISED, DOUBLE BLIND, PLACEBO-CONTROLLED MULTICENTRE STUDY. G. Comi[1], M. Filippi[2] for the Copaxone MRI Study Group. [1]Clinical Trials and [2]Neuroimaging Research Unit, Department of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, Italy.

Glatiramer acetate is a mixture of synthetic polypeptides which suppresses both acute and chronic experimental allergic encephalomyelitis. Two double-blind, placebo-controlled trials demonstrated that glatiramer acetate reduces relapse rate in patients with relapsing-remitting multiple sclerosis (RRMS). The aim of this study was to determine the effects of daily s. c. injection of 20 mg glatiramer acetate on MRI-measured disease activity in RRMS, during a 9-month double blind placebo-controlled phase, followed by a 9-month open label phase. One or more relapses in the two years prior to study entry and at least one enhancing lesion on the screening MRI scans were required for enrollment. Brain MRI was performed monthly during the double blind phase. The primary end-point was the total number of enhancing lesions. Two hundred thirty-nine patients were enrolled (119 received glatiramer acetate and 120 placebo). There was a significant reduction in the total number of enhancing lesions in the treated group (29% reduction in LOCF adjusted mean, $p=0.003$, 35% reduction on data as is $p=0.0007$). Differences in favor of glatiramer acetate were also found for: mean number of new enhancing lesions (30% reduction, $p=0.0029$), number of new T2 lesions (35% reduction, $p= 0.001$), median change from baseline in volume of enhancing lesions ($p=0.0098$), median change from baseline of T2 lesion load ($p=0.0245$). The relapse rate was also reduced in glatiramer acetate compared to placebo group (-33%, $p=0.0117$). In RRMS glatiramer acetate significantly reduced the MRI disease activity and burden. This effect mirrored the reduction of clinical activity.

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T-CELL DEPLETED AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR MULTIPLE SCLEROSIS; TRANSPLANTATION RELATED TOXICITY AND EARLY RESULTS IN THREE PATIENTS. J. P. A. Samijn, M. R. Schipperus, P. A. van Doorn, J. J. Cornelissen, J. W. B. Moll, C. A. M. Huisman, B. Löwenberg and F. G. A. van der Meché. Department of Neurologyand hematology, Erasmus Medical Center Rotterdam.

Based on animal models and clinical observations autologous stem cell transplantation and bone marrow transplantation (BMT) may be effective therapies for several autoimmune diseases. Phase II studies with different conditioning regimens have been initiated worldwide to evaluate if BMT can halt disease progression in patients with malignant multiple sclerosis (MS). We selected patients by predefined criteria: definite MS according to Poser's criteria, an expanded disability status score (EDSS) ≥ 3 within two years and progression of disability in the years prior to inclusion. Current EDSS had to be between 5 and 7. The patients received total body irradiation (2x5Gy) and cyclophosphamide (120 mg/kg). Anti-thymocytic immunoglobulins were administered for in vivo T-cell depletion. This was followed by CD34 selected autologous BMT. Supportive care and isolation methods were according to standard procedure. In three patients (m, 30 yr; m, 39 yr; f, 48 yr) the transplantation procedure has been completed. All patients suffered from general malaise. Liver function disturbances and moderately severe toxicodermia were observed in two patients. Two

patients needed parenteral feeding because of severe mucositis. There were no serious infections. After 4 months there are no changes on the EDDS although a decrease in general functioning is reported due to fatigue and increased muscle spasms. We conclude that autologous bone marrow transplantation for multiple sclerosis can be performed safely with acceptable toxicity. Evaluation of effectiveness needs a longer follow-up period, comparison of results with other centers and randomised studies

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MRI/CLINICAL CORRELATIONS IN THE PHASE III TREATMENT TRIAL OF INTERFERON BETA-1B IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS. Molyneux PD, Miller DH, Kappos L, Polman C, Pozilli C, Thompson AJ, Dahlke F, Ghazi M, Wagner K. European Study Group on Interferon β-1b in Secondary Progressive MS

The recently completed placebo controlled multicentre randomised trial of interferon beta-1b (betaferon) utilised both clinical and MRI outcome outcomes, allowing an opportunity to assess the level of relationship between these parameters in a large cohort of secondary progressive MS patients. The trial design and clinical outcomes have been published elsewhere [Lancet 1998;352:1491-1497]. Brain T2 weighted lesion load was measured annually in all 718 patients, together with visual analysis to identify any new or enlarging (active) T2 lesions at each annual timepoint. A subgroup of 125 patients had monthly gadolinium enhanced imaging T1 weighted imaging at months 0-6 and 18-24. For the annual MRI outcomes, a significant but modest correlation was identified between the change in T2 lesion load and change in expanded disability status scale (EDSS) over the study duration ($r=0.17$, $p < 0.0001$); simple visual analysis of the same T2 weighted scans revealed significant correlations for the cumulative number of active T2 lesions against (i) change in EDSS ($r=0.18$, $p < 0.0001$) and (ii) relapse rate ($r=0.25$, $p < 0.0001$). In the subgroup of 125 patients undergoing monthly imaging, a significant correlation was also identified between monthly MRI activity and relapse rate over months 0-24 ($r=0.21$, $p=0.008$). These results both confirm that the clinical/MRI relationship identified in relapsing remitting MS is still apparent in the later SP phase of the disease, and support the use of MRI as a relevant surrogate in SP MS. The relatively modest nature of the correlations highlights the appropriate role of clinical outcomes as primary trial endpoints.

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MITOXANTRONE (MX) IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS (MS): CLINICAL RESULTS AND THREE YEAR FOLLOW-UP OF A PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND PHASE III TRIAL. H. P. Hartung, Graz, Austria; R. Gonsette, Melsbroek, Belgium; and the MIMS-Study Group

A phase III study was conducted in 17 centers from 4 European countries to evaluate the effects of MX in MS. Eligible patients had relapsing-progressive or secondary-progressive MS in an active stage of the disease and with an EDSS from 3 to 6.194 patients were randomized to 12mg/m^2 Mitoxantrone (MX12), 5mg/m^2 Mitoxantrone (MX5) or Placebo (PLC) given intravenously every 3 month for two years. EDSS and Ambulation Index (AI) were assessed by a blinded observer. 188 patients were evaluable. Baseline parameters showed no difference between the groups. All efficacy endpoints defined in the protocol were significantly better in MX12. EDSS was decreased by 0.12 in MX12, 0.23 in MX5 and increased by 0.23 in PLC ($p < 0.038$). AI was increased with 0.2, 0.4 and 0.8 in MX12, MX5 and PLC, ($p < 0.040$). The mean number of treated relapses were 0.4 in MX12, 0.7 in MX5 and 1.2 in PLC ($p < 0.0002$). There was a statistically significant difference in the time to first treated relapse ($p < 0.0004$). Three year follow-up data will be presented. Adverse events reported more frequent in the MX groups were nausea, alopecia, urinary tract infections, menstrual disorders, amenorrhea, transient leucopenia and increase of γ-glutamyltransferase. Most adverse events were mild to moderate intensity. The trial showed that MX is an effective and usually well tolerated treatment for progressive MS and should be considered as an important therapeutic option in this patient population. *Supported by Wyeth Lederle Germany and Belgium*

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MITOXANTRONE (MX) IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS (MS): MRI RESULTS OF THE EUROPEAN PHASE III TRIAL. H. Krapf, Tübingen, Germany; S. P. Morrissey, Munich, Germany; O. Zenker, Münster, Germany; T. Zwingers, Augsburg, Germany; R. Gonsette, Melsbroek, Belgium; H. P. Hartung, Graz, Austria; and the MIMS-Study Group.

A recently completed Phase III trial (MIMS-trial) showed that MX had a significant beneficial impact on disease progression and relapse rate in progressive MS. Patients were treated with Mitoxantrone 12mg/m^2 (MX12), Mitoxantrone 5mg/m^2 (MX5) or placebo (PLC) intravenously every three month for two years. In a subgroup of 110 patients non-enhanced T2 and Gadolinium enhanced (Gd-enh) T1 MRI was obtained at months (M) 0, 12 and 24. MRI were jointly analyzed by two readers blinded to clinical results. Comparing M24 to M0, the mean number of Gd-enh lesions per patient diminished from 1.88 to 0.03 in MX12 ($p < 0.049$), from 3.23 to 0.11 in MX5 ($p < 0.039$) and from 0.44 to 0.28 in PLC ($p < 0.385$). The number of patients with Gd-enh was more or less unchanged in the placebo group (M0: 22,2%, M: 12: 19,4%, M: 24: 15,6%), whereas there was a marked reduction in MX5 (47.5%, 15.0%, 10.8%) and in MX12 (29.4%, 14.7%, 3.2%). The mean change in number of T2-weighted lesions at M24 was significant smaller in MX12 vs. PLC (+0.29 vs +1.94; $p < 0.012$). The mean intraindividual change of the total lesion load at M24 was significantly greater in PLC ($p < 0.009$), while it remained stable in MX5 and MX12. These MRI results confirm the beneficial clinical effects of MX on progressive MS. *Supported by: Wyeth Lederle Germany and Belgium*

General Neurology – 2

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TNF-RI ARE DECREASED IN MIGRAINE PATIENTS. Empl M, Förderreuther S, Riedel M*, Müller N*, Straube A, Department of Neurology, Department of Psychiatry*, Ludwig-Maximilians-University, Munich, Germany.

Recently, some cytokines (TNF-alpha and Interleukin-6) have been recognised as pain mediators in addition to their immunologic function. Following the hypothesis of neurovascular inflammation in migraine, a contribution of cytokines to the pain generation in migraine seems possible. We analyzed IL-6 and its soluble agonistic receptor sIL-6R and the antagonistic receptor spg130 as well as TNF-alpha and its soluble receptor TNF-RI in 27 migraine patients. 8 headachefree persons served as controls. Migraine patients (with and without aura, most of them in the headache free intervall) showed significantly decreased TNF-RI (769±142 pg/ml) compared to controls (945±136 pg/ml; p=0,01). Patients with aura (n=8) showed beside the decreased TNF-RI also decreased levels of sgp130 (246±40 ng/ml) compared to 296±41 ng/ml in controls (p=0,05). Patients with migraine without aura (n=19) also had lower TNF-RI levels (775±152 pg/ml; p=0,01), but the decrease in sgp 130 failed to reach stasticical significance. No differences in cytokine concentrations could be observed. As TNF-RI block TNF-alpha action, it could be speculated, that migraine patients lack a sufficiant quantitiy of antagonistic TNF-RI to neutralize hyperalgesic TNF-alpha during a migraine attack. In the same way, the decrease of antagonistic spg130 in patients with aura could be explained. However, detailed study of the time course of cytokine levels during a migraine attack should be performed, in order to confirm the postulated rise in TNF-alpha and IL-6 during a migraine attack.

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A NEW mtDNA MUTATION ASSOCIATED WITH MELAS SYNDROME AND UNUSUAL NEURORADIOLOGICAL FINDING. C. Clerc (1), P. Laforet (2), L. Rumbach (3), O. Joyeux (4), P. Richard (1), M. Bataillard (1), T. Maisonobe (2), A. Lombes (2), (1) Service De Neurologie Ch Montbeliard, (2) Institut De Myologie Groupe Hospitalier Pitie-Salpetriere Paris, (3) Service De Neurologie CHU Besancon, (4) Service De Neurologie C H Valence France

The majority of patients with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and strokelike episodes) have an A to G transition of nucleotide 3243 in the leucine (UUR) mitochondrial transfer RNA (tRNA). However, approximately 10 other mutations have been reported in MELAS syndrome, most of them located in leucine tRNA gene. We describe a new mtDNA mutation associated with MELAS syndrome and unusual neuroradiological lesions. A 47-year-old patient presented with right hemiplegia and aphasia. Right-side focal seizures occured 3 years later. Bilateral deafness has been present since the age of 20. The family history was negative. Brain computed tomography (CT) scan showed large calcifications affecting basal ganglia and dentate nuclei. Magnetic resonance imaging (MRI) showed diffuse leucoencephalopathy with cerebellar cystic lesions. Cerebrospinal fluid (CSF) lactate was elevated. Muscle histology showed numerous ragged-red fibres with a mosaic pattern of cytochrome oxidase (COX) activity. A large scale deletion of

mtDNA was excluded by Southern Blot analysis. A heteroplasmic mutation in glutamine tRNA gene was detected by DGGE (denaturating gradient gel electrophoresis). It was identified by sequencing of a G to A transition at nucleotide 4332. This mutation destroyed one of the hydrogen bonds in the tRNA aminoacyl stem, thus disrupting a highly conserved secondary structure. Direct pathogenic potential of the mutation is under analysis.

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M-CHLOROPHENYLPIPERAZINE INDUCES MIGRAINE ATTACKS
Leone M, Attanasio A, Croci D, Filippini G, D'Amico D, Grazzi L, Nespolo A, Bussone G. Neurological Institute "C. Besta", Via Celoria, 11-20133 Milan, Italy.m-Chlorophenylpiperazine (mCPP), a $5HT_{2B/2C}$ receptor agonist, may be used to induce headache. The advantages of the mCPP experimental headache model are: (1) the headache is provoked by the stimulus of specific 5HT subreceptors and (2) it is possible to correlate headache occurrence with plasma levels of the stimulating substance. The primary aim of the present study was to further explore the use of mCPP as a migraine provoking agent in a large sample of subjects. We studied 75 subjects: 20 healthy controls, 19 migraineurs, 22 episodic cluster headache sufferers in remission and 14 low back pain patients. Each underwent two challenges, one with 0.5 mg/Kg of oral mCPP and the other with placebo separated by 4-8 days. Headache appearance in the following 24 hours was noted. Blood samples were taken at –30, 0, 30, 60, 90, 120, 150 and 180 minutes. The area under the mCPP curve was similar in the four groups. The overall occurrence of headache was similar after mCPP (29/75) and after placebo (24/75). The headaches were classifiable as migraine or tension type headache according to IHS criteria. A significantly increased risk of developing a migraine attack was found in the mCPP group (27/75) compared to the placebo group (6/75) (odds ratio 5.06; 95% confidence interval: 2.34, 10.92). This study shows that mCPP is able to provoke migraine attacks and reinforces the hypothesis that $5HT_{2B/2C}$ receptors are involved in migraine pathophysiology.

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HYPERACTIVITY OF NITRIC OXIDE PATHWAY IN MIGRAINE AND CLUSTER HEADACHE. D. D'Amico, Alessandra Ferraris, Anna Catania*, Andrea Carlin*, Massimo Leone, Licia Grazzi, Gennaro Bussone-Neurological Institute "C. Besta", Via Celoria, 11 - 20133 Milan, Italy - -* 3rd Medical Department, Ospedale Maggiore, Milan, Italy.

Nitric oxide (NO) is a messenger molecule which may be involved in aspects of migraine (M) and cluster headache (CH), as suggested by its roles in the vasodilation of intracranial arteries, perivascular neurogenic inflammation, and nervous transmission in CNS areas (brain stem, hypothalamus) involved in head pain. The aim of this study was to explore the NO involvement in M and CH by measuring plasma nitrites (stable products of NO metabolism). We studied 169 patients, 100 with M (60 without and 40 with aura) and 69 with episodic CH (32 in active phase, 37 in remission phase), and 112 healthy controls. Blood was sampled outside headache attacks. Plasma nitrites were determined by the Griess technique. Nitrites plasma levels were significantly higher in headache patients than controls (Mann-Whitney Rank Sum Test, $p < 0.0001$); this remained the case when the data were analysed by subgroup: M without aura, $p < 0.044$, M with aura p o. 015, CH in remission $p < 0.004$, CH in active phase $p < 0.011$. This finding suggests a basal activation of NO-producing mechanisms in M and CH outside attacks. Hyperactivity in systems in which NO is involved as a messenger may play a role in the pathophysiology of vascular primary headaches.

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WHAT CLINICAL FEATURES PREDICT DIAGNOSIS OF ACUTE DISSEMINATE ENCEPHALOMYELITIS (ADEM)?- N. Levin MD, A. Lossos MD, O. Abramsky MD, PhD.-Neurology Dep., Hadassah University Hospital, Jerusalem, Israel.

Objectives: To evaluate what initial clinical features may predict the diagnosis of ADEM. Background: ADEM is an uncommon inflammatory disorder of the central nervous system (CNS) white matter, sharing many similarities with acute form or initial attack of multiple sclerosis (MS) and with acute hemorrhagic leukoencephalitis. Based on a history of prior infection and on usually monophasic course, diagnosis of ADEM requires pathological confirmation and remains essentially retrospective since no clinical or imaging feature is consistently pathognomonic. Design And Methods: We reviewed the files of 148 patients who where categorized in our institution under the diagnosis of demyelinating disease of the CNS between 1980-1999. Eleven were suspected to have ADEM at their first admission. We examined their clinical features, laboratory and imaging findings and their long-term outcome. Results: Nine women and 2 men at the mean age of 43y (16 - 77y) were identified. Presenting symptoms included: focal neurological deficits (10), headache (4), confusion (3), fever (2), GI complaints (2) and dystonia (1). None had prior vaccination. All had brain MRI on admission: multifocal lesions were present in 8 and single in 3.Ten had lesion enhancement. Cerebrospinal fluid was available in 9 patients and was abnormal in 2. One had elevated protein level and oligoclonal antibodies band and the other showed a monoclonal band. Mean follow up was 1.52 years. Only 4 patients diagnosis of ADEM was established prospectively, 2 based on biopsy and 2 based on clinical follow up. Five patients had recurrent episodes and were subsequently diagnosed as MS. The long-term diagnosed ADEM patients were all females, over 52 years of age. Three out of 4 had a single MRI lesion and 3 out of 4 presented with confusional state. Conclusions: ADEM present a problematic diagnosis on first admission. Most of the patients believed to be ADEM patients on their presentation were finally diagnosed as MS. Common characteristics of the patients who were consistently diagnosed as ADEM was female gender, old age, confusional state on admission and a single lesion on MRI.

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CLINICAL, MORPHOLOGICAL AND BIOCHEMICAL STUDY OF THE CONGENITAL MYASTHENIC SYNDROME WITH END-PLATE ACETYLCHOLINESTERASE DEFICIENCY (TYPE Ic).- A. Pou-Serradell*, J. Pascual**, B. Eymard**, M. Fardeau**, S. Bon***. *Service of Neurology, Hospital del Mar, Barcelona. **INSERM U153, Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, ***Laboratoire de Neurobiologie Cellulaire et Moléculaire, CNRS 1857, Ecole Normale Supérieure, Paris.

Congenital myasthenic syndrome (CMS) with end-plate acetylcholinesterase (AchE) corresponds to CMS type Ic. The first genetic defect causing CMS-Ic is a mutation in the Human Acetylcholinesterase-Associated Collagen Gene (COLQ) (Am. J. Hum. Genet. 63:967-975, 1998). The objective is to present the clinical, morphological and biochemical aspects in a family (the same where the genetic defect was described) with CMS type Ic. Method/Patients: We analysed the clinical and follow-up studies in 6 members (4 males and 2 females, ages 43-61 years) belonging to a large Spanish familiy with fatigability on exertion. Electrophysiological studies were performed on four patients. Morphological and biochemical analysis were performed in biopsies of deltoid muscles in the end-plate region, obtained from two patients. AChE was extracted from muscle biopsies. Results: The onset of myasthenic symptoms occurred at age 6-10 years, in four patients fatigability improves spontaneously and two patients present permanent weakness, one of them with myopathy. They present double CMAP evoked responses to single-nerve stimuli. The morphological studies showed very small end plates, low AchE activity, nerve terminals reduced in size and marked degenerative changes at the functional folds. Analyses of AchE showed the presence of a normal complement of A12 and A8forms. Conclusions: We emphasize about the main clinical features that allows to define this CMS-Ic as a mild form of the disease. According to the fact that a mutation of the COLQ is the primary defect for this CMS-Ic we discuss the possibility that morphological changes were secondary.

Epilepsy

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EFFICACY AND TOLERABILITY OF LEVETIRACETAM (LEV) AS ADD-ON TREATMENT IN REFRACTORY SEIZURES: NO-NEED FOR AN UP-TITRATION STEP. Tim Betts, Birmingham – UK; Anne Danniau, Tony Waegemans and Peter Verdru, UCB S. A. Pharma Sector, Braine-l'Alleud, Belgium.

In previous trials LEV has shown efficacy at 1g, 2g, and 3g. In these trials the majority of patients received an effective dose (1g) without up-titration. One of the aims of this study was to further investigate the tolerability and efficacy of higher doses of LEV when given without up-titration. Methods: This was a multicenter, double blind, parallel group study comparing the tolerability and efficacy of LEV 2g and 4g with placebo in patients with refractory partial or generalized seizures. Criteria for inclusion were at least four seizures during the 24-week period prior to the inclusion. Results: Somnolence and asthenia were the most common AEs reported, most of them were mild or moderate in severity and occurred in the

first days after initiation of LEV. The median seizure frequency was reduced for all seizure types. The analysis of the responder rate confirmed the results of previous studies with 48.1% in the 2g group, 28.6% in the 4g group and 16.1% in the placebo group. A similar responder rate (43%) was observed during the open label (LEV 4g) follow-up period. Conclusions: This study confirms that 2g and 4g of LEV can be given without major safety concern. This trial confirmed the efficacy of LEV in partial seizures and showed a tendency towards efficacy for generalized seizures.

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LONG-DURATION EPILEPTIC SEIZURES: ELECTROCLINICAL FEATURES OF 5 PATIENTS. A. Biraben, D. Taussig, C. Le Berre, J. P. Vignal, A. M Bernard, P. Chauvel, E. Seigneuret, J. M. Scarabin

Epileptic seizures usually last less than 5 minutes. We report on the electroclinical features of 5 patients with usual non convulsive epileptic seizures of long duration. Patients and methods: We selected among the patients undergoing presurgical evaluation for drug-resistant epilepsy those having seizures lasting more than 5 minutes, as reported by history and as confirmed on video-EEG recording. We excluded patients with prolonged tonic-clonic generalisation as well as patients with unusual long lasting features during video EEG recording possibly due to drug tapering. One to 3 seizures were recorded for each patient. None of them were cluster. 4 ictal SPECT were performed. Results: Two patients have apparently generalised or bifrontal epilepsy with long-lasting seizures (30 minutes) close to non convulsive status. The most prominent feature is fluctuation of consciousness. One of them have ring 20 chromosome which has been associated with long-duration seizure close to status; caryotype will be performed in the second one. The 3 other patients have partial epilepsy, temporal lobe epilepsy in 2, perisylvian in the 3rd. Seizure duration was 6 to 23 minutes. Ring Chromosome 20 is negative in 2 of them, and not yet tested for the other. Discussion and conclusion: Brief duration of the fit is often a diagnosis element for epileptic seizures. However, long lasting epileptic seizures does exist in apparently generalized and in partial seizures. Some genetic factors including chromosomal abnormalities could favour long-duration seizures or alter seizures termination system.

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LATERALIZING SEIZURE PHENOMENA IN FRONTAL AND TEMPORAL LOBE EPILEPSY. Soheyl Noachtar[1], Mona Pfänder[1], Stephan Arnold[1], Konrad J. Werhahn[1], Anja Henkel[1], Ilonka Eisensehr, Peter A. Winkler[2],Hans O. Lüders[3] [1] Dep. of Neurology and [2] Neurosurgery, University of Munich, Munich/Germany, [3] Cleveland Clinic Foundation, Cleveland/Ohio

This study evaluates the seizure evolution in a consecutive series of patients with frontal (FE) and temporal epilepsy (TE) considered for resective epilepsy surgery. 232 consecutive patients with TE (n=163) and FE (n=69) were included in this prospective study. Patients underwent ictal EEG-video recordings (n=232), MRI (n=230), interictal FDG-PET (n=148) and ictal ECD-SPECT (n=28). The lateralizing seizure phenomena of 2947 seizures were analyzed. Lateralizing seizrue phenomena were observed in 67% (n=110) of the TE patients and74% (n=51) of the FE patients. The frequency and positive predicitive values (PPV) of the lateralizing seizure phenomena in TE and FE were significantly diferent: dystonia (TE 32%, PPV 98%; FE 9%, PPV 100%; $p < 0.01$), verion (TE 31%, PPV 96%; FE 36%, PPV 96%), unilateral cloni (TE 31%, PPV 98%; FE 48%, PPV 97%; $p < 0.01$), and postictal aphasia (TE 19%, PPV 83%; FE 0%; $p < 0.01$). Preserved responsiveness (TE 3%, FE 0%), unilateral somatosensory aura (TE 2%, FE 15%, PPV 100%; $p < 0.01$), and unilateral tonic seizures (TE 2%, FE 25%, PPV 100%; $p < 0.01$) were rare phenomena in TE, but lateralized always correct. We conclude from our results that lateralizing seizure phenomena are common in patients with FE and TE and reliably lateralize the epileptogenic zone. The occurrence of different lateralizing seizure phenomena helps differentiate TE from FE. This clinical information should be included in the evaluation of FE and TE patients considered for resective epilepsy surgery.

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ANTI GLUR3 ANTIBODIES IN RASMUSSEN'S ENCEPHALITIS AND CONTROLS. R. Mantegazza, P. Bernasconi, N. Aurisano, C. Antozzi, T. Granata, C. Frassoni, R. Garbelli, L. Angelini, F. Cornelio, R. Spreafico. Istituto Nazionale Neurologico "C. Besta", Milan, Italy.

Rasmussen's encephalitis (RE) is a serious encephalopathy associated with epileptic seizures which are poorly responsive to anti-epileptic drugs. An autoimmune hypothesis has been proposed on the basis of brain pathological alterations, response to plasmaexchange or protein A immunoadsorption, and presence in patients' sera of anti glutamate receptor type 3 (GluR3) antibodies. We tested serum and CSF samples from 8 RE patients and 123 controls for GluR3 epitope mapping by ELISA (positivity was given as OD above the mean ± 2SD of healthy controls). Peptide GluR3A and B, GluR3-L29 (near N-term domain), GluR3-A162 (large hydrophilic domain), GluR3-W553 (cytoplasmic domain) and GluR3-I866 (C-term domain) were used. Controls included: partial epilepsy without CNS lesions (n. 11), partial epilepsy with CNS lesions (n. 3), neuronal migration defects with epilepsy (n. 6), early-onset epileptic encephalitis (n. 4), young-onset myasthenia (n. 6), young-onset SLE (n. 10), degenerative diseases (n. 2), and healthy controls (n. 81). RE patients' sera reacted with a similar positivity to the 6 different GluR3 epitopes thus suggesting that the anti GluR3 antibody population in each patient is heterogeneous with regard to the epitope mapping. As far as the specificity is concerned, RE patients showed a positivity ranging from 50 to 67% whereas healthy controls ranged from 7 to 8%.

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A REDUCED K^+ CURRENT DUE TO A NOVEL C-TERMINAL MUTATION IN KCNQ2 CAUSES BENIGN FAMILIAL NEONATAL CONVULSIONS. H. Lerche[1,2], C. Biervert[3], A. Alekov[1,2], L. Schleithoff[1], O. K. Steinlein[3], F. Lehmann-Horn[1] - Departments of Applied Physiology[1] and Neurology[2], University of Ulm, D-89069 Ulm, Germany: Institute of Human Genetics[3], University of Bonn, Wilhelmstr. 31, D-53111 Bonn, Germany

Benign familial neonatal convulsions (BFNC) is a rare dominantly inherited epileptic syndrome characterized by frequent brief seizures within the first days of life. The disease is caused by mutations in one of two recently identified voltage-gated potassium channel genes, KCNQ2 or KCNQ3. Here, we describe a four generation BFNC family carrying a novel mutation within the distal, unconserved C-terminal domain of KCNQ2, a one base pair deletion, 2513delG, in codon 838 predicting substitution of the last seven and extension by another 56 amino acids. Three family members suffering from febrile but not from neonatal convulsions do not carry the mutation, confirming that febrile convulsions and BFNC are of different etiology. Functional expression of the mutant channel in Xenopus oocytes revealed a reduction of the potassium current to 5% of the wild type (WT) current, while the voltage sensitivity and kinetics were not significantly changed. To explore whether the loss of the last seven amino acids or the C-terminal extension due to 2513delG causes the phenotype, a second, artificial mutation was constructed yielding a stop codon at position 838. This truncation increased the potassium current by twofold compared to the WT, indicating that the pathological extension produces the phenotype, and suggesting an important functional role of the distal, unconserved C-terminal domain of this channel. Our results indicate that BFNC is caused by a decreased potassium current impairing repolarization of the neuronal cell membrane which results in hyperexcitability of the central nervous system within the neonatal period.

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AURAS OF ECSTASY AND PLEASURE: REPORT OF FIVE NEW CASES, ANALYSIS OF THE LITERATURE AND A PRECIS OF A NEW HYPOTHESIS. Martínez, JVL; Palmini, A*; Bezerra, MLS, Da-Costa, JC*; Paglioli-Neto, E*; Calcagnotto, ME*; Paglioli, E*; Portuguez, MW*; Raupp, S*. *Porto Alegre Epilepsy Surgery Program, São Lucas Hospital, Rio Grande do Sul Catholic University (PUCRRS), Porto Alegre-RS, Brazil. Neurology Department, Fluminense Federal University, Niterói-RJ, Brazil.

The experiential phenomena are perhaps the most intriguing of the epileptic manifestations. And among these, no epileptic manifestation has caused more controversy than the ecstatic auras or consisting of pleasurable feelings. We present here five patients whose auras consisted of ecstatic and pleasurable sensations. We also discuss the cases described in the literature and draw a hypothesis regarding these manifestations. Material And Methods: We report five male patients with epilepsy and auras consisting of 'ecstasy' or 'good feelings'. Sexual auras were excluded. They all were refractory to medical treatment were submitted to pre-operative evaluation and later to epilepsy surgery. They all had cranial MRI, chronic video-EEG monitoring and neuropsychological evaluation. One of them had invasive EEG monitoring and extra-operative cortical stimulation. Four of them had temporal mesial lesions and the 5th had orbito-frontal lesion. Discussion: Our data here presented are in accordance with

the hypothesis that the limbic structures are the neural substrate of the religious and pleasure sensations. These two types of aura (ecstasy and pleasure –without sexual connotations) are more common in men, although orgasmic auras are almost exclusive in women. "These features compatible with the assumption that localized epileptic neuronal discharge involving some limbic structures could create a matrix representing features of individual experience of the kind activated in the curse of limbic seizures. "

Peripheral neuropathy – 3

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THE ABSENCE OF PO PRODUCES A NOVEL MOLECULAR PHENOTYPE IN SCHWANN CELLS- Daniela Maria Menichella, MD [1], Wenbo Xu, MD [2], Jean-Michael Vallat, MD[3], Pier Luigi Baron, MD, PhD[1], Elio Scasrpini, MD[1], Guglielmo Scarlato, MD[1], John Kamholz, MD PhD[2] and Michael Shy, MD[2]. 1IRCCS, Policlinico Hospital University of Milan-Italy; 2 Wayne State University, Detroit, USA; 3University Hospital, Limoges, France.

Myelination is a regulated process involving coordinated expression of a set of myelin-specific genes and coordinated assembly of a set of myelin-specific proteins. Protein Zero (PO), the most abundant protein of PNS myelin, is necessary for normal myelination, since mice lacking this protein (PO-/-) develop a severe dysmyelinating neuropathy. Recent evidence suggests that PO mediates myelin compaction, but it may also have a regulatory role in the myelination process. In order to unravel the potential regulatory role of PO, we analyzed both the pattern of myelin-specific gene expression and localization in the sciatic nerve of adult PO-/- mice and during development. Northern blot analysis of sciatic nerve mRNA demonstrates a 5 to 7-fold increase in MAG and PLP/DM20 steady state levels, while MBP mRNA levels are unchanged. In contrast, PMP-22 mRNA levels are undetectable. These results have also been confirmed by in situ hybridization in frozen sections of sciatic nerve. Immunohistochemical analysis of teased fiber preparations demonstrate further that PLP/DM20 and MAG localization is altered. PLP/DM20 is found mainly in the perinuclear cytoplasm, while MAG is found diffusely throughout the nerve. No MAG is localized at either the Node of Ranvier or the Schmidt-Lanterman incisors. E-cadherin and β catenin, also normally localized to the NR and SL incisors, are also diffusely distributed throughout the nerve in the PO-/- animals. Taken toghether, these data demonstrate that PO plays an important role, either directly or indirectly, in the regulation of myelin gene expression as well as the process of myelin assembly.

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ALTERED PROTEIN SYNTHESIS BY TRANSGENIC OVEREXPRESSION OF PERIPHERAL MYELIN PROTEIN 22 KD (PMP22) IN A RAT MODEL OF CHARCOT-MARIE-TOOTH DISEASE. [1]Michael Sereda, [1]Stephan Niemann, [2]Ueli Suter, [3]Ian Griffiths, and [1]Klaus-Armin Nave - [1]Zentrum für Molekulare Biologie (ZMBH), University of Heidelberg, Germany. [2]Department of Cell Biology, Swiss Federal Institute of Technology, ETH-Hoenggerberg, CH-8093 Zürich, Switzerland. [3]Department of Veterinary Clinical Studies, University of Glasgow, U. K.

Peripheral myelin protein 22 kD (PMP22) is a peripheral myelin protein that is produced by Schwann cells and has been associated with different inherited demyelinating neuropathies in humans. Among these Charcot-Marie-Tooth disease (CMT) is the most common and has been associated with a partial duplication of chromosome 17 (CMT type1A). We have generated a transgenic rat model of this disease and provide experimental evidence that CMT1A is caused by increased expression of the PMP22 gene. The heterozygous transgenic rats develop gait abnormalities caused by a peripheral hypomyelination, 'onion bulb' formation, and muscle weakness at the age of approximately 4 weeks. Reduced nerve conduction velocities closely resemble recordings in human patients with CMT1A (Sereda et al., Neuron, 16, 1049-1060, 1996). In sciatic nerves of young transgenic animals, PMP22 is increased at the mRNA level and also the protein level when compared to other myelin proteins such as Protein Zero ($p < 0$). At later disease stages $p < 0$ and PMP22 are decreased reflecting demyelination. However, in the myelin compartment PMP22 is increased at this disease stage when compared to wildtype littermates, demonstrating that the relative abundance of PMP22 is increased in the myelin sheath. By deglycosylation assays we show that PMP22 and $p < 0$ in transgenic animals almost exclusively contain complex oligosaccharides and therefore are not aberrantly retained in the endoplasmatic reticulum, but have reached at least the medial Golgi compartment. Furthermore, Western blot analysis revealed that LAMP-1 protein, a marker for the lysosomal/endosomal compartment, is more abundant in 6 week old transgenic animals, but not in earlier disease stages (postnatal day 6). To analyze protein synthesis in CMT rats we performed ex vivo pulse-chase experiments in isolated sciatic nerves. Using 3H labeled fucose we show that label incorporation into TCA precipitable protein is increased 3 fold in total nerve homogenates indicating an increased overall protein synthesis. Interestingly, proteins of the myelin fraction only show a moderatly increased incorporation of label. This suggests that most of the newly synthesized proteins do not reach the myelin compartment. We hypothesize that abnormal trafficking of myelin proteins in PMP22 overexpressing Schwann cells accounts for abnormal protein turnover and degradation in the lysosomal/endosomal compartment. The biochemical and and morphological observations in our rat model, when taken together, let us propose a cellular disease model of PMP22 mediated neuropathies.

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SEVERE CMT1 DISEASE WITH CRANIAL NERVE INVOLVEMENT AND A MUTATION IN THE *EGR2* GENE. D. Pareyson, S. Botti, G. Lauria, C. Ciano, M. Morbin, F. Taroni, A. Sghirlanzoni. Milan, Italy.

The transcription factor Early Growth Response-2 (EGR2) is a zinc-finger protein which binds DNA. Its murine orthologue *Krox-20* is involved in PNS myelinogenesis and hindbrain development. The homozygous knockout animal shows PNS amyelination and cranial nerve abnormalities. Recently, *EGR2* gene mutations have been reported in a few patients with peripheral myelinopathies of different severity. We report clinical findings of a family in which a 66-year-old man and his 32-year-old daughter had a severe early-onset neuropathy associated with a heterozygous missense mutation (Arg381His) in the *EGR2* gene. The more severely affected father, chairbound since age 55, had also proximal muscle weakness and cranial nerve involvement (oculomotor paresis with diplopia, vocal cord paresis requiring tracheostomy). Motor conduction velocities were 16-28 m/sec in upper limbs, no M-response could be obtained from lower limbs, and sensory action potentials were absent in both patients. In the daughter, electrophysiologic studies of facial and spinal accessory nerves and blink reflex were abnormal. No significant abnormality was found at brain MRI in both patients. Sural nerve biopsy in the daughter demonstrated severe loss of myelinated fibers with several complex onion bulb formations. This family shows severe Charcot-Marie-Tooth type I with cranial nerve involvement consistent with a role of EGR2 in cranial nerve development. Supported by Telethon-Italy grants to A. S and F. T.

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INFLAMMATORY CELL INFILTRATION AND DEATH IN THE NERVE OF DIABETIC PATIENTS. Conti G., Scarpini E, Baron PL, De Riz M., Clerici R, Siglienti I, Piccio L, Livraghi S, Erba M, Scarlato G. IRCCS Osp. Maggiore Policlinico, Dino Ferrari center, University of Milan, Italy

The recent observation that inflammatory cells infiltrate the nerve of diabetic patients suggests that immune mechanisms may contribute to the pathogenesis of diabetic neuropathy, playing a possible role in chemotaxis and regeneration. This study analyzed infiltration of T-cells and macrophages in nerves obtained from a series of diabetic patients affected by distal symmetrical polyneuropathy. Furthermore, apoptosis was detected on teased nerve fibers by TUNEL and DAPI staining combined with cell phenotype characterization. We observed that macrophages and T-cell infiltrate in some extent the endoneurium of diabetic nerves, and about the 20% of these cells undergo apoptosis, while Schwann cells do not. These processes may play an important role in the pathogenesis of diabetic neuropathy regulating nerve damage and regeneration, and suggesting a potential effect of anti-inflammatory and/or anti-immune drugs in the treatment of diabetic neuropathy.

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CHRONIC CRYPTOGENIC POLYNEUROPATHY: A PROSPECTIVE STUDY. Jann S, Beretta S*. Dept of Neurology, Niguarda Cà Granda Hospital, Milano, Italy. *Dept of Neurology, Valduce General Hospital, Como, Italy.

Thirty patients with chronic sensorimotor polyneuropathy of undetermined cause were followed up in order to detect the progression and the prognosis of the disease. 22 males (age ranging from 52 to 80) and 8 females (64-78), previously healthy, underwent clinical examination, exten-

sive laboratory tests, neurophysiological examination, and, in some cases, CSF examination and sural nerve biopsy. They had neurological symptoms suggestive of symmetric polyneuropathy (distal paresthesias, pain or burning sensation in the lower limbs, mild weakness) lasting from more than one year before the first neurological examination (mean 2 years). Neurophysiological examination showed in all patients a chronic axonal degeneration and these results were confirmed by sural nerve biopsy when performed. Patients were reviewed every three months. Laboratory tests were performed every six months for the first two years and then every year. Neurophysiological examination was performed every year in all patients. Patients were followed up for at least three years (range 3-5 years). In no case a possible aetiological factor was detected during the follow up. Neurological condition had a very slowly progressive course in few cases and remained unchanged in the others. Neurophysiological examination showed only a slight progression. Our study suggests that patients referred to a neuromuscular centre and affected by a chronic cryptogenic polyneuropathy, need only to be reassured. No extensive laboratory tests and neurophysiological studies are necessary during the follow up.

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LIGHT-CHAIN AMYLOID NEUROPATHIES: STUDY OF A COHORT OF 20 PATIENTS. Rerat K, Adams D, Labauge P, Lacroix C, Said G. CHU de Bicêtre. France.

Light-chain amyloidoisis (AL) is an uncommon multisystemic disease which may cause neuropathies by endoneurial amyloid light-chain protein deposition. The main objective of the study was to report the main characteristics and course of acquired amyloid neuropathies in a cohort of 20 patients, mean age 60 years (extremes: 37-75), 12 males/8 females. Amyloidosis was associated with multiple myeloma in 5; Waldenstrom's macroglobulinemia in 3. Clinical presentation was sensory polyneuropathy (6/20), sensorimotor polyneuropathy (13/20) with autonomic dysfunction (12/20). Sensory loss predominantly affected temperature and pain sensations (10/19). Motor deficit was severe in 4 patients. Electrophysiological study showed signs for axonal neuropathy (9/13). On nerve biopsy, amyloid deposits were found in 16/18 patients, allowing diagnosis of amyloidosis in 10, with progressive wallerian degeneration (15/15) in association with demyelination in 2/15. Amyloid deposits were located mainly around endoneurial blood vessels. Neuropathy was preceded by major weight loss in 14 patients, nephrotic syndrome related to amyloïdosis in 6 (30%). The course was marked by seve pains (5), progressive motor deficit (5), postural hypotension (12), and heart and kidney complications failure (8). Neuropathy remained isolated in 7 patients (35%). Eighteen patients received chemotherapy including 3 with autologous blood stem-cell transplantation. 16/20 patients died 34 months on verage after first neuropathic symptoms (extremes : 11-120). Intensive chemotherapy needs to be assessed in patients with AL amyloid neuropathy.

Neuro-ophthalmology

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ACTIVATION OF CEREBELLAR STRUCTURES DURING OPTOKINETIC STIMULATION AND VOLUNTARY SACCADES (AN FMRI STUDY). M. Dieterich[1], S. F. Bucher[1], K. C. Seelos[2], Th. Brandt[1]. Departments of [1]Neurology and [2]Neuroradiology, Klinikum Grosshadern, Ludwig-Maximilians-University Munich, Germany

Aim of this fMRI study was to investigate noninvasively the activation pattern of cerebellar structures during small-field optokinetic stimulation (OKN) compared to that during voluntary saccades and fixation suppression of OKN. Eight healthy, right-handed volunteers (4 m, 4 w, mean age 29.6 y, range 25-37 y) were examined during horizontal OKN and horizontal saccades, vertical OKN and vertical saccades, and fixation suppression of OKN. OKN was elicited by viewing a rotating drum while wearing prism glasses (stimulated field: 20° in the horizontal, 15° in the vertical direction). Voluntary saccades were executed at a rate of 1-2 Hz and with an amplitude of 10°. Functional images were acquired from oblique transverse slices using a radio-frequency-spoiled single-slice FLASH (fast low angle shot) pulse sequence on a Siemens Vision Scanner (TR/TE=63/30 ms, voxel size=0.65x0.45x3 mm, field of view=200-250 mm, thickness = 4 mm, bandwidth=32 Hz/Pixel). Horizontal OKN and saccades were associated with bilateral activity in the cerebellar hemispheres (superior semilunar lobule, simple lobule, quadrangular lobule, inferior semilunar lobule), the middle cerebellar peduncle, the dentate nucleus, and medially in the culmen and uvula of cerebellar nuclei. The pattern and extent of activation were independent of the stimulus direction for OKN and saccades. During fixation suppression, the extent of activation was significantly diminished (hemispheres) or even absent (uvula, culmen). FMRI revealed that there is a complex sensorimotor network in the cerebellum as has also been found in the cortex.

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INFLUENCE OF VISUAL DYSFUNCTION ON EXECUTION OF MOVEMENT IN PARKINSON'S DISEASE (PD). Thomas Müller, Wilfried Kuhn, Thomas Büttner & Horst Przuntek. Department of Neurology, St. Josef-Hospital, Ruhr-University of Bochum, 44791 Bochum, Germany

The objective of the present study was the evaluation of a putative association of distorted colour vision and delayed initiation and execution of movement in PD. We performed the Farnsworth-Munsell 100-Hue Test and estimated the total error score in 30 previously untreated parkinsonian patients and 30 age- and sex matched controls. Then we assessed reaction time and movement time. Significant differences ($p = 0.007$) appeared between parkinsonian patients' (mean: 333.23 ± 63.82 SD, range 240 - 469 ms) and controls' reaction time (mean: 293.46 ± 44.86 SD, range 223 - 408 ms). The difference between parkinsonian subjects' (mean: 241.53 ± 85.70 SD, range 120 - 417 ms) and controls' movement time (mean: 179.92 ± 53.24 SD, range 96 - 329 ms) was significant ($p = 0.001$). Parkinsonian patients' total error score (mean: 79.4 ± 50.6 (SD), range 10 – 237) was significant ($p = 2.2268E-08$) higher compared to the ones of controls (mean: 18.4 ± 9.6 (SD), range 0 – 41). A significant association between movement time and total error score appeared ($p = 0.008$; Spearman $R = 0.473$), but not between reaction time and total error score ($p = 0.166$; Spearman $R = 0.259$). Visual dysfunction and execution of movement are more influenced by altered dopaminergic neurotransmission in PD in comparison to initiation of movement.

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MEMANTINE VS. GABAPENTIN IN ACQUIRED PENDULAR NYSTAGMUS: AN OBSERVER-BLIND CROSS-OVER STUDY. Starck, M.[1], Albrecht, H.[1], Pöllmann, W.[1], Dieterich, M.[2], Straube,A.[2] - [1]Marianne-Strauss-Klinik, Milchberg 21, D-82335 Berg - [2]Departement of Neurology, University Hospital Großhadern, Marchioninistr. 15, D-81377 München

One of the most disabling oculomotor syndroms in patients with multiple sclerosis is acquired pendular nystagmus (APN) causing oscillopsia. Recently two independent studies proved the effectiveness of Memantine, a weak NMDA-antagonist, and Gabapentin, a substance with no known specific action up to now, in therapy for APN. To compare both drugs, we treated 9 patients with clinically definite multiple sclerosis (mean age 45,5 yrs, mean duration of disease 14,1 yrs, mean disability score EDSS 6,1) and stable APN for at least one year in a cross-over study with Gabapentin versus Memantine. The dosage of Memantine was 40-60 mg/d PO and that of Gabapentin 900-1200 mg/d PO. Each treatment was followed by a wash-out period. The patients were evaluated by DC-EOG or search coil recording, clinical neuro-ophthalmological examination including visual acuity testing. The EOG/search coil recordings were evaluated independently by 2 blind observers. A reduction of the amplitude of nystagmus by at least 50% was considered a positive treatment effect. There was no effect of the drugs on frequency of nystagmus. Eight of 9 patients taking Memantine and 4 of 8 on Gabapentin showed a decrease or cessation of APN. While none of the patients on Memantine reported major side effects, 5 patients on Gabapentin complained of muscular weakness and 3 of a worsening of ataxia. Conclusion: Both drugs can have a positive effect on APN. However, Memantine seems to reduce APN more consistently and also causes less side effects than Gabapentin in multiple sclerosis patients.

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UNILATERAL LESIONS OF THE INTERSTITIAL NUCLEUS OF CAJAL (IC) IN THE ALERT MONKEY DO *NOT* ELICIT SEESAW NYSTAGMUS. C. Helmchen, H. Rambold, U. Büttner. Dept. of Neurology, Klinikum Großhadern, University of Munich, Germany

Seesaw nystagmus (SSN) is a unique binocular disorder characterized by alternating vertical skew deviation and conjugate ocular torsion. Jerk and pendular SSN must be distinguished since they may be caused by different lesion sites (Rambold et al. 1998). It has been proposed that jerk SSN is elicited by a unilateral lesion of the midbrain interstitial nucleus of Cajal (iC) (Halmagyi et al. 1994). iC is part of the neural integrator for vertical

and torsional eye movements (Crawford and Vilis 1993, Helmchen et al. 1998). Accordingly, experimental lesions in iC elicit vertical and torsional nystagmus. To test this proposed hypothesis, for the first time, we studied the effect of unilateral reversible midbrain inactivations in the alert monkey on *binocular* vertical-torsional eye movements using the three-dimensional search coil technique. Seven unilateral reversible iC inactivations were performed (microinjections of muscimol; 0.1 %, 0.5 µl). All injections elicited vertical and torsional nystagmus but all nystagmus components had conjugate directions on both eyes, i. e. there was no SSN. We conclude that - unlike proposed elsewhere (Halmagyi et al. 1994) - a unilateral iC lesion alone is not sufficient to cause jerk SSN. *Supported by the Deutsche Forschungsgemeinschaft*

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VISUAL DISORDERS AFTER TRAUMA IN CHILDREN: A CLINICAL SURVEY. E. Castelli, G. Poggi, C. Triscari, G. Mancarella. IRCCS "Eugenio Medea", Bosisio Parini (Lc), Italy.

Traumatic brain injury (TBI) is the most common cause for disabilities acquired in developmental age. Visual function deficits are often associated with head trauma in adults. The visual system is vulnerable to injury from the cornea to the visual cortex. Goals: The aim of our paper is the study of visual system lesions and its dysfunction after TBI occurring in developmental age. Method: 58 children who suffered nonpenetrating TBI were selected. Data collected on each patient concerned the age of onset, type and severity of the insult, presence of cranial fractures, site of neuroradiological anomalies. In the framework of a complete multidisciplinary evaluation patients underwent an accurate visual, clinical and instrumental assessment. Results: The mean age of onset was 7.2. The mean GCS was 6.3.59 % of babies and toddlers presented an increase in intracranial pressure. Lesions to the fronto-temporal lobes were present in more than 75% of cases independent of age, whereas brainstem damage was rarer at a younger age. The neurological outcome ranged from complete recovery to vegetative state. More than 2/3 patients presented visual disorders. We found impairment of visual acuity, ocular posturing, pursuit, saccades, stereopsis, fundus oculi, visual field and also a case of visual agnosia. The study highlighted a significant correlation between the GCS score, the age of the insult, the intracranial hypertension and the presence of visual deficits.

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INFRARED OCULOGRAPHY IN THE DIAGNOSIS OF OCULAR MYASTHENIA. Gschwandtner, U. *; Fuhr, P. and Steck, A. J. ***Psychiatric Outpatient Clinic of the University of Basel, . **Clinic of Neurology of the University of Basel, Switzerland.

Patients: In this study we applied infrared oculography to examine 12 patients (7 females, 5 males, aged 25 to 75, average age 55 years) diagnosed with suspected ocular myasthenia and compared the results with a group of control subjects who were free of neurological symptoms. Methods: An analysis of saccades, an eye tracking paradigm (sinus 0.33 Hz) and an eye muscle fatigue test were performed using an infrared-controlled, non-invasive analysis of eye movement (IROG). Saccades were characterized in terms of amplitude, duration, speed and intersaccadic variabilities (occurrence of glissades, saccadic stuttering, saccadic slowing). Eye tracking measured the number of corrective saccades, and the fatigue test measured the increase in saccade duration. An EMG and determination of Ach-receptor antibodies were performed on all subjects. Statistical analysis was conducted using the Student t-test. Results: Ach-receptor antibodies were absent in all patients. Two patients showed a decrement when exposed to repetitive stimuli in the EMG. In 6 of the 12 patients, infrared oculography revealed pathological saccadic patterns (glissades, saccadic stuttering, saccadic slowing) and an increased number of pathological patterns in the eye muscle fatigue test. These two parameters combined - pathological saccadic patterns and pathological fatigue tests – significantly distinguished patients suspected of suffering from ocular myasthenia from the control group ($p < 0.01$). In addition in 4/6 patients the tensilon-test was positive. No significant difference was found in the number of corrective saccades recorded during eye tracking (sinus 0.33 Hz) in the patients as compared to the controls. Conclusion: Saccade analysis and measurement of eye muscle fatigue by infrared oculography are important supplementary diagnostic parameters is assessing patients suspected of suffering from ocular myasthenia, especially if the results of an EMG and antibody test are negative.

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CLINICAL, BIOCHEMICAL AND MOLECULAR GENETIC CHARACTERISTICS OF TYROSINE HYDROXYLASE DEFICIENCY. Wevers RA[1], Rondot P[2], Hoffmann GF[3], Bräutigam C[3], Smeitink JAM[1], van den Heuvel LPWJ[1], Steenbergen-Spanjers GCH[1], Gabreëls FJM[1], A. Verrips[1] - [1]University Hospital Nijmegen, 6500 HB Nijmegen, The Netherlands, [2]CHU Bicêtre, Le Kremlin-Bicêtre, France, [3]University Children's Hospital, Marburg, Germany.

Tyrosine Hydroxylase (= TH) deficiency was recognized recently as an inborn error of the CNS metabolism. As yet only two families with this defect have been described in literature. TH deficiency affects the biosynthesis of catecholamines including dopamine, norepinephrine and epinephrine as important neurotransmitters. Inheritance is autosomal recessive. Clinically patients with TH deficiency have a dopamine-deficiency syndrome characterized by extrapyramidal signs and symptoms. Onset of the disease is in the first year of life. It may either present as a progressive dystonia of the limbs (starting in the lower limbs / this is a recessive variant of Dopa-responsive dystonia) or as a hypokinetic rigid parkinsonism syndrome. Patients generally show a spectacular clinical response to low-dose L-Dopa treatment. Cases with severe mutations in the gene, however, only have a limited response to this therapy. The biochemical hallmark of the disease is low HVA and MHPG with normal 5-HIAA in CSF. Urine HVA and VMA may be fully normal. We have characterized 11 cases from 10 families and found mutations in the TH gene in 19 of the 20 alleles in all cases. In this presentation the clinical, biochemical and molecular genetic characteristics of the disease are presented.

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GENETIC ANALYSIS OF THE PARKINSONISM DEMENTIA COMPLEX OF GUAM AND EXCLUSION OF THE *TAU* GENE- HR Morris, R Crook, AJ Lees, NW Wood, J Hardy, JC Steele, J Perez-Tur. Institute of Neurology, Queen Square, London, UK

The parkinsonism dementia complex of Guam (PDC) is a neurodegenerative condition which involves the deposition of tau protein neurofibrillary tangles. We are engaged in a search for a genetic cause for PDC. The *tau* gene itself has recently been shown to be of importance in neurodegenerative tauopathies: both pathogenic mutations and a predisposition effect have been described. We have therefore evaluated the role of the *tau* gene and genetic locus in the development of PDC. We are studying the genotypes of 24 apparently unrelated cases and 20 controls in a genome wide association study, assuming that the genetic cause for the disease will be consistent among affected Guamanian Chamorros. Analysis of eight markers spanning a 30 centimorgan region around the *tau* gene, together with a ninth intragenic *tau* marker, the intronic marker described to be associated with progressive supranuclear palsy, showed no association effect between these markers and disease status. Additionally, direct sequencing of the *tau* gene in two affected and two control individuals revealed no sequence variation that could account for the disease. This study demonstrates a novel approach to the genetic analysis of neurodegenerative disease in an isolated population and excludes the involvement of the *tau* gene in PDC.

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TWO LARGE BRITISH KINDREDS WITH AUTOSOMAL DOMINANT PARKINSON'S DISEASE. N. L. Khan, P. Piccini, E. A. Graham, J. R. Vaughan, J. D. Gayton, D. Nicholl, D. J. Brooks, N. W. Wood. Institute of Neurology, London, UK- MRC Cyclotron Unit, Hammersmith Hospital, London, UK

We have identified two large British kindreds with autosomal dominant Parkinson's disease which is indistinguishable, both clinically and pathologically, from sporadic PD. An extensive genealogical search has been performed on both kindreds in order to detect further affected members. A novel approach using $_{18}$ Fluorodopa PET scans performed on unaffected relatives has been employed; those with statistically abnormal PET scans have contributed to linkage analysis. Genealogical data on kindred A is available over four generations and all members can be traced back to a family from the county of Lincolnshire. Affectation status in generations 1-3 has been based on historical account only. Twenty-five affected members have been identified; of which five are living today. In a further two members the diagnosis is inconclusive. The phenotype is identical to the sporadic form of PD with a mean age of onset of 53 (range 42-70 years) with asymmetrical rest tremor being the most common feature. PET stud-

ies have been statistically abnormal in both an affected and an unaffected member of this kindred. Genealogical data is available on kindred B across sixteen generations. Eight affected members in two generations have been identified; all are levodopa responsive, clinically and pathologically indistinguishable from sporadic PD with a mean age of onset of 64 years (range 42-53 years). PET studies have also been statistically abnormal in both an affected and an unaffected member in this family. This is a novel approach of using clinically unaffected members with statistically abnormal scans to contribute to linkage analysis in order to identify further PD loci.

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PARTIAL LAMININ α 2 IN DEFICIENCY IN A PATIENT WITH LEUCOENCEPHALOPATHY AND VACUOLAR MYOPATHY. Di Blasi Claudia, Nicolas Vignier, Morandi Lucia, Pareyson Davide, Sghirlanzoni Angelo, Guicheney Pascale, Mora Marina - Milano, Italy; Paris, France

It is becoming evident that clinical phenotypes associated with partial laminin α 2 deficiency are variable. We have recently observed a 29 year-old man patient with leucoencephalopathy and vacuolar myopathy resembling inclusion body myositis. Neurological examination revealed pes cavus, mild muscle weakness and wasting. CK levels were high. EMG revealed myopathic abnormalities and prolonged F-latencies; SEP latencies were prolonged. Muscle biopsy showed myopathic features, mononuclear cell infiltration and autophagic vacuoles. Filamentous nuclear inclusions were observed by electron microscopy. MRI showed diffuse and symmetrical signal hyperintensity (T2-weighted images) in supratentorial white matter and some broadening of the gyri. Laminin α 2 immunohistochemical analysis with two antibodies showed reduction of the protein on muscle fibers surfaces. Molecular analysis revealed two novel compound heterozygous mutations in the LAMA2 gene. These were: a missense mutation, a T→C transition at position 4405 in exon 29, and a nonsense mutation, a C→T transition at position 4645 in exon 31. The missense mutation affects a conserved cysteine-rich repeat of domain IIIa on the short arm of laminin α 2 chain. Although this change should result in normal synthesis of the α 2 chain and formation of the heterotrimeric laminin molecule, it is likely to cause protein instability or increased proteolysis sensitivity. This is the first report linking a mutation in the LAMA2 gene with leucoencephalopathy and inclusion body-like myositis.

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α•-SYNUCLEIN MUTATION ASSOCIATED WITH FAMILIAL PARKISON'S DISEASE IN TWO NEW GREEK KINDRED. S. Veletza*#, S. Bostatzopoulou+, G. Hantzigeorgiou#, A. Kazis+ and A. Papadimitriou#. *Hellenic Red Cross and #Red Cross Hospital, Athens, +Papanikolaou Hospital, Thessaloniki, Greece

We report two Greek kindred with early onset familial Parkinson's Disease (PD), presenting the autosomal dominant mode of inheritance, who carry a G209A mutation at exon 4 of the α-synuclein gene. In family I two siblings, carry the mutation, whereas PD has been known in two generations, that is to both the siblings and their father. In family II, also two siblings with PD were affected; both carry the mutation, whereas the disease had been pronounced in their father and paternal aunt. The disease was manifested at ages 38, 39, 47 and 49, respectively. Both families originate from the area of Larissa, in Central Greece and are apparently unrelated, whereas in previously reported kindred both by our group (2 families) and by others (5 families), Greek families originate from the same greater area of Southern Greece. This finding brings the total number of PD families with the mutation up to 9, worldwide. As numerous persistent efforts of scientific teams could not identify the mutation in any PD families in Europe or the US (with the exception of the Southern Italian Contursi family), the presence of the G209A mutation and its association with PD seems to refer almost exclusively to Greek families. This raises the possibility of founder effect. We are also planning a large scale epidemiological study in the Greek population.

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MUTATIONS IN LAFORA ASSOCIATED PROTEIN TYROSINE PHOSPHATASE (LAFPTPASE) IN PROGRESSIVE MYOCLONUS EPILEPSY OF THE LAFORA TYPE. JM Serratosa[1], P Gómez-Garre[1], ME Gallardo[1], B Anta[1], D Beltrán-Valero de Bernabé[1], D Lindhout[2], PB Augustijn[3], CA Tassinari[4], R Michelucci[4], A Malafosse[5], M Topcu[6], D Grid[7], C Dravet[8], SF Berkovic[9] and S Rodríguez de Córdoba[1]. [1]Madrid, Spain, [2]Rotterdam, The Netherlands, [3]Heemstede, The Netherlands, [4]Bologna, Italy, [5]Geneve, Switzerland, [6]Ankara, Turkey, [7]Evry, France, [8]Marseille, France and [9]Melbourne, Australia

Progressive myoclonus epilepsy of the Lafora type or Lafora disease (EPM2) is an autosomal recessive disorder characterized by epilepsy, myoclonus, progressive neurological deterioration and glycogen-like intracellular inclusion bodies (Lafora bodies). We have recently cloned a gene responsible for the majority of EPM2 patients. This gene encodes LAFPTPase, a protein with amino acid sequence identities to protein tyrosine phosphatases (PTPases). METHODS: Thirty-eight families with the clinical diagnosis of EPM2 and a biopsy of skin, muscle, liver, or brain showing the characteristic periodic acid-Schiff-positive Lafora bodies were screened for mutations by SSCP and direct sequencing. RESULTS: We describe three new mutations in the EPM2 gene encoding LAFPTPase: a homozygous loss-of-function mutation consisting of the sustitution of a C to a G changing a tyrosine residue to a stop codon (Y5fs) and 2 missense mutations (F3L and G159L). CONCLUSION: Our findings provide further evidence that progressive myoclonus epilepsy of the Lafora type results from the mutational inactivation of a PTPase activity that may be important in the control of glycogen metabolism.

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MUTATIONS IN THE SCHWANN CELL TRANSCRIPTION FACTOR *EGR2/KROX-20* IN PATIENTS WITH SEVERE HEREDITARY DEMYELINATING NEUROPATHIES. Taroni F., Botti S., Fiocco R., Sghirlanzoni A., Ciano C., Nemni R., Riva D., Pareyson D., Mostacciuolo M. L. ; Milan, Italy; Padua, Italy.

Hereditary demyelinating neuropathies are a heterogeneous group of disorders usually associated with mutations in the *PMP22*, *MPZ*, and *Cx32* genes. In a number of patients, however, no alterations in these genes can be found. We have screened 30 patients from this group for mutations in the *EGR2* gene. This gene, also known as *Krox-20* in the mouse, encodes a zinc-finger protein which is thought to be a transcription factor involved in the myelination of PNS and in the regulation of hindbrain development. Sequence analysis of *EGR2* uncovered two novel mutations in two patients. Pt 1 was a child with Dejerine-Sottas disease (DSD). Sural nerve biopsy showed dramatic loss of myelinated fibers with numerous basal-lamina onion bulbs. Interestingly, he had signs of 5th and 7th cranial nerve involvement. This patient carried a *de novo* dominant missense mutation (R359W). Pt 2 was an adult with an autosomal dominant early-onset form of CMT1. His daughter was similarly affected. Notably, he also exhibited signs of cranial nerve involvement with diplopia and vocal cord palsy. Both patients from this family were heterozygous for a dominant missense mutation (R381H). SSCP analysis of the zinc-finger region showed an abnormal migration pattern in two other patients, one with CMT1 and one with DSD. Sequence analysis is under way. These results confirm the crucial role of EGR2 in myelinogenesis and show that, as observed in the *Krox-20* KO mouse, *EGR2* mutations may also cause cranial nerve involvement, consistent with a role of this gene in human hindbrain development. Furthermore, the data extend the phenotypic spectrum of *EGR2* mutations to include DSD. Mutation analysis in a number of additional families is under way. (Telethon grant to F. T.)

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MUTATIONS OF SURF-1 GENE IN CYTOCHROME- C- OXIDASE DEFICIENCY. Tiranti V, Galimberti C, Carrara F, Lamantea E, Hoffmann S, Meitinger T, Bertini E, Comi G, Uziel G, M. Zeviani - Milano, Roma. (Italy); München (Germany)

We have recently identified mutations of SURF-1, a gene located on chromosome 9q34, in patients affected by Leigh syndrome (LS), or subacute necrotizing encephalomyelopathy, associated with deficiency of cytochrome c oxidase (COX), the terminal component of the mitochondrial respiratory chain. To invbestigate to what extent SURF-1 is responsible for LS $_{COX}$, or other human disorders due to COX deficiency, we undertook sequence analysis of the SURF-1 gene in 46 unrelated patients. Frameshift, stop, and splice mutations of SURF-1 were detected in 18/24 (75%) of the LS $_{COX}$ cases. No mutations were found in the LL $_{COX}$ and non -LS $_{COX}$ group of patients. Rescue of the COX phenotype was observed in transfected cells from patients harbouring homozygous and heterozygous mutations, as well as in three patients with a mutation found in a single allele. By contrast, no complementation was observed in transfected cell lines from one LS $_{COX}$ - and one LL $_{COX}$ - patient, in both of

whom no mutations were detected by sequence analysis. Loss- of-function of SURF-1 protein is specifically associated with LS_{COX}, although a proportion of LS_{COX} cases must be due to abnormalities in gene (s) other than SURF-1. SURF-1 is the first nuclear gene to be consistently mutated in a major category of respiratory chain defects. DNA analysis can now be used to accurately diagnose LS_{COX}, a common subtype of Leigh syndrome.

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TUBEROUS SCLEROSIS GENE 2 (TSC2) DEFECTS CORRELATE WITH A MORE SEVERE NEURO-CUTANEOUS PHENOTYPE THAN TSC1. N. Migone, L. Longa, S. Polidoro, S. Padovan, A. Allavena, A. Brusco, E. Grosso, M. Ruggieri, C. Carbonara. Dept. of Genetics, Biology and Biochemistry, Torino University, Italy; and the Italian TSC collaborative group.

We investigated the genotype-phenotype correlation in 51 TSC families assigned to either *TSC1* (16) or *TSC2* (35) by protein truncation test, LOH, heteroduplex analysis, fluorescence assisted mismatch analysis and southern blot. Interestingly, the large majority of *TSC1* probands had one or more affected relatives (13 of 16), whereas most *TSC2* probands appeared sporadic (25 of 35; $p < 0.01$). This phenomenon suggested a lower fitness of *TSC2* mutations compared to *TSC1*. Including the affected relatives, the clinical data from 40 *TSC1* and 48 *TSC2* patients were available for the analysis. Overall, *TSC2* patients showed a higher prevalence of mental disabilities (60% vs. 23%, $p < 0.01$; this difference persists (P=0.03) if we consider only sporadic patients), retinal hamartomas (37% vs. 9%; P=0.01) and facial angiofibromas (73% vs. 45%; P=0.01). The age distribution at the neurocutaneous examination and the possible bias of proband selection in the multiplex families did not seem to account for such findings. *Work supported by the "Associazione Emma & Ernesto Rulfo per la Genetica Medica" and by Telethon, Italy (Project E. 730).*

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IDENTIFICATION OF SIX NOVEL MISSENSE MUTATIONS IN THE HUMAN SPHINGOMYELINASE GENE (SMPD1) IN GERMAN PATIENTS AFFECTED WITH NIEMANN-PICK TYPE B DISEASE. Rolfs, Arndt (1), Hufen, Antje (1), Harzer, Klaus (2), Bauer, Peter (1). (1) Klinik für Neurologie, Universität Rostock, Rostock, Germany; (2) Institut für Hirnforschung, Universität Tübingen, Tübingen, Germany; Study supported by Genzyme., Germany (Dr. Stefan Maeser)

Niemann-Pick type B disease (NP-B) phenotype represents the visceral variant of the deficiency of sphingomyelinase (SMPD1). NP-B is characterized by hepatosplenomegaly, pulmonary infiltrations and impaired vision. Biochemically, the patients lack sufficient activity of sphingomyelin phosphodiesterase 1 (SMPD1) which usually catalyzes the cleavage of sphingomyelin to phosphorylcholine and ceramide. Genetically, SMPD1 coding sequence with an open reading frame of 1509 bp is covered by six exons within the locus. Up to now, 11 missense and four nonsense mutations clustering in exon 2 and 6 are described. We have completely sequenced SMPD1 from leukocyte preparations obtained from three individuals affected with NP-B. Patient 1 shows heterozygousity at Val36Ala and Gly245Ser, patient 2 is heterozygous for Arg289Val and Arg440Ter and patient 3 is homozygous for a 6 bp deletion Val36 and Gly292Lys. Thus, six novel missense mutations could be detected in our patients. Val36Ala and 6 bp deletion Val36 are the only known mutations in exon 1 so far. Since up to now no curative therapy is available for NP-B patients, direct sequencing of SMPD1 in patients and affected families represents a valuable tool for genetic counseling and prenatal diagnostics. as well as genotpye-phenotype correlation studies.

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TWO NOVEL MUTATIONS IN SPANISH PATIENTS WITH MCARDLE`S DISEASE. J. Gamez, AL. Andreu, C. Cervera, C, Bruno, R. Fernandez, C. Navarro, S. Schwartz, S. DiMauro. Barcelona, Spain. New York. USA.

Miophosphorylase deficiency (McArdle`s disease) is a common muscle glycogenosis that typically affects young adults and causes exercise intolerance, myalgia, cramps and episodic myoglobinuria. The myophosphorylase gene has been cloned, sequenced, and assigned to chromosome 11. Recent molecular genetic studies have identified more than fifteen different mutations in patients with McArdle`s disease. The nonsense point mutation in exon 1 (R49X) accounts for approximately 80% of mutant alleles in American and British patients, but appears to be less common in other ethnic groups. A correlation between the phenotype and genotype is not clearly demonstrated in this disease, although some mutations are correlated to specific clinical types. Objective: We present two novel mutations causing McArdle's disease. Methods: Two unrelated male patients, aged 28 and 55 years. They showed myalgia, exercise intolerance and high CK levels. The diagnosis was established by histochemical demonstrations of myophosphorylase deficiency in muscle biopsies. Genomic DNA was extracted from leukocytes and amplified by polimerase chain reaction (PCR). Digestion with diagnostic restriction enzymes for restriction fragment length polymorphism (RFLP) analyses and sequencing were performed by described methods (*Tsujino*). We screened for all previously described genetic errors. Results: We found two new mutations: A missense point mutation at codon 115 in exon 3. This changes an encoded leucine to a proline . The second mutation was a missense mutation at codon 684 in exon 17. This changes an encoded asparagine to a tyrosine. Conclusions: This study confirms the molecular heterogeneity of McArdle`s disease. Further studies are necessary to characterise these specific mutations and determine their correlation with ethnic origin.

Functional imaging

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VESTIBULAR CORTEX: DOMINANCE OF THE NON - DOMINANT HEMISPHERE (PET STUDY). M. Dieterich[1], S. Bense[1], Th.,Brandt[1], M. Schwaiger[2], P. Bartenstein[2] . Departments Of [1]Neurology, Ludwig-Maximilians-University Munich, And [2]Nuclear Medicine, Technical University Munich, Germany

The posterior insula and retroinsular regions are the human homologues of the parieto-insular vestibular cortex (PIVC) in monkeys which is apparently an integration center for several multisensory vestibular areas of the temporoparietal cortex. In an earlier PET activation study monaural vestibular stimulation induced a bilateral activation of cortical and subcortical areas. The aim of this PET study was the functional differentiation of vestibular and ocular motor activity with respect to hemispherical dominance. Therefore, seven right-handed and seven left-handed (laterality quotient –100 to –80; Edinburgh inventory test) healthy volunteers were examined in a Siemens 951 R/31 PET scanner using a O-15 water-bolus technique. Vestibular stimulation was induced by caloric irrigation of the right or left ear (100ml water at 44°C). The data were realigned, anatomically standardized in the stereotaxic Talairach space, and smoothed before statistical group analysis (SPM96 software package). Caloric irrigation caused bilateral activation that was mainly localized in the middle and posterior parts of the insula and the adjacent temporoparietal cortex of the *non-dominant* hemisphere in all 14 subjects, independently of which ear was stimulated. These activated areas include, e. g., the PIVC, visual posterior sylvian area, areas 6 and 7. Conversely, insular activation showed a

significant right hemispherical dominance in the right-handed (1152 vs 57 voxels) and left-hemispherical dominance in left-handed subjects (621 vs 0 voxels). This PET study clearly shows a hemispherical dominance of the non-dominant hemisphere for cortical processing of vestibular information.

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FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) OF THE HUMAN SENSORIMOTOR CORTEX DURING WHOLE-HAND AFFERENT ELECTRICAL STIMULATION. S. Golaszewski[1], M. M. Dimitrijevic[3], Ch. Kremser[1], F. Zschiegner[2], M. Hackel[1], S. Lechner-Steinleitner[2], M. Berger[2], F. Gerstenbrand[2], F. Aichner[1,2], S. Felber[1], M. R. Dimitrijevic[3]. [1]Depts of Magnetic Resonance and [2]Neurology, University, Innsbruck, 6020, Austria. [3]Division of Restorative Neurology and Human Neurobiology, Baylor College of Medicine, Houston, Texas

In this fMRI study we wanted to find a new paradigm for fMRI studies of the sensorimotor cortex in stroke patients for monitoring of the poststroke rehabilitation and understanding of the mechanisms of poststroke motor recovery. With active motor paradigms these studies are often difficult to perform because of impairment of motor functions. Therefore, for the fMRI evaluation of stroke sensory electrical stimulation would be of great importance, because the collaboration of the subject under examination is not requested. Methods, Results: All experiments were performed on a 1.5 Tesla MR-scanner (Magnetom VISION, Siemens, Germany) with an echo planar imaging sequence. For electrical stimulation of the right whole-hand, a mesh-glove and a two-channel stimulator (Medtronic Model 3128 Respond II) was used. A first fMRI measurement was performed with electrical stimulation until the right forearm flexors showed rhythmical contractions with a frequency of 2 Hz. Then we performed a second fMRI measurement with finger-to-thumb tapping. Eight healthy, right handed male and female volunteers (age range 20 - 45 years) were included in the study. Data analysis was performed using SPM96. In six out of the eight subjects contralateral activation of the primary motor cortex (MI) within the gyrus precentralis, the primary somatosensory cortex (SI) within the gyrus postcentralis, the frontal cortex ventral to the MI area within the superior and middle frontal gyrus, which can be associated with the prefrontal cortex (PFC) and the somatosensory association cortex (SII) corresponding to the caudal parietal operculum and the anterior part of the superior parietal lobule was found. An ipsilateral activation focus was seen within the SI, SII and PFC cortex, which was weaker but nevertheless well pronounced. The strongest activation was found within the contralateral SI and SII followed by the MI. Subject 7 had activation only within the contralateral SI and SII and Subject 8 showed only a weak activation spot within the contralateral SI. Conclusion: Whole-hand afferent electrical stimulation on motor level for the forearm flexors can elicit cortical activation within main areas of the sensorimotor cortex such as SI, SII, MI and PFC similar to active motor paradigms such as finger-to-thumb tapping but without the need of the collaboration of the patient. The SI, SII and PFC is activated even bilaterally. Thus, this kind of electrical stimulation may be an alternative paradigm in fMRI testing of sensorimotor functions in poststroke patients or patients with severe motor deficits. The ipsilateral activations of sensorimotor cortex may be due to callosal projections from contralateral somatosensory cortex. In this case, whole-hand afferent electrical stimulation can be used as paradigm for testing corpus callosum functions for instance in posttraumatic vegetative state for the prediction of the recovery in addition to conventional cerebral MRI.

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DIFFERENT FMRI ACTIVATION PATTERNS OF AUTOMATED AND NON-AUTOMATED HANDWRITING MOVEMENTS. [1]I. Yousry, [1]M. Wiesmann, [1]A. Nolte, [2]T. Schenk, [1]G. Fesl, [1]T. A. Yousry, [2]N. Mai. [1]Department of Neuroradiology, [2]Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians University Munich, Germany

Automated movements such as normal handwriting are characterized by invariant features in the kinematic analysis. In contrast, non-automated movements are associated with irregular and multiple peaked velocity profiles. We questioned whether automated movements involve different areas of the brain than non-automated movements in functional magnetic resonance imaging (fMRI). Methods: The task for automated movements was to draw circles (1cm diameter) at normal writing speed in the scanner (1.5 T). For non-automated movements the subjects had to mentally track the curve of the circle, concentrating on the top of it. We trained 11 healthy right- handed volunteers until the kinematic criteria were stable. fMRI was performed using echo-planar sequences. Image analysis was performed using SPM. Results: Group analysis showed clear differences between automated and non-automated movements. During the non-automated task there was significant additional activation on the right (ipsilateral) hemisphere in the precentral and postcentral gyri. On the left (contralateral) hemisphere there was additional activation in the precentral, middle frontal and middle occipital gyri. Conclusion: This is the first study to demonstrate significant differences between automated and non-automated movements as defined by kinematic parameters. Such analysis might help to identify motor problems in neurological patients and monitor these patients during treatment.

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EXAMINATION OF CORTICAL CONNECTIVITY WITH TRANSCRANIAL ELECTRICAL STIMULATION (TES) DURING FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI). Brandt SA, Niehaus L, Röricht S, BrockeJ, Ploner CJ, Villringer A, Meyer BU. Department of Neurology, Charité, Berlin, Germany.

This is an attempt to further our studies about assessment of local brain activation elicited by TES and simultaneous fMRI. Distant effects on functionally connected areas, effects of stimulus intensity and location of stimulation electrodes were examined. Four healthy volunteers were scanned at 1.5 T (Siemens Vision) with echo-planar imaging (18 axial slices). TES (Digitimer D180) was performed with 0.5 Hz over the hand area of the right motor cortex at intensities below and just above the motor threshold. The anode was placed over the hand area and the cathode either over the vertex or 4 cm anterior to the hand area. Activations were evaluated with a cross-correlation analysis using the BrainVoyager® software. During suprathreshold TES over the right primary motor cortex a transient signal intensity increase in T2*-weighted images in the area beneath the electrodes was observed. Further stimulus correlated activation was found contralaterally to the stimulation site in the somatosensory cortex of the left hemisphere, the supplementary motor areas, bilaterally in primary somatosensory cortex, the basal ganglia and thalamus. Thus we were able to elicit distant stimulation effects in functionally connected areas. Distant effects may be due to transcallosal and cortico-cortical spread of excitation. TES during fMRI might be a suitable tool for studying functional connectivity in the human brain.

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FUNCTIONAL BRAIN MAPPING OF LANGUAGE AREAS BY MEANS OF A LEXICAL DECISION TASK. Gianpaolo Basso[1], Maria Luisa Gorno Tempini[1], Giovanna Calandra[1], Marco Serafini[2], Giuseppe Pagnoni[1], Luciano Mavilla[2], and Paolo Nichelli[1] - [1]Universita' degli Studi di Modena e Reggio Emila, Modena; [2]Azienda Policlinico, Modena.

Language localization is important in presurgical assessment of brain tumors and epilepsy. We developed a lexical decision task to explore the sensitivity of functional magnetic resonance imaging (fMRI) in the localization of language related areas in single subjects. Three females and three males, (right handed; age range: 23-36 years) were asked to discriminate between real words and pseudowords by pushing or pulling a small lever with their right hand. On a control task, subjects discriminated between strings of either japanese graphemes or italian consonants. All strings were composed of 7 characters. Words were composed of three syllables and were controlled for frequency and imageability. Each subject performed 8 runs during which lexical decision and control tasks alternated 3 times every 33 s. Data analysis was performed with SPM96. Group analysis showed activity in the left inferior frontal, left middle temporal, left SMA and bilateral occipital gyrus. Single subject analysis revealed highly significant activity in the left middle temporal gyrus in 6 subjects (100%) and in the left inferior frontal gyrus in 5/6 subjects. We suggest that the task developed is a sensitive method to localize language in single subject. We are currently extending the sample to confirm our results.

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THE SPATIAL FUNCTIONS OF THE PARIETAL CORTEX IN VISUAL PERCEPTION AND IMAGERY: AN FMRI STUDY OF THE MENTAL CLOCK TEST. D. E. J. Linden, F. Di Salle, E. Formisano, D. Grossi, H. Steinmetz, R. Goebel, L. Trojano. Department of Neurology, Johann-Wolfgang-Goethe-Universität, Frankfurt-am-Main, Germany.

Parietal lobe lesions often affect the patients' capacity for visuospatial analysis and imagery. We used functional magnetic resonance imaging (fMRI) to determine whether areas in the parietal lobe that have been im-

plicated in the spatial transformation of visual percepts are also activated during the generation and spatial analysis of imagined objects. Methods. FMRI was performed at 1.5 Tesla on a Siemens Magnetom Vision clinical scanner (TE=66ms; TR=5s;FA=90°;voxel-size=1.6x1.6x5mm^3;15 axial slices). Functional time-series were analysed and visualized using the BrainVoyager software package (Goebel 1998). Subjects were presented acoustically with pairs of clock times and required to choose the one in which the hour and minute hand formed the smaller angle. Task- difficulty was varied parametrically. Results. Spatial operations on mental representations were accompanied by a robust and specific activation along the intraparietal sulcus and in the prefrontal cortex in both hemispheres. The strength of this activation increased with increasing difficulty of the spatial matching task. The difficulty-matched non-spatial control task showed the same activation pattern in the prefrontal cortex, but no significant activation of the parietal lobes. Conclusions. Our results clarify the nature of top down processes in the dorsal stream of human cerebral cortex and provide evidence for a specific convergence of the pathways of imagery and visual perception within the parietal lobes.

Extrapyramidal disorders – 1

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REDUCED STRIATAL DOPAMINE TRANSPORTERS IN IDIOPATHIC REM SLEEP BEHAVIOR DISORDER. Eisensehr I[1], MD, Linke R[2], MD, Tatsch K[2], MD, Noachtar S[1], MD. Department of Neurology[1], Department of Nuclear Medicine[2], Klinikum Grosshadern, Ludwig-Maximilians University, Munich, Germany

REM sleep behavior disorder (RBD) is characterized by complex behavior and lack of skeletal muscle atonia during REM sleep. The underlying cause is yet unknown, but a recent prospective study showed that 38% of the patients with RBD eventually developed Parkinson's disease (PD). Therefore we studied central pre- and postsynaptic dopamine receptor density in patients with idiopathic RBD. We investigated the striatal postsynaptic dopamine D2-receptor occupancy with ^{123}I labeled (S)-2hydroxy-3iodo-6-methoxy-(1-ethyl-2-pyrrolidinylmethyl) benzamide (123I-IBZM) and the presynaptic dopamine reuptake site occupancy with ^{123}I labeled (N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane (123I-IPT) using the single photon emission computer tomography (SPECT). Five patients (4 men, 1 woman, mean age: 68.5 a 7.5 a) with polysomnographically confirmed RBD and 7 age- and sex-matched controls without a specific history for any sleep disorder were participating the study. All RBD patients had significantly reduced mean specific uptakes of IPT in the striatum (S), caudate (NC) and putamen (P) (RBD: 2.81 ± 0.44 to 3.44 ± 0.45 vs comtrols: 4.31 ± 0.18 to 4.72 ± 0.28, $p < 0.001$). IBZM uptakes were not significantly lower in the RBD group ($p < 0.07$). Striatal dopamine transporters are usually reduced in PD. This study for the first time demonstrates reduced striatal dopamine transporters as possible pathophysiologic mechanism for idiopathic RBD. Results are given as mean SD

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STRIATAL 1H-MAGNETIC RESONANCE SPECTROSCOPY (MRS) IN TARDIVE DYSKINESIA AND DYSKINETIC PARKINSON'S DISEASE (PD). H Wilson, C Ellis, A Simmons, SCR Williams, B Toone, PN Leigh, K Ray Chaudhuri. London, UK.

Objective: To assess whether there is MRS evidence of striatal neuronal dysfunction in schizophrenic patients rendered dyskinetic following neuroleptic use and comparison with a group of dyskinetic PD patients on chronic l-dopa therapy. Background: The pathogenesis of tardive dyskinesia (TD) arising from neuroleptic use remains obscure In PD dyskinesia also occurs although secondary to dopamine simulation by chronic l-dopa therapy. Although striatal alterations in N acetyl aspartate (NAA), thought to be a neuronal marker, have been reported in PD, similar studies have not been reported in tardive dyskinesia. Methods: We studied 7 schizophrenic patients with TD (Shooler and Kane Criteria) with a mean age of 44.8 ± 11.5, 7 PD patients with dyskinesia, mean age 58 ±13, and 8 controls, mean age 48 ±10 using single voxel proton MRS (1.5T GE Signa system, TR=200ms, TE=136ms, 256 averages, 2048 points, PRESS pulse) localised to the putamen bilaterally. Peak areas and ratios were determined for NAA, choline (Cho) and creatine and phosphocreatine (Cr + PCr). Data were analysed using SAGE/IDL software. Results: There were no significant differences from the putamen in NAA/Cho, NAA/Cr+PCr and Cho/Cr+PCr between TD, PD and controls. Conclusion: Putaminal NAA levels in dyskinetic PD patients and schizophrenic patients with TD are not significantly different from those in healthy volunteers.

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ANXIETY, DEPRESSION, AND PARKINSON'S DISEASE: A POPULATION-BASED CASE-CONTROL STUDY. Rocca WA*, Shiba M*, Bower JH**, Maraganore DM**. Department of *Health Sciences Research and **Neurology, Mayo Clinic and Mayo Foundation, Rochester, MN, U. S. A.

The purpose of this study was to investigate the association between preceding psychiatric disorders and Parkinson's disease (PD). We studied 196 incident cases of PD in Olmsted County, MN between 1976 and 1995 and 196 age- and sex-matched controls from the same population. We used the medical records-linkage system of the Rochester Epidemiology Project to detect psychiatric disorders preceding the onset of PD (or the index year for controls). All medical records were reviewed by a psychiatrist using DSM-IV criteria. The frequency of anxiety disorder and depression was higher in cases than in controls; the odds ratio was 2.3 for anxiety disorder (confidence interval = 1.5 - 3.6; p value = 0.0002) and 2.1 for depression (confidence interval = 1.2 - 3.6; p value = 0.008). When we restricted our analyses to disorders present five years or more before the onset of motor symptoms of PD (prodromal period), only the association with anxiety disorders remained significant. Our results indicate that anxiety disorder may be either a risk factor for PD or an early non motor manifestation of PD. By contrast, since depression occurred more commonly within the prodromal period, it is more likely an early manifestation of PD.

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THE PREVALENCE OF DYSTONIA IN EUROPE. TT Warner and Y Ben-Shlomo on behalf of the Epidemiological Study of Dystonia in Europe (ESDE). London, UK.

There have been few epidemiological studies of dystonia, the majority of which rely on estimates based on a small number of cases. The Epidemiological Study of Dystonia in Europe (ESDE) was established to produce stable, precise but conservative prevalence rates of dystonia. Ascertainment was based on diagnosed cases by neurologists with specialist movement disorder (and botulinum toxin) clinics. Ten European centres in eight countries covering a population of 5.7 million participated. The crude prevalence rate for primary dystonia was 152 per million (95% CIs 142-162). Prevalence rates per million for generalised, multifocal and segmental dystonia were 0.9 (0.3 to 2.0), 2.4 (1.3 to 4.1) and 31.6 (27.2 to 36.5) respectively. The commonest form of dystonia was focal with rate of 117 per million (108-126). The overall prevalence rates for cervical dystonia, blepharospasm and writer's cramp were as follows: 57.0 (51.0 to 63.5), 35.6 (30.9 to 40.8), and 13.6 (10.8 to 17.0). The age-adjusted relative rates for women compared to men were significantly elevated for segmental and focal dystonias with the exception of writer's cramp. The ESDE prevalence estimates are the most precise currently available for primary dystonia and its subtypes, and are comparable with previous studies in the world literature. Due to under-ascertainment of cases, the rates presented should be seen as conservative and an under-estimate of the true prevalence of dystonia.

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CLINICAL DIFFERENCES BETWEEN TARDIVE AND IDIOPATHIC CERVICAL DYSTONIA. V. Kiriakakis, E. Caputo, K. P. Bhatia, N. P. Quinn, C. D. Marsden. Institute of Neurology, Queen Square, London, UK.

Tardive dystonia (Tdyt) is the most common cause of secondary dystonia and the cervical region is most commonly involved. Despite the belief that Tdyt is phenomenologically indistinguishable from primary (idiopathic) dystonia, recent reports have suggested that there may be differences between the two conditions. The aim of our study was to compare these two disorders in a large cohort of patients. We therefore reviewed the medical records of 69 patients with tardive and 425 with idiopathic cervical dystonia seen in our movement disorders clinic between 1972 and 1996. There was no difference in the mean follow-up time from dystonia onset between the two groups. There were more females in idiopathic (58%) than in tardive group (42%, p = 0.02). Rotational torticollis was more common in the idiopathic group (90% versus 81%, p = 0.04) with left-sided predominance of rotation (in 60%) compared with right-sided predominance in the tardive group (70%; Odds Ratio 3.5, 95% Confidence Interval 1.8-6.7, p = 0.0002). Retrocollis was more common in tardive than in idiopathic group (36% vs. 22%, OR 2, 95% CI 1.2-3.4, p = 0.01) as also was anterocollis (33% vs. 10%, OR 4.3, 95% CI 2.4-7.8, p < 0.0001). Extracervical involvement was found in 88% of the tardive and 24% of the idiopathic

group ($p < 0.0001$). These differences between tardive and idiopathic cervical dystonia may help to improve diagnostic accuracy and to better understand the pathophysiology of these disorders.

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DETERIORATION OF DYSTONIA AFTER HYPOXIC-ISCHEMIC DAMAGE OF THE STRIATUM. S. Sangla, G. Gallouedec, S. Bakchine[1],J. M. Netter[2], E. de Ferron[3], M. Vidailhet. Neurology departments Saint-Antoine Hospital, 1-Salpétrière Hospital, 2-CCN, 3-Nantes Hospital. France.

We analysed, on a long term follow-up, the clinical characteristics and the pattern of evolution of six patients presenting a dystonic syndrom after a hypoxic/ischemic injury. Patients and methods: Mean age at onset was 32 years, the follow-up was 6.6 years (range 2-17). Hypoxy/ischemy was secondary to cardiac arrest associated with drug abuse, asthma, wasp sting and cardiac surgery (n=2). The pattern of distribution and progression of dystonia was assessed once a year and sequencial video recordings were taken . Analysis of the striatum lesions on MRI was performed. Results: Dystonia appeared after recovery from hemiparesis. Delay of onset of dystonia was one year. Dystonic postures were initially unilateral, in the upper limb. We observed: a) worsening of the initial posture, b) spreading to the lower limb, c) involvement of the controlateral side. The sequence could take up to 4 years. Akinesia with severe freezing was present at onset of dystonia (n=1) or could appeared later (n=1). MRI showed bilateral lesions of the striatum, more pronounced in the putamen. Conclusions: Despite a "static" hypoxic-anoxic damage, the dystonia is worsening over the years and could be associated with akinesia, freezing and postural instability. These various movement disorders could be related to secondary neurodegeneration and/or striatal reorganisation as observed in animals.

Extrapyramidal disorders – 2

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GROWTH-HORMONE RESPONSE TO APOMORPHINE - A SIMPLE TEST TO DIFFERENTIATE IDIOPATHIC FROM NON-IDIOPATHIC PARKINSON SYNDROMES. E. Friess, MD, T. Kümpfel, MD, J. Winkelmann, MD, D. Schmid, F. Holsboer, MD, PhD, R. Rupprecht, MD, and C. Trenkwalder, PhD. Max-Planck-Institute of Psychiatry, Neurological Department, 80804 Munich, Germany

The early distinction of Parkinson's disease (PD) from parkinson syndromes (PS) of other etiologies gains growing importance with respect to putative neuroprotective agents. We investigated the dopaminergic sensitivity in patients with "de novo" PS through measurement of the growth hormone (GH) response to a subthreshold dose of the D1/D2-receptor agonist apomorphine (0.005mg/kg BW s. c.). The study group consisted of 10 patients clinically diagnosed as PD (7m, 3f; 61.2±13.4 yrs), 10 as multiple system atrophy (MSA, 3m, 7f, 64.±7.1 yrs) and 11 healthy controls (6m, 5f, 58.3±11.3 yrs). The enhanced maximum GH release significantly differentiated the patients with PD from patients with MSA and the control group (45min. p. i.; PD: 8.6±5.9ng/ml; MSA: 2.5±2.6ng/ml; HC: 2.4±1.6 ng/ml; p=0.001, ANOVA). Interestingly, we found no significant group differences in the release of prolactin, cortisol or adrenocorticotropin, nor in the GH release to a higher dose of apomorphine (3mg s. c.) or to growth hormone releasing hormone (1µg/kg BW i. v.). Thus, the GH response within the "low-APO-test" appears to be a useful tool to identify the specific deficit of the central dopaminergic systems in PD versus MSA patients suggesting that an hypersensitivity of the extrastriatal dopamine receptors seemed to present only in PD.

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DIFFERENTIATION OF ATYPICAL PARKINSONIAN SYNDROMES WITH ROUTINE MRI. A Schrag[1], T Good [2], C Miszkiel[2], Morris H [2], CJ Mathias[1], AJ Lees', NP Quinn[1]. 1 - Dept. of Clinical Neurology, 2 - Dept. of Neuroradiology, 3 - Autonomic Unit, Institute of Neurology, Queen Square, London, UK

We evaluated the value of abnormal findings in the basal ganglia, the midbrain, and supra and infratentorial structures on routine magnetic resonance imaging in differentiating between progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and control subjects. Two neuroradiologists blindly and independently rated axial T2-weighted and proton density MRI scans of 54 patients with MSA, 39 patients with PSP, and 44 controls. High field (1.5 T) scans were available in 23 MSA patients, 15 PSP patients and 14 controls. All other patients had 0.5 T scans. More than 70% of patients with PSP and more than 80% of patients with cerebellar predominant MSA could be correctly classified with 0.5 or 1.5 T scans, and no patient in these groups was misclassified. In the remaining patients an unequivocal differentiation could not be made. However, only about 50% of patients with parkinsonism-predominant MSA could be correctly classified and 19% of them (all of whom had had 0.5 T scans) were misclassified. We conclude that specific findings on routine MRI can contribute to the identification of MSA and PSP. However, in a minority of patients no unequivocal diagnosis can be made using MRI findings alone.

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DONEPEZIL FOR THE TREATMENT OF DYSKINESIAS IN PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE (IPD). Catherine ML Foy, Harvey J Sagar. Section of Clinical Neurology, Royal Hallamshire Hospital, Sheffield, UK.

IPD is associated with a reduction in striatal dopamine. Dopamine replacement therapy inhibits acetylcholine release leading to hypoactivity of cholinergic neurones and this has been associated with dyskinesia. Attention and sleep may also be affected by disruption of these neurotransmitter systems. We assessed the effect of donepezil, an acetylcholinesterase inhibitor, on motor control, sleep and attention in patients with IPD and dyskinesia. Thirteen dyskinetic patients with IPD were studied. Patients were treated with 5mg of donepezil for 2 weeks. Other treatment was maintained. Tests took place before treatment commenced (visit 1), after 2 weeks of treatment (visit 2) and 2 weeks after withdrawal of treatment (visit 3). Assessments included the Unified Parkinson's Disease Rating Scale (UPDRS), the Goetz Scale for measurement of dyskinesias, a sleep diary over 4 nights and the Triesman's test of attention. On donepezil, the patients showed a reduction in dyskinesia ratings on the UPDRS and Goetz scale ($p < 0.05$) but the duration and severity of off periods did not alter ($p > 0.05$). Total UPDRS score showed no change ($p > 0.05$). Donepezil also increased sleep duration ($p < 0.01$) and improved reaction time on Triesman's test ($p < 0.005$). The benefits reversed on drug withdrawal. Test practice effects were excluded by the effects of drug withdrawal and also serial testing in control subjects. Donepezil improves dyskinesia, sleep and attentional deficits in IPD without compromise to motor control.

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INTRACEREBRALLY GRAFTED NEURONAL PROGENITOR CELLS (ST14A) EXPRESS NEURONAL MARKERS AND AMELIORATE ROTATIONAL BEHAVIOR IN A RAT MODEL OF PARKINSON DISEASE. Bauer, Peter (1), Haas, Stefan (2), Weinreich, Carola (2), Koblich, Rupert (1), Cattaneo, Elena (3), Benecke, Reiner (1), Wree, Andreas (2) and Rolfs, Arndt (1) - Dept. of Neurology, University of Rostock, Rostock, Germany; (2) Dept. of Anatomy, University of Rostock, Rostock, Germany; (3) Institute of Pharmacological Sciences, University of Milan, Milan, Italy

For analyzing in vivo effects of transplanted pluripotent, neuronal ST14A-cells in a rat parkinson model we lesioned the pars compacta of the substantia nigra unilaterally with 6-OH-dopamine. 12 days after the lesion, apomorphine-induced rotations were assessed, and 100.000 ST14A cells were transplanted bilaterally in the striatum; prior transplantation the cells have been stabely labeled with PKH-26 fluorescent dye. Six weeks after transplantation, the apomorphine-test was reevaluated and the rotations were measured. Animals were sacrified and the migration pattern and differentiation of the transplanted cells were characterized by cell-specific antibodies against GFAP, vimentin, tyrosinhydroxylase, NSE, NeuN and neurofilament 200. The number of apomorphine-induced rotations was reduced in the transplanted group compared with lesioned animals without cell grafting. Immunocytochemistry demonstrated that the majority of the transplanted cells were positive for GFAP. However, a small proportion were positive for neuronal markers. Also a few tyrosinhydroxylase-positive transplanted cells were found. The amelioration of the rotational behaviour could be explained by the migration, neuronal differentiation and functional integration of the grafted cells. The data demonstrates the potential benefit of transplanted cells in neurodegenerative diseases.

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SEX DIFFERENCES IN PARKINSON'S DISEASE, CONSEQUENCES FOR DOPAMINERGIC THERAPY. Kraus PH Klotz P Przuntek H. St. Josef-Hospital, Universitätsklinik der Ruhr-Universität Bochum, Dept. Neurology, Bochum, Germany

Sex differences in Parkinson's disease were until now not of interest for research as most epidemiological studies do not show such effects concerning prevalence and incidence of Parkinson's disease (PD). But there are some biochemical findings suggesting possible differences such as weight, height and also in age for the normal population. Therefore for examination of sex differences for therapeutic parameters in PD those variables have to be taken into consideration. We analyzed two settings to work out possible consequences for therapeutic decisions. Materials and Methods: 1. In a double blind cross over examination 28 male (age 6014 years) and 19 female (age 5911 years) PD-patients were treated with 1.5 mg apomorphine (or equivalent NaCl-solution) s. c.. Patients were randomized on two different days and the treatment effect on blood pressure was examined. 2.We also explored data of a long term multicentric trial (L-DOPA vs. L-DOPA plus bromocriptine) with initial 603 de novo PD patients (284 male / 319 female) over 4 years for differences during course of the disease. Results: 1. We found a significant sex difference: mean decrease of systolic blood pressure for men was 10.20.99 and for women 5.61.5 in our apomorphine trial. 2. The long term trial data showed significant sex differences for improvement after initiation of therapy (Webster rating scale, ANOVA, repeated measures, p=0.010, age as covariate: p=0.022) as well as during the course (deterioration) after reaching the therapeutic optimum. Conclusion: Our data show clear sex differences for dopaminergic drugs concerning therapeutic response and course under therapy as well as decrease in blood pressure as a side effect. Therefore sex has to be taken as one parameter for randomization in clinical trials. Since the influence of sex seems to be higher than that of age its role for therapeutic management has to be discussed.

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THE TREATMENT OF PARKINSON'S DISEASE WITH DEEP BRAIN STIMULATION. Broggi G*, Franzini* A, Servello* D, Dones* I, Genitrini° L, Girotti° F. * Neurosurgical Dep. ° Neurological Dep. Istituto Nazionale Neurologico "C. Besta". Milan – Italy.

Since the beginning of stereotactic surgery for Parkinson's disease it is well known that electrical stimulation of selected targets interferes intraoperatively with major symptoms of the disease. Aim of this presentation is to report of the results obtained in series of parkinsonian patients which underwent chronic stimulation of Vim, Gpi and STN to treat respectively tremor, DOPA-induced dyskinesias and rigidity. Our series (January 1995 – December 1998) include 41 patients, mean age 64 years, 21 males. The heralding symptoms occurred 3-10 years before surgery (mean duration of the disease 6 years). All were under controlled medical treatment. Twenty patients were affected by parkinsonian tremor and underwent Vim implant. Ten patients were mainly affected by hypokinesia and dopa-related on-off phenomena and underwent Gpi implant. Eleven patients were affected by severe rigidity and akinesia and underwent STN implant. The stereotactic surgery has been performed by CRW-Stereoplan apparatus (radionics, USA) and/or MS-DOS based dedicated softwere implemented electronic on-line atlases. Implanted electrodes and impulse generator have been supplied by Medtronic. Morbidity and mortality were nil. Control of tremor was obtained in 90% of patients at 24 months follow-up. Control of on-off phenomena was obtained in 70% of patients. The last group (STN target) shows excellent short term results with a possible decrease of medical treatment. The choice of this target seems to be promising for the future to treat all parkinsonian symptoms. In conclusion neurostimulation allowed to treat the major parkinsonian symptoms and DOPA-related phenomena without lesioning of brain nuclei. Bilateral procedures are allowed without the well known adverse effects of bilateral radiofrequency lesions.

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INFLUENCE OF PALLIDAL STIMULATION ON GAIT IN PARKINSON'S DISEASE USING THE OPTOELECTRONIC VICON SYSTEM. P. Krystkowiak, L. Defebvre, J. L. Blatt, J. L. Bourriez, M. Perina, S. Blond, A. Destée. Lille, France.

Chronic bilateral internal globus pallidus (GPI) stimulation allows the control of Levodopa induced dyskinesias (LID) and motor symptoms in severe Parkinson's disease (PD). The effect on gait is not clearly established. Different results have been reported, mostly clinical data. The aim of this study was to evaluate, by using a video motion analysis system (optoelectronic VICON system), the influence of bilateral GPI stimulation on gait in PD. Seven patients underwent bilateral GPI stimulation. The preoperative and postoperative (3 months after surgery) clinical gait disturbances (items 29 and 30 of the motor UPDRS), and gait kinematic parameters (cadence, velocity, stride and step times, single and double supports times, stride and step lengths) were analysed in off-drug and on-drug conditions. After surgery, the clinical data were improved in both conditions. All the mean values of the kinematic parameters were improved in off-drug condition whereas in on-drug condition, only the step and the stride length was not modified. This study confirms that bilateral GPI stimulation can induce beneficial effects on gait disturbances in Parkinson's disease.

Poster Session – 1

Neurobiology

P205
ASSESSMENT OF THE GLUTAMATE TRANSPORTER SUBTYPE IN SYNAPTOSOMES ISOLATED FROM THE RAT CEREBRAL CORTEX K. Kuroda[1], H. Homareda[2] and Y. Yoshino[1]. [1]The First Department of Internal Medicine and [2]The First Department of Biochemistry, Kyorin University School of Medicine, Tokyo, Japan.

Although synaptosomes have often been used in experiments studying glutamate (Glu) uptake, the Glu transporter subtype in synaptosomes is not known. The synaptosome fraction was prepared from the rat cerebral cortex by discontinuous density-gradient centrifugation according to the method of Dunkley et al. (1988). This fraction, consisting of vesicles with some mitochondria, was stained by an antibody to synaptotagmin, a specific protein of synaptic vesicles, whereas it was not stained by an antibody to glial fibrillary acidic protein, suggesting the absence of glial components. Immunoblotting of the synaptosome fraction by using specific antibodies to the 3 Glu transporter subutype proteins (GLT-1, GLAST and EAAC1) showed that GLT-1 was strongly positive, while the other two were weakly positive. Km calculated from the uptake of L-[^{3}H]Glu into the synaptosome fraction was 7.5 ± 0.4 μM, and the concentration of dihydrokainate for half-maximal inhibition of L-[^{3}H]Glu uptake into the synaptosome fraction was 90 μM. These values are not so dissimilar to the reported values of GLT-1, namely 1–2 μM and less than 20 μM, respectively. Our results indicate that GLT-1 may be the main Glu transporter subtype in synaptosomes, suggesting a possibility of the presence of GLT-1 in presynaptic nerve terminals.

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ROSTRAL THORACIC MOTONEURONS INNERVATE CAUDAL LUMBAR VENTRAL ROOTS AND THEIR TARGET MUSCLE *VIA* A NERVE AUTOGRAFT IN ADULT PRIMATES AFTER SPINAL CORD INJURY. Song LIU,[1] Gérard SAID[2] and Marc TADIE[1]. [1]Lab. of Experimental Neurosurgery; Dept. of Neurosurgery; [2]Lab. of Neurobiology, Dept. of Neurology; Hospital of Bicêtre, 94275 Le Kremlin Bicêtre, France.

To restore the hind limb motor deficits after lower thoracic spinal cord injury, a nerve autograft (NAG) was used to promote the rostral motoneurons innervating the caudal denervated territory in adult primates (*Callithrix jacchus*). Nine monkeys underwent a left spinal cord hemisection at T12 and intradural section of all ipsilateral lumbar ventral roots. In repaired animals (n = 5), a NAG from the right peroneal nerve was connected with the left L3 and L4 ventral roots selected by electrophysiology, then ventrolaterally implanted into the T10 cord. In control animals (n = 4), no sectioned ventral root was repaired. All animals were followed nine months. Three repaired animals out of five showed the clinical improvement of their paralyzed limb. Muscle action potential and motor evoked potential were recorded from the denervated/reinnervated quadriceps of all repaired animals with the mean amplitudes of 1023 ± 361 μV and 256 ± 137 μV respectively. Horseradish peroxidase retrograde labeling from the denervated/repaired ventral roots traced 234 ± 178 μV labeled neurons in the rostral ipsilateral thoracic ventral horn nearby the NAG tip. Histological analysis evidenced numerous regenerating axons in this nerve pathway and many new endplates in the denervated/reinnervated quadriceps. No positive result was obtained in the control animals. These data indicate that rostral thoracic motoneurons can regrow into the caudal denervated lumbar ventral roots via a NAG and innervate their target muscle in adult primates after spinal cord injury and suggest a possible surgical repair strategy.

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ROSTRAL THORACIC MOTONEURONS INNERVATE CAUDAL LUMBAR VENTRAL ROOTS AND THEIR TARGET MUSCLE*VIA*

AN IMPLANTED NERVE AUTOGRAFT IN ADULT RATS AFTER SPINAL CORD INJURY. Song LIU,[1] Gérard SAID[2] and Marc TADIE[1], [1]Lab. of Experimental Neurosurgery, Dept. of Neurosurgery; [2]Lab. of Neurobiology, Dept. of Neurology; Hospital of Bicêtre, 94275 Le Kremlin Bicêtre, France.

Intraspinally implanting a nerve autograft (NAG) to promote axonal regeneration towards periphery was investigated as a surgical treatment for spinal cord injury in adult rats. Fifteen animals first underwent a left hemisection of the T12 cord and intradural section of all ipsilateral lumbar ventral roots. In repaired animals (n = 9), a NAG from the right peroneal nerve was anastomosed to the electrophysiologically selected left L3 and L4 lumbar ventral roots supplying the quadriceps, then ventrolaterally implanted into the T10 cord. In control group (n = 6), no sectionned lumbar ventral root was repaired. Nine months later, five repaired rats out of nine showed the clinical improvement of their paralyzed hind limb. The mean amplitudes of muscle action potential and motor evoked potential recorded from the denervated/reinnervated quadriceps were 918 ± 329 μV and 216 ± 40 μV respectively in the repair group. HRP retrograde labeling from the denervated/repaired lumbar ventral roots evidenced 146 ± 112 labeled neurons ipsilaterally located in the thoracic ventral horn near the implantation site. Histological analysis demonstrated numerous myelinated axons in the NAG and denervated/repaired lumbar ventral roots. Also many new endplates were seen in the denervated/reinnervated quadriceps. No regeneration was detected in controls. These data indicate that rostral thoracic motoneurons can regrow into the caudal denervated lumbar ventral roots via a NAG and innervate their target muscle in adult rats after spinal cord injury.

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THE EFFECT OF TREATMENT WITH CITICOLINE ON PILOCARPINE SEIZURE SUSCEPTIBILITY IN HYPERGLYCAEMIC MICE AFTER BRAIN OLIGEMIC-HYPOXIC INSULT. 1 Rejdak K.1, Rejdak R.1, Sieklucka-Dzluba Stelmaslak Grieb, Kleinrok Z. 1. Departments of 'Pharmacology, ' Hygiene and 3 Neurology, Medical University in Lublin; 3 Laboratory of Experimental Pharmacology Polish Academy of Sciences Medical Research, Centre, Warsaw, Poland,

Transient hyperglycemia aggravates brain damage due to cerebral ischemia or hypoxia, and induces delayed seizures. The aim of the study was to examine the effects of citicoline (CDP-choline) on seizure susceptibility of transiently hyperglycemic mice exposed to oligemic-hypoxic insult.1 METHODS: Under pentobarbital anaesthesia, right carotid artery was occluded and 24 hours later hyperglycaernia was induced by oral administration of 40% glucose solution (4g/kg). 30 min. later the animals were exposed to hypoxia (5% oxygen) for 6 min. Pharmacological treatment with CDP-choline (300mg/kg, Lp) started 1 hr after the insult and was given daily for 6 1 days. Seizures were induced with pilocarpine (200 mg/kg i.p.) 6 days after hypoxia. N-methylscopolamine (1 mg/kg s.c.) was iiljected 30 min. prior to pilocarpine. Seizure activity was assessed during 1 hour after induction and defined as latency to first generalised seizures, severity score and frequency of clonic and tonic convulsions. RESULTS: Compared to SHAM-operated mice, animals exposed to oligemia-hypoxia displayed 11 increased pilocarpine seizure susceptibility. The treatment with CDP-choline modestly diminished the frequency of clonic seizures and severity score, but also increased latency to first generalised seizures in transiently hyperglycemic mice exposed to oligemic-hypoxic insult. CONCLUSION: While CDP-choline does not have anticonvulsant activity in normal animals, it shows some protective. anti-seizure activity in hyperglycemic mice subjected to oligemic-hvpoxic insult.

P209
SIGNALLING MOLECULES FOR PROLIFERATION OR DIFFERENTIATION IN THE BRAIN.L. Conti, C. De-Fraja, M. Peschanski[1], B. Haddad[1] and and E. Cattaneo. Istituto di Scienze Farmacologiche, Univ. di Milano, Via Balzaretti 9, 20133 Milano; [1]INSERM U421, Creteil, France.

In the last few years the events occurring at the transition from proliferation to differentation of brain neuroblasts has attracted a lot of attention, also for the growing interest in the use of neuroblasts as donor cells in intracerebral transplantation in neurodegenerative disorders. Much has been learnt of the biological effects of soluble molecules, such as neurotrophins and cytokines onto CNS cells. How the same factor may elicit different biological responses is, however, still poorly understood.Molecules like the EGF or FGF (as well as the neurotrophins) are known activators of the Shc-Ras-MAPK pathway. Shc is an adaptor protein connecting the activated RPTKs with downstream components of the signalling cascade (Cattaneo and Pelicci, TINS, 1998). In vivo and in vitro studies conducted by our group have demonstrated that expression of ShcA adaptor proteins in the developing rodent brain is tightly regulated and strictly associated with the immature dividing cell state (Conti et al., PNAS, 1997). ShcA is absent from mature neurons, suggesting an important role for this adaptor protein during the proliferative phases of the embryonic brain. No other known intracellular signalling protein shows similar expression profile. The recent cloning of two other Shc-like genes (ShcB/Sli and ShcC/Rai) has greatly increased the interest on the role of these connector molecules in the specification of the cell responsiveness.We have utilized cultured human CNS progenitor cells (from cortex or striatum, age 8-9 weeks post conception) to investigate the role of Shc members in proliferating neuroblasts and differentiated neurons. We observed important changes in ShcA content during the in vitro differentiation of the human cells. Remarkably, ShcA is replaced by ShcC in mature neurons. This switch in the availability of these two adaptor proteins leads to different degrees of activation of the MAPK(s) upon exposure of the human cells to growth factors. Variations in the intracellular levels of adaptor proteins may thus represent one of the mechanisms by which cells change their ability to respond to a given factor, allowing to choose between proliferation and differentiation. (Supported by Telethon-Italy E733 to LC and AIRC, Italy #442/96 to EC).

Higher function disorders

P210
THE ANATOMY OF MEMORY DISORDERS IN STROKE PATIENTS.I. Declercq, 0. Godefroy, C. Delmaire, V. Petit, M. Roussel, D. Leys, France.

Although memory disorders have been reported in mediotemporal and thalamus damage, memory has not been systematically assessed in focal lesions. Thus its frequency and anatomy remain unclear. This study examined (1) the influence of periventricular and white matter abnormalities (PVWMA) on memory and (2) the location of lesions inducing memory disorders. The study population included 89 stroke patients, examined in the acute stage by MRI. Signal abnormalities were rated in 60 regions of interest by 3 examiners blinded to neuropsychological data. Short term memory (STM) was assessed by digit span; verbal and visual long term memory (LTM), by Signoret Battede. Lesions predicting memory disorders were selected using stepwise regression. Memory did not depend on PVWMA (P>0A, all). STM disorder (n=7) depended on left insular lesions (P=0.0003). Disorder of verbal UM (n=35) depended mainly on right mediofrontal, or left thalamic, medioparietal or mediotemporal lesions (model: P=0.01). Disorder of visual UM (n=23) depended mainly on right frontomedial, or left striatal or centrum semiovale lesions (model: P=O. 04). This study shows that (1) STM syndrome depends on insular lesions; (2) UM disorders occur frequently in stroke patents, (3) without hemisphere dominance for the material to be memorised; and (4) in addition to mediotemporal and thalamic regions, frontal lobes are involved in UM, supporting recent PET findings.

P211
THE ANATOMY OF APHASIA REVISITED.Kreisler A, Godefroy 0, Delmaire C, Pruve, JP, Debachy B, Leej ere M, Leys D. Lille - France

Lesion locations determining aphasic disorders remain unclear. Controversies are mainly due to the methodology of brain-behavior relationships study. The aim of the study was to determine lesion locations associated with disorder of oral expression, comprehension, repetition and naming. The population included 107 consecutive stroke patients examined using a standardised language evaluation and magnetic resonance imaging (MRI). Language was assessed with a standardised battery using subtests from Montreal -Toulouse and Boston Diagnostic Aphasia Examination. Three examiners blinded from clinical data rated signal abnormalities in predetermined regions of interest (n=69) (interobserver agreement: K=0.55, P < 0.00001). Statistical procedure used classification trees tests which selected regions associated to each deficit. The clinicalradiological correlation study showed that (1) fluent aphasias were related to posterior damage; (2) nonfluent aphasia, to frontal or putamen damage; (3) repetition deficit, to insula-external capsule damage; (4) comprehension deficit, to posterior lesion of temporal gyri; (5) phonemic paraphasia, to insula and temporal damage; (6) verbal paraphasia, to temporal or caudate nucleus damage; (7) perseveration, to caudate nucleus damage. Each analysis classified correctly 67 to 94% of the patients (all P values 0.02 or lower). Age

did not correlate to aphasic disorder. This work demonstrates that (1) it is possible to draw the anatomy of aphasia; (2) lesion location is the main determinant of aphasic disorders, when general factors are secondary; (3) most lesion locations associated to specific disorders fit classical data.

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THE EFFECT OF DONEPEZIL ADMINISTRATION ON P300 POTENTIAL. Thomas A., Paci C, Melchionda D, D'Andreamatteo G, Toma L, Onofrj M. Department of Oncology and Neuroscience, University "G. D'Annunzio" Chieti, Italy.

An alteration of the cholinergic system is thought to be the likely cause of cognitive decline in Alzheimer Disease (AD) patients. We evaluated 20 AD patients (9 men, 11 women), 58 to 73 years old (mean 65±8.9 years), group I: 10 "probable" AD patients, group II: 10 "possible" AD patients. P300 recordings and neuropsychological examinations were performed at baseline. Donepezil was administered orally in a single evening daily dose of 5 mg for 3 months. ERPs recordings were performed at 3-9 days, 2-4-6-10-12 weeks, after the baseline recording. The difference in P300 latencies and amplitudes between I and II groups was significant ($p < 0.01$ latency in I vs II; $p < 0.01$ amplitude in I vs II) at baseline. Group I recordings after drug administration showed a progressive reduction of the P300 latency in 6 patients, with an average latency recovery of 20.7±8.3 msec at the last recording session, in 2 patients latency and amplitudes showed oscillations that were in the range of baseline variations and 2 patients have a latency increasing of about 9.7±3.5 msec and an amplitude decreasing of about 2.5±0.7 V. Group II recordings were suitable to those shown in group I, with a latency decrement and an amplitude increment in all patients; latency reductions of 14.4±5.8 msec were significant at the 2nd week in 4 AD patients ($p < 0.01$) and 4th week in 6 ($p < 0.01$), and amplitude showed significative increment in all patients ($p < 0.02$), average increment of 1.8±0.7 V. We show that donepezil administration reduces the latency and increases the amplitudes of the P300 component and that ERPs recordings are a useful tool to evaluate the pharmacological response to a specific drug administration in patients affected by cognitive impairment.

P213
ACCELERATED AGING PROCESS OF MOTOR FUNCTION IN DOWN'S SYNDROME (DS): COMPARISON WITH ALZHEIMER'S DISEASE (AD). M.F. Ghilardi, S. Marelli, G. Squintani, M. Alberoni, M. Rossi, C. Mariani, F. Fazio, M. Franceschi.INB-CNR, H.S.Raffaele, IRCCS Don Gnocchi, Univ. di Milano, Italy.

Motor slowing is reported in elderly DS together with increased prevalence of cognitive decline. We have recently shown that without visual monitoring, movements in AD are abnormally slow and inaccurate. Here we compare motor performance of AD and DS patients to age-matched controls.Subjects were: 11 AD with mild to moderate dementia (mean age 66 yrs); 12 DS (mean age 28), 14 young (mean age 28) and 18 elderly normal controls (mean age 73). Subjects moved a cursor to targets at 3 distances in 2 orthogonal directions on a digitizing tablet, without seeing their limb. They were said to make 'single, uncorrected movements as fast and as accurate as possible'. Target and starting location were always visible on a screen, while, during movement, cursor position was either visible (FB) or blanked (NoFB).With FB, the main transport phase was severely shortened in both DS and AD patients compared to age-matched controls ($p <• 0.001$). With NoFB, DS trajectories were highly curved with increased directional asymmetry, indicating abnormal inter-joint coordination. In AD and older DS subjects, movements were slower and inaccurate with asymmetrical velocity profiles.We conclude that DS subjects: 1) undergo accelerated aging of motor function; 2) may have impaired integration of proprioceptive information; 3) in older age may show motor abnormalities similar to AD patients.

P214
EFFECT OF LEVODOPA ON COGNITIVE FUNCTIONS AND EVENT RELATED POTENTIALS (P-300) IN PARKINSONIAN PATIENTS. A.Molochnikov, C. Klein, J.M. Rabey, Zerifin, Israel

Background: Levodopa (LD) is considered the gold standard treatment for the management of motor features in Parkinson's disease (PD). However its effects on cognitive functions are still controversial.Aims: To evaluate the effect of LD on cognition and event related potentials (P-300) in PD patients. Methods: We included 31 consecutive PD patients (mean age 69 y, mean disease duration 8.4 y) chronically treated with LD (mean daily dose 618 mg). Eleven of the patients suffered also from dementia (DSM IV criteria). Each patient was examined in the early morning (after 12 hours off medication). The study included recording of P-300 (Medelec /Teca Saphire premiere;H-filter 50 Hz;sensitivity-50 mv;70db above auditory threshold; 8 target among 50 non-target average stimulus) and Mattis test for scoring of mental functions. Both examinations were repeated 90 minutes after the ingestion of 125 mg LD. Results: Mean P-300 significantly improved after the ingestion of LD (Before 351.6 ms; after LD 337.85 ms; $p < 0.05$).Mattis on the contrary did not substantially change. Similar results were observed while PD patients were clustered among those with and without dementia. Conclusions: Although LD seems to improve ERP (P-300) it does not modify the cognitive performance in PD patients (as measured with the Mattis test).

P215
CREUTZFELDT-JAKOB DISEASE IN THE FRENCH WEST INDIES. D.Caparros-Lefebvre,V.Sazdovitch,M.Roudier,J.P.Brandel,J.L.Laplanche, J.P.Deslys, J.J.Hauw -CHU Pointe à Pitre, CHU Pitié-Salpêtrière, Inserm U360, CHU Lariboisière, CEA Orsay, France

Objective: To report the first case of Creutzfeldt-Jakob disease (CJD) in West Indies (W.I.).Background: The CJD, which has an incidence of 1 case per million in Europe, had never been reported in the W.I. Case study: A 75 year old black guadaloupean woman had been admitted for gait disorders, associated with dementia. She never left the W.I. before 1990, when she spent few weeks in Paris. She had no history of ophthalmologic surgery or neurosurgery. Neurological examination revealed cerebellar symptomes including instability, falls, and action tremor with myoclonic jerks predominating on the right arm. Cognitive testing showed memory impairment and apraxia. Electroencephalogram showed a diffuse slowing with few biphasic slow waves. There was a subcortical atrophy on brain CT-scan. She died in June 1998, after a one-year-long course. Neuropathological examination confirmed the diagnosis of CJD, with predominant cerebellar lesions. There was diffuse spongiform changes with astrogliosis, involving the whole neocortex, limbic cortex, caudate nucleus and substantia nigra. Cerebellum contained a large amount of Kuru plaques. Immuno-histochemical staining with anti-PrP antibodies was positive on plaques, perivacuolar deposits and in a synaptic pattern in the cerebellum and the neocortex. Discussion: This first pathologically proven case of CJD in W.I. is a sporadic case. The european survey for prion diseases associates the French W.I. The detection of this case of CJD in W.I. is likely related to the recent setting up of neurologists with a clinical experience of neurodegenerative disorders.

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Abstract withdrawn by author

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NEUROPSYCHOLOGICAL EVIDENCE FOR PREFRONTAL CORTICAL DYSFUNCTION IN TOURETTE SYNDROM. M Vérin, S Caloone, C Teixeira, B Pillon, B Dubois, Y Agid, G Edan, Rennes & Paris, France; Rio, Brazil.

Although several evidences are in favour of frontal lobe dysfunction in Tourette syndrom (TS), the respective role of the cortical and/or subcortical part of the frontal-subcortical circuits in the emergence of tics remains under debate.Involvement of prefronto-striatal loops in a temporo-spatial delayed response paradigm has been recently demonstrated in human by our group by testing the integration of both temporal and spatial coordinates of internal representation of environmental informations. A set of sequencing tasks was designed which incorporate the dissociation of spatial and temporal parameters and analysis of the role of the delay.The same paradigm was applied to patients with TS (n = 15), prefrontal cortical (PFC) lesions (n = 8) or basal ganglia (BG) dysfunction (Parkinson's disease, n = 12) compared to healthy control groups.TS and PFC groups presented the same pattern of response. In the spatial and temporo-spatial recall tasks the effect of the delay was significant in all the patient groups (TS, PFC and BG), whereas in the temporal recall task this effect was evident only in the BG group.These results in man: 1) confirm during a delay the role of both PFC and BG in the processing of spatial informations and the implication of BG in the processing of temporal informations; 2) provide neuropsychological evidence for PFC and no BG dysfunction in TS.

P218
COGNITIVE DEFICITS IN HOMOZYGOUS BETA-THALASSEMIA: RELATIONSHIP TO SECONDARY HEMOCHROMATOSIS. Roberto Monastero, Gaia Monastero, Deborah Recca, Gabriella Farinella, °Alessandro Padovani, Lawrence Camarda and Rosolino Camarda. Department of Neurology, University of Palermo, Palermo, Italy; °Department of Neurology, University of Brescia, Brescia, Italy.

To identify cognitive changes in patients with homozygous beta-thalassemia (β-th) by using a wide neuropsychological battery and to relate such findings to peripheral hemochromatosis, chronic ipoxic states or to deferoxamine (DFO) neurotoxicity. Forty-six homozygous beta-thalassemia patients and 46 age, sex, and education matched controls were evaluated with an extensive neuropsychological battery for the assessment of short and long term memory, attention, visuospatial skills, abstract reasoning, language and executive functions. All patients underwent medical and routine laboratory analyses as well as dosages of mean serum ferritin levels (SFm), mean hemoglobin plasmatic levels (Hbm), and mean deferoxamine dosages (DFOm). The following clinical parameters were also recorded: onset of blood transfusions, time interval between birth and onset of blood transfusions (BTy), time interval between onset of blood transfusions and onset of DFO treatment (TDFOy), years of blood transfusions (Ty) and DFO treatment (DFOy). Compared to controls, β th patients showed a significant impairment on all neuropsychological tests (p. from.003 to.00001). The performance on the Mini Mental State Examination (MMSE), used as a measure of global cognitive functioning, significantly correlated with TDFOy (p.01) but not with clinical and laboratory variables such as DFOy, Ty, BTy, SFm, Hbm and DFOm. These findings suggest that β -th is associated with cognitive disturbances which might be mainly due to secondary hemochromatosis following blood transfusions rather than to chronic ipoxic states or to DFO neurotoxicity.

P219
ACQUIRED HEPATOCEREBRAL DEGENERATION PRESENTING AS A MYOCLONIC ENCEPHALOPATHY. Y Boukriche, H Gervais, C Masson. Department of neurology, Beaujon Hospital, Clichy, France.

Many disorders may produce a syndrome of myoclonic encephalopathy in an elderly patient. In this case, confusion, myoclonus and pseudorythmic sharp waves on EEG were the presenting symptoms of acquired hepatocerebral degeneration. MRI findings were contributing to the diagnosis. Case report: A 77-year old woman was admitted because of confusion and arrhythmic myoclonic jerks of limbs and face, worsened by movement. There was a 4 months history of gait disturbances and memory impairment. EEG showed slow waves and pseudo-rhythmic sharp waves. CT scan and CSF were normal. Tl -weighted MRI without contrast showed bilateral hyperintense signal of globus pallidi. Laboratory tests showed low serum V factor, hemolysis without anemia, neutropenia and thrombocytopenia. Abdominal ultrasonography examination demonstrated dysmorphic liver and portal hypertension. Liver biopsy showed evidence of cirrhosis. Ammonia was elevated. There was no alcoholism. Viral and autoimmune hepatitis, Wilson' s disease and idiopathic hemochromatosis were excluded. Lamotrigine was effective for the treatment of myoclonus. Conclusion: Acquired hepatolenticular degeneration is an uncommun nonhereditary disorder in which a primary derangement of the liver affects cerebral function. Neurological symptoms are rarely the presenting signs as in the present case. MRI is then useful for diagnosis when revealing a hyperintense Tl signal in the pallidum, putamen, subthalamic region or dentate nuclei.

P220
THE FUNCTIONAL ANATOMY OF INHIBITION PROCESSES INVESTIGATED WITH THE HAYLING TASK. F.Collette[1], M. Van der Linden[1], G. Delfiore[2], C. Degueldre[2], E. Salmon[2]- [1]Department of Neuropsychology, [2]Cyclotron Research Centre. University of Liège, Belgium

Introduction. Burgess and Shallice (1996) have described a task (the Hayling task) designed to explore initiation and inhibition processes. In the initiation condition, the subjects have to complete sentences with a word clearly suggested by the context. In the inhibition condition, they have to complete the sentences with a word unrelated to the context of the sentence. The aim of the present study is to examine the cerebral areas involved in the inhibition process measured by the Hayling task. Method. A PET activation study was performed with 12 right-handed subjects using the two conditions of the Hayling task (initiation and inhibition). In each condition, sentences with the last word omitted were visually presented and remained on the screen until the subject's response. Data were analysed with SPM 96.Results. In comparison to the initiation task, the inhibition task induced a bilateral activation in the middle (BA 9/10) and the superior (BA 47) frontal gyrus.Discussion. Our study demonstrates the involvement of the prefrontal cortex in the inhibition processes elicited by the Hayling task. These results differ from those obtained by Nathaniel-James et al. (1998) who did not observe prefrontal activation using the same task. Contrary to our study, they presented each sentence during 6 seconds, which could make the task less sensitive to the inhibition processes.Burgess, P.W., Shallice, T. (1996), Neuropsychologia, 34, 263-273Nathaniel-James, D.A., et al. (1997); Neuropsychologia, 35, 559-566

P221
CLINICO-METABOLIC CORRELATION FOR WORD RECOGNITION TASK IN ALZHEIMER'S DISEASE. CONTRASTED EFFECTS OF FAMILIARITY AND NOVELTY. F. Lekeu[1 2], M. Van der Linden[3], E. Salmon[1 2], F. Collette[3],C. Degueldre[1], C. Lemaire[1] & G. Franck[1] [1]Cyclotron Research Centre, University of Liège, [2]Department of Neurology, CHU of Liège, [3]Department of Neuropsychology, University of Liège, Belgium

The aim of our study was to investigate the neural substrate of verbal recognition task in AD, contrasting the effects of familiarity and novelty of the material.Subjects and Method: Seventeen subjects (mean age 69.9 +/- 6.1 years; mean MMSE score 22.8 +/- 3.9) who met the NINCDS-ADRDA criteria for probable AD underwent resting 18 FDG-PET, that was analized with SPM 96.We developped a verbal recognition word paradigm adapted from Tulving et Kroll (1995). Results The performance for correctly rejecting familiar non studied words and for correctly accepting familiar studied words was significantly related to left anterior cingulate metabolism. Correct reject or acceptance of novel words (studied or not studied) was related to cerebral metabolism in left postcentral gyrus and right superior parietal lobule.ConclusionThese results highlight several cerebral regions involved in verbal memory recognition. Left anterior cingulate gyrus was implicated when stimuli were familiar, suggesting a response selection process in relation to a context of list. Regions like left postcenral gyrus and right superior parietal lobule appeared more implicated when stimuli were novel, suggesting involvement of attentional or perceptive general processes. Tulving, E. Et Kroll, N., Psychonomic Bulletin & Review, 1995 2 (3): 387-390.

P222
IDENTIFYING PREDICTORS OF DEMENTIA SEVERITY UPON AD DIAGNOSIS: RESULTS OF AN OBSERVATIONAL STUDY. Annick Alperovitch, Olivier Guard, Patrick Blin, Sylvia Goni, Pierre Hinault, Paris, France.

Objectives: To identify factors associated with dementia severity at AD diagnosis. Methods: A French observational study in which 231 private neurologists submitted data (including demographics) collected at baseline on the first 5 AD patients whom they saw within the first 2 months of the study. The odds ratio of an MMSE score19 (OR^{MMSE19} [95% confidence intervals]) for those patients diagnosed 1 year previously and with MMSE scores10 was calculated using logistic regression. Results: 566 patients

had MMSE scores 10 and a 1-year-old diagnosis. Of these 62.9% were female, 56.2% aged 70-79 years and 27.9% aged >80 years. In the total cohort (n=1053) the mean baseline MMSE scores of the male and female patients were 17.25.8 and 16.55.7, respectively, while 81.0% of males and 48.0% of females were primarily cared for by their spouse. For all patients OR^{MMSE19} was significant for age>80, social class and educational level. Multivariate analysis showed that for male patients, education was the only independent factor associated with MMSE19 (OR^{MMSE19}=2.1[1.0-4.4] for men with a primary as opposed to a secondary or third-level education). Education had no effect for women, but age80 years and a low social class were both independently associated with MMSE19. Conclusions: Patients are referred to neurologists at a later stage in the dementia process when they are of low socioeconomic status. For female patients old age is a further factor.

P223
LONG-TERM SAFETY AND TOLERABILITY OF DONEPEZIL IN ALZHEIMER'S DISEASE PATIENTS.John R Ieni, Carlos A Perdomo and Raymond D Pratt, New Jersey, USA

Objective: To examine the safety and tolerability of long-term donepezil treatment in patients with mild to moderately severe Alzheimer's disease (AD). Methods: Two open-label, multicenter extension trials; from one Phase II and two Phase III double-blind studies. In the Phase II trial, patients (n=133) initially received 3 mg/day donepezil, which could be increased to 10 mg/day in a step-wise fashion. Patients were treated 240 weeks. Patients (n=760) from the two Phase III trials received 5 mg/day donepezil for 6 weeks, after which a dose increase to 10 mg/day was encouraged. Patients were treated 152 weeks. Tolerability and safety were evaluated by the assessment of adverse events (AEs), physical examinations and clinical laboratory tests. Results: The incidence of AEs remained low throughout the duration of both trials, contributing to only 17% of patient discontinuations. The most common adverse events, those associated with the nervous and digestive systems, were generally mild and transient, and resolved without any dose modifications. There were no clinically significant effects on vital signs or laboratory test values. In particular, liver function parameters remained unaffected in both trials, despite long-term donepezil treatment. Conclusions: The excellent profile of donepezil demonstrates that, for the first time, there is an acetylcholinesterase inhibitor that the majority of AD patients can tolerate, at effective therapeutic doses, over the long-term.

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DONEPEZIL SAFETY AND EFFICACY IN A LARGE, COMMUNITY-BASED, OPEN-LABEL TRIAL Thomas McRae and John Orazem, New York, USA

Objective: To evaluate the safety and efficacy of donepezil in treating Alzheimer's disease (AD) using mostly community-based sites yielding a broad sample of patients. Methods: 256 sites enrolled patients meeting standard criteria for mild to moderate probable/possible AD. Patients received 5 mg/day of donepezil for 4 weeks, then 10 mg/day, if tolerated, for 8 weeks. Evaluations were every 4 weeks. Results: 1034 patients enrolled, with a mean age = 74.9 years (7.84). and mean baseline SMMSE* = 19.77 (5.45). 86.5% of patients completed 12 weeks, 6.2% withdrew due to adverse events. At Week 12, 89% were on 10 mg/day. 97% had prior or comorbid medical conditions, 94% were taking concomitant medications. The incidence of cholinergic side-effects were lower than those reported in previous trials after a 1-week interval prior to dose increase. Neither aspirin nor NSAID use significantly increased risk ratios for GI side-effects. Beta-blocker, calcium channel blocker, or digoxin use did not significantly increase risk ratios for bradycardia. At Week 12, mean SMMSE change from baseline was 1.28 on 5 mg (n=97; SD3.0; $p < 0.0001$) and 1.57 on 10 mg (n=798; SD3.1; $p < 0.0001$). Conclusions: The results of this study support both the safety and efficacy of donepezil as seen in the pivotal trials. Cholinergic side-effects appear directly related to the time to dose increase from 5 mg to 10 mg, and do not appear to be increased by concomitant medication use. *Molloy DW, et al. Am J Psychol 1991; 148:102–105.

P225
DONEPEZIL TREATMENT OF ALZHEIMER'S DISEASE IN NURSING HOME PATIENTS.Jacobo Mintzer, Carlos Perdomo, Ed Whalen and Elias Schwam, South Carolina, USA

Objective: Evaluate the safety and efficacy of donepezil in the treatment of Alzheimer's disease (AD) in nursing home patients. Methods: In-patients with AD were randomized to receive donepezil 10 mg/day (D, n=103) or placebo (P, n=105) for 24 weeks. Results: Baseline mean age = 85.7 years (64–102); mean MMSE = 14.4 (5–26); 83% female. Prior and current medical problems at screening were categorized by the Cumulative Illness Rating Scale for Geriatrics (CIRGS): heart (59%D/62%P), respiratory (28%D/31%P), upper-GI (25%D/34%P) and lower-GI (54%D/60%P). Concomitant medication use included beta blockers (16%D/12%P), CCBs (23%D/16%P), antacids (54%D/62%P), analgesics (70%D/78%P), antidepressants (29%D/37%P), antipsychotics (18%D/14%P), anxiolytics (22%D/19%P), and sedative hypnotics (8%D/7%P). 82%D and 74%P of patients completed the trial, with AEs being the primary reason for discontinuation (11%D/18%P). Nausea, anorexia, abdominal pain, diarrhea and weight loss, usually mild, were reported more frequently in the D group (9–19%D/04%P). Differences in mean change from baseline for MMSE favored D at each 4-week assessment, with significance ($p < 0.05$) at Wks 8, 16 and 20. 51%D and 36%P patients had a 3-point improvement for at least one time point ($p < 0.05$). The difference in mean change from baseline in the Clinical Dementia Rating (Nursing Home) sum of the boxes favored D at each 12-week assessment (Wk 12, $p < 0.10$; Wk 24 $p < 0.05$). Conclusions: Donepezil was well tolerated and improved cognition and global function in this elderly population, in a long-term care environment, with high comorbidity and concomitant drug use.

P226
OPTIMAL DONEPEZIL EFFICACY IN ALZHEIMER'S DISEASE IS DEPENDENT ON CONTINUED ADMINISTRATION. Rachelle S Doody, David S Geldmacher, Raymond D Pratt, Carlos A Perdomo, Houston, USA

Objective: To assess the effect of temporary drug withdrawal on donepezil efficacy. Methods: This was an open-label extension of two multicenter, Phase III, double-blind, placebo-controlled clinical trials: Study 301 comprising 12 weeks treatment followed by 3 weeks placebo washout, and Study 302 comprising 24 weeks treatment followed by 6 weeks placebo washout. During the double-blind phase, patients received donepezil (5 or 10 mg/day) or placebo. Following washout, all patients (n=760) received donepezil 5 mg/day for 6 weeks, after which an increase to 10 mg/day was encouraged. Efficacy and safety evaluations were undertaken at Baseline, Weeks 6 and 12, and at 12-week intervals up to 144 weeks. Results: After the double-blind phase, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) change scores for patients treated with donepezil were close to baseline values. Following the 3-week washout in Study 301, ADAS-cog change scores remained above baseline and, following resumed treatment, were maintained for a further 12 weeks; Clinical Dementia Rating-Sum of the Boxes (CDR-SB) change scores also remained close to baseline which, after resuming treatment, were maintained for a further 24 weeks. For Study 302 patients, ADAS-cog and CDR-SB change scores dropped below baseline after the 6-week washout. When treatment was resumed, both ADAS-cog and CDR-SB change scores improved, but never regained baseline levels. Conclusion: These data provide evidence that prolonged drug withdrawal affects efficacy, as the level of cognitive function achieved previously does not seem to be reattained.

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HDS: A SCREENING TEST FOR SUBCORTICAL DEMENTIA? Barbera van Harten[1], Marise NJ Courant[2], Henry C Weinstein[1]. Department of Neurology[1] and Neuropsychology[2], Sint Lucas Andreas Hospital, Postbus 9243, 1006 AE Amsterdam, NL.

Introduction The clinical features of subcortical dementia are disturbances in attention, concentration and memory with intact recognition, slowness in motor speed and problems with executive functions. In spite of these problems, patients with subcortical dementia do not often fulfill the clinical criteria of dementia according to DSM-IV, while having problems in daily life. In addition to the presence of subcortical dementia ancillary investigations are necessary. The purpose of this study is to investigate if the HIV-dementia scale (HDS) is sen-sitive for identifying subcortical dementia in an older population, caused by other diseases than HIV-dementia.Patients and methods Patients, who were sixty-five years or older and suspected of cognitive impairment with a subcortical profile caused by vascular white matter disease and normal pressure hydrocephalus in most cases, were included. Thirty-six patients and seventeen control patients were evaluated by the HDS and the Mini Mental State Examination (MMSE). Neuropsychological investigation was used as a reference test

for both groups. Results The mean HDS score (maximum 16) for the patients was 5.6± 3.7 and for the controls 14.1± 2.1 (p 0.05). The mean MMSE score(maximum 30) for the indexgroup was 26.7± 2.3 and for the controls 29.1± 1.1. The sensitivity of the HDS was 94% (CI 80-99%) and the specificity was 78% (CI 40-97%).Conclusion The limited number of included patients precludes firm conclusions at this time, but these interim results suggest that the HDS may be a sensitive screeningtest for identifying subcortical dementia, irrespective the underlying disease.

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DELAYED VERBAL REACTIONS IN EPILEPTIC PATIENTS. Ceriani F., Pinelli P., Poloni M., Piazzini A.*, Canger R.*, Maggiori G.*, Canevini M.P.*Cl.Neurologica III and Regional Epilepsy Center* – Osp. San Paolo – Milano – ITALY

We have applied a battery of neuropsychological and delayed verbal reaction tests, with variable foreperiods (FP of 0, 0.1, 0.5, 1.5 and 4 s), to 15 patients (17-43 year old): 11 cases of generalized seizure and 4 with temporal lobe epilepsy compared to a group of 15 age matched normal controls. All the investigations were carried out before and 4 weeks after the beginning of the antiepileptic therapy. Mean verbal reaction times (RT) have been calculated on both electromyographic (surface EMG from orbicularis oris muscle) and voice (ACG) recordings. We have considered two indexes: IR (Interference Ratio) and TB (Temporal Bridging Ratio). The former represents the ratio between RT in short (FP=0.1s) delayed reactions and RT in immediate task reactions, while TB identifies the ratio between RT for longer foreperiods and the same denominator. In basal conditions a significant difference is found only for the IR reflecting a defeat of lateral inhibition processes. During the therapy, we detect a significant increase of the 1.5 s foreperiod TB index, that corresponds to a remarkable reduction in the facilitation processes. This change can be attributed to the antiepileptic effect induced by the drug.

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DECREASED GLUTAMATE UPTAKE IN PLATELETS FROM ALZHEIMER (AD) AND DOWN (DS) PATIENTS.C. Canevari[1], B. Begni, S. Pirola[1], R. Riva, M. Frigo, L. Frattola, C. Ferrarese. Dept. of Neurology, University of Milan, Monza, and [(1)] IRCCS E. Medea, Bosisio Parini, ITALY.

Decreased glutamate uptake can be linked to altered Amyloid Precursor Protein (APP) metabolism in AD and DS and is involved in excitotoxicity and neurodegeneration. Since abnormal APP processing and secretion have been described not only in brain, but also in peripheral tissues, in present study we investigated possible modifications of glutamate uptake in platelets, as peripheral markers of excitotoxicity in vivo.32 AD, 18 aged DS and 50 age-matched normal controls were selected for the study. Diagnosis of probable Alzheimer's disease was made according to DMS-IV and NINCDS-ADRDA criteria, MMSE was applied to all patients to assess the degree of dementia. Uptake experiments were performed using [^{3}H]glutamate, according to the method previously described (Mangano and Schwarz, 1981). Glutamate uptake was decreased by 50 % ($p < 0.0001$) in platelets from Alzheimer's patients, compared to age matched controls, although neither correlated with the severity of dementia nor with the duration of the disease. Preliminary data indicate decreased uptake also in DS patients, suggesting systemic impairment of glutamate uptake in both syndromes and the validity of platelets as peripheral markers of excitotoxicity.

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ASSOCIATION OF EARLY ONSET ALZHEIMER'S DISEASE WITH AN INTERLEUKIN-1 α POLYMORPHISM. V. M. Casadei, C. Ferri, F. Veglia, M.C. Cavallini, F. Licastro, G. Annoni, I. Biunno, G. De Bellis, S. Sorbi, C. Mariani, M. Franceschi, L. M. E. Grimaldi. Milan, Bologna, Florence, Italy.

To assess the role of inflammation in Alzheimer's Disease (AD), we analyzed the interleukin-1 (IL-1) α, IL-1 β and IL-1 receptor antagonist (IL-1Ra) genes for their association with occurrence or clinical variables of AD in 318 clinically diagnosed AD patients and 357 age- and ethnicity-matched non demented controls. We found a significant overall association between AD and IL-1α A2/A2 genotype (ApoE ε4-independent odds ratio = 2.03; p=0.003). This effect was entirely due to patients with early onset AD (onset at 65 years and over) (odds ratio 5.36; $p < 0.001$). IL-1α A2/A2 AD patients had a lower mean age at onset (61 years; 95% CI 59-63) compared to A1/A2 (62 years; 95% CI 61-67) and A1/A1 (69 years; 95% CI 67-71) (p=0.0002) subjects. IL-1β and IL-1ra were not associated with the occurrence of AD. A region on chromosome 2, close or coincident to the IL-1α gene was found in linkage disequilibrium with the disease (lod score 2.06). We conclude that IL-1α is a new genetic marker for early onset AD. AD patients discordant for IL-1α genotypes develop the disease a mean of 9 years apart. Inflammatory mechanisms under genetic control are likely to modulate the neurodegenerative processes involved in AD pathogenesis and might represent a new potential target for its treatment.

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UNUSUAL PRESENTATION OF GENERAL PARESIS IN A 50 YEAR OLD MAN. Roze E, Azria A, Améri A, Dunand JF, Chédru F, Department of Neurology, Meaux, France

A 50 year-old man was admitted because he had run away from home for 4 days without any apparent reason. One year before admission, a first fugue was thought to be related to an acute alcoholic intoxication. He was treated 30 years ago for secondary syphilis. His medical history was otherwise unremarkable. On examination, he had dysarthria, bucco-lingual masticatory movements, diminished reaction to the light in his left pupil and impaired cognitive functions (Mini Mental Status =24/30). The patient suffered from delusion with grandiose ideas of religious nature and emotional lability. Cerebral MRI and EEG were normal. Syphilis blood serology disclosed positive VDRL (1/64), TPHA (1/20480) and FTA. HIV test was negative. CSF examination showed: 33 white cells/mm^3 with 98% lymphocytes,. normal glycorachia (3,2 mmol/L), increased proteinorachia (0,75g/L) with an elevated oligoclonal γ-globuline level, VDRL (1/8), TPHA (1/20240) and FTA. A diagnosis of General Paresis (GP) was done and a treatment with intravenous penicillin was given for 3 weeks. A month later, the patient's cognitive and psychiatric symptoms had resolved and there were no relapse within the next 2 years. As GP has became nowadays exceptional, this diagnosis is often delayed or not done. Moreover, this case is remarkable because of unusual presenting manifestations for neurosyphilis: onset with a fugue and facial movement disorders with bucco-lingual masticatory movements.

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DEMENTIA AND CELIAC DISEASE. A CASE REPORT. C. Clerc (1), M. Bataillard (1), M-H Bentz (1), L. Rumbach (2), (1) Service De Neurologie Ch Montbeliard, (2) Service De Neurologie, CHU Besancon, France.

A 73-year-old-man presented a 6-month history of progressive difficulty of memory and language accompagnied by diarrhoea.The neurological exam revealed grasping reflex. His Mini Mental State Examination was 28/30. Neuropsychological tests demonstrated subcortical cognitive impairment. Magnetic resonance imaging showed cerebral and cerebellar atrophy. T2 weighted sequences showed lacunar lesions on the white matter and basal ganglia, which were sometimes confluent. Cerebrospinal fluid was normal. Folic acid, thiamine and vitamine B12 deficiencies were demonstrated, homocysteine was elevated in the blood. The search for antigliadine and antiendomysium antibodies were found positive in the serum but not in the cerebrospinal fluid. Findings from duodenal biopsy revealed histological evidence of celiac disease. Several cases of dementia in association with celiac disease have been reported. Pathogenesis is unclear. Carencial, toxic and immunologic factors were considered. In our patient, radiological aspects, normality of the cerebrospinal fluid analyse and increased rate of homocysteine were in favor of ischaemic mechanism.

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Severe dysexecutive syndrome consecutive to bilateral pallidal stimulation: a case study. Dujardin K, Krystkowiak P, Defebvre L, Blond S, Destée A. CHRU Lille, France

In treatment for severe Parkinson's disease (PD), a recent procedure was developed which consists of implanting electrodes in the internal globus pallidus (GPi) for chronic electrical stimulation. The consequences on cognitive function of such an intervention remain sparsely documented. The present study reports the case of a PD patient who underwent bilateral implantation of deep brain stimulation electrodes in the GPi and who, 6 months after surgery, suffered from a severe dysexecutive syndrome. An extensive neuropsychological examination was conducted 1 month before and 6 months after surgery. Before surgery, whatever the test, the patient showed normal performance. At 6 months after surgery, almost all tests

were performed at the same level as before surgery, except those evaluating or depending on executive function. Such results underline the role of the GPi in executive function.

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INTRAVENOUS IMMUNOGLOBULIN PREPARATIONS MAY CONTAIN ACTIVATING NEUTROPHIL ANTIBODIES. Raymond Voltz, MD, Jurgen Beck MD, Manfred Wick MD, Reinhard Hohlfeld MD, Walter Stummer MD.From the Department of Neurology and Institute for Clinical Neuroimmunology (RV, RH), the Department of Clinical Chemistry (MW) and Neurosurgery (JB, WS) at the Klinikum Grosshadern, 81366 München, Germany

Treatment with intravenous immunoglobulin may be complicated by an aseptical neutrophil meningitis. Recently, we described a patient with severe cerebral vasospasm and neutrophil CSF pleocytosis following immunoglobulin treatment for Guillain BarrÈ syndrome (Neurology 1996; 46:250-251). *Methods:* In vivo neutrophil activation was tested in a gerbil animal model. Anti-neutrophil cytoplasmic antibodies (ANCA´s) were tested with a commercially available immunofluorescence assay. Anti-proteinase 3 and anti-myeloperoxidase antibodies were measured by ELISA. Results: The immunoglbulin preparation that had caused cerebral vasospasm in our patient lead to a significant increase of the number of neutrophil "stickers" in cerebral vessels compared to NaCl infusion at 120 and 180 minutes ($p < 0.05$). There was a trend to increased numbers of neutrophil "rollers". In addition 5/5 different immunoglobulin preparations tested proved positive for ANCA´s (all negative for proteinase 3 and myeloperoxidase); the patient´s preparation had the highest ANCA titer (1:2048). *Conclusions:* Preparations of intravenous immunoglobulins may stimulate neutrophils in vivo. Whether this functional effect is related to the presence of ANCA´s is currently being investigated.

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COMPARISON OF THE EFFECTS OF DOPAMINERGIC AND SEROTONERGIC ACTIVITY IN THE CENTRAL NERVOUS SYSTEM ON THE ACTIVITY OF NATURAL KILLER CELLS OF THE IMMUNE SYSTEM. R Shahien[1], S Badarni[2], V Weksler[1], V Weispapir[1], A Mizruchin[1], AI Kook[1]. [1]Rebecca Sieff Government Hospital, Safed Israel, [2]Carmel Medical Center, Haifa, Israel.

Major depression is linked to decreased serotonergic activity in the central nervous system (CNS). There is a link between reduced natural killer cell cytolytic activity (NKCA) and depression. We investigated another neurotransmitter, dopamine, which is involved in several CNS pathologies, including Parkinson's Disease (PD) and schizophrenia. We examined NKCA in 3 groups: Schizophrenic patients treated with D2 blockers, depressed patients treated with selective serotonin reuptake inhibitors (SSRIs) and patients with PD treated with L-DOPA and dopaminergic agonists, to explore the relative importance of dopaminergic activity compared to serotonin activity in regulating NK activity. A control group was made up of 45 healthy volunteers. NKCA in the group of depressed patients was significantly lower ($p < 0.01$) than that of healthy controls. During treatment with SSRIs, NKCA was clearly improved. In contrast, NKCA in PD and schizophrenic patients showed no significant difference from that of normal controls. There were no significant changes in NKCA during treatment with D2 blockers or L-DOPA. Our findings suggest that NKCA is correlated with serotonergic activity in the CNS, but not directly with dopaminergic activity. Further investigations concerning different groups of PD patients are needed.

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THYMECTOMY FOR MYASTHENIA GRAVIS: FACTORS INFLUENCING OUTCOME OF THE TREATMENT. Lodi Gogovska, Risto Ljapcev. Clinic of Neurology, Faculty of Medicine, Skopje, Macedonia

Objective: To evaluate the therapeutic impact of thymectomy combined with medical therapy in the treatment of Myasthenia Gravis (MG) and to determine the factors that influence outcome. Background: Thymectomy has gained increasing acceptance as a therapeutical modality in the treatment of MG, but factors that influence the response are still matters of contraversy. Method: Fifthy-two patients (15 male and 37 female) with generalized MG who underwent thymectomy through a median sternotomy, were retrospectively reviewed. Clinical staging was determined before and at month 1, 6, and 18 postoperatively using a modified Osserman's classification. The outcome measures were changes in clinical stage and medication requirement before and after thymectomy, effect of patient age, sex, stage of the disease, histopathology of the thymus and the duration of the disease. Results: At last follow-up, 46 patients (88,6 %) were improved. Complete remission was achieved in 21 % and pharmacologic remission in 67,6 % (48 % were still needed anticholinesterase and 19,6 % additional immunosupressive agents). Patients in preoperative stages IIa and IIb, hyperplastic or regressive thymus, female sex, age less than 45 years and thymectomy performed whithin the first year of the disease showed the greatest improvement. Conclusions: Thymectomy is beneficial and should be considered in all patients with generalized MG as soon as possible after the diagnosing of the disease. Optimal results are to be expected in the younger population, especially female patients with IIa and IIb stage preoperatively.

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ENDOCRINE FUNCTION IN LAMBERT-EATON MYASTHENIC SYNDROME (LEMS). Paul Maddison, Ashwin Pinto, John Newsom-Davis. University Department of Clinical Neurology, Radcliffe Infirmary, Oxford OX2 6HE, UK.

Voltage-gated calcium channels (VGCCs), classified into several major subtypes, are important in stimulus-secretion coupling in endocrine tissues: L- and P/Q-type channels are thought to play a significant role in insulin secretion. Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder in which antibodies to VGCCs are thought to be responsible for neuromuscular weakness. LEMS IgG has been shown to reduce hormone release in rats from both anterior pituitary cells and insulinoma cells. However it is unclear whether LEMS patients have evidence of subclinical endocrine dysfunction. We obtained blood samples from 10 LEMS patients and 5 control patients with myasthenia gravis (MG): all LEMS patients had raised titres of P/Q-type anti-VGCC antibodies. Measurements of fasting, early morning glucose, insulin, and pituitary hormones were made in all patients. There was no evidence of impaired pancreatic β cell function in LEMS patients. MG and LEMS patients taking steroids showed evidence of insulin resistance with a compensatory increase in β cell function, whereas LEMS patients not taking prednisolone had normal values of insulin resistance and β cell function. Prolactin, growth hormone, TSH, cortisol and gonadotrophin measurements were within normal limits in all patients. We have found no clinical or laboratory evidence of endocrine dysfunction in LEMS patients. This may be in part due to upregulation of non-P/Q-type VGCCs in pancreatic and pituitary cells, or to antigenic differences between isoforms of P/Q-type VGCCs expressed in neurons and endocrine cells. The apparently normal endocrine function demonstrated here is reassuring because LEMS patients often require corticosteroid treatment that can have adverse effects on glucose metabolism.

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ANTI-EXCITATORY PROPERTIES OF THE CEREBROSPINAL FLUID IN NERVOUS DISEASES. F. Weber[1], H. Brinkmeier, P. Aulkemeyer, K. H. Wollinsky[2], and R. Rüdel. Abt. Allgemeine Physiologie, Universität Ulm, D-89069 Ulm/Donau, and [1]Abt. für Neurologie, Bundeswehrkrankenhaus Ulm, [2]Abt. für Anästhesie, Rehabilitationskrankenhaus Ulm, Germany.

The cerebrospinal fluid (CSF) of patients with Guillain-Barré syndrome (GBS) contains factors having sodium channel blocking activity. The objective of this study was to investigate whether such activity also exists in the CSF of patients with other neurological diseases. Existence of sodium channel blocking activity was tested in 37 native CSF samples of three patient groups (group 1: GBS, n = 13; group 2: other inflammatory diseases, n = 7; group 3: non-inflammatory diseases, n = 17). NH15-CA2 neuroblastoma x glioma cells in the whole-cell recording configuration were used to assess the sodium channel blocking activity of CSF specimens. The CSFs shifted the steady-state inactivation curve of the sodium channels reversibly by (means SD) -10.2 4.4 mV in group 1; by -6.4 4.1 mV in group 2, and by -4.9 3.8 mV in group 3 (p 0.01). The shift was larger in demyelinating (9.1 4.6 mV) than in non-demyelinating (5.5 4.1 mV) diseases (p 0.02). The reduction of sodium current might provide a supplementary explanation for clinical symptoms in these diseases.

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UNUSUAL CD4/CD8T LYMPHOCYTES ARE ELEVATED IN MYASTHENIA GRAVIS AND RETURN BACK TO NORMAL AFTER THYMECTOMY: FUNCTIONAL DISCREPANCY BETWEEN THYM-

IC HYPERPLASIA AND THYMOMA. Carsten Reinhardt, MD and Arthur Melms, MD. Max Planck Institute of Psychiatry, Munich and Department of Neurology, University of Tübingen, Germany.

T cell dependent B cell help is likely to be of major importance in the pathogenesis of myasthenia gravis (MG). In this study we investigated the occurrence of recently identified CD4 /CD8T lymphocytes (DN-T cells) a unique population which has been implicated not only in immunoregulation but also in antibody augmentation. Comparison with healthy controls showed increased frequencies of DN-T cells in peripheral blood of MG patients but failed to reach significance (.66% vs..44%; p=0.068). When differentiating between patients with lymphofollicular hyperplasia (LFH) and patients with thymoma, however, we found a significant increase in LFH (.84%; $p < 0.01$) not only compared to control but also versus thymoma (.49%). Moreover thymectomy led to a strong reduction of DN-T cells in our LFH patients (.41%; $p < 0.01$) but not the thymoma patients (.44%) which correlates with the clinical notion that thymectomy is most efficient in patients with thymic hyperplasia. DN-T cells of our patients vigorously secreted both IFN and IL-4 and frequently exhibited an $TCRV24^{+}CD56^{+}$ phenotype. Taken together our data suggest that CD4 /CD8 T lymphocytes are of pathogenic relevance in patients with LFH but not in patients with thymoma.

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HIGH PREVALENCE OF GANGLIOSIDE ANTIBODIES IN INCLUSION BODY MYOSITIS. Swanson NR, Phillips B, Mastaglia FL Department of Medicine, The University of Western Australia, Nedlands, Australia.

Inclusion body myositis (IBM) is generally considered to be a myopathy and most likely autoimmune in nature. However, it has long been recognised that certain pathologic and electromyographic findings suggest a neurogenic component to the disorder. Ganglioside antibodies are associated with different lower motor neurone syndromes but have not previously been investigated in IBM. In the present preliminary study we measured serum antibodies to gangliosides and sulfatides in 13 IBM patients, 9 patients with polymyositis (PM), 4 patients with dermatomyositis (DM) and 20 healthy controls. Antibodies were detected using a sensitive immunoblot assay incorporating purified gangliosides (G_{M1}, asialo-G_{M1} [G_{A1}], G_{D1a}, G_{D1b}) and sulfatides. Antibodies to G_{A1} and sulfatides were found in all 13 IBM patients, each of whom fulfilled the recognised clinicopathological disease criteria. Antibodies were independent of isotype (IgG and/or IgM) and were considered significant on the basis of titre (eg 1:2560 to 20560 for G_{A1}). No reactivity was observed against either G_{D1a}, or G_{D1b} and only 2 cases showed weak reactivity with G_{M1}. By contrast, G_{A1} and sulfatide antibodies were found in only 1 PM (11%) and 2 DM (50%) patients in low titre. Healthy control subjects showed no significant reactivity to any of the 5 antigens. We conclude that the pathogenetic significance of ganglioside and sulfatide antibodies in IBM warrants further investigation.

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A FLOW CYTOMETRIC METHOD FOR THE ANALYSIS OF CYTOKINE PRODUCING CEREBROSPINAL FLUID (CSF) CELLS. Kerstin Hellwi, Volker Hoffmamv, Maike Riek&,-*, Sebastian Schimrigk-,,, Maike Krane–, Horst Przuntek~, Dieter Pöhlau~,* - #Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital, Gudrunstr.56, D-44791 Bochum, Germany - *Sauerlandklinik Hachen, Sundem-Hachen, Germany

The cytokine network is essential for the pathogenesis of autoimmune diseases. The analysis of the cytokine pattern of peripheral blood cells with intracellular cytokine staining and flow cytometrical analysis is already well established. In inflammatory diseases of the central nervous system, the analysis of cells in the CSF is of interest. We extended the method of intracellular cytokine staining in CSF cells for various cytokines. Method: After lumbar puncture, 5-10 nil of CSF are collected and immediately centrifugated. The cell pellet is washed with culture-medium. After resuspending in culture-medium the cells are incubated with phospho-myristate-acetate (PMA) and ionomycin for cytokine stimulation and with monensin for secretion inhibition. Afterwards fixation with paraformaldehyde and permeabilisation with saponin buffer for two hours follows. Then the cells are incubated with fluorescence-conjugated anti-Interferon-y-, transforming growths factor, -tumor necrosis factor, -Interleukin 4 (IL-4), -IL-12, -IL-8 monoclonal antibodies. For analysing we use three-color-flowcytometry (FACScan@, Becton Dickinson). Results: Using this technique we found fluorescence signals for various cytokines in CSF cells qualitatively comparable with those found in peripheral blood cells. Due to the simultaneous analysis of the T-cell subset by surface markers (CD4, CD8), it is possible to identify the cytokine producing subpopulations. This method may be a useful tool to evaluate the role of immunemediators secreted by CSF cells in pathogenesis and disease activity of different neurological diseases.

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Influence of high-dose methylprednisolone treatment on the expression of adhesion molecules in multiple sclerosis. J. Kraus*, P. Oschmann*, B. Engelhardt°, S. Kuehne*, J. Tofighi*, N. Chatzimanolis*, C. Laske*, A. Kern*, W. Dorndorf*- Justus-Liebig-Universität Gießen/ Germany, Department of Neurology, Clinical Research Group for Multiple Sclerosis*; Max Planck/ W.G. Kerckhoff-Institut Bad Nauheim/ Germany, Department of molecular cell biology°;

Objective: Intercellular adhesion molecule -1 and -3 (ICAM-1 and -3), both members of the Ig supergene family, can be induced on the cell surface of various cells. Upregulation of cell bound and soluble ICAM-1 (c- and s-ICAM-1) is an important early marker of immune activation and response, whereas ICAM-3 can be found in relatively high levels in the period between two acute inflammatory processes. The aim of this study was to investigate the influence of methylprednisolone (MP) therapy on c- and s-ICAM-1 and -3 expression in patients with multiple sclerosis (MS). Materials and Methods: 24 patients (12 females, 12 males) with relapsing-remitting MS were included into the study. All of them were treated with high-dose MP (for five days 1 g intravenously, then for nine days 1 mg/ kg orally) with intent to improve their clinical symptoms. In order to detect the influence of this treatment on the expression of c- and s-ICAM-1 and -3 blood was drawn before and at the tenth day of the therapy. Results: At the tenth day of high-dose MP we found a significant decrease both for the expression of c-ICAM-1 on monocytes in blood ($42,3 \pm 9,3$ to $38,3 \pm 6,0$; $p < 0,05$) and the concentration of s-ICAM-1 in serum (571 ng/ml 116 to 435 ng/ ml 106 ; $p < 0,0005$). In contrast to this the values for the expression of c-ICAM-3 on T cellls ($14,9 \pm 2,7$ to $22,7 \pm 7,1$; $p < 0,0005$) as well as on monocytes ($65,8 \pm 25,3$ to $97,8 \pm 34,5$; $p < 0,001$) were increased at the tenth day of treatment. Conclusion: We found significant changes of the expression of both adhesion molecules after ten days of MP treatment. The simultaneous decrease of ICAM-1 and the increase of ICAM-3 levels might indicate the antiinflammatory effect of this therapy. It could be interesting to search for similar effects investigating the new immunmodulatoring therapies of MS.

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DEXAMETHASONE SUPPRESSION OF BETA CHEMOKINE EXPRESSION IN LEWIS RAT BRAIN ENDOTHELIUM. K.A.C.Harkness, J.D.Sussman, G.A.B.Davies-Jones and M.N.Woodroofe

Recent studies have demonstrated differential elevation of CSF chemokines in a range of neuroinflammatory diseases. The cellular source of CSF chemokines has not yet been clearly identified. The vascular endothelial cells of the blood-brain-barrier are ideally situated to express and present chemokines to circulating leukocytes. We therefore studied the *in-vitro* expression of MCP-1 and RANTES by the Lewis rat brain endothelial cell line, GP8 (kind gift from DR J Greenwood). Resting cells constitutively express MCP-1 and RANTES as assessed by Immunofluoresence and ELISA, suggesting a role in physiological immune surveillance. The expression of MCP-1 and RANTES is significantly upregulated following stimulation with the proinflammatory cytokines TNFα, IL-1β and IFN-γ at a concentration of 10ng/ml. Addition of the immunosuppressant agent dexamethasone (1μM) leads to downregulation of both constitutive, and proinflammatory cytokine induced chemokine expression *in-vitro* and may account for some of the clinical effects of steroids *in-vivo*.

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AUTOANTIBODIES TO PERIPHERAL MYELIN PROTEIN 22 IN PATIENTS WITH HEREDITARY AND ACQUIRED NEUROPATHIES. M.-F. RITZ, J. LECHNER-SCOTT, R. J. SCOTT, P. FUHR, N. MALIK, B. ERNE, V. TAYLOR*, U. SUTER*, N. SCHAEREN-WIEMERS, A. J. STECK. Basel and *Zürich, Switzerland

To investigate the possibility that an autoimmune mechanism may play a role in the hereditary neuropathy Charcot-Marie-Tooth type 1A (CMT1A), sera were analysed by Western blot for anti-peripheral myelin protein 22 (PMP22) autoantibodies. In addition, sera from healthy controls were

compared with sera from patients with CMT type 2 (CMT2), acquired peripheral neuropathies such as chronic inflammatory demyelinating neuropathy (CIDP), anti-MAG neuropathy, Miller-Fisher syndrome (MFS) and diabetic neuropathy. Anti-PMP22 positive sera were detected in 70% of patients suffering from CMT1A and unexpected also in CMT2. Interestingly, 44% of the patients with other peripheral neuropathies and 23% of the apparently healthy controls also contained anti-PMP22 antibodies. Immunohistochemical analysis of the anti-PMP22 antisera on healthy sural nerve sections and on PMP22-expressing COS cells revealed that these sera did not recognize endogenous PMP22 within plasma membranes. Our results indicate that anti-PMP22 antibodies are found by Western blot in different types of peripheral neuropathies but their role in the pathogenesis of these conditions remains to be determined.

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TREATMENT OF HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS WITH INTERFERON β-1A, GLATIRAMER ACETATE AND IMMUNOGLOBULINS DOES NOT INTERFERE WITH MITOGEN-INDUCED PROLIFERATION *IN VITRO*. Stephan Schmidt[1], Sonja Balzer[1], Christiane Nüllen[1], Axel von Rücker[2], Thomas Klockgether[1]. Department of Neurology[1] and Clinical Biochemistry[2], University of Bonn

Interferon beta-1a (IFN β-1a) and glatiramer acetate are effective in the treatment of relapsing-remitting Multiple Sclerosis (RR-MS). Several reports indicate that intravenous application of 7S-immunoglobulins (IvIg) might also be useful in RR-MS. Though the exact mode of action of either IFN β-1b, glatiramer acetate and IvIg in MS has remained unclear, all of these therapies interfere with antigen-presentation, T- and B-cell proliferation and switch cytokine profiles towards a Th2-type milieu. To test the usefulness of combining immunomodulatory treatments, we stimulated peripheral blood mononuclear cells (PBMCs) from 10 MS patients and 10 healthy controls with phytohemagglutinin (PHA), pokeweed mitogen (PWM) and lipopolysaccherides (LPS) adding either IFN β-1a, glatirameracetate or IvIg alone or combinations of either IFN β-1a plus glatiramer acetate, IFN β-1a plus IvIg, glatiramer acetate plus IvIg, or IFN β-1a plus glatiramer acetate plus IvIg. Out of the 10 MS patients, one had been previously treated with IFN β-1a, one with IFN β-1b, one with glatiramer acetate, and one with IvIg. Proliferation was measured by standard ^{3}H-thymidine incorporation assays after 24, 48 and 72 hours. Though the stimulatory capacity differed significantly between the different mitogenes, no effect on PBMC proliferation was observed for any of the immunomodulatory drugs used alone or in combination. Further analysis will reveal if a treatment effect is demonstrable on cytokine profiles.

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SERUM TRANSFORMING GROWTH FACTOR-1 (TGF-1) IN MULTIPLE SCLEROSIS (MS) AND ITS RESPONSE TO INTRAVENOUS METHYLPREDNISOLONE (IVMP). MT Boylan, GV McDonnell, SA Hawkins, AD Crockard. Belfast, Northern Ireland.

Objective: To measure serum TGFβ-1 across the clinical spectrum of MS and assess the effect of IVMP on TGFβ-1 in relapse. Background: TGFβ-1 is a strongly immunosuppressive cytokine, inhibiting expression of pro-inflammatory cytokines and blocking cytokine induction of adhesion molecules. Data in MS has been conflicting with higher and lower levels of TGFβ-1 reported in relapse and it has been postulated that increased E-selectin in primary progressive MS (PPMS) may reflect a relative lack of TGFβ-1. Methods: Serum was obtained from 15 relapsing-remitting (RRMS) patients in relapse, 15 RRMS patients in remission, 15 PPMS patients, 15 secondary progressive (SPMS) patients and 14 normal controls. Serum was also obtained from 10 patients in relapse and undergoing IVMP therapy (1g daily for 3 days), pre-treatment, 4 and 24 hours into treatment and 48 hours post-treatment. TGFβ-1 was measured by solid-phase ELISA (Genzyme, Cambridge, MA). Results: Mean (SEM) TGFβ-1 levels were (ng/ml): RRMS relapse - 37.9 (4.7); RRMS remission - 56.0 (3.8); PPMS - 58.4 (3.5); SPMS - 57.6 (7.0); Controls - 52.1 (4.1). This represents significantly lower levels during relapse: vs RRMS remission ($p=0.0060$); vs PPMS ($p=0.0017$); vs SPMS ($p=0.0265$); vs controls ($p=0.0255$). IVMP treated patients exhibited a trend towards rising TGFβ-1 levels during and post-treatment which did not reach statistical significance: pre-treatment - 26.4 (4.5); 4 hours - 31.5 (7.4); 24 hours - 35.5 (12.5); 48 hours post-treatment - 34.5 (7.7). Conclusions: Serum TGFβ-1 is reduced during MS relapse and the upward trend with IVMP indicates another possible mechanism by which corticosteroids mediate immunosuppression in MS.

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THERAPEUTIC TRANSFER OF HSV-DERIVED VECTOR CONTAINING IL-4 GENE IN THE CENTRAL NERVOUS SYSTEM PROTECTS MICE FROM EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS PROGRESSION. R Furlan, PL Poliani, PC Marconi, A Bergami, G Desina, S Smiroldo, L Adorini, G Comi, G Martino, Milan, Italy

We previously demonstrated that herpes simplex virus (HSV)-type 1-mediated cytokine gene transfer via intracisternal (i.c.) injection is a safe and feasible procedure for the production of "therapeutic" cytokines within the central nervous system (CNS). We also showed that preventive i.c. administration of interleukin (IL)-4 gene using HSV-derived vectors delays the onset and ameliorates the symptoms of experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice. We now report that the same vector protects from EAE progression also when administered at the time of disease onset. We found that none of the spinal cord homogenate (SCH)-immunized BiozziAB/H mice treated with the IL-4 containing vector (12 mice) died from EAE compared to 53% (10/19 mice) of the control mice (immunized with the same emulsion but treated with an empty vector). Morevoer, IL-4-treated mice had a milder and shorter course of EAE attack compared to surviving control mice. We found that CNS recrutiment of blood-borne macrophage was impaired in IL-4-treated mice compared to controls and that this was possibly caused by the IL-4-mediated downregulation of two macrophage-attractant chemokines such as RANTES and MCP-1. In CNS-infiltrating cells from IL-4 treated mice we also found decreased levels of pro-inflammatory cytokines mRNA (IL-1β, IL-6, TNFa, IFN?) confirming that IL-4 delivery decreased also the in situ proinflammatory cytokine network. Our results indicate that the therapy of the acute phase of autoimmune demyelination can be succesfully accomplished by using non replicative HSV-1derived viral vector containing the IL-4 gene. The efficacy of this therapeutic protocol is mainly due to the decreased production in the CNS of chemokines and pro-inflammatory cytokines regulating the recruitment of effector macrophages from the periphery.

P248
FACIAL NERVE DIPLEGIA WITHOUT OPTHALMOPLEGIA IN A PATIENT WITH ANTI GQ1B ANTIBODIES. De Riz M, Clerici R, Carpo M, Siglienti I, Conti G, Scarpini E, Baron P, Silani V, Cappellari A, Nobile-Orazio E, Scarlato G. IRCCS Ospedale Maggiore, Dino Ferrari Center, University of Milan, Italy

Anti GQ1b IgG antibodies have been often observed in the serum of patients with Miller-Fisher syndrome, and they may partecipate in the development of ophtalmoplegia. We report a 56-year-old woman that was admitted because of peripheral facial nerve dyplegia, dysphagia, dysphonia and mild strenght impairment of the limbs. Superficial and deep sensation were normal except for paraesthesia in her hands, and deep reflexes were abolished. Gait and ocular motility were normal and she did not refer diplopia. CSF, EMG and MRI of the cervical spinal cord were normal, while GQ1b antibodies (1:1600), were found in the serum. Starting by day 4 after admission, the patient was treated with six plasma-exchanges, over a three-week period. By day 9, facial nerve diplegia, dysphagia and dysphonia started to improve. By day 35, there were no clinical deficits, and by day 45 deep tendon reflexes could be elicitable again. Plasma exchange was dramatically effective in the treatment of this patient. This clinical case shows that anti GQ1b IgG antibodies may be detectable in acute demyelinating polyradiculoneuropathy with bulbar signs and without ataxia and ophtalmoplegia.

P249
MRNA LEVELS OF CASPASE-1 MRNA IN PERIPHERAL BLOOD LYMPHOCYTES OF MULTIPLE SCLEROSIS PATIENTS CORRELATE WITH CLINCAL AND MRI MARKERS OF DISEASE ACTIVTY. R Furlan, M Filippi, A Bergami, M Rocca, V Martinelli, L. Moiola, M. Gironi, PL Poliani, LME Gtrimaldi, G Comi, G Martino, Milan, Italy

The cysteine protease caspase-1 plays a crucial role in the inflammatory processes due to its proteolitic activity on proinflammatory cytokine precursors such as interleukin (IL)-1β and IL-18. Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervosus system (CNS). We measured caspase-1 mRNA levels in peripheral blood mononuclear cells (PBMC) from 8 patients with relapsing-remitting MS every 15 days over a one-year period and compared its fluctuations with clinical and magnetic resonance imaging (MRI) evidence of disease activ-

ity. Caspase-1 mRNA levels were measurable in all the 169 MS samples tested and tended to fluctuate over time in all the MS patients.The levels of caspase-1 mRNA ranged between 0,17 to 88,03 AU. The calculated mean (± SE) was 12,67 AU (± 1,30). The mean was significantly higher than that found in healthy donors ($p < 0,001$) which originated from the mean value measured in healthy donors ± 3 SD. The relationship between caspase-1 fluctuations and clinical attacks was calculated on data obtained in the month preceeding the attack and in the week immediately thereafter. In MS patients, a two fold increase of caspase-1 mRNA mean levels was observed in the week preceeding an acute acttack ($p = 0.05$). The caspase-1 mRNA levels tended to return in the 1st week following the attack to the basal values. We found a statistically significant relationship between the number of new gadolinium-enhancing brain-MRI lesions and caspase-1 PBMC mRNA levels ($r = 0,67$; $p=0.01$). However, when we correlated caspase-1 mRNA levels with the number of persisting lesions from the previous scan we found no correlation ($r = 0,10$; $p = 0.49$). Our results show that PBMC elevation of caspase-1 trascription rate correlate with disease activity in MS patients thus suggesting that caspase-1 might represent a suitable peripheral marker of CNS inflammation in MS.

P250
ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) ASSOCIATED WITH TRANSFUSIONS AND HEPATITIS C VIRUS (HCV) INFECTION: CASE REPORT. S.Sacconi, A.Costa, E. Merelli. Department of Neurology - University of Modena - Italy

A 46-year-old woman, HCV negative, underwent to a gastroresection for duodenal ulcera with massive blood and hemoderivatives transfusions for hemorrhagic shock; fifty days later she was admitted to the Neurological Department for the onset of occipital headache and recurrent generalized epileptic crisis; she was cachectic, somnolent but arousable, with mild right hemiparesis, she alternated stupor with psychomotor agitation; there was not evidence of meningeal signs. Cerebral MRI showed foci of abnormal T2-weighted signal in the parieto-occipital regions, left greater than right, and multifocal areas within the white matter and in the deep gray matter characteristics of ADEM. Some lesions presented enhancement after gadolinium administration. HCV antibody titer and PCR for HCV RNA was positive. On the day of admission, she began Dexamethasone 0.6 mg/Kg daily for 15 days followed by tapering per os. Twentyfour days after, at the discharge the MRI revealed a remarkable improvement with foci of abnormal signal in left parietal region and right periventricular white matter associated to signs of old hemorrhage in right lenticulo-capsular region. The patient's neurological conditions showed only generalized weakness and mild impairment in walking. Taking into account the recent infection of transfusional HCV, we suppose that the virus had a role in the development of ADEM; to our knowledge, this is the first reported case of ADEM with HCV infection following to surgical procedures.

P251
IDENTIFICATION OF RESIDENT MACROPHAGES IN THE NORMAL AND INJURED RAT PERIPHERAL NERVOUS SYSTEM. Marcus Müller, Karin Wacker, William F. Hickey*, E. Bernd Ringelstein and Reinhard Kiefer. Dept. of Neurology, Univ. of Münster, Münster, Germany, and *Dept. of Pathology, Dartmouth Medical School, Lebanon, U.S.A.

Resident macrophages of the peripheral nervous system are an endoneurial cell population of monocytic origin. Their function is largely unknown due to difficulties in identifying and differentiating them from hematogenous macrophages as there are no reliable differentiating cellular markers. Radiation bone marrow chimeric rats may overcome these problems but existing models depend on low abundance surface antiges that require stimulation with cytokines for the detection of the discriminating antigen. We developed a method allowing for the differentiation between hematogenous and resident macrophages using a stable genetic marker requiring no further manipulation of the animals for detection. Chimeric rats were created by transplanting bone marrow from wildtype Lewis rats into irradiated transgenic Lewis rats carrying the functionally silent TK-tsa transgene. Resident endoneurial macrophages were identified by genomic in-situ hybridization and colocalization with macrophage markers on 1 µm thick serial sections of methylmethacrylate-embedded tissue. This method proved to be superior to several other embedding media, including paraffin, LR White, LR Gold, glycol methacrylate, and lowicryl. This system thus allows for the detection of resident endoneurial macrophages in vivo avoiding cytokine stimulation that might alter the biological behaviour of theses cells. Preliminary results following a sciatic nerve crush injury indicate that resident endoneurial macrophages are preserved distal to the lesion and can be distinguished from infiltrating hematogenous macrophages.

P252
ASSOCIATION OF ANTI-GM1 ANTIBODIES WITH ANTI-C.JEJUNI ANTIBODIES IN GUILLAIN-BARRÉ SYNDROME. I. Tripkovic, S. Aleksic, D. Lange, R. Trikic, Lj. Suturkova, S. Apostolski. Belgrade, Yugoslavia; Hamburg, Germany; Skopje, Macedonia.

Patients with Guillain-Barré syndrome (GBS) subsequent to *Campylobacter jejuni* (Cj) enteritis often have IgG anti-GM1 antibodies. The relationship between preceding infections and antibodies to ganglioside GM1 was investigated in 22 Yugoslav patients with GBS. Twelve (55%) patients were severely affected with tetraplegia and two of them (9%) needed artificial respiration. Cranial nerve involvement was found in 6 (27%) patients. EMG and nerve conduction studies showed primary axonal, predominately motor neuropathy in 9 (41%), and demyelinating sensorymotor neuropathy in 13 (59%) patients. CSF protein content ranged from 0.74 – 3.3.g/L. Pre-treatment serum samples were tested using an anzymelinked immunosorbent assay (ELISA) and Western blot for the presence of IgA, IgM and IgG antibodies to 63 kDa flagellar protein (fp) from Cj serotype 0.19. An ELISA was also used to detect IgM and IgG antibodies to ganglioside GM1. Elevated titers of anti-GM1 antibody were found in 14 (63.6%) and antibodies to Cj 63 kDa fp were detected in 11 (50%) patients. Ten patients (45.5%) showed an association of both types of antibodies. Five (55.5%) of the 9 axonal GBS had anti-GM1 antibodies in comparison to 9 (69%) of the 13 demyelinating GBS patients. IgG anti-GM1 antibodies were associated with IgG anti-Cj 63 kDa fp antibodies in only two patients (22%) with axonal GBS. Nine (69%) patients with demyelinating GBS had IgG antibodies to Cj 63 kDa fp and in eight of them (89%) these antibodies were associated with elevated antibody titers to GM1. We conclude that anti-GM1 antibodies are closely associated with antecedent Cj enteritis not only in patients with axonal but also in patients with demyelinating GBS.

P253
EFFECTS OF IFN TREATMENT ON LEUKOCYTE ADHESION TO BRAIN VESSELS IN MULTIPLE SCLEROSIS PATIENTS. M.Zaffaroni[1], S.Martinazzi[1,2], A.Zampieri[2], F.Crivelli[2], A.Ghezzi[1], A.Zibetti[1, 1] Centro Studi SM and [2] Pathology Unit, Hospital of Gallarate, Italy

The mechanims of action of Interferon (IFN) in preventing multiple sclerosis (MS) relapses are unknown. Conversely, leukocyte adhesion to cerebral endothelium is a well known early key event in MS lesion pathogenesis. We developed an improved frozen section assay for studying blood mononuclear cell adhesion to cryostat sections of normal human brain. We previously showed that immunocytochemically detectable CD45+ cells from MS patients bind to blood vessels more than cells from controls. Aim: To investigate whether long-term IFN treatment in MS patients can modify the adhesion potential of blood mononuclear cells at basal conditions and after TNF or IFN stimulation. Subjects & methods: We are following up 20 relapsing-remitting definite MS patients (10 men and 10 women, mean age 30,5 yrs, mean disease duration 3,9 yrs, mean disability 1,68 EDSS). They were randomly allocated to a treatment with IFN-1a (8 M.I.U./week) or IFN-1b (6 M.I.U./A.D). The adhesion assay is performed before the treatment, one and ten months after treatment onset. Results & Comment: Preliminary results from 17 patients at 1 month and 5 patients at 10 months suggest that mononuclear cell adhesion decreases progressively during IFN treatment. Significantly reduced values were found after 10 months for cytokine stimulated cells. These findings suggest that IFN may reduce leukocyte adhesion to brain vessels, particularly pro-inflammatory cytokine-dependent adhesion.

Amyotrophic lateral sclerosis and Motor neuron disease

P254
AXONAL TRANSPORT IS IMPAIRED IN SPORADIC AND FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS. Jun Kadekawa, Harutoshi Fujimura, Saburo Sakoda, Misako Kaido, Takehiko Yanagihara. Osaka, Japan.

To explore the presence of the impairment of fast axonal transport and investigate its mechanism in amyotrophic lateral sclerosis (ALS), we examined the ventral roots derived from the anterior horn cells of the spinal

cord obtained at autopsy from patients with ALS. Nine cases with ALS (2 familial cases associated with different SOD1 mutations and 7 sporadic cases), 2 cases with peripheral nerve diseases and 5 normal controls were studied. A light microscopic examination showed focal axonal swelling of large myelinated fibers in the ventral roots from ALS cases, which reacted with anti-phosphorylated neurofilament and anti-§-tubulin antibodies. Ultrastructurally, focal axonal swelling of large myelinated fibers consisted with vacuolated axon containing degenerated organelles and displaced axoplasm, with an increase in the number of microtubules and axoplasmic reticulum. These observations suggested that the impairment of fast axonal transport might have been caused by degeneration of axons per se and that it might be causally associated with motor neuron death in ALS.

P255
RILUZOLE HAS ONLY A MILD EFFECT ON HUMAN MUSCLE SODIUM CHANNELS. B. Mohammadi[1], N. Lang[1], D. Franzius[1], F. Lehmann-Horn[2], R. Dengler[1], A. Würz[1]. [1] Department of Neurology, Medizinische Hochschule, 30623 Hannover, Germany. [2] Department of Applied Physiology, University of Ulm, 89069 Ulm, Germany

The effects of riluzole on the human skeletal sodium channels were studied using the whole-cell patch clamp technique. Riluzole has neuroprotective, anticonvulsant, anxiolytic and anesthetic qualities. These effects are mediated by blockade of glutamate transmission, stabilizing of sodium channels and blockade of gamma-aminobutyric acid (GABA) reuptake. Riluzole has been suggested to be effectiv in amyotrophic lateral sclerosis, in HIV-induced neurocortical lesions and in animal models of ischaemic and traumatic neuronal damage. It has been already shown, that riluzole blocks the Rat Brain IIA sodium channel subunit (10µM: 45%, Benoit 1991). Asthenia is reported to be one of adverse events using riluzole. We studied human skletal sodium channels subunit expressed in HEK 293 cells applying various riluzole conzentrations (10, 100, 1000 and 2000 µM). Follwing data show the block (%) after application of riluzole (µM): 10 µM: 4.13%, 100 µM: 13.13%, 1000 µM: 34.84% and 2000 µM: 60.55%. We have also seen a dosis dependent shift of steadystate inactivation in hyperpolarizing direction. We conclude that the blockade of neuronal sodium channels is significantly greater than of muscle sodium channels. At common serum conzentration (2,0 µM) a relevant effect on muscular sodium channels contributing to asthenia seems unlikely.

P256
RELIABILITY OF COMMONLY USED MEASURES FOR DISEASE PROGRESSION IN MND-PATIENTS. Beck M, Magnus T, Auer A, Giess R, Puls I, Ochs G, Toyka KV. Department of Neurology, Julius-Maximilians-University, Wuerzburg, Germany

The ALS Functional Rating Scale (ALSFRS) and the Forced Vital Capacity (FVC%) are well-established tools for measuring disease progression in MND-patients. Their predictive power in estimating strength loss compared to objective strength assessment methods, such as the manual muscle testing ought to be proved. Methods: In a retrospective study development of the ALSFRS and FVC% were compared to the decrease in muscle strength, measured by a newly formed MRC-Mean-Score (MMS). MMS was calculated from a eigth step MRC scale, used for strength assessment in a total of 32 muscle groups. Results: Two hundred and fifteen MND-patients were analysed retrospectively using our database population. Mean age at disease onset was 53.9+/–12.3 years. The interval between disease onset and first contact in our outpatient clinic was 7 to 18 months. ALSFRS at entry was 30.9+/–6.1, FVC% 84.3+/–19.2 and MMS 3.9+/– 0.7 with an almost linear decline within 18 months. Pearson correlation of ALSFRS vs. MMS and FVC% vs. MMS revealed $r_{ALSFRS} = 0.71$ (p 0.01) and $r_{FVC\%} = 0.56$ (p 0.01). Conclusion: The ALSFRS and the FVC% are suitable instruments to assess disease progression in MND-patients as well as semiquantitative strength measurement methods. Furthermore, they give to some extent information about total strength loss in the ongoing disease process.

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AN ISOLATED PARANEOPLASTIC SYNDROME INAUGURATING BREAST CANCER. P Corcia*, J Honnorat**, AM Guennoc*, B de Toffol*, C Hommet*, C Prunier*, A Autret*. *: Clinique Neurologique, C.H.U. Bretonneau, Tours, France. **: Hopital Neurologique, Lyon, France.

The simultaneous appearance of a visceral cancer and neurologic disorder suggests a paraneoplastic origin but diagnosis is often difficult to establish since there are no pathognomonic markers available and in more than 80% neurologic symptoms appeared before the cancer is discovered. Upper motoneuron disease have been recently reported associated with neoplasm (Forsyth et al, 1997). We report the case of a 71 year-old, hypertensive but well treated, woman who suffers from a upper motor neuron disease compatible initially with primitive lateral sclerosis until she developed six years later breast cancer. Although cancer was treated and in remission, neurologic symptoms worsen. MRI revealed symmetrical lenticular hypersignals. Although breast cancer was extremely frequent, the rarity of primitive lateral sclerosis suggests that a chance association is unlikely. Moreover, Forstyth et al reported 5 cases similar our. Consequently, a systematic search of breast cancer should be undertaken in all woman presenting a upper motor neuron disease. Ref: Forsyth PA, Dalmau J, Graus F, Cwik V, Rosenblum K, Posner JB. Motor neuron syndromes in cancer patients. Ann Neurol 1997 ;41:722-30.

P258
CLINICAL, NEUROPHYSIOLOGICAL AND MAGNETIC RESONANCE IMAGING (MRI) FINDINGS IN PRIMARY LATERAL SCLEROSIS (PLS). J Kuipers-Upmeijer, AEJ de Jager, JM Hew*, TW van Weerden. Departments of Neurology and Neuroradiology*, University Hospital Groningen, The Netherlands

The clinical, neurophysiological and MRI signs of 9 patients with PLS were studied. Diagnosis was made according to standard criteria. Final diagnosis was reached 1-6 (mean 3.5) years after the first symptom. All patients were male. Mean age was 42.5 year. The mean duration of the disease was 12.5 years. On clinical examination, 4 patients had slight weakness of the legs only; 2 patients showed severe quadriparesis. All patients had marked spasticity, especially in the legs. Four patients had spastic dysarthria and 5 patients demonstrated pseudobulbar affect. Muscular wasting and fasciculations were absent. Deep tendon reflexes were extremely brisk. Babinski's sign was present bilaterally. Intellect was preserved in all patients. Motor Evoked Potentials (MEP) were prolonged or gave no response. Somatosensory Evoked Potentials (SSEP) were borderline in 4 patients. Electromyography (EMG) showed no evidence of acute denervation. In 6 patients a cranial MRI was made, showing cerebral atrophy, most prominent in the precentral gyrus. This study confirms the clinical studies in other groups of PLS patients. Remarkable is the division in 5 patients with and 4 patients without pseudobulbar symptoms, whereas in other aspects no differences could be found. Five patients were misdiagnosed and in 3 patients it took more than five years before the right diagnosis was established. Spasticity had a profound effect on the patients' ability to function.

P259
NON INVASIVE VENTILATION IN TREATING RESPIRATORY FAILURE IN ALS. Mora G, Mazzini L*, Braghiroli A°. Division of Neurology, *Division of Physical Therapy, °Division of Pulmonary Disease. "S. Maugeri" Foundation, IRCCS, Rehabilitation Institute of Veruno –NO- (Italy)

Respiratory failure is the most common cause of death during the course of amyotrophic lateral sclerosis (ALS). To improve quality of life and prolong survival different non invasive approaches (volume-cycled ventilators, bi-level devices, pressure-cycled ventilators), using nasal or facial masks, are advocated, but the exact timing and mode of ventilation in ALS patients is still not clear. To investigate the efficacy of different approaches in non invasive ventilation (NIV), during the years 1992-1997 we evaluated 533 ALS patients. All patients underwent Pulmonary Function Tests, arterial blood gas analysis, nocturnal pulse oxymetry and polisomnography. Entry criteria for proposing NIV were: FVC50%, pCO2>45 mm Hg, SaO290%, AHI>10. 65 patients were able to adapt to the ventilator and started home NIV; in 14 of these PEG was performed. We performed survival analysis on all ventilated patients and compared the survival among the different modalities of ventilation. We conclude that NIV gives the patient the opportunity to postpone the decision about tracheostomy to a more advanced stage of the disease. The use of volume-controlled pressure-cycled ventilators provided with full face masks appears the best solution in terms of easy adaptation, dyspnoea reduction, and prolongation of survival.

P260
KENNEDY'S DISEASE - SPECTRUM OF SUBCLINICAL LESIONS. Koelmel C, Ciccotti P, Lindemuth R, Dillmann U, Department of Neurology, University of Saarland, Germany

Kennedy's Disease is a x-linked bulbospinal muscular atrophy caused by a trinucleotid repeat expansion of the androgen receptor gene. Because of the wide representation of the androgen receptor in the CNS we examined whether there are additional pathways involved in Kennedy's Disease. Therefore we looked in 6 patients with documented mutations for subclinical brainstem lesions by means of blinkreflex, auditory evoked potentials, masseter reflex and nystagmography. The cerebellar function was examined by posturography. In addition we performed tests of the autonomic nervous system including measurement of the serum catecholamines (noradrenalin, adrenalin, dopamin). In result the masseter reflexes showed prolonged latencies in 3 of 6 Patients. AEP revealed altered configurations of the waves II-V in 2 patients. Blinkreflex showed abnormalities in terms of missing or prolonged R_1-component in one patient. Concerning the studies of the autonomic nervous system there were pathological results especially in subtests measuring the parasympathic nervous system. The serum catecholamines were within normal range. The posturography confirmed afferent ataxia. Furthermore there were signs of cerebellar lesions. Our data suggests that in patients with Kennedy's Disease there are subclinical brainstem and cerebellar lesions together with an involvement of the autonomic nervous system.

P261
MONITORING ALS-PROGRESSION AND ANALYSIS OF SUBGROUPS. Magnus T, Beck M, Giess R, Puls I, Toyka KV.Department of Neurology, Julius-Maximilians-University, Wuerzburg, Germany

Several rating scales have been established for the assessment of clinical status and therapeutic success. Bulbar onset, primary low FVC values, and greater age are associated with shorter survival. However, there exists no systematic study that correlates younger age of onset with slower rate of disease progression. Methods: We performed a retrospective study with our ALS database population by using the internationally accepted ALS Functional Rating Scale (ALSFRS) and forced vital capacity (FVC%) to compare the rate of disease progression within different age subgroups. Over a 15-month period data were collected in three month intervals. Results: One hundred sixty-nine patients were analyzed. Mean age at first contact was 53.9+/–12 years. The deterioration of the two parameters followed a nearly linear pattern. After dividing the patients into age subgroups (>55 years and 56 years) we found no significant difference within the decline of ALSFRS (31.3+/–6.3 to 23.6+/–6.5 and 31.3+/–5.2 to 23.7+/–5.4 respectively) and FVC% (78+/–17 to 61+/–27 and 82+/–21 to 64+/–20 respectively). Conclusion: Our results show no significant difference in disease progression between older and younger ALS patients. The shorter survival time of older patients observed in other studies is probably not directly related to the rate of disease progression. Other factors like smaller vital capacity, substantially decreased muscle volume, and coexisting diseases may influence the length of survival in these patients.

P262
METABOLIC IMPAIRMENT OF THE LIMBIC SYSTEM IN THE DEMENTIA ASSOCIATED WITH MOTOR NEURON DISEASE: A POSITRON EMISSION TOMOGRAPHY STUDY.G. Garraux, E. Salmon, G. Franck. Cyclotron Research Centre and Department of Neurology, University of Liège, Sart Tilman B35, Belgium.

Some patients with frontotemporal dementia (FTD) develop early in the course of the disease clinical features compatible with a motor neuron disease (FTD/MND). Some neuropathological studies in FTD/MND suggest that neuronal loss is predominant in the limbic system. Using statistical parametric mapping (SPM96), we compared the metabolic patterns obtained at rest with positron emission tomography (PET) in 46 healthy subjects (HS) with that obtained in 10 FTD patients and 3 FTD/MND patients. Mean age, duration of illness and dementia intensity did not differ statistically between FTD and FTD/MND groups. When the FTD/MND group was compared to the FTD group, significant hypometabolism was only observed in bilateral amygdala, bilateral hippocampus, and bilateral enthorinal and parahippocampal regions (Brodmann's areas, BA 28/36) at p 0.005 (Z score > 2.58). In the reverse contrast, when FTD patients were contrasted to FTD/MND patients, we found no significant differences in the regional glucose uptake. Our results suggest statistically comparable frontal and lateral temporal hypometabolism in both conditions but greater impairment of limbic system in FTD/MND especially in medial temporal lobe regions. Further neuropsychological studies in FTD/MND should concentrate on the involvement of the limbic system.

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DIAGNOSIS AND MONITORING OF UPPER MOTOR NEURON DEGENERATION BY PROTON MAGNETIC RESONANCE SPECTROSCOPY. C. Pohl, MD, W. Block*, PhD, MD, J. Karitzky, NM, F. Trdber*, PhD, S. Schmidt, MD, H. Schild*, MD, Thomas Klockgether, MD.

Objective: To evaluate diagnosis and monitoring of upper motor neuron (UMN) degeneration in motor neuron disease by proton magnetic resonance spectroscopy ('H-MRS). Methods: 52 patients with amyotrophic lateral sclerosis (ALS), 6 patients with spinal muscular atrophy (SMA) and 48 healthy controls were examined by short and long echo-time 'H-MRS of the right and the left motor cortex, fifteen patients were followed up longitudinally over a period of 4 to 32 months. Results: There were reduced NAA/Cho and NAA/(P)Cr ratios in ALS patients. In addition, elevated Cho/(P)Cr and Ins/(P)Cr ratios were found in ALS while Glx/(P)Cr ratios were unchanged. No changes occurred in patients with SMA. NAA/Cho was the most sensitive metabolite ratio to detect UMN degeneration in ALS patients and revealed clinically silent UMN loss in patients with suspected ALS. This ratio was distributed asymmetrically in the motor cortex with lowest values contralateral to the predominately affected extremities. Longitudinal 'H-MRS measurements as well as correlation of clinical with 'H-MRS findings revealed a considerable interindividual variability of NAA/Cho deterioration corresponding to the clinical heterogeneity of motor neuron disease. Defining limits for pathological measurements (mean ± 2 standard deviations of healthy controls) 'HMRS showed a 60% sensitivity for detection of UMN degeneration. Sensitivity was increased by bilateral measurements and by follow-up examinations (71 %). Conclusion- 'H-MRS of the motor cortex can be used as a diagnostic tool for detection of UMN degeneration and adds important information upon the natural history of neurodegeneration in patients with MND.

P264
PLATELET GLUTAMATE UPTAKE AND GLT-1 EXPRESSION IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENTS. G.Sala, B.Begni, C.Zoia, I.Rivolta, G.Galimberti, R.Riva, E.Beghi(*), L.Frattola, C.Ferrarese. Dept. of Neurology, University of Milan, Monza, and (*) the Italian Study Group for ALS, Milan, ITALY.

Decreased glutamate uptake has been shown in synaptosomes from spinal cord and motor cortex of ALS patients. A loss of the astrocytic glutamate transporter EAAT2 (GLT-1), linked to abnormal mRNA splicing, was also observed. To assess whether glutamate uptake can be a marker of disease progression and/or is observed in genetically susceptible individuals, we used platelets, which possess a high-affinity glutamate uptake, similar to that described in brain synaptosomes. Glutamate uptake was determined in platelets from 41 ALS patients, 20 relatives and 32 age-related normal controls, as Na^+-dependent [^{3}H]glutamate influx. GLT-1 transporter expression was investigated by Western blot analysis using polyclonal rabbit antibodies. A 38% reduction of glutamate uptake ($p < 0.005$) was observed in ALS patients, compared to controls; the decrease was not correlated with the disease severity, measured by the Norris scale, suggesting that glutamate uptake decrease could be an early marker of ALS. A 43% reduction of glutamate uptake ($p < 0.005$) was also observed in relatives of ALS patients, compared to controls. Preliminary studies in 10 ALS patients have shown an increased GLT-1 expression which could be a mutated-non functional protein or a compensatory phoenomenon for decreased activity of other transporters. Our data support a possible use of platelets as peripheral model of excitotoxic phoenomena in ALS.

P265
A PSYCHOLOGICAL SUPPORT SERVICE IN THE PALLIATIVE CARE OF ALS PATIENTS. E Bertuzzi, M Giuliani, A Cucatto, AA Terreni, A Chiò. Department of Neurosciences, University of Turin, Italy

Introduction: ALS is a rapidly progressing fatal disease interfering with a wide variety of patients activities. Patients intellective abilities are usually not impaired: therefore, till death, they are aware of the disease progression. Objective: The aim of the psychological support service is to promote (*a*) an effective cooperation within the various specialists involved in the case management; (*b*) the expression of the patient and his/her family feelings concerning the diagnosis and/or the disease progression, in order to help them to face the disease meaning and to promote remaining potentialities; (*c*) the reorganization of a new patient's identity that includes the acceptance of the impairment due to the disease; (*d*) an ethic reflection

about the various helps available for improving the patient's quality of life. Methods: the psychologists activity is based on periodical meetings with the patient and his/her caregiver; monthly meetings between neurologists and psychogists; quarterly meetings with all the specialists involved in the patient care. Results and comments: seventy percent of patients accepted a psychological help. These patients generally cooperated better with caregivers and physicians, they felt able to influence their environment, being confirmed in their dignity and personally validated, and they better cope with the burden determined by their progressive disability. In future, a home psychological support for patients who cannot deambulate and self-help family groups will be activated.

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A LEUKAEMIA INHIBITORY FACTOR (LIF) GENE MUTATION IN PATIENTS WITH SPORADIC AMYOTROPHIC LATERAL SCLEROSIS (ALS). Giess R, Beck M, Goetz R, Schrank B, Ochs G, Toyka KV, Sendtner M. Department of Neurology, Julius Maximilians University, Würzburg, Germany

LIF belongs to a family of cytokines including CNTF (ciliary neurotrophic factor) and Cardiotrophin I. It is a potent survival factor for motoneurons in cell culture and *in vivo*. Whereas inactivation of the *lif* gene does not lead to a significant postnatal motoneuron loss, double knockout of the *lif* and the *cntf* gene results in a potentiated motoneuron degeneration in mice. Methods: We screened 104 German patients with sporadic ALS for mutations in the *lif* gene. Polymerase chain reaction products were screened by single stranded conformation polymorphism analysis. Those PCR products showing abnormal band patterns were sequenced. Results: A G to A point mutation at position 3400 of the *lif* gene was identified in four ALS patients. The mutation leads to an amino acid exchange from Valine to Methionine at position 64 of the LIF protein. This mutation was not identified in our control group (n=131) consisting of patients with genetically proven muscular dystrophy or ischemic cerebrovascular disorders. Conclusion: Sporadic degenerative disorders of motoneurons may be based on multifactorial defects which individually do not result in disease. In analogy to results obtained in knockout mice this *lif* gene mutation might be of pathogenic significance in patients with sporadic ALS when combined with other as yet unidentified gene defects.

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CLINICAL COURSE OF ALS: FINDINGS OF THE IRISH ALS REGISTER OVER A SIX YEAR STUDY PERIOD 1993 – 1998. BJ Traynor, MB Codd, B Corr, E Frost, C Forde, O Hardiman.

We describe the clinical features and outcome of all individuals with amyotrophic lateral sclerosis (ALS) enrolled on a population-based register during the period 1993 - 1998. Three hundred and eighty-eight residents of Ireland with ALS were diagnosed between 1st January 1993 and 31st December 1998 and followed through 31st December 1998. The median age at diagnosis of ALS patients in Ireland was 63.2 years (range, 29.0 – 91.6) for men and 66.7 years (range, 29.0 – 92.6%) for women. There was a preponderance of males among the incident cases: 220 men versus 168 women. Twenty-five patients (6.4%) were familial ALS compared to 363 sporadic cases. At onset of symptoms, 124 (32.0%) patients had bulbar dysfunction, 209 (53.9%) commenced with limb symptoms and 55 (14.1%) had symptoms referable to both bulbar and limb musculature at onset. Over the six-year study period 253 patients died and one patient was chronically ventilated giving a median survival time of 1.49 years. Older age (Cox model hazard ratio for 10-year increase in age, 1.17) and site of onset (adjusted hazard ratio for bulbar onset disease, 1.24) were independently associated with impaired survival ($p < 0.0001$). In conclusion, our study confirms the poor prognosis associated with older age of onset and bulbar onset disease, and reveals a higher rate of bulbar symptoms at onset than reported in most other countries.

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AMYOTROPHIC LATERAL SCLEROSIS FOLLOWING CONSUMPTION OF ECHINACEA: A POSSIBLE ASSOCIATION. C H Hawkes & A Hensiek

The aetiology of sporadic amyotrophic lateral sclerosis [ALS] is unknown. The presence of monclonal paraproteinaemia, antibodies to calcium-channels, ganglioside [GM-1] or neurofilament protein and immune-mediated models all imply the disease might have an immune basis. Another pathogenic mechanism of relevance here, is oxidative damage.. We report a 45 year old man who developed classical ALS after prolonged exposure to Echinacea Purpurea. He was a keen marathon runner who consumed Echinacea to help avoid infection. Echinacea Purpurea is a medical herb used for its observed effect in stimulating the immune system. If may also affect the generation of free radicals. Echinacea has been found to increase the number and activity of macrophages and granulocytes, activate cell growth factors, increase T-cell proliferation and increase levels of Interleukins IL1, 5, 6 and Interferon α, β.. It is also claimed to elevate tumour necrosis factor [TNFa] which has been found to be raised in animal models of ALS. In view of the immune stimulant effect of Echinacea and generation of reactive oxygen intermediates a causal relationship between this herb and ALS is possible.

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COPPER/ZINC SUPEROXIDE DISMUTASE I AND ALS: A POPULATION ANALYSIS. B.J.Traynor[1], B.Corr[1], E.Frost[2], A.Green[3] O.Hardiman[1]. [1]Dept.Neurology, Beaumont Hospital Dublin; [2]Irish Motor Neurone Disease Association, [3]Dept.Genetics, University College Dublin, Ireland.

ALS is a degenerative disorder of unknown cause affecting motor neurones and characterised by a combination of upper and lower motor neurone signs with progression. 90% of cases of ALS are sporadic (SALS), and the remaining 10% pare familial (FALS). Mutations in the Cu/Zn SOD1 gene have been identifying as the underlying cause in approximately 20% of FALS cases, and have been found in a small percentage of apparently sporadic cases. The frequency of sporadic SOD1 mutations in the Irish ALS population has not been established. We have screened 76 sporadic and 4 familial cases, representing approximately 50% of the Irish ALS population by single-strand confirmation polymorphism and heteroduplex analysis. Point mutations in exon 4 and exon 2 have been identified in 2 cases. This population-based study of ALS represents the most complete analysis of an ALS population in a defined region, and provides an accurate assessment of the occurrence of SOD1 mutations in Ireland.

Multiple Sclerosis

P270
APOE GENOTYPE AND CLINICAL COURSE OF MS: A CROSS-SECTIONAL STUDY. S. Strasser-Fuchs, H. Schmidt, F. Fazekas, C. Enzinger, A. Lechner, E. Flooh, R.. Schmidt and H.P. Hartung. Department of Neurology and Institute of Medical Biochemistry, Karl-Franzens University Graz, Austria

Different patterns of the ApoE genotype have been associated with susceptibility for and course of various disorders of the central nervous system. We therefore wanted to determine if there exists also a relation between the ApoE genotype and MS. Methods: We performed ApoE genotyping in 137 consecutive patients admitted to our MS outpatient clinic. Mean patient age was 38 years (range 17 –70) and EDSS scores ranged from 0 to 8.5 (mean 2.6). Pertinent clinical and demographic variables were recorded and compared between different ApoE genotypes. Results: The distribution of ApoE genotypes was not significantly different from that in the normal population. Patients with ApoE-ε3/ε4 (n=25) were younger (35.0+/–9.6 yrs.), had a somewhat higher EDSS (2.7+/–2.2), a faster progression rate (progression index 0.69+/–1.2) and included a higher proportion of individuals with chronic progressive disease (28%) than patients with the 2/3 (n=17; 41.1+/–11.8; 2.3+/–1.5; 0.46+/–0.7, 12%) and patients with the ε3/ε3 genotype (n=84; 38.7+/–9.9; 2.1+/–1.5; 0.43+/–0.2, 20%). Due to marked variance none of these differences reached statistical significance. In a logistic regression analysis, however, the ApoE genotype entered the model as a significant predictor of progression as reflected in the progression index besides relapse rate ($r=0.29$; $p=0.035$). Conclusion: These data suggest a moderate modifying effect of the ApoE genotype in MS with a more rapid course of the disease in patients with the ε4 allele.

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VENTRICLUAR SIZE MEASUREMENT BY TRANSCRANIAL ULTRASOUND CORRELATES WITH CLINICAL DISABILITY AND COGNITIVE DYSFUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS. Mäurer M., D. Berg, M. Warmuth-Metz, P. Rieckmann, G. Becker. Department of Neurology, University of Würzburg, 97080 Würzburg, Germany

Recent studies demonstrated, that progression of CNS atrophy in multiple sclerosis (MS) patients correlates with worsening disability. Therefore

measurement of CNS atrophy has been proposed as a surrogate marker for disease progression. We evaluated the enlargement of the ventricular system as a marker for brain atrophy with magnetic resonace imaging (MRI) and transcranial sonography (TCS) to look for an association between ventricular system diameter and disability, cognitive performance and mood in a group of MS patients. Methods: 74 MS patients (48 f, 26 m, mean age 42 y) were included. Disability was assesed by the expanded disability status scale (EDSS). Neuropsychlogical test batteries and routine depression scales were administered. All patients were submitted to a standardized TCS and MRI-protocol. For TCS we applied a color-coded- phased array ultrasound system with a 2.5 MHz transducer (Siemens Sonoline Ellegra). Ventricular width of the third ventricles and the frontal horns were measured by two independent investigators. Results: Interobserver reliability was high for the measurement of ventricle size (MRI r = 0.9, TCS r = 0.8 III. for ventricle). Comparison of the data for the diameter of the ventricular system obtained by TCS and MRI yielded a significant correlation (r = 0.9 III. for ventricle). There was a significant correlation between the diameter of the third ventricle and disability measured by EDSS. In addition TCS and MRI data correlated significantly with the neuropychological tests. Correlation with the with of the frontal horns was substantially lower for both imaging techniques. No correlation was found between diameter of the ventricles and depression scales. Conclusion: The study demonstrates a correlation between ventricular size, disability and neuropsychological performance and suggests that the ventricular size in MS is a robust parameter for the purpose of such correlative studies. Moreover it was shown that TCS is a valuable method for the assessment of the ventriclular system in MS patients. Therefore this easy applicable technique will be further evaluated in serial studies to elucidate the relation between inflammation and tissue destruction and for the evaluation of putative treatments.

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ORAL FUMARIC-ACID ESTER THERAPY (FAE) INFLUENCE T-HELPER CELL APOPTOSIS IN PERIPHERAL BLOOD LYMPHOCYTES (PBLS) AND SOLUBLE INTERCELLULAR ADHESION MOLECULE-I (SICAM-1) IN SERUM OF PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS). Brune N, Schimrigk S, Meier D, Krane M, Rieks M*, Hoffmann V, Hellwig K, Pöhlau D*, Przuntek H. Department of Neurology, St. Josef Hospital, 44791 Bochum, Ruhr University Bochum, Germany, * Sauerlandklinik Hachen, Germany

Relapses in RRMS are assumed to be induced by autoreactive TH_1-type lymphocytes whereas remissions are associated with TH_2-type cytokine pattern, a deletion of autoreactive T-cells and decline of inflammation. Th_2-type cytokines are able to induce apoptosis in autoreactive T-cells and down regulate inflammatory processes mediated by adhesion molecules like sICAM-1., FAE (Fumaderm®) a potent immunomodulator known to alter TH_1- towards a TH_2-type cytokine pattern in vitro and in vivo. We investigated the influence of oral FAE therapy, as a possible treatment for patients with RRMS during an open phase II prospective study. Materials and Methods: We examined 10 patients with definitive RRMS. The investigation over 28 weeks was divided into a baseline section (6 weeks), a treatment period (18 weeks) and a post-study section (4 weeks). During the investigation, we detected T-cell apoptosis of PBLs using the annexin-V-binding-method by flowcytometry. Additionally we measured serum levels of sICAM1 by enzyme linked immunosorbent assay (ELISA). Results: Operating with those techniques, we were able to correlate the alteration in T-helper cell apoptosis with the observed TH_2 -type cytokine shift under drug therapy. We found an increased (50%) rate of apoptosis in T-helper cells after 6 weeks of treatment which declined to baseline levels afterwards in accordance to the IL-10 producing lymphocytes. Serum concentrations of sICAM-1 remained stable throughout the entire investigation. Conclusion: FAE (Fumaderm®) seem to have beneficial effects on the disease course during the study. Soluble ICAM-1 as a proposed long-term marker of the disease activity remains stable. The rate of T-helper cell apoptosis correlates directly with the observed IL-10 induction.

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IN VITRO STIMULATION OF PERIPHERAL BLOOD LYMPHOCYTES WITH CALCIUM MONOMETHYLFUMARATE (CAMF) INFLUENCE PRODUCTION OF INTRACELLULAR TH_1- AND TH_2-TYPE CYTOKINES IN A SPECIFIC MANNER.Schimrigk S, Krane M, Hellwig K, Hoffmann V, Rieks M*, Pöhlau D*, Przuntek H. Department of Neurology, St Josef Hospital, 44791 Bochum, Ruhr University Bochum, Germany; * Sauerlandklinik Hachen, Germany

T-helper lymphocytes classified as TH_1- and TH_2-type lymphocytes, depending on their different cytokine pattern, have different functions in the immune system. TH_1-type cytokines like IFN-γ and TNF-α are predominantly pro-inflammatory and TH_2-type cytokines like IL-4 and IL-10 can down regulate inflammation. We investigated the influence of CaMF on the TH_1- and TH_2- type cytokine pattern of peripheral blood lymphocytes in vitro. Methods: PBLs from healthy donors were stimulated in vitro with CaMF in different concentrations (50, 100 and 200μM) and with different incubation times (24, 48 and 72h). Controls without stimulation were included. Cytokines were measured after single stimulation in culture plates. TH_1-type cytokines (IL-2, IFN-γ, TNF-α) and TH_2-type cytokines (IL-4, IL-10, TGF-) were detected intracellular by flowcytometry. Results: We found a dose dependent influence on intracellular TH_1- and TH_2-type cytokine production. There is a marked decrease in the production of TH_1-type cytokines and a significant increase of TH_2-type cytokines after a 24h incubation time. The substance affected primarily CD4 positive cells. Discussion: The changes in the intracellular cytokine pattern after stimulation of PBLs in vitro with CaMF are reproducible and suggest a possible protective role of this substance in inflammatory diseases.

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INTERFERON BETA-1B IN THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS: CLINICAL AND MRI RESULTS. Ozakbas S, Idiman E, Cakmakci H, Yener GG, Kovanlikaya I.Dokuz Eylul University, School of Medicine, Departments of Neurology and Radiology.Izmir Turkey

Several evidences suggest that immunopathological factors are critically involved in the pathogenesis of multiple sclerosis (MS). Some clinical trials demonstrated that interferon beta-1b reduces the frequency and severity of exacerbations, slow the accumulation of disability and supressed magnetic resonance imaging (MRI) activity and lesion accrual. In this study, seventeen relapsing-remitting MS patients (2 male and 15 female), who has short disease period and 2 relapse in the last two years, have received 8 million unit interferon beta-1b every other day subcutaneously for nine months. They are evaluated clinically and on the base of MRI in the second, forth, sixth and ninth months. Clinical evaluation was performed with expanded disability status scale (EDSS). Mean age was 32.29 ± 5.45, mean disease duration was 2.44 ± 0.61 years, mean EDSS score was 2.20 ± 0.41 and mean relapse rate was 2.06 ± 0.90 in the last two years. Mean MRI score (which was assigned depending on the volume and number of lesions) was 44.12. EDSS scores were significantly decreased in the forth (p=0.0277), sixth (p=0.0015) and ninth (0.0015) months of the treatment. MRI scores were significantly decreased in the forth (p=0.0409), sixth (p=0.0019) and ninth (p=0.0007) months. No serious side effect was seen during the therapy. We concluded that interferon beta-1b might decrease both clinical disability and MRI lesions.

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CORTICOSTEROID INDUCED GENE EXPRESSION IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF MULTIPLE SCLEROSIS PATIENTS DETECTED BY cDNA MICROARRAYS. Weilbach F.X., Gold, R. and Toyka K.V.Department of Neurology, Julius-Maximilians-Universität, Würzburg, Germany.

The cDNA microarray technique is a recently introduced method to simultaneously survey the expression of multiple genes synchronously. This method has been applied to cell cultures and tissue specimens to detect transformation- or differentiation-induced gene expression. Using Clontech microarrays we have monitored the change of gene expression patterns induced by standard intravenous steroid pulse therapy for treatment of MS relapses in human PBMCs ex vivo. Total RNA was isolated from density gradient purified lymphocytes of freshly accessed blood samples. $dCTP^{32}$ labeled cDNA was then hybridized to human cDNA expression array membranes. Simultaneous autoradiographic analysis of 588 genes indicated an increase in the expression of several transcription, differentiation and proliferation factors in 5 patients. Upregulated genes included granulocyte colony stimulating factor receptor-1, LFA-1, interferon gamma induced protein, PDGF, IL-2, Interleukin-1 Receptor Type II, whereas prothymosin alpha, calgranulin B, thymosin-beta and connective tissue growth factor were downregulated. Amongst these are genes hitherto not described as steroid-responsive in lymphocytes or PBMCs. This technique may be applied to PBMCs ex vivo and allow to detect and monitor disease specific or treatment induced gene expression patterns in a easily accessible material. *Funding: University Research Funds*

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MULTIPARAMETRIC MRI STUDY OF FRONTAL LOBE DEMENTIA IN MULTIPLE SCLEROSIS. G. Comi, M. Rovaris*, F. Possa, G. Iannucci*, G. Santuccio, L. Minicucci*, M. Filippi*. Clincal Trials and *Neuroimaging Research Units, Dept. of Neuroscience, H San Raffaele, Milan, Italy.

New magnetic resonance imaging (MRI) measures, such as the estimation of MS lesion load on T1-weighted and fast fluid-attenuated inversion recovery (fast-FLAIR) images and the histogram analysis of magnetization transfer (MT) ratio (MTR) maps, improved the degree of the correlations between clinical and MRI findings in multiple sclerosis (MS). We assessed their relationship with the presence of MS-related cognitive decline. Dual echo, T1-weighted, fast-FLAIR and MT brain MRI scans were obtained in 11 MS patients with and in 11 without frontal lobe dementia, matched for age, sex, education and disability. Total (TLL), frontal (FLL) and subcortical (SLL) lesion loads were assessed from fast-FLAIR, T2- and T1-weighted images. The degree of brain atrophy was measured from T1-weighted scans. On MT scans, MTR histogram analysis was performed for the whole brain, the frontal lobe, the subcortical regions and the cerebellum. Multiple, subcortical MS lesions were visible on all the scans obtained from cognitively impaired patients with any MRI technique, whereas 4/11 unimpaired patients did not show any subcortical lesions on any scans. Average TLL, FLL and SLL were significantly higher in cognitively impaired patients for all the imaging techniques. The MRI measure that better discriminated the two groups of patients was fast-FLAIR TLL. Brain atrophy was significantly more severe in cognitively impaired patients. Average MTR, peak height and location of overall brain, frontal lobe and subcortical MTR histograms were significantly lower for cognitively impaired patients. The presence of cognitive decline in MS is associated with the extent and pathological severity of brain MRI abnormalities. A regional analysis of these abnormalities does not significantly improve the relationship between MRI and cognitive findings.

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MAGNETIZATION TRANSFER HISTOGRAM ANALYSIS OF NORMAL APPEARING BRAIN TISSUE FROM PATIENTS AT PRESENTATION WITH CLINICALLY ISOLATED SYNDROMES SUGGESTIVE OF MULTIPLE SCLEROSIS. M. Filippi, C. Tortorella, G. Iannucci, M. Rovaris, M.A. Rocca, M. Bozzali, G. Comi*. Neuroimaging Research And *Clinical Trials Units, Dept Of Neuroscience, H San Raffaele, University Of Milan, Italy.

In this study, we obtained magnetization transfer (MT) histograms of normal appearing brain tissue (NABT) from patients with clinically isolated syndromes (CIS) suggestive of multiple sclerosis (MS) to evaluate whether tissue outside lesions visible on conventional magnetic resonance imaging (MRI) scans is damaged in the early phases of MS. Twenty-four patients with CIS, with the first clinical attack in the preceding three months and at least four focal abnormalities on T2-weighted scans, were included in the study. Twenty healthy subjects served as controls. To create MT histograms of the normal-appearing cerebral tissue, MS lesions were segmented from dual-echo scans and superimposed automatically and nulled out from the co-registered and scalp-stripped MTR maps. For each magnetization transfer ratio (MTR) histogram, the following parameters were analyzed: the peak height and the peak position and the mean average MTR value. T2 and T1 lesion loads, brain volume and average lesion MTR were also assessed. Compared to controls, CIS patients had lower average MTR ($p < 0.0001$) and peak position ($p=0.002$). No differences in brain volume were found between patients with CIS and controls. No correlation was found between NABT-MTR, average lesion MTR and T2 lesion load, while a correlation was found between NABT-MTR and brain volume ($r=0.5$; $p=0.01$). CIS are characterized by subtle abnormalities in the NABT which go undetected when using conventional MRI. Small focal abnormalities, beyond the resolution of conventional scanning, located in the normal appearing white or grey matter might explain these changes.

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MRI AND MTI CHANGES IN THE BRAIN AND SPINAL CORD FROM PATIENTS WITH DEVIC'S NEUROMYELITIS OPTICA. M. Filippi, M.A. Rocca, L. Moiola, V. Martinelli, A. Ghezzi, F. Salvi, R. Capra, G. Comi. Neuroimaging Research Unit, Dept. of Neuroscience, H San Raffaele, Milan, Italy.

Devic's neuromyelitis optica (DNO) is a syndrome in which a severe myelopathy is associated with an optic neuritis. In DNO, magnetic resonance imaging (MRI) shows a severe damage of the cervical cord with virtually no brain abnormalities. In multiple sclerosis (MS), magnetization transfer imaging (MTI) is sensitive in detecting microscopic abnormalities in the white matter which appears to be normal on conventional MRI scans. In this study, we compared MRI and MTI changes of the normal appearing white matter (NAWM) in the brain and in the cervical cord from DNO patients with those from MS patients and controls. Brain and cervical cord MRI and MTI scans were obtained from 8 DNO, 10 MS patients and nine controls. No significant difference was found for any of the brain NAWM MTR histogram metrics between DNO patients and controls. Compared to controls, brain NAWM histograms from MS patients had lower average MTR ($p=0.02$), peak height ($p=0.001$) and number of pixels ($p=0.01$). Compared to DNO, MS patients had lower average MTR ($p=0.006$) and peak position ($p=0.012$). Cervical cord MRI was abnormal in all DNO and in nine MS patients. DNO and MS patients had lower average cervical cord MTR ($p=0.02$) than controls. MS patients had also lower peak height than controls ($p=0.03$). There was no difference in cervical cord MTR histogram metrics between DNO and MS patients. DNO is a disorder characterized by a sparing of the brain white matter. In spite of the different appearance on conventional MRI scan of the cervical cord lesions in patients with DNO and MS, analysis of the cervical cord MTR histograms suggests that the overall damage is comparable between the two groups.

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MRI ASSESSMENT OF MACRO- AND MICROSCOPIC BRAIN PATHOLOGY IN PATIENTS WITH MULTIPLE SCLEROSIS AND VASCULITIDES. M. Rovaris, B. Viti, G. Ciboddo*, R. Capra, G. Comi** C. Tortorella, M. Filippi. Neuroimaging Research and **Clinical Trials Units, Dept. of Neuroscience and *Dept. of Internal Medicine, H San Raffaele, Milan, Italy.

Magnetization transfer imaging (MTI) has a higher pathological specificity than conventional magnetic resonance imaging (MRI) and can provide information on the "invisible" lesion load affecting the normal appearing white matter (NAWM). We compared brain MRI and MTI findings in patients with multiple sclerosis (MS) and different vasculitic diseases of the CNS. Brain dual-echo and MTI scans were obtained in patients with systemic lupus erithematosus (SLE) without clinical CNS involvement (n=15), SLE with CNS involvement (NSLE) (n=9), Behcet disease (BD) (n=5), Wegener granulomatosis (WG) (n=9), antiphospholypid antibody syndrome (APLA) (n=6) and MS (n=10). T2-weighted and MT-calculated images of the same subject were co-registered and post-processed to obtain MT histograms of the whole brain and of the NAWM. Hyperintense T2-weighted lesions were found in all MS and NSLE patients and in 5/15 SLE, 5/9 WG, 1/5 BD and 3/6 APLA patients. The burden of T2-weighted hyperintense lesions was significantly higher in MS patients. All MTR histogram parameters were significantly different among patient subgroups. MS patients had significantly lower average MTR than all but NSLE patients and significantly lower peak height and location than SLE patients. NSLE patients had significantly lower average MTR than SLE patients. Microscopic NAWM damage is relevant in MS patients, but, apart from patients with NSLE, seems to be absent in other systemic vasculitic disorders, even in the presence of macroscopic lesions seen by T2-weighted MRI or symptoms/signs of CNS involvement.

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HASTE-FLAIR AND EPI-FLAIR SEQUENCES IN THE IMAGING OF MS PATIENTS: A COMPARISON WITH FAST-FLAIR. M. A. Rocca, G. Mastronardo, C. Pereira, I. Yousry*, T. A.. Yousry*, M. Filippi. Neuroimaging Research Unit, Dept Of Neuroscience, H San Raffaele, Milan, Italy; *Dept Of Diagnostic Radiology, Klinikum Grosshadern, University Of Munich, Germany.

Fast fluid-attenuated inversion recovery (FLAIR) sequences are very sensitive in detecting lesions in patients with multiple sclerosis (MS) with reduced acquisition time as compared to conventional spin-echo sequences. Aim of this study was to compare the sensitivities of fast-FLAIR, fast-FLAIR with half-fourier acquisition single-shot turbo gradient spin echo (HASTE) and echo planar imaging (EPI) -FLAIR sequences in detecting MS patients' lesions. Fourthy-six MS patients entered the study. Magnetic resonance imaging (MRI) of the brain was performed using two 1.5 Tesla machines. Areas of high signal intensity thought to represent lesions were marked on the hard-copies and each lesion was scored according to size and site. A total of 1905 lesions were detected on fast-FLAIR, 1175 on HASTE-FLAIR and 1134 on EPI-FLAIR scans. HASTE-FLAIR and EPI-

FLAIR sequences detected similar numbers of lesions, except for the infratentorial regions (p=0.006). Morever, they detected fewer number of lesions than fast-FLAIR ($p < 0.0001$). This was due to the poor sensitivity of HASTE-FLAIR and EPI-FLAIR in detecting small lesions. The image quality of EPI-FLAIR was inferior to that of HASTE-FLAIR and both of them had an image quality worse than that of fast-FLAIR sequences. HASTE-FLAIR and EPI-FLAIR sequences are as sensitive as fast-FLAIR in detecting large MS lesions. Since their time acquisitions are only a fraction of that needed for fast-FLAIR sequences, they might be used for making a rapid diagnosis of MS in uncooperative patients.

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REPRODUCIBILITY OF MTR HISTOGRAM-DERIVED MEASURES OF THE BRAIN IN HEALTHY VOLUNTEERS. M.P. Sormani, G. Iannucci, M.A. Rocca, M.A. Horsfield*, G. Mastronardo, M. Filippi. Neuroimaging Research Unit, Dept Of Neuroscience, H San Raffaele, Milan, Italy; *Division Of Medical Physics, Leicester, Uk.

Magnetization transfer ratio (mtr) histogram analysis is a promising technique for the monitoring of multiple sclerosis (ms). In this study, we evaluated the intra-observer, the inter-observer, the scan-rescan and the inter-scanner variabilities in the assessment of mtr histograms obtained monthly on four occasions from five healthy volunteers using two scanners. We obtained two sets of mtr histograms. The first consisted of mtr histograms obtained from the whole imaged tissue without any human intervention. This allowed to assess the 'pure' scan-rescan and the inter-scanner variabilities. The second consisted of mtr histograms obtained by three observers, who segmented the brain from the surrounding tissue using a semi-automated segmentation technique. One of the three observers repeated this procedure on two occasions. This allowed to assess the intra-observer, the inter-observer variabilities and the scan-rescan and the inter-scanner variabilities with multiple observers. The mean coefficients of variations (covs) ranged from 1.0% to 2.3% for 'pure' scan-rescan variability, from 1.2% to 4.9% for inter-observer variability and from 2.1% to 4.9% for scan-rescan variability with multiple observers. Mean intra-observer covs were always lower than 1%. Mean cov ranged from 11.2% to 13.7% for 'pure' inter-scanner variability and from 8.6% to 14.3% for inter-scanner variability with multiple observers. Inter-scanner variability accounted for 96.0% of the overall variability of average mtr, 96.7% for that of peak location and for the 41.1% of the peak height. The use of different mr scanners is the main source of variability when obtaining mtr histograms. This claims for a careful standardization of the mt acquisition procedures when performing multi-center studies in ms.

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MAGNETIZATION TRANSFER HISTOGRAMS OF THE CERVICAL CORD FROM PATIENTS WITH MULTIPLE SCLEROSIS. M. Bozzali, M.A. Rocca, C. Tortorella, C. Pereira, G. Comi*, M. Filippi. Neuroimaging Research and *Clinical Trials Units, Dept. of Neuroscience, H San Raffaele, Milan, Italy.

Spinal cord damage is a common feature of multiple sclerosis (MS) and might contribute to the development of severe and fixed neurological deficits. Magnetization transfer (MT) imaging is sensitive to the more destructive aspects of MS and MT histogram analysis provides accurate estimates of the overall (macro- and micro-scopic) disease burden of the brain. Aim of this study was to evaluate, using MT histograms, the amount of the macro- and micro-scopic damage in the cervical spinal cord from patients with MS and different disease evolutions. Cervical cord T2 weighted and MT scans were obtained from seventy-eight MS patients (51 with a relapsing-remitting [RR], 18 with a secondary progressive [SP] and 9 with a primary progressive [PP] course) and 21 age- and sex-matched controls. Quantitative MTR maps and MTR histograms were derived. In MS patients, the median number of lesions on the T2 weighted scans was 2 (range 1-5). Compared to controls, the overall MS population and each of the clinical subgroup considered had lower MTR (p= 0.009), MTR_{25} (p= 0.003), and the MTR_{50} (p= 0.002) than controls. Patients with PPMS had the lowest peak height and location. In patients with RRMS there was a significant correlation between average spinal cord MTR and EDSS (r value= -0.3; p=0.04). This study shows that it is possible to obtain MT histograms of the spinal cord and that this technique is helpful in improving the understanding of the different factors underlyng the clinical manifestation of MS.

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CHANGES IN THE NORMAL-APPEARING BRAIN TISSUE AND COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS. M. Filippi, C. Tortorella, M. Rovaris, M. Bozzali, F. Possa*, G. Iannucci, G. Comi*. Neuroimaging Research and *Clinical Trials Units, Dept. of Neuroscience, H San Raffaele, Milan, Italy.

The contribution of normal-appearing brain tissue (NABT) and normal-appearing white matter (NAWM) changes to the impairment of cognition in multiple sclerosis (MS) patients is still unknown. We assessed a) whether the changes in the NABT/NAWM, as revealed by magnetization transfer (MT) histogram analysis, correlates with cognitive dysfunction in MS patients and b) the relative contribution of these changes in comparison to that of MS lesions visible on conventional magnetic resonance imaging (MRI) scans. Dual echo, T1-weighted and MT scans of the brain were obtained in 12 MS patients with and in 7 without cognitive impairment. Patients were matched for demographic and other disease-related variables. Lesion loads were assessed from T2- and T1-weighted scans. MT histogram analysis was performed for the NABT and the NAWM. Average lesion MT ratio (MTR) and brain size were also measured. T2- and T1- lesion loads were significantly higher and the average lesion MTR and brain size were significantly lower in the group of cognitively impaired patients. Patients with cognitive deficits also had significantly lower MT histograms values for all the variables tested (except peak height) in the NABT and NAWM. Logistic regression analysis showed that 68% of the total variance was explained by MTR of MT histograms from NABT alone and 43% by MTR of MT histograms from NAWM alone. Multivariate regression model showed that these two measures were the only factors that significantly predicted cognitive impairment in our patients (p=0.001). The extent of abnormalities which go undetected when using conventional MRI scanning is relevant in determining cognitive impairment in MS.

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AUTOLOGOUS BLOOD STEM CELL TRANSPLANTATION FOR PROGRESSIVE MULTIPLE SCLEROSIS: INTERIM ANALYSIS OF EFFICACY AND TOXICITY. Fassas A[1], Kazis A[2], Anagnostopoulos A[1], Kapinas K[2], Sakellari I[1], Kimiskidis V[2], Tsimourtou V[2]. Depts of Haematology[1] and Neurology[2], G.Papanikolaou Hospital, Thessaloniki,Greece

Autologous BSCT is a novel treatment for severe autoimmune diseases, including progressive MS (pMS). We now report an interim analysis of our two pilot studies. In the first one, 15 patients with pMS were treated with BEAM, autologous BSCT and Anti-thymocyte Globulin (ATG) whereas in the second one, which included 9 further patients, additional $CD34^+$ selection of the graft was performed. Median follow up is 30 months (range=9-39). Out of 23 surviving patients, 18 responded (18/23, 78%) in the sense of getting improved or stabilised on EDSS whereas the remaining 5 progressed. Four out of these 5 had primary pMS. Out of 18 responders, 12 patients (12/18, 58%) have maintained a stable condition whereas 6 developed relapses or slowly progressed after initial improvement. $CD34^+$ selection appeared to give a higher (albeit statistically non significant) percentage of patients maintaining a stable condition (75 vs 40%). However, it resulted inpotent immunosuppression with the subsequent death due to aspergillosis (1/24, 4%). Other adverse effects of BSCT included fever, allergy, bacteremia and transient neurotoxicity. These encouraging results wait confirmation by a currently ongoing multi-center study of BSCT in MS.

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SKEWED T-CELL RECEPTOR V USAGE OF CD8+ BUT NOT CD4+ T-CELLS IN CEREBROSPINAL FLUID FROM MULTIPLE SCLEROSIS PATIENTS. B. Hemmer, M. Jacobsen, S. Schock, B. Osburg, W. H. Oertel, N. Sommer. Clinical Neuroimmunology Group, Department of Neurology, Marburg University, Rudolf-Bultmann-Str. 8, 35033 Marburg, Germany

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system. Inflammatory changes of brain lesions strongly suggest that T cells are involved in MS pathogenesis. However, it is not clear, whether specific T-cell populations are enriched in brain and cerebrospinal fluid (CSF) compared to peripheral blood. Methods: We have used a novel multiparametric flow-cytometry technique to determine T-cell receptor (TCR) Vβ expression on T cells from CSF and blood using a panel of 22 TCR Vβ antibodies in combination with CD4 and CD8 markers. Thirty patients with probable or definite clinical MS and oligo-

clonal IgG expression in the CSF were included in the study. TCR profiles for CD4+ and CD8+ T cells from CSF and blood were compared in each individual patient to detect repertoire changes. Results: We found only minor differences of TCR Vβ expression on CD4+ cells in patients' CSF compared to peripheral blood. In contrast, remarkable and highly significant differences were detected for the Vβ expression on CD8+ T-cells, with individually variable over-expression of one or few Vβ chains in the CSF. Conclusions: The results demonstrate that specific CD8+ T-cell populations are selectively enriched in the CSF of MS patients suggesting their relevance to the disease process. The technique used here is a novel and powerful approach to determine, characterise, and isolate T-cell populations from the CNS likely to be related to MS pathogenesis.

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LONG-TERM CHANGES OF INTERFERON GAMMA PRODUCTION IN BLOOD LYMPHOCYTES OF PATIENTS UNDER INTERFERON BETA TREATMENT. H.F. Petereit, S. Bamborschke, W.D. Heiss. Department of Neurology, Cologne, Germany.

Interferon beta therapy has been shown to be effective in reducing disease activity in patients with multiple sclerosis (MS). A reduction of proinflammatory cytokine production by T lymphocytes has been discussed as one possible mechanism. Until now it is unknown if these immunological changes are temporary effects or if they persist during long-term therapy. Here we present data of 12 patients with relapsing remitting MS who were followed up during the first two years of interferon beta treatment. Exacerbation number and frequency, disability and interferon gamma producing blood lymphocytes were measured before therapy and after one and two years of treatment. Disability was assessed according to the expanded disability status scale (EDSS). Interferon gamma production (IFG) was detected in stimulated CD3+ blood lymphocytes. Before therapy, the mean exacerbation frequency was 1,67/year. The EDSS was between 1.0 and 4.5 with a mean of 2,33 and the mean IFG was 11,9% (standard deviation SD 6,80%). After one year of therapy, the mean IFG was reduced to 9,49% (not significant), after 2 years of therapy to 6,61% (SD 4,17%, $p < 0,02$). Mean EDSS did not change significantly. The mean exacerbation frequency decreased significantly in the first (0,5/year, $p < 0,005$) and second year of therapy (0,25/year, $p < 0,005$). Our results suggest that the reduction of interferon gamma producing lymphocytes is a persistent effect of clinically successful interferon beta therapy.

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ISOLATED CRANIAL NEUROPATHY AS INITIAL SYMPTOM OF MULTIPLE SCLEROSIS: CLINICAL FEATURES AND PROGNOSIS. R. Gil de Castro, C. de Andrés, A. Guillem and S. Giménez Roldan. Department of Neurology. HGU Gregorio Marañón, Madrid. Spain

Isolated cranial neuropathy as the initial symptom of multiple sclerosis (MS) is unusual. The objective is to establish clinical features of these patients and to evaluate potential prognostic factors. Patients and method: 30 patients (63% female, 27% male), both prospective (70%) and retrospective (30%), followed-up during a mean period of 5 years (range 2-17). All prospective patients had MRI performed after the first bout, evoked potentials were also available in every case and CSF analysis in 95,2%. Results: Cranial nerves affected were: V(56,6%), VI(23,3%), VII(23,3%), VIII(10%), III(10%), IV(6,6%), IX(3,3%), XII(3,3%) and more than one (26,6%). MRI showed disseminated lesions in 85,7% of prospects and localized affected nerves in 40%. CSF analysis detected an increase of IgG index and/or presence of oligoclonal bands in 47,6% of cases. Neurophysiology was MS compatible in 62,5% of cases, showing topographical dissemination in 68,7%. Bout rate of occurrence was 0,5/year. Poser criteria of clinically defined MS were met by 43,3% after the first two years of control and by 81,8% after the first five. Mean Expanded Disability Status Scale (EDSS) was 1 (range 0-4) at the end of the period. Conclusions: Unusual symptom with good prognosis in the short timeframe. No correlation found between EDSS and CSF abnormal findings. These patients should be considered for early treatment therapies.

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VENTRICULAR VOLUMES IN MULTIPLE SCLEROSIS: WHICH LINEAR MEASURES CORRELATE BEST WITH 3D VOLUMES AND CLINICAL PARAMETERS ?BP Turner, N Ramli, T Jaspan, LD Blumhardt. University of Nottingham, UK

MRI and pathological studies have demonstrated the role of axonal loss and atrophy in multiple sclerosis (MS). Estimated ventricular enlargement may usefully index axonal loss, but conventional imaging methods employed in MS trials to date permit measurements only in 2D. Aim To investigate the relationship between 3D and 2D measures of ventricular volumes and clinical parameters. Methods: Linear measurements of the ventricles on conventional T_1-weighted images were compared with volume estimates obtained by stereology on 3D T_1-weighted MRI scans in 40 MS patients and 10 healthy controls. Associations with age, symptom duration and clinical disability were investigated. Results: Our ventricular volumes in healthy controls were similar to published normative data. Third ventricle width was strongly correlated with 3D volume estimates of the third ($r=0.81$, $p < 0.0001$) and lateral ventricles ($r=0.79$, $p < 0.0001$). The best 2D lateral ventricular measure was the oblique anterior horn width ($r=0.69$, $p < 0.0001$). Third ventricular volumes significantly correlated with symptom duration ($r=0.52$, $p=0.0007$) with trends for EDSS ($r=0.36$, $p=0.0222$) and Scripp's Neurological Rating Scale ($r=-0.38$, $p=0.0175$). Conclusion: Third ventricle width and oblique anterior horn width are simple and easily applicable measures that will accurately predict ventricular volumes from 2D images. In addition, third ventricular volumes, as reflected by third ventricular width, are significantly associated with the clinical stage of disease, symptom duration and disability.

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MACROPHAGIC MYOFASCIITIS (MMF) ASSOCIATED WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT. Authier FJ, Créange A, Bonnotte B, Ranoux D, Abdelmoumni A, Vogel R, Chérin P, Gherardi RK. For the GERMMAD (Groupe d'Etudes et Recherche sur les Maladies Musculaires Acquises et Dysimmunitaires), Association Française contre les Myopathies (AFM), PARIS, France.

Objective: To describe central nervous system involvement (CNS) in 5 patients with macrophagic myofasciitis (MMF). Introduction: MMF is a newly described inflammatory myopathy of unknown origin, emerging in Europe (Gherardi et al, Lancet 1998;352:347-52). It is characterized by highly specific myopathological alterations, that have been observed in patients with poorly specific muscle symptoms, most often arthromyalgias and mild muscle weakness. Methods: Retrospective evaluation of 26 French patients with biopsy-proven MMF collected from 1993 to 1998. Results: 7/26 patients with MMF had CNS involvement, including 5 with avalaible clinical data (4 women, 1 man; aged 29-72 ys). Presenting CNS manifestations were sensory or sensorimotor hemisymptoms (4/5) and marked fatigue (4/5). Two had a relapsing course. Other neurological manifestations included bilateral pyramidal signs (3/5), cerebellar signs (2/5), cranial nerve involvement (1/5) and aphasia (1/5). Brain T2-weighted MRI showed hypersignal areas in in sustentorial white matter (4/4) and atrophic corpus callosus (1/4). Evoked potential were abnormal in 2/3 patients, and CSF in 1/3 (oligoclonal bands). Four patients were considered to have multiple sclerosis (MS). Four patients also complained of myalgias (3/4) or myopathic proximal weakness (1/4). Most patients had normal CK levels (4/5) and EMG (4/5). Muscle biopsy showed massive macrophage infiltrates in epi-, peri- and endomysium with typical osmiophilic intralysosomal apatite-like crystals, sparse CD8+ T-cells, and minimal myofiber damage. Intestinal biopsies (5/5) did not show pathological features of Whipple's disease. A combination of antibiotics and steroids improved symptoms in 3/4 patients. Conclusion: Typical MMF may be associated with a MS-like CNS involvement of an unknown significance.

P290
UVEITIS AND RETINAL INFLAMMATION IN MULTIPLE SCLEROSIS. Stephan Schmidt[1], Ludger Wessels[2], Albert Augustin[2], Thomas Klockgether[1]Departments of Neurology[1] and Ophthalmology[2], University of Bonn

Multiple Sclerosis (MS) is a chronic putatively autoimmune demyelinating disease of the central nervous system (CNS). Though ocular manifestations are common in MS, only few studies have systematically investigated the presence of ocular inflammation apart from optic neuritis. We performed a prospective study in 50 consecutive patients with clinically definite MS to determine the frequency of uveitis and retinal inflammation. 6/50 patients showed evidence of retinal inflammation on slit lamp examination. In 2/6 patients acute inflammation was confirmed by fluoresence angiography. In addition, we reviewed the history of 11 patients with manifest uveitis [anterior uveitis (n=8), intermediate uveitis (n=1) and posterior uveitis (n=2)] and clinically definite MS. Systemic vasculitis and sarcoidosis had been previously excluded in all patients. The onset of uveitis (mean age 27.9±8.2 years) consistently preceded the onset of neu-

rological symptoms (mean age 35.4±7.9 years). The distribution of lesions on cranial MRI did not differ between patients with and without uveitis. These clinical observations confirm experimental studies demonstrating that T-cells specific for antigens co-expressed in the eye and the CNS may induce both encephalitis and uveitis. The delayed onset of the neurological symptoms in the 11 MS patients with concomitant uveitis may even indicate that an autoimmune response primarily directed against uveal antigens might be pathogentically relevant in a small subgroup of MS patients.

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(Abstract P291 added in proof – see page I/185)

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P292
NUCLEAR AND FASCICULAR THIRD NERVE LESION, A CASE REPORT: Nagbhushan S. Rao. Olean Medical Group, Olean, N.Y. U.S.A.

Well documented nuclear or fascicular 3rd nerve lesions are very rare.Rostral nuclear lesions may not produce bilateral ptosis due to sparing of a singal caudal central nucleus.We report a case of combined nuclear and fascicular 3rd nerve lesion. A 59 year old white man status post prostatic carcinoma developed severe headache, nausea, ataxia and altered sensorium over a few hours. Patient was arousable,had severe dysarthria, complete left 3rd nerve palsy, right superior rectus palsy, normal left 6th nerve,2mm reacting right pupil and right hemiparesis. CT reveled a left cerbellar infarct. Next day MRI showed additional left thalamic and paramedian midbrain infarct extending anteroposteriorly. Lumbar puncture was normal. Several days later right hemiparesis improved but showed significant ataxia for hand movement and gait. Visually guided rightward saccades were impaired. Oculocephalics towards right revealed normal abduction but absent adduction. Right superior rectus palsy remained. Total left 3rd nerve palsy did not resolve. MRA was normal. A month later patient was home ambulating. Oculomotor abnormality did not resolve.Thalamic lesion resulted in impairment of visually guided saccades towards right side. Right superior rectus palsy was related to left 3rd nerve nuclear involvement.Complete left 3rd nerve palsy was related to fascicular involvement in the midbrain. In summary we report a patient with a combined nuclear and fascicular 3rd nerve lesion based on MRI, hitherto undescribed.

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VERTICAL SEMICIRCULAR CANAL FUNCTION BY THE CALORIC TEST-A STUDY ON PATIENTS WITH BENIGN PAROXYSMAL POSITIONAL VERTIGO - Masahiro Iida, M.D.Department of Otorhinolaryngology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-1193, Japan

The morbidity of benign paroxysmal positional vertigo (BPPV) was investigated from the functional standpoint by analyzing nystagmus elicited by the caloric test. The subjects of the study consisted of two males and 4 females with posterior semicircular canal variants of BPPV. An infrared CCD camera and a personal computer system were used to analyze the nystagmus. For the caloric test, a small quantity (5 cc) of cold water (20°C_) was used as the stimulus. The test was performed with the head tilted at 30°C forward from the supine position. At this time, the CCD camera was attached over the left eye. As a result of an investigation of the three (horizontal, vertical and torsional) components of the nystagmus elicited by the caloric stimulus, the directions of the horizontal and torsional nystagmus were found to be symmetric between the left and right ears in all 6 cases. Regarding vertical nystagmus, there were differences between the left and right ears, with upward vertical nystagmus found on the affected sides in all 6 cases. The activity of the anterior semicircular canal should exceed that of the the posterior semicircular canal in the affected ear. The vertical nystagmus elicited by the caloric stimulus reflected the functions of the anterior and posterior semicircular canals, and investigation of the difference in function between the anterior and posterior semicircular canal from the direction of the vertical nystagmus appeared to be feasible _

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INVESTIGATION OF EYE MOVMENTS IN PARKINSONS'S DISEASE AND HEREDITARY CAREBELLAR ATAXIA. S. Cherninkova, V. Dimova / University Alexander Hospital, Department of Neurology, Sofia, Bulgaria

Electro-oculographic study of saccadic and smooth pursuit eye movements was performed in 21 Parkinsonian patients / 12 male and 9 female, mean age = 56,8 years / and 7 patients with hereditary cerebellar ataxia / 3 male and 4 female, mean age = 46,2 years /. The results were compared with two groups of 20 age matched healthy subjects. The peak velocity of horizontal and vertical saccades was significantly slowed both in parkinsonians and in patients with hereditary cerebellar ataxia. The most typical morphological feature of smooth pursuit eye movments was saccadic pursuit, abnormal configuration of single waves, witch was found in almost all patients of both groups. The patients did not have clinically apparent oculo-motor disorders. Electro-oculographic findings are related with subclinical lesion of ocular mobility.

P295
GALVANIC STIMULATION IN BILATERAL VESTIBULAR FAILURE: OCULAR MOTOR EFFECTS. Reto Zink, Alexander Weiss, Thomas Brandt, Marianne Dieterich/Department of Neurology, Ludwig-Maximilians-University, Munich, Germany

Since 3-D analysis of eye movements is possible, galvanic vestibular stimulation is increasingly being used to test vestibulo-ocular function. In normal subjects galvanic stimulation at the mastoid level elicits tonic ocular torsion of 2.8° ± 0.8° toward the anode with low current strength (≤ 3 mA) and superimposed dynamic torsional-horizontal nystagmus at higher current intensities (≥ 3 mA). It remains unclear which peripheral and/or central vestibulo-ocular structures are stimulated by this method and to what extent galvanically elicited eye movements can be used for clinical testing. Eight patients (2 females, 6 males; mean age 50 years) with bilateral vestibular failure (BVF) underwent binaural galvanic mastoid stimulation (rectangular, unipolar, 1.0 – 3.0 mA) during 3-D monocular video-oculography (60 Hz). The patients exhibited three major differences from the normal controls: (1) Tonic ocular torsion was significantly smaller (1.3° ± 0.6° at 3 mA), (2) rotatory nystagmus was stronger and occurred with lower current intensities in 7 of 8 patients, and (3) a "rebound nystagmus" was recorded at the end of stimulation in 6 of 8 patients. It must be assumed that the ocular motor effects of galvanic stimulation in patients with bilateral vestibular failure indicate excitation of central vestibulo-ocular brainstem structures despite the peripheral vestibular loss and that these structures exhibit an overexcitability. Overexcitability may be explained by the absence of spontaneous resting discharge due to peripheral deafferentation, which normally reduces the effects of disturbing impulses and thus helps to maintain balance.

P296
NEUROVASCULAR RELATIONSHIPS OF THE ABDUCENS NERVE USING 3DFT-CISS AND TOF SEQUENCES. I. Yousry[1], S. Camelio[1], M. Wiesmann[1], B. Moriggl[2], H. Brückmann[1], T. A. Yousry[1/1]Department of Neuroradiology, Department of Anatomy[2], Ludwig-Maximilians University, Munich, Germany.

It was recently shown that using the three-dimensional Fourier transformation constructive interference in steady-state (3DFT-CISS) sequence the abducens nerve (NVI) could be reliably identified. In a further step, we wanted to assess the neurovascular relationship of NVI using time of flight (TOF) sequences for magnetic resonance (MR) angiography as well as 3DFT-CISS sequences. Materials: In 20 volunteers we obtained a 3DFT-CISS, in 10 a TOF sequence. We noted whether the vessel was "anterior" or "posterior" to NVI. We measured the distance between the area of contact and the pontomedullary sulcus. Results: NVI could not be identified using TOF sequences.. In the 3DFT-CISS sequence the blood vessel most often identified was the anterior inferior cerebellar artery (AICA) (n=47). It was in contact with NVI in 76.6%. The AICA passed anterior to the nerve in 63.8% and posterior in 29.8%. The mean distance between the pontomedullary sulcus and the area of contact was 5.9 mm for vessels anterior and 8.9 mm for vessels posterior to NVI. Discussion: MR imaging reliably identifies the neurovascular relationship of NVI when using 3DFT-CISS sequences. MR angiography can assist in identifying the arteries but failes to visualize NVI.

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INFLUENCE OF CIGARETTE SMOKING ON BALANCE: CORRELATION OF NICOTINE-INDUCED NYSTAGMUS AND POSTURAL BODY SWAY. CB Pereira, M Strupp, A Holzleitner, and Th Brandt, Dept. of Neurology, Munich, Germany

Smoking may cause transient dizziness and nystagmus, especially in nonsmokers. The aim of this study was to correlate the anterior-posterior (AP)

and lateral body sway with the intensity and direction of the nicotine-induced upbeat nystagmus. Postural body sway and eye movements were recorded simultaneously before and 1, 5, and 10 min after smoking a cigarette (containing 0.9 mg nicotine) in 4 healthy non-smokers, who had been found in an earlier study to regularly develop a nicotine-induced upbeat nystagmus. Eye movements were measured by videonystagmography and postural body sway by posturography as AP-, lateral, and total "sway path values" (SP) while the subject stood on a compliant, foam rubber-padded platform in the dark. Nicotine caused significant increases in SP in all subjects. AP-SP increased from 1.80 ± 0.26 m/min (x SE) before smoking to 2.31 ± 0.33 m/min 1 min after smoking ($p < 0.001$, $n = 4$) and the lateral SP from 0.98 ± 0.11 m/min to 1.38 ± 0.12 m/min ($p < 0.01$). Subsequently there was a gradual decrease of SP, which reached normal values within 10 min after inhalation. There was a high correlation between the SP and the intensity and time course of the pharmacologically induced upbeat nystagmus. Thus, (1) nicotine caused a significant and transient increase in SP in all directions; (2) the close correlation of the intensity, and time course of the SP, and the nystagmus supports the interpretation that nicotine acts primarily on the vestibulo-ocular and vestibulospinal systems rather than on the ocular motor system alone.

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NICOTINE-INDUCED NYSTAGMUS: THREE-DIMENSIONAL ANALYSIS OF EYE MOVEMENTS AND DEPENDENCE ON HEAD POSITION. CB Pereira, M Strupp, Th Eggert, A Straube, R. Zink, and Th Brandt, Dept. of Neurology, Munich

Smoking may induce different forms of nystagmus, due to the action of nicotine. There is some controversy in the literature about the direction of nicotine-induced nystagmus (which is mainly reported as upbeat) and, so far, three-dimensional eye movement analysis has not been performed. Further, it is unclear whether nicotine-induced nystagmus is an ocular motor or a vestibular phenomenon. If vestibular, a tone imbalance of the vestibulo-ocular reflex is the most likely cause. This should be modulated by otolith input. Therefore, two- or three dimensional eye movement recordings (videonystagmography or search coil technique) were made in 42 healthy, occasional smokers or non-smokers before and 1, 5, and 10 min after smoking a cigarette (containing 0.9 mg nicotine). These measurements were made with the subjects in standing and supine positions in order to evaluate the influence of varying otolith input on the nystagmus. Twenty of the 42 subjects showed a nicotine-induced nystagmus, which occurred 1 to 5 min after smoking. Only 5 of these 20 persons exhibited an upbeat, 6 a horizontal, 2 a diagonal nystagmus, and in 7 a transition was observed from upbeat to horizontal nystagmus within 5 min. A torsional component was found in 4 subjects. The influence of changes in head position was evaluated in 14 of these 20 subjects. In 10, the peak slow phase velocity increased by 100 to 300% after transitions from the standing to the supine position. The two major findings of this study are as follows: (1) Contrary to previous descriptions, nicotine not only causes upbeat, but also horizontal nystagmus, both frequently combined with torsional components. (2) Nystagmus intensity in most subjects increased after transition from standing to supine position (i.e., modulation of otolith input), The latter finding supports the view that nicotine-induced nystagmus reflects pharmacologically induced vestibulo-ocular tone imbalance.

P299
EVALUATION OF VISUAL FIELDS PERFORMED WITH AUTOMATED PERIMETRY IN OPTIC NEURITIS. N. Georgiadis*, C. Terziclou*, I. Milonas**, M. Paschalidou**, S. Lake*. Eye Univ. Clinic, AHEPA Hospital, Thessaloniki, Greece B' Univ. Department of Neurology, AHEPA Hospital, Thessaloniki, Greece

Purpose: To evaluate the sensitivity of the automated perimetry in the diagnosis and follow up of optic neuritis. Method: 24 patients were examined with the Octopus 500EZ perimeter. Sixteen patients suffered from multiple sclerosis, 6 from retrobulbar neuritis and 2 from attypical optic neuritis. Using the G1 program and the "Peridata 6,1 c" soffware, 32 pairs of visual fields (v.f.) examinations were performed. 1) The 64 v.f. were evaluated for each of the following parameters. Gray scale/relative sensitivity map, Bedie curve, MD, LWCLV, topographical indices. 2) We compared the first v.f. pairs of the 24 patients with their visual acuity. Results: 1)Debie curve and MD proved to be the most sensitive indices in the evaluation of a v.f. especially with v.a. > 0,9. 2) We found that no patient with visual acuity 1.0 in one eye had normal v.f. in either eye. From the 14 patients with visual acuity 1.0 in both eyes, only 2 had normal v.f. in one eye. Conclusion: Automated perimetry is a sensitive, reliable, quick and inexpensive method for the diagnosis and follow up of optic neuritis in every day clinical practice.

P300
THE INFLUENCE OF VISUAL EXTINCTION ON VISUAL FIELD TESTING IN PATIENTS WITH VISUAL NEGLECT AND HEMIANOPIA. E.M. Müller-Oehring, E. Kasten, T. Schulte & B.A. Sabel. Institute of Med. Psychology, Medical Faculty, Otto-von-Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany.

Perimetric data of the visual field are difficult to interpret in patients with neglect syndrome. Misses of visual stimuli can either due to primary visual field loss or deficits of spatial attention. Hemi-neglect and hemianopia can occur simultaneously, but in some cases hemianopia was simulated by visual neglect (Walker, 1991). We suppose that this is a problem of "visual extinction".. That means, fixation point and light stimuli appear as a condition of "double simultaneous stimulation" (DSS), which implies that a patient with neglect would extinct left stimuli. Subjects. We investigated sixteen patients with hemianopia and visual neglect disorder after damage of occipital and/ or parietal brain areas. Methods. Patients performed standard perimetric testing and high resolution campimetry. We designed a visual search task with three conditions: 1. target and fixation point, 2. target without fixation point, 3. target and distractor stimuli in the opposite hemifield. *Results*.. Most patients with visual neglect showed visual field defects in perimetric and campimetric testing. All patients had prolonged reaction times in the defect hemifield, which were much more pronounced in neglect patients. Under the DSS-condition hemianopic patients and neglect patients only had prolonged visual search, when additional stimuli appear ipsilesionally. This showed that neglect patients behave in fact hemianopicly under DSS-conditions.. Without fixation point reaction time became shorter in some parts of the contralesional hemifield in neglect patients. It is argued that primary vision was intact in these parts of visual field.

P301
SPONTANEOUS AND TRAINING-INDUCED RECOVERY FROM BILATERAL LOWER QUADRANOPIA IN A PATIENT WITH A SHOTGUN LESION. Poggel DA[1], Kasten E[1], Müller-Oehring EM[1], Sabel BA[1] & Brandt SA[2]. [1]Otto-von-Guericke University, Institute of Medical Psychology, Magdeburg, Germany. [2]Department of Neurology, Charité, Humboldt-University, Berlin, Germany

Over a period of over three years, we investigated visual functions in a patient suffering from a visual field defect after a shotgun lesion affecting the upper calcarines. Initially, our patient had been completely blind before he showed a spontaneous partial recovery over a periode of six month leaving him with a bilateral lower quadranopia. Over the next year high-resolution campimetry documented a 20% gain increase in light perception in the lower visual fields. When visual field size was finally shown to be stable after 18 months of spontaneous recovery, a computer-based visual restitution training (Kasten et al., 1998, Nat-Med. 4) was started. Visual field size increased significantly over a training period of one year. In comparison with most hemianopic patients, our patient showed an unusually long period of spontaneous recovery. Additionally, he was able to increase his intact visual field by systematic training. In spontaneous as well as in training-induced recovery, progress was mainly observed in partially defective areas (transition zones). We hypothesize that mechanisms underlying spontaneous recovery could also be responsible for training-induced increase of visual field size and that spontaneous recovery might be a good predictor for training-induced recovery from visual field defects.

P302
SUBJECTIVE PHOTIC SENSATIONS ELICITED BY RTMS OF THE VISUAL CORTEX IN BLIND PERSONS. Gothe J [1], Meyer B-U [2], Kasten E [1], Sabel BA [1] & Brandt SA [2]. [1] Institute of Medical Psychology, University of Magdeburg, Germany. [2] Department of Neurology, Charité, Humboldt University, Berlin, Germany

In normal subjects, repetitive transcranial magnetic stimulation (rTMS) over the occipital lobe induces phosphenes in the contralateral visual field. We investigated subjective photic sensations elicited by rTMS in 24 blind patients (visual acuity reduced at least to light/dark perception) with different prechiasmatic pathologies. All patients were normal on neuropsychological testing. Focal rTMS (Dantec, MagPro) was performed on the intersections of a skull surface grid (1x1 cm) covering the occiput and by

this the visual areas V1, V2, V3 and V5. Seven 15-Hz stimuli were applied with an intensity of about 1.2 times the individual thresholds to elicit hand muscle twitches by single pulse stimulation over the motor cortex. The additionally blindfolded subjects were asked to report any induced visual perception. Eleven patients reported white or yellowish phosphenes varying in size, form and location depending on the stimulation sites. Six patients reported a prolonged subjective light sensation during the stimulation session and after the end of stimulation an increase of the ability to perceive visual schemes which lasted 15 minutes to 3 hours. This phenomenon might be related to long term potentiation of cortical excitability induced by rTMS.

P303
MOTION-INDUCED TRANSIENT ROOM TILT ILLUSION IN AN OTHERWISE HEALTHY SUBJECT. Veronika Schlamp, Thomas Schenk, Thomas Brandt. Department of Neurology, University of Munich, Marchioninistr. 15, Munich, Germany

Room tilt illusion (RTI) – transient upside-down vision or apparent 90° tilt of the visual scene –has been described in patients with acute lesions of the brainstem, the parieto-occipital region, or the frontal lobe. Published cases so far have been based on patient histories taken after the event. A 31-year-old, otherwise healthy subject repeatedly over about twelve years experienced upside-down vision for seconds. To elicit RTI in this subject, we applied various precipitating stimuli in the pitch, roll, or yaw plane after a period of visual occlusion. Shutter glasses were used to determine the duration of the illusion and of its reversion. RTI could be induced in 65-100% of trials by changes in head or body position or by large-field visual motion stimulation following a period of visual occlusion of at least 15s. Angles of tilt were confined to 90° or 180°.. The direction of tilt was identical to the direction of the preceding body motion in the roll plane but opposite to the direction of visual pattern motion in the roll plane. RTI was stable for more than one second; then it gradually reverted to normal within six seconds. A hypothetical mechanism in this exceptional subject is a cortical mismatch of vestibular and visual spatial 3D-coordinate frames due to a delayed computation of a newly acquired body position in space.

P304
SLOWING OF HORIZONTAL SACCADES NOT ONLY IN CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA BUT ALSO IN ISOLATED MITOCHONDRIAL MYOPATHY. V. Schlamp, Th. Klopstock, Th. Eggert, M. Dieterich, A. Straube. Department of Neurology, University of Munich, Marchioninistr. 15, D-81366 Munich

Mitochondrial diseases may manifest as myopathies with (chronic progressive external ophthalmoplegia, CPEO) or without (mitochondrial myopathy, MM) obvious involvement of the extraocular muscles. We investigated visually guided, horizontal saccades in 12 patients (ages 28 to 75, mean 48) with mitochondrial disease by using an infrared reflection device (IROG). Moreover, neuro-ophthalmologic and electro-oculographic testing (EOG) with calorics was done. Ten of these patients with typical muscle biopsy and mitochondrial DNA findings had been previously classified as CPEO and two as MM. Saccadic peak velocity (PV) of nine patients (including the two patients with MM), as recorded by IROG, was compared to that of amplitude-matched saccades from a pool of eight normal subjects (ages 38 to 58, mean 49). Every patient showed significant saccadic slowing for abduction and/or adduction with PV reaching 43% to 89% of that of the matched controls. This reduction in PV was also significant for the patient group. Saccadic gain and latency did not differ between patients and controls. The PV of horizontal saccades in the three remaining patients could be determined by EOG data only; they also showed reduced values. The saccadic slowing found in all patients – even in the two with clinical sparing of the extraocular muscles - supports the hypothesis of a subclinical continuum between MM and CPEO.

Neuro-oncology

P305
NEUROMUSCULAR INVOLVEMENT IN PATIENTS WITH ERYTHRODERMIC CUTANEOUS T-CELL LYMPHOMAS. M Desi*, L Laroche**, D Adams*, C Lacroix*, L Nahum-Moscovici*, AM Heudes**, G Said*. *Department of Neurology, Hopital de Bicêtre, Univ. Paris Sud, 94270 Kremlin Bicêtre, France. **Department of Dermatology, Hopital Avicenne, Univ. Paris XIII, Bobigny, France

Neurological involvement is uncommon in patients with cutaneous T-cell lymphoma (CTCL) and virtually unknown in patients with generalized erythroderma which includes Sezary syndrome and erythrodermic *mycosis fungoides*.. Among 41 erythrodermic CTCL patients treated in one center by extracorporeal photochemotherapy (between 1988 and 1998), 11 patients presented with neurological manifestations. Four patients are described: a 50-year-old woman with meningeal and peripheral nervous system Sezary cells infiltration, demonstrated by CSF analysis and nerve biopsy; a 55-year-old man with thoracic radiculopathy related to an epidural infiltration; a 71-year-old man with a symmetric sensorimotor neuropathy and normal nerve biopsy; a 68-year-old woman with a myositis and Sezary cells infiltrate on muscle biopsy. Two other patients had an asymmetric sensorimotor neuropathy suggesting radicular infiltration, four presented with a symmetric sensory neuropathy with a gloves and stocking distribution and one had an isolated agueusia. No central nervous system involvement was observed. These data show that neurological involvement also occurs in this specific form of CTCL. The incidence, the type, the pronostic significance and the response to treatment of these different neurological complications will be discussed.

P306
LYMPHOMATOUS BILATERAL OPTIC NEUROPATHY AFTER COMPLETE NON-HODGKIN'S INTESTINAL LYMPHOMA REMISSION. Munteis E, Roquer J, Rodriguez-Campello A, Gomis M, Aduna M(*), Pou A. Serveis de Neurologia i RNM(*). Hospital del Mar. Barcelona. Spain.

Optic neuropathy (ON) is rarely seen during the evolution of non Hodgkin's lymphomas (NHL). In some cases it may precede the systemic disease, but it is exceptional after a complete remission. ON may be classified into two groups according to the type of nerve optic lesion: a.- mainly it's related to the lymphoma orbital infiltration; b.- less usual infiltration affects the chiasma/optic nerves. We report a patient who was in complete remission from treatment of a HNL who developed a bilateral ON as the first manifestations of a lymphomatous meningitis (LM). A 31-year-old woman with known stage IV-B NHL, who was in complete remission from November 1998, complains in January 1999 a subacute bilateral visual loss with retro-orbital pain followed after four days by confusional state and epileptic fits. Incomplete right third nerve palsy, neck rigidity and drowsiness were present at neurological examination, but no papilledema was seen. CSF showed atypical lymphocites. Brain MRI demostrated multiple nodular lesions some of them involving optic chiasma and both optic nerves supporting the diagnosis of LM. Patient was treated with radiotherapy and intrathecal chemoteraphy. Our case suggests: 1.- ON may be the first manifestation of LM despite complete clinical remission. 2.-Early recognition of visual disorders in HNL patients it's important because the prompt treatment may lead to improve the visual loss.

P307
IMPLICATION in TUMOR PROGNOSIS OF ANTI-CV2 ANTIBODIES IN PATIENTS WITH PARANEOPLASTIC NEUROLOGICAL SYNDROMES AND SMALL-CELL LUNG CARCINOMA. C. Khouatra[1], P. Adeleine[2], P.J. Souquet[1], J.C. Antoine[3], P. Trouillas[4], J. Honnorat[4]. - [1]Service de Pneumologie, Lyon, France, [2]Service de statistique médicale, Lyon, France, [3]Service de Neurologie, Saint-Etienne, France, [4]Service de Neurologie B, Lyon, France

Anti-CV2 antibodies (CV2Ab) are a recently described paraneoplastic antibodies that react with a 66 kDa developmentally regulated protein. Small cell lung cancer (SCLC) is the cancer the most frequently associated with CV2Ab. Several studies suggest that tumor growth is slow down in patients with paraneoplastic neurological syndromes (PNS). We studied if the presence of CV2Ab is associated with a slow growth of the tumor. The tumor outcome of 9 patients with PNS, SCLC and CV2Ab (CV2Ab+) was compared with that of 20 patients with SCLC without CV2Ab or PNS. Stastitical analysis was performed by using the log Rank test, Kaplan-Meyer survival curves and likelihood Ratio chi-Square. The disease was limited to the thorax in 8/9 $CV2Ab^+$ patients and in 8/20 $CV2Ab^-$ patients. Median survival time was 24±8 months in the $CV2Ab^+$ group versus 10±1 months in the $CV2Ab^-$ ($p < 0.01$). After treatment, a complete response was observed in 88.9% of $CV2Ab^+$ patients versus 35.0 % in $CV2Ab^-$ patients ($p < 0,02$). In conclusion, the presence of CV2Ab at diagnosis of SCLC is related with complete response to treatment. The difference of median survival time between each group suggest a more indolently growth of the tumor in $CV2Ab^+$ patients.

P308
UNILATERAL HEMISPHERIC MENINGIOMATOSIS: ABOUT A CASE IN A PREGNANT WOMAN.S. LITRICO** - D. VON LANGSDORF* - M. LONJON* - Ph. PAQUIS* - M. CHATEL** *Service de Neurochirurgie - Hôpital Pasteur - NICE (France)/**Service de Neurologie - Hôpital Pasteur - NICE (France)

Meningioma growth may be influenced by hormones and pregnancy. We report the case of a 40 years old woman who presented during the 1980-1989 years period many losses of consciousness. In her gynaecological past, she had an abortion by RU-486 and a treatment by progesterone. In February 1989, she presented an epileptic seizure and was admitted for diagnosis. The clinical examination revealed no cutaneous abnormality. An electroencephalogram showed slow delta waves on the right side. A CT-scan revealed several lesions strictly localised over the right hemisphere. At operation, the meninges appeared thickened and rough between tumours; eleven lesions were resected which were confirmed as fibroblastic meningiomas. The post surgery CT-scan showed several remaining meningiomas. The patient was put under Phenobarbital (100mg/d). No further epileptic seizures was observed. In 1995, one frontal lesion grew and led to a second surgery where seven of the remaining lesions were resected. Three meningiomas were unresectable. An hormonal study of tumour samples confirmed the presence of progesterone receptors. In 1997, the patient got pregnant. Fœtal caryotype by amniocentesis was normal. No serious events during pregnancy were observed, despite remaining intracranial meningiomatosis with hormonal receptors.. She gave birth by caesarean section to a child weighing 2580g - Apgar score 10. A control MRI showed a moderate increase of the residual meningiomas. This case raises several questions: - the oncogenesis of a strictly unilateral and supratentorial location of meningiomatosis; - the problems of pregnancy and of adequate gynaecological and neurological follow up of such a patient.

P309
QUALITY OF LIFE IN MALIGNANT BRAIN TUMOUR PATIENTS AFTER DISEASE RECURRENCE A.R. Giovagnoli, A. Silvani, B. Muolo, A. Boiardi. National Neurological Institute C. Besta, Milano, Italy

In selected brain tumour patients, combined treatment by surgery, chemotherapy and radiotherapy can lengthen survival and preserve quality of life (QOL). However, after disease recurrence, the effects of therapeutic insistence on QOL are closely stressed by the perspective of poor survival. We, therefore, evaluated QOL in malignant brain tumour patients at different time intervals after disease recurrence to investigate cognitive, emotional, and physical dimensions, and to explore what factors influence QOL in these patients. Sixty-five patients affected by recurrent malignant tumour were evaluated by neuropsychological tests for abstract reasoning, attention and memory, and self-administered questionnaires for daily autonomy, anxiety and depression. The Functional Living Index – Cancer (FLIC) was used as a global index of QOL. The mean interval between disease recurrence and evaluation was shorter than six months in fourty-one patients, 6-12 months in 14 patients and longer than 12 months in 10 patients. Thirthy-six healthy subjects served as controls for emotional aspects and cognitive performance. With respect to controls, the three patient groups showed higher levels of anxiety and depression and poorer attention and memory. Married patients were less anxious and depressed than unmarried patients. Patients with recurrence interval shorter than six months showed worse mood state than the others. Factor analysis of the neuropsychological tests and scale scores provided two factors: Cognition/Autonomy and Mood. Regression analysis of the FLIC score showed significant associations with Mood, Cognition/Autonomy, and age. Cognition/Autonomy was associated with age, and Mood was associated with the time interval between disease recurrence and evaluation, and marital status. These results suggest that, in brain tumour patients undergoing chemotherapy after disease recurrence, QOL is mainly affected by depressed mood and reduced daily autonomy determined by cognitive impairment. The appraisal of disease recurrence and loneliness seem to play a major role in determining depression in these patients.

P310
THE ROLE OF THE NEUROLOGIST IN ONCOLOGY. A PROSPECTIVE STUDY. Augusto Caraceni, Sivana Scolari, Fabio Simonetti, National Cancer Institute, Milan, Italy.

The impact of neurological diagnosis (ND) on the management of patients with systemic cancer was prospectively assessed. Between April 98 and December 98, 497 consecutive, adult patients with solid tumors, were referred for ND. Other 57 (total 554) were discarded because affected by brain tumors. ND was sought because of, limb pain (18.9 %), back or neck pain (14.2%), segmental weakness (18.7 %), limb sensory disturbances (16.7%), visual disturbances (9.4%), other cranial complaint (8.0%), headache (7.8%), gait disturbance or ataxia (6.6%), vertigo (5.2%), other symptoms were present with a frequency 5%. The most frequent metastatic ND were, brain (11.8% of patients), and meningeal metastases (7.2%), tumor plexopathy (6%), epidural invasion or spinal cord compression (5.6%), radiculopathy (5.6%), only bone pain (5.2), seizures (3.2%). Toxic/metabolic encephalopathy was the most common (6.2%) non metastatic ND. Cancer-treatment related ND included, toxic peripheral neuropathy (7.6 %), postRT syndromes (2.0 %), postsurgery syndromes (3.4%). Non cancer-related ND were found in 308 cases (61.9%), ND demonstrated progression of the oncological disease (PD) in 162 pts (44.2%), the diagnosis could not be established in 27 pts (5.5%). Considering only the patients with metastatic disease at referral, ND showed PD in 59% and only in 9.4% of the non-metastatic-ones. ND prompted specific antineoplastic treatment for 15.5% of patients and supportive therapies for 30%.

P311
PRIMARY NON-HODGKIN LYMPHOMA OF THE SPINAL CORD: A CASE REPORT. H. Pels, I. Vogt and T.Klockgether. Department of Neurology, University of Bonn, 53105 Bonn, Germany.

Primary intramedullary malignant lymphomas of the spinal cord are rare with only a few cases reported. Case report: A 75-year old woman suffered from subacute and progressive lower extremity weakness and numbness associated with fecal and urinary incontinence developing over one month. On admission she was unable to walk, deep tendon and anal reflexes were absent, sphincter tone was reduced and proprioceptive and vibration sense were impaired below level T10. Lumbar puncture revealed 25 cells/mm^3 and a total protein of 70 mg/100 ml. MRI of the thoracolumbar region disclosed a contrast enhancing intrinsic lesion of the spinal cord extending from the T7 to the T11 level. An open biopsy of the lesion was carried out and a neuropathological examination revealed a lymphoplasmacytoid lymphoma. MRI of the brain and cervical spine were normal. Further staging revealed no evidence of extramedullary lymphoma manifestation. Treatment consisted of radiotherapy, 30 gy administered in 15 fractions, from the T5 to the T12 level, followed by a combination chemotherapy with vincristine (2mg i.v.), lomustine (50 mg/m^2 p.o.) and procarbazine (75 mg/m^2 p.o.). Bowel dysfunction resolved under therapy and paresis of the left leg improved markedly, however the patient is not able to walk without assistance one month after completion of radiotherapy. Myelopathy of undetermined etiology may be due to primary intramedullary lymphoma of the spinal cord. Prompt diagnosis and initiation of therapy is essential, since outcome after successful treatment of a spinal tumor mainly depends on the patient´s status prior to therapy.

P312
AMAUROSIS AND ENLARGED EXTRAOCULAR MUSCLES FROM METASTATIC SIGNET RING CARCINOMA Clerici R., De Riz M., Siglienti I, Piccio L., Tadeo S., Conti G., Scarpini E., Baron PL., Scarlato G. IRCCS Ospedale Maggiore, Dino Ferrari Center, University of Milan, Italy

We report a case of a 49 year-old woman who noted progressive loss of vision in the right eye, up to amaurosis in one month. She had smoked 20 cigarettes per day for 30 years. At the time of the first neurological examination, she presented amaurosis with a restriction of lateral and upward movements of the right eye, and bilateral exophathalmos more evident in the right eye. The remaining opthalmologic and the neurologic examination were normal. The laboratory exames demonstrated a hight erythrocyte sedimentation rate (82 mm/h). An orbital computer tomography scan showed pathological swelling of right ocular muscles with a dislocation of optic nerve. The magnetic resonance with gadolinium revealed infiltrative processes with unhomogeneous enhancement in the right medial rectus, right lateral rectus and left medial rectus muscles. Cerebrospinal fluid examination was normal. Three subcutaneus nodes without lymphadenopathy were observed, and a bioptical examination demonstrated fibroadipose and muscular tissue infiltrated by adenocarcinoma. The gastroscopy showed multiple localizations of signet ring carcinoma. The woman died three mounths after the onset of the ocular symptoms with the presence of metastatic localizations at the lung, bone and liver. Many conditions such as Graves' thyroid ophthalmopathy or inflammatory myositis, produces extraocular enlarged muscle, but the rare instances of metastatic carcinoma carries a grim prognosis.

Pain & Headache

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ZICONOTIDE, A NOVEL NON-OPIOID ANALGESIC, DOES NOT PRODUCE RESPIRATORY DEPRESSION. Robin Dean, Ph.D., Vandana Mathur, MD, and Scott Bowersox, Ph.D. Elan Pharmaceuticals, 3760 Haven Avenue, Menlo Park, CA 94025, USA

Patients with chronic pain refractory to systemic analgesic therapies are often treated with intraspinally delivered opioids. However, it is estimated that 1% of patients treated with conventional doses of spinal opioids develop the potentially lethal side effect of respiratory depression severe enough to require medical intervention. Ziconotide (Elan Pharmaceuticals, Inc. South San Francisco, CA) produces analgesia by binding neuronal-specific voltage-sensitive calcium channels. Ziconotide, administered intrathecally, was highly efficacious in producing analgesia in prospective, controlled trials of patients with chronic nociceptive, neuropathic, and central pain, including those refractory to intraspinal opioids. To determine whether ziconotide induced respiratory depression, we administered ziconotide in analgesic doses as a 0.1 μg intrathecal bolus (with or without induction of respiratory depression by morphine 10 mg/kg sc) or as a continuous intrathecal infusion (0.1 or 0.3 μg/hr) to Sprague-Dawley rats and measured minute ventilation (tidal volume x respiratory rate) by plethysmography. Ziconotide did not alter minute ventilation on room air or during 10% CO_2 inhalation either when given alone or when given following the development of respiratory depression with morphine. Unlike opioids, ziconotide does not produce respiratory depression. Ziconotide may be superior to opioids in the treatment of chronic pain both because of its efficacy in opioid-refractory pain and because of its freedom from this potentially lethal side effect of opioids.

P314
PAIN DUE TO TISSUE ACIDOSIS IN COMPLEX REGIONAL PAIN SYNDROME (CRPS) F. Birklein,M. Ernst, B. Riedl. Neurologische Universitätsklinik Erlangen, Schwabachanlage 6, D-91054 Erlangen, Germany

CRPS is a disabling complication occuring after noxious events such as trauma, surgery, myocardial and brain infarction. Beside sympathetic vasomotor disturbances long standing pain and hyperalgesia are the most crippling symptoms. The pathogenesis of the disorder still remains unclear. The aim of this study was to investigate the influence of low pH in the pathophysiology of pain in CRPS under the hypothesis that tissue acidosis due to vasomotor abnormalities is one important factor for pain in CRPS. We investigated 7 patients with CRPS at the upper extremity with a mean duration of the disease of 25 weeks (range 8-50 weeks) and 10 control subjects. A motorized syringe pump was used to infuse an acid buffer solution (pH 6,1) intradermally on the back of hand and thereafter into the interosseus I muscle on both sides. A flow rate of 30 ml/h was chosen for intradermal and 7,5 ml/h for intramuscular infusion over a period of 10 minutes. The magnitude of pain was rated on a visual analogue scale, patients were requested to give their rating every 10 seconds. We found a significant hyperalgesia to protons on the affected side. Low pH in the skin (affected: 21.% VAS, unaffected: 5.2% VAS; $p < 0,05$) and in the muscle (affected: 33.3% VAS, unaffected: 19% VAS; $p < 0,05$) elicited significantly more pain on the affected side. In controls there was no significant right vs. left difference. The pain quality at infusion into the muscle was described as being nearly the same "deep" pain present in CPRS. In conclusion these results suggest that pain and hyperalgesia due to tissue acidosis is an important factor in CRPS. Whether this depends on a decreased buffer capacity in CRPS tissue or a sensitization of nociceptive function needs to be clarified. *Supported by Deutsche Forschungsgemeinschaft SFB 353,C3*

P315
BEHAVIOUR AND PERSONALITY TRAITS OF STUDENTS WITH TENSION-TYPE HEADACHE (T-TH) Dubojska A. M.[1], Split W.[1], Rostowski J.[2] [1]Department of Neurology, Institute of Dentistry, Medical University of Lodz, [2]Department of Psychology, University of Lodz, Poland.

The aim of this study was to asses the personality traits of students with T-TH and the influence of T-TH on their school behaviour. The students personality was investigated using the Eysenck Personality Questionnaire EPQ-R. The internal-external locus of control was investigated using I-E Rotter Scale. State anxiety and trait anxiety using the Selfassessment Questionnaire of Spielberger et all. The level of depression was assessed using the Beck Depression Inventory, the level of perceived stress using Cohen Scale of Perceived Stress PSS-10. The results obtained were statistically evaluated using computer programme SPSS/PC+. Ninety students having T-TH (60 females and 30 males) in the age range 16 to 19 years (SD 17.2) were investigated. In 39% of the group headache occurred on more then 50 days over the year. In the control group were 38 headache-free students (HF) (19 females and 19 males) with the same age range as those having T-TH (SD 17.34). When compared to the HF, it was shown that T-TH influences emotional balance, trait anxiety, level of depression and level of perceived stress. Tension-type-headache did not seem to have significant influence on the school behaviour of students having such personality traits as internal locus of control and those students who are ambiverts with extravertive tendencies. When compared to HF, T-TH students have a more negative opinion of their school-place and also negative opinion of requirements given them by their teachers (requirements that offences students capabilities).

P316
TENSION-TYPE HEADACHE: ITS INFLUENCE ON SCHOOL ACHIEVEMENTS. Dubojska A.M., Split W. Department of Neurology, Institute of Dentistry, Medical University of Lodz, Poland.

The aim of this study was to investigate if tension-type headache (T-TH) affected school absenteeism and academic achievements. An analysis of school records revealed the number of days a student was absent, a number of individual hours away from school-lessons, the number of unsatisfactory school-work marks occurring over the school-year, the overall arithmetical average for all semester marks over the year. State anxiety and trait anxiety was measured using the Selfassessment Questionnaire of Spielberger et all. The level of depression was assessed using the Beck Depression Inventory, the level of perceived stress using the Cohen Scale of Perceived Stress PSS-10. The results obtained were statistically evaluated using computer programme SPSS/PC+. Ninety students having T-TH (60 females and 30 males) in the age range 16 to 19 years (SD 17.2) were investigated. In 39% of the group headache occurred on more that 50 days over the year. In the control group were 38 headache-free students (HF) (19 females and 19 males) with the same age range as those having T-TH. When compared to the HF controls, the T-TH group had significantly more days of absence from school (T-TH - 10.1 days, SD=6.7; HF - 5.4 days, SD=4.3), and significantly more individual hours away from school-lessons (T-TH - 11.9 individual hours, SD=7.5; HF - 1.1 individual hours, SD=1.6). Although the T-TH group also had the highest number of unsatisfactory marks in a school-year, the overall arithmetical average for all semester marks for individual students were not statistically different. T-TH was seen to have the effect of significantly influencing trait anxiety, level of depression and level of perceived stress.

P317
EFFECTIVENESS OF GABAPENTIN IN THE TREATMENT OF POSTZOSTERIC AND TRIGEMINAL NEURALGIA:AN OPEN LABEL THERAPEUTIC TRIAL Lisch,S;[1] Hengge, U;[2] Scholten, A;[1] Hufnagel, A[1] - Dept. of Neurology,[1] Dept. of Dermatology,[2] Univ. of Essen, Essen, Germany

Postzosteric neuralgia occurs in about 50% of patients following an infection with the varicella zoster virus. It is known to be difficult to treat as typical analgetics proved to be relatively ineffective. The common therapy with antidepressants and antiepileptics is limited by the side effects especially in elderly patients. Gabapentin is a novel, well tolerated anticonvulsant which has no cardiac or hematological adverse effects and has shown to be effective in neuropathic pain. In an open label therapeutic trial we administered gabapentin as add-on drug with stepwise increment of dosage to patients refractory to monotherapy with carbamazepine. Eight patients (aged 41-84yrs, mean age 63) with postzosteric neuralgia received doses of gabapentin ranging from 1200 and 2400mg. Three patients with trigeminal neuralgia (aged 60-86yrs, mean age 72,6) received 800 to 2400mg gabapentin. After 3 weeks of titration 5 weeks of continuation followed. Pain intensity was assessed 3 times daily with the visual analogous scale (VAS). Out of these 11 pat. 7 improved considerably with a mean reduction of the VAS-score from 7,7 to 2,7 points, 1 showed no effect, 3 dropped out (inefficency N=2, adverse effects N=1). In conclusion, our pilot study demonstrated effectiveness of gabapentin in the majority of patients with postzosteric and trigeminal neuralgia.

P318
INHIBITION OF INFLAMMATORY HYPERALGESIA BY SUMATRIPTAN IN THE MOUSE PAW: ROLE OF 5-$HT_{1B/1D}$ RECEPTORS. Davey, P, Raval, P., Sammons, M., Hunter, A.J., Bingham, S. & Parsons, A.A. Neurosciences Research, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Harlow Essex, CM 19 5 AW, UK

Sumatriptan has marked anti-hyperalgesic properties during morphine withdrawal (1). The aim of the current study was to evaluate the effects of sumatriptan in a model of inflammation-induced thermal hyperalgesia in the mouse. Methods: Female mice (20-27g) were habituated to a test environment and baseline paw withdrawal latencies (PWL) to an infra red stimulus were assessed (plantar test). The next day, carrageenan (2%w/v) or saline was injected into the plantar surface of the left paw and PWL assessed 240min post-administration. The effects on paw volume were assessed by plethysomometer. Sumatriptan 30 or 300 g kg^{-1} (i.p) was given 15 min pre-plantar. In separate experiments, the effects of the mixed 5-$HT_{1B/1D}$ receptor antagonist, GR-127935 (3mg/kg i.p) administered 60 min pre-sumatriptan was investigated either alone or in combination with sumatriptan (300 g kg^{-1} i.p. 15 min pre-plantar) on carrageenan induced hyperalgesia. Results: Sumatriptan (300 g kg^{-1}) produced a significant attenuation of hyperalgesia (PWL: vehicle 3.1 $\pm$ 0.4s, n=16; sumatriptan 5.6 $\pm$ 0.95s, n=16). Sumatriptan 30 g kg^{-1} had no effect. GR-127935 had no significant effect on thermal hyperalgesia alone, but produced a significant reversal of the sumatriptan induced responses (PWL: sumatriptan 6.3 $\pm$ 0.7 s, n=25; sumatriptan & GR-127935, 4.5 $\pm$ 0.6s, n=25). Sumatriptan had no significant anti-inflammatory properties under these conditions. Conclusions: Sumatriptan has marked anti-hyperalgesic properties which are inhibited by 5-$HT_{1B/1D}$ receptor blockade. These data show a novel analgesic profile for sumatriptan which may explain its efficacy as an anti-migraine therapeutic. Ghelardini et al., 1996, Fun Clin Pharmacol 10:192

P319
PREVALENCE OF PRIMARY HEADACHE IN CENTRAL REGION OF THAILAND: A CROSS-SECTIONAL SURVERY. Kammant Phanthumchinda, Pirom Kamolratanakul, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Epidemiologic studies can contribute to the understanding of headache. However, epidemiology of this disorder especially in community remains in its infancy. This is the first large community survey study of primary headache in middle region of Thailand. Materials and Methods: Sampling technique in this study was multi-stage sampling. All provinces (25) of central region were stratified by geographical stratification. Then, two provinces in each part were selected using simple random sampling. All villages in each selected province were stratified into 2 parts: urban and rural villages. Simple random technique was used to select 15 samples, aged 13-59 years from each village. The selected population was interviewed by well-trained interviewers and physical examinations were performed by well-trained physicians. The questionnaires had been tested and used in previous headache survey both in community and in hospital bases. International Headache Society criteria were used to diagnose various types of primary headache. Result: 621 from 720 samples participated in this survey and the response rate was 86.3%. The sampling population consisted of 197 males and 424 females. The average age of this population was 35.64± 13.63 years. The overall prevalence of primary headache in the previous year was 37.2%. The prevalence of migraine, tension-type of headache and combined headache were 17.4%, 27.2%, 7.4% respectively. The mean age of primary headache was 36.26± 13.68 years. The percentage of male to female was 26.4% versus 73.6%. The educational levels in the primary and secondary school was 84.0%. The percentage of farmer, businessmen and workers were 17.7%, 16.9%, and 26.8% respectively. The average age of onset of headache was 24.75+ 12.71 years. The percentage of population who have several attacks per month was 8.2% and percentage of population who have disabling headache was 22.9%. The most common precipitating factors of headache were stress (10.8%) and sleep deprivation (4.8%) and most of them used pain killer (30.7%). The headache population who considered themselves as analgesic abuse was 8.2%. Lack of exercise and recreation were detected in 46.3% and 12.1%. Medical consultation and the diagnosis of headache were noted in 37.2% and 17.7%. Medical and non-medical treatment were 96.5% and 3.5%. Satisfactory results from medical and non-medical treatment were 61.1% and 2.6%. The primary headache population who thought that they had intracranial diseases was 29.4% and the serious diseases they concerned were intracranial tumor (13.9%) and cerebrovascular disease (7.8 %). Conclusion: Primary headache is a common problem and has an important impact on individuals and society. The disorder is still underdiagnosed and undertreated. The burden of headache disorders provides an important target for public health intervention in Thailand.

Extrapyramidal disorders

P320
PALATAL TREMOR AND OLIVARY HYPERTROPHY: A CLINICO-PATHOLOGICAL STUDY.Makoto Nishie1), Yasuji Yoshida2), and Muneo Matsunaga1)Department of Neurology, Hirosaki University School of Medicine, Hirosaki, Japan - 2) Department of Pathology, Research Institute for Brain and Blood Vessels, Akita, Japan

To determine the relationship between palatal tremor and olivary hypertrophy, we have investigated clinical findings and pathology in the inferior olive in 19 autopsied cases with cerebral infarct and hemorrhage in the dentate-olivary tracts. Palatal tremor appeared 30-50 days after cerebrovascular accidents. Palatal tremor worsened and reached to the maximal level one year after the accidents, that remained until death. The size of the olivary nucleus increased up to one year after cerebrovascular accidents, and then decreased gradually below the normal range. Hypertrophic olivary neurons were not seen in patients who died within 10 days but observed 20-40 days after the accidents. Hypertrophic changes were maximum 6-7 months after the accidents. The number of olivary neurons including the hypertrophic neurons decreased to less than 10% of controls in long survivors. In patients who survived longer than five years, 50-80% of remaining neurons looked normal. Most of the normal neurons were surrounded by enlarged axons and synaptic clusters. These results suggest that the size of the olivary nucleus and the number of hypertrophic olivary neurons may be related to the emergence of palatal tremor but not to its continuation.

P321
ROLE OF SEROTONERGIC NEURONS IN THE CONVERSION OF EXOGENOUS L-DOPA TO DOPAMINE IN THE STRIATUM WITH DOPAMINERGIC DENERVATION. H. Tanaka, K. Kannari and M. Matsunaga. Department of Neurology, Hirosaki University School of Medicine, Hirosaki, Japan

To test the hypothesis that the conversion of exogenously administered L-DOPA to dopamine (DA) in the striatum of Parkinson's disease occurs in the serotonergic neurons, we examined L-DOPA (50 mg/kg i.p.)-induced changes in extracellular DA levels in the striatum of 6-hydroxydopamine (6-OHDA)-lesioned hemiparkinsonian rats using in vivo brain microdialysis. Experiments were performed on three groups of rats. Group 1: single 6-OHDA-lesioned rats; group 2: 6-OHDA-lesioned rats treated with 5,7-dihydroxytryptamine (5,7-DHT; 10 mg i.c.v.) that produces additional serotonergic denervation; group 3: 6-OHDA-lesioned rats treated with p-chlorophenylalanine (PCPA; 200 mg/kg i.p. x 2) that reduces serotonin content without serotonergic denervation. In serotonergic denervation group (group 2), L-DOPA-derived extracellular DA was reduced to 21% of that in single 6-OHDA lesion group (group 1) (p 0.05). However, there was no statistical difference in L-DOPA-derived extracellular DA between PCPA treatment group (group 3) and single 6-OHDA lesion group (group 1). These results suggest that in the striatum with dopaminergic denervation, exogenously administered L-DOPA is converted to DA mainly in the serotonergic neurons and that serotonin itself does not modulate the release of striatal DA derived from exogenous L-DOPA.

Poster Session – 2

Neurobiology

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EFFECT OF RECOMBINANT HUMAN NERVE GROWTH FACTOR ON CISPLATIN NEUROTOXICITY IN RATS. G. Tredici 1, M. Braga 1,2, G. Nicolini 1, M. Miloso 1, P. Marmiroli 1, L. Frattola 3,4, G. Cavaletti 1,3 - 1- Istituto di Anatomia Umana, L.I.T.A., Segrate; 2- Clinica Neurologica, I.R.C.S.S. Ospedale Maggiore Policlinico, Milano; 3- Clinica Neurologica, Monza; 4- Fondazione "Don Gnocchi", I.R.C.S.S., Milano, Italia

The neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor, (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) are a family of growth factors which play an important role in regulating developmental processes in the nervous system. Although their role in adult life is still not completely understood, it has been suggested that they might represent a tool in the treatment of disorders of the peripheral nervous system. We evaluated the effect of recombinant human NGF

(rhNGF, gifted by Boehringer Mannheim Germany) on cisplatin (CDDP)-induced sensory neuronopathy. Young adult female Wistar rat were treated with CDDP (2 mg/kg i.p. twice weekly for 9 times) alone or in combination with rhNGF (1 mg/kg s.c. on alternate days). The effect of CDDP (NGF treatment was evaluated with behavioral (tail-flick test) and neurophysiological (nerve conduction velocity in the tail) methods immediately after treatment and after a follow-up period of 6 weeks. Pathological and morphometrical examinations of the dorsal root ganglia (DRG), sciatic and saphenous nerves were also performed. rhNFG treatment induced a signficant reduction in the CDDP-induced decrease in nerve conduction velocity ($p < 0.05$), and this was associated with a significant protection against the decrease in somatic ($p < 0.05$), nuclear ($p < 0.05$) and nucleolar size ($p < 0.01$) caused by CDDP treatment. However, for each of the parameters examined the neuroprotection obtained with rhNGF treatment was not complete. At the follow-up examination no differences between the 3 groups were observed in tail-flick test and nerve conduction velocity. We conclude that rhNGF exerts a biologically significant neuroprotective effect against CDDP peripheral neurotoxicity. These data, however, suggest that the combination of rhNFG with other pharmacological agents might be necessary in order to completely prevent this serious adverse effect of CDDP.

P323
REGULATION OF CHEMOKINE EXPRESSION IN HUMAN CEREBRAL ENDOTHELIAL CELLS. O. Klein, V. Hummel, B. Kallmann, N. Kruse, K.V. Toyka, P. Rieckmann. Clinical Research Unit for Multiple Sclerosis and Neuroimmunology, Department of Neurology, University of Würzburg, Germany

Objective: To examine chemokine expression in human cerebral endothelial cells under different proinflammatory conditions. Background: Chemokines are proposed to play an important role in defining the cellular composition of inflammatory infiltrates in the CNS. To date, it is known that in the CNS these factors can be expressed by different cell types including astrocytes, microglia and invading leukocytes. In animal models of inflammatory CNS disorders (e.g. acute EAE) chemokines were also detected in endothelial cells. Methods: After isolation from human brain specimens the cerebral phenotype of the endothelial cells was demonstrated by immunofluorescence-staining with monoclonal antibodies against Glucose-transporter-1, Factor-VIII and specific lectin binding. Subconfluent cell cultures were incubated with the proinflammatory cytokines TNF-α, IL-1, IFN-γ or lipopolysaccharide (LPS). After 4, 12 and 24 hours of incubation cell culture supernatants were removed and chemokines (IL-8, IP-10, RANTES, MCP-1 and MIP-α) were measured by ELISA. In addition, total RNA was extracted from cerebral endothelial cells and the chemokine m-RNA levels were determined by quantitative RT-PCR. RESULTS: We detected different patterns of chemokine expression in human cerebral endothelial cell cultures under proinflammatory conditions. IL8 was strongly induced by LPS and TNF-α. RANTES expression occured at later time points, mainly by LPS and TNF-α. Low levels of MCP-1 were already secreted under basal conditions and significantly induced by IFN-γ. IP-10 was only induced by IFNγ. MIP-1 was not detectable under any conditions used. Conclusion: Human cerebral endothelial cells are potent producers of chemokines which may have important implications for the recruitment of different immune cells into the CNS.

P324
CHARACTERIZATION OF AN "IN VITRO" MODEL TO STUDY THE MIGRATORY ACTIVITY OF LHRH NEURONS AND ITS PATHOLOGICAL DISFUNCTION PRESENT IN KALLMAN'S DISEASE. Federica Pimpinelli, Laura Molteni and Roberto Maggi Dept. of Endocrinology, University of Milan, 20133 Milan, Italy

The normal development of reproductive functions depends on the correct of LHRH neurons from the olfactory placode to the hypothalamus. We have tested the use of two cell lines (GI-7 and GNI 1) of immortalized LHRH neurons as an "in vitro" model to investigate the factors possibly involved in such migratory activity. In fact, GTI-7 cell line has been derived from post-migratory LHRH neurons, while GNI I cell line derives from LHRH neurons blocked at an early stage of migration. The analysis of the expression of differentiation markers shows that GT 1 -7 cells represent mature LHRH neurons, while GN I I cells represent an immature form. GN11, but not GTI-7, cells show an elevated motility and capacity to migrate in a collagen-gel matrix and on glass fibers. GN11 cells also show a significant chemotactic response to fetal bovine serum (FBS) which can be blocked by pertussis toxin. GTI-7 cells show very low spontaneous motility and appeared to be insensitive to the FBS chemotactic stimulus. In conclusion, these results indicate that GN I 1/GT 1 -7 cells may be a useful models to clarify several aspects of the migratory process of the LHRH neurons and consequently the pathological disfunctions possibly present in Kallmann's disease (Supported by Telethon, E.523, and by MURST).

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DIFFERENTIAL EXPRESSION OF L- AND S-MAG IN HUMAN AND MOUSE MODELS OF PERIPHERAL NEUROPATHIES. N. Schaeren-Wiemers, R. Lützelschwab, B. Erne, S. Atanasoski*, S. Sancho*, U. Suter*, A.J. Steck. Department of Research and Neurology, University Hospital Basel, Switzerland, *Institut of Cell Biology, ETH-Hönggerberg, Zürich, Switzerland

Myelin associated glycoprotein (MAG) is a glycoprotein located in the periaxonal membranes, in paranodal loops and in non-compacted myelin sheaths of the peripheral and central nervous system. MAG is expressed as two developmentally regulated isoforms, L- and S-MAG. The aim of the present work is to elucidate a possible functional role of MAG in demyelinating diseases. We focused on the analysis of the differential expression pattern of L- and S-MAG in human sural nerve biopsies of Charcot-Marie-Tooth 1A (CMT1A) and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) patients and in the corresponding mouse models for these demyelinating neuropathies. These examinations revealed that a higher number of L-MAG positively stained nerve fibres were detectable in nerves from HNPP and CMT1A patients compared with controls. Furthermore, a significant correlation (p 0.05) between L-MAG positively stained nerve fibres and large fibre diameter could be observed. Quantitative, competitive PCR and immuhistochemical characterization of 3 different mouse lines (heterozygous and homozygous PMP22 knock out mice and PMP22 overexpressing mice) at different developmental time points showed that L- and S-MAG mRNA and protein expression levels vary in PNS and also in CNS. Within the PNS, S-MAG appears to assume a compensatory role for the loss of PMP22 function.

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ELECTRODERMAL RESPONSE IN LEXICAL PROCESSING: AUTONOMIC "RECOGNITION" OF WORDS IN APHASIA.B.Roesing1, F. Schaefer2, W. Huber1. 1Neurolinguistics/Neurology Department, RWTH Aachen, Germany. 2Psychophysiology Department, University of Wuppertal, Germany

It has been previously shown that patients with cognitive impairment due to circumscribed cerebral lesions can autonomically distinguish information which they cannot when asked to give conscious verbal response.Electrodermal reaction is one of the most reliable parameters to show autonomic nervous system activity.We studied the autonomic reaction to auditory verbal stimuli in a group of 15 aphasic patients and a control group of 16 healthy subjects. Presented stimuli were single words and pseudowords as targets and distractors in a lexical descision task requiring selective attention. We wondered whether access to the phonological input lexicon was still available in all clinical conditions of aphasia. All participants (aphasic patients and normal subjects) discriminated well between targets and distractors autonomically, as revealed by their electrodermal reaction to the stimuli. A subgroup of patients had difficulties to distinguish words and pseudowords overtly. This correlated to their low performance in auditory verbal comprehension as assessed by the Aachen Aphasia Test (AAT). Despite their low overt performance these patients did neither differ from the other aphasic patients nor from normal subjects in amplitude of specific electrodermal reaction. All groups showed significantly higher amplitudes to targets than to distractors.We hypothesize that the phonological input lexicon is still active though conscious access is impaired.

Clinical neurophysiology

P327
ELECTROMYOGRAPHIC ASSESMENT OF SKELETAL MUSCLE IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY: EVIDENCE OF SUBCLINICAL MYOPATHY AND ITS RELATION TO FAMILY HISTORY OF SUDDEN DEATH. Nikos Karandreas', Pantelis Stathis2, Aris Anastasakis', Angelos Rigopoulos3, Perry. Elliot4' Panayiotis Piperos', Artemis Theopistou3, Chris Stefanadis3, William. McKenna4, Pavlos Toutouzas3. Dept. of Neurology-EMG Lab., 3. Dept.of

Cardiology- University of Athens, 2. Dept. of Neurology- Hospital of Social Security Services- Athens, 4. Dept of Cardiology-St. George's Hospital Medical School, London.

Backround.-Hypertrophic Cardiomyopathy (HCM) is a complex and heterogeneous heart muscle disease. It is an important cause of arrhythmias, syncope and sudden death, affecting both children and adults and it caused by mutations in cardiac contractile protein genes such as B-cardiac myosin, troponin T etc. Because B-myosin is a constituent of slow skeletal muscle the question has arisen whether skeletal muscle is also affected by mutations in this protein. Methods: In 46 unrelated consecutive patients (pts) with HCM (26 male, 49±18 years) and no clinically detectable muscle weakness and in 10 matched healthy volunteers, deltoid, quadriceps, tibialis anterior, and soleus muscles were investigated using convetional and quantitative electromyography (EMG). Results: Using convetional EMG, myopathic findings were demonstrated in 12 (26%) pts, 25 pts had normal studies and in 9 pts EMG was unconclusive. Pts with normal EMG had a high prevalence of sudden death in their family (9/25). In contrast, pts with myopathy had no family history of sudden death (0/12) ($p < 0,05$). Quantitative EMG had an adjuctive role on convetional EMG findings. Conclusion: A substantial minority of patients with HCM have subclinical myopathy detectable with conventional EMG. The higher prevalence of a family history of sudden death in pts with normal EMG may reflect a higher prevalence of high risk mutations that are not expressed in skeletal muscles (eg troponin T).

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Abstract withdrawn by author

P329

SYMPATHETIC SKIN RESPONSE STUDY IN EPILEPSY. J.Kapustecki,J.Kowalski,K.Pierzchala.Ii Department Of Neurology, Silesian School of Medicine, Zabrze, Poland

The electrophysiologic parameter to objective assese of postganglionic sympathetic fibres functions is sympathetic skin response (SSR) resulting from the changes in skin electric resistance due to several endo- and egzogenous impulses. The aim of this study was to estimate the correlations between SSR parameters (latency and amplitude) and epilepsy clinical picture. Methods: 30 patients with non-symptomatic epilepsy, 20 women and 10 men in mean age 34,2±10,72 years, without neurological deficit, were examinated. The control group consisted of 28 healthy subjects aged 35,35± 6,18 years. SSR was recorded from palmar surface of the right hand and plantar surface of the right foot, elicited by electrical stimulation of contrlateral median nerve. The examined factors were as follows: 1/ age, epilepsy duration, 2/ seizure types, 3/ anti-epileptic drugs. Results: Significantly diminish mean amplitude and prolonged mean SSR latencies in the whole group of epileptic patients were found. Epileptics with partial seizures had more frequently prolonged SSR latencies compared to the other patients. There was no differences in SSR parameters between patients on monotherapy and combination of two or more anticonvulsants. Less prolonged SSR latencies of shorter duration of treatment were found. Conclusions: Results suggest that disturbances of sympathetic functions are various among the epileptic syndromes probably by a lesion various central autonomic structures.

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FACIAL CORTICAL SILENT PERIOD IN PATIENTS WITH CRANIAL DYSTONIA A.Currà, A.Romaniello, G.Cruccu, A.Berardelli Department of Neuroscience, University of Rome "La Sapienza"

We studied the cortical silent period (SP) in the upper and lower face muscles in patientswith cranial dystonia (n=23) and age-matched controls (n=10). High intensity magnetic stimulation was delivered with a round coil centered at the vertex during maximal contraction of the upper and lower facial muscles. Simultaneous recordings from perioral muscles and orbicularis oculi showed SPs of similar duration in the upper and lower face muscles in both groups. Patients with cranial dystonia had shorter SPs in the facial muscles than normal subjects.In order to investigate whether the SP duration varied according to the muscles involved in dystonic movements, further analysis was performed on patients with cranial dystonia classified as having blepharospasm only (n=13), and blepharospasm plus oro-mandibular dystonia (n=10). Patients with blepharospasm plus oro-mandibular dystonia had shorter SP than patients with blepharospasm only. We conclude that in patients with cranial dystonia the duration of the SP is shortened in the orbicularis oculi and the perioral muscles. Moreover, when dystonia affects both upper and lowerfacial muscles, the SP induced by magnetic stimulation is even shorter.

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MODIFICATIONS OF CORTICAL. EXCITABILITY AFTER MAGNETIC REPETITIVE STIMULATION OF CORTICAL MOTOR AREAS. S. Romeo, F. Gilio, F. Pedace, M. Inghilleri, C. Lorenzano, A. Berardelli. Dpt of Neurological Sclenses, University of Rome "La Sapienza", Rome, 00 185 Italy.

The éffect of repetitive transcranial magnetic stimulation (rTMS) on the cortical silent period (SP) was studied in humans. Cortical stimuli were delivered in trains at frequencies of 1, 2, 3, 5, 10 and 15 Hz and intensities of 110% and 140% of motor threshold (MTh) while the subjects moderately contracted the forearm flexor muscles. The cortical SP was also recorded after single magnetic stimuli.Trains of 20 stimuli at 110% above MTh prolonged significantly the cortical SP at 2, 3, 5, 10 and 15 but not at 1 Hz. Higher intensity of stimulation (140%) evoked SPs of longer duration but the lenghtening of the duration produced by the train of stimuli was similar to that seen with trains delivered at 110% of MTh. The peak-to-peak amplitude of motor evoked potentials that preceded 0 14- each SP did not change over the cours of the train. We conclude that rTMS delivered at frequencies over 1 Hz prolongs the cortical SP by activating intracortical inhibitory interneurones.

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IMPAIRMENT OF PRESYNAPTIC INHIBITION OF IA FIBRES ELICITED BY GROUP III AFFERENT INPUT IN DYSTONIA. C. Lorenzano *, A. Priori.**, S. Ozkaynak ***, A. Berardelli *Dpt. of Neurological Sciences, University of Rome "La Sapienza", Italy, ** Ospedale Maggiore(IRCCS) Milan, *** Dpt. of Neurology, Akdeniz University, Antaha, Turkey

Presynaptic inhibition exerted by group III afferents on la fibres (Priori A. et al, Brain 1998) was studied in nine patients with generalized dystonia and in ten normal healthy subjects. Electrical stimuli (70 mA, 0. 1 ms) were delivered over the tendon of the extensor carpi radialis muscle at the wrist with surface electrodes at an intensity subthreshold for pain. The EMG signal during steady isometric contraction (50% of the maximum) was recorded by a pair of surface electrodes over the extensor carpi radialis, rectified and averaged (100 sweeps). In. normal subjects the EMG signal after tendon stimulation showed two excitatory (E I, E2) and one inhibitory phases (11). In the patients perceptive threshold, background EMG level and the latencies and durations of these phases did not differ from control values, but the 11 area excedeed the control value (controls: 0.004775±0.004080, Vs -1 patients: 0.01092±0.006296 Vs-, mean±SD, p=0.01 17, in Mann-Whitney test). In conclusion, the EMG suppression (11) after tendon stimulation is reduced in dystonia, indicating a wide dysfunction of presynaptic inhibitory mechanisms in the spinal cord, involving L. both group 1 and 111 afferents.

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TRANSCRANIAL MAGNETIC STIMULATION DURING THE TREATMENT WITH BOTULINUM TOXIN-A IN PATIENTS AFFECTED BY POST-STROKE SPASTIC HEMIPARESIS Flavia Pauri1,2, Laura Boffa1, Emanuele Cassetta1, Patrizio Pasqualetti1,2 and Paolo Maria Rossini1,2- 1: AFaR-CRCCS Centro di Ricovero e Cura a Carattere Scientifico: Divisione di Neurologia, Ospedale Fatebenefratelli, Isola Tiberina 39, 00186 Roma 2: IRCCS Centro S Giovanni di Dio - FBF, Brescia

Eight patients affected by spastic hemiparesis due to stroke were treated with Botulinum toxin type- A in the muscles of the affected calf and forearm in order to reduce spasticity. Clinical evaluation included Ashworth scale to test the spasticity. The patients were clinically and neurophysiologically evaluated before treatment, one day, two weeks and 1 month after injections.Motor evoked potentials (MEPs) were recorded from lower and upper limbs from both sides (affected and unaffected), as well as F-wave, compound Motor Action Potentials (cMAP), H-reflex..The following parameters were taken into account: latency and amplitude of MEPs from each muscle, latency and amplitude of F-waves, Central Conduction Time (CCT) calculated by means of F-wave formula, latency and amplitude of H reflex, latency and amplitude of cMAP, H amplitude/ cMAP amplitude ratio. Clinical evaluation showed a clinical improvement in both treated upper and lower limbs two weeks after the injection and this effect persisted several months. No patients complained side effects.Neurophysiological follow-up showed reduction of MEPs latency and CCT in both upper and lower limbs.

P334
SPASTIC PARAPARESIS IN MULTIPLE SCLEROSIS TREATED WITH BOTULINUM TOXIN: A TRANSCRANIAL MAGNETIC STIMULATION STUDY. Flavia Pauri1,2, Laura Boffa1, Emanuele Cassetta1, Patrizio Pasqualetti1,2 and Paolo Maria Rossini1,2-1: AFaR-CRCCS Divisione di Neurologia, Ospedale Fatebenefratelli, Isola Tiberina Roma 2: IRCCS Centro S Giovanni di Dio - FBF, Brescia

Botulinum toxin type A (BoNT-A) has been recently used as aspecific treatment of spasticity.In this study fifteen patients affected by spastic drop foot due to Multiple Sclerosis received BoNT-A injections (Dysport(: 500 UI/2.5 ml), under EMG guidance, in one or both calf according to the clinical picture. In all patients, gastrocnemius muscle was treated, in some cases soleus or tibialis posterior muscles were treated too. The total doses/session of the drug varied, ranging from 150 to 700 IU. All patients had a clinical benefit as documented by a standardised scale (Ashworth), which started about two weeks later and lasted about four - six months. When the treatment was repeated (9 patients) the clinical improvement reoccurred. No patient complained side effects. Neurophysiological investigations, performed before the treatment and 1 day, two weeks and 1 month later, included: Motor Evoked Potentials, F-wave and Compound Motor Action Potential (cMAP) from gastrocnemius and tibialis anterior of both sides, H-reflex from soleus of treated and non-treated legs. MEPs latency and Central Conduction Time increased two weeks after the treatment, only when recorded from the treated gastrocnemius. These data, not explainable only by the peripheral effects on the {-motoneurons terminals, are consistent with the hypothesis of a central role of BoNT-A.

P335
SIMULATION OF STATIC VESTIBULO-OCULAR SYNDROMES BY A 3-D MATHEMATICAL MODEL.Stefan Glasauer, Marianne Dieterich and Thomas Brandt. Dept. of Neurology, Ludwig-Maximilians-University Munich, D-81377 Munich, Germany

Patients with peripheral or central unilateral vestibular lesions present with various static vestibulo-ocular syndromes: skew deviation (a vertical disconjugacy of the eyes), ocular torsion, and a gain asymmetry of static ocular counterroll (OCR) in response to lateral head tilt in the frontal plane. A basic version of a 3-D mathematical model for simulating otolithic control of binocular static eye position was extended by introducing the electrophysiologically demonstrated force-response relationship of utricular primary afferents. This modification appeared necessary to adequately simulate OCR gain asymmetries in patients with peripheral vestibular lesions. The current model can adequately simulate clinically observed OCR gain asymmetries in patients with unilateral utricular loss. It predicts similar OCR gain asymmetries following vestibular nuclei or central graviceptive pathway lesions. The direction of simulated skew deviation and ocular torsion correspond exactly to the published human data in normals and neurological patients with acute vestibular loss. However, the extent of deviations in simulated static eye position deviations is smaller than that observed clinically. This result, together with recent data on galvanic stimulation of the vestibular nerve, suggests that part of the static ocular deviations is caused by the loss of semicircular canal function.

P336
DEPENDENCE OF H REFLEX BEHAVIOR ON DIFFERENT STIMULUS DURATION IN PATIENT WITH PARKINSON'S DISEASE IN COMPARISON TO NORMAL SUBJECTS. Kushnir M, Klein C, Rabey J.M.. Department of Neurology Assaf Harofe Medical Center Zerefin, Sackler School of Medicine, Tel - Aviv University, Israel.

Electrical stimulus, starting at 0.1 and gradually increased to 1.0 ms was used for eliciting the H reflex in 21 normal subjects and 48 patient with Parkinson disease (PD). In 19 normal subjects (90.5%) the threshold for sensory fibers was lower than for motor fibers and the H reflex was obtained before the M response for all duration stimuli. In 19 PD patients (39.6%) with mild and moderate rigidity (according to the motor part of UPDRS) the threshold for the H reflex and M response was the same or the M response threshold was lower in at least one of the legs for short stimulus duration. In 15 (31.2. %) PD patient (most of them with severe rigidity) the threshold for M response was lower for all stimulus duration and it was obtained before H reflex. In 14 PD (29.2%) patient the H reflex behavior was the same as in most normal subjects in one or both legs. This very significant different behavior (Fisher exact test, $P = 0.0000$) of the H reflex in PD patient could possibly be explained by changes in agonist - antagonist inhibition and could be used as another parameter in the clinical assessment of extrapyramidal rigidity in PD patient.

P337
HYPEREXCITABILITY OF FACIAL MOTONEURONS CONTRALATERAL TO FACIAL NERVE PALSY. Manca D, Valls-Solé J, Marchetti P, Valldeoriola F. Department of Neurology. Hospital Clinic. Barcelona. Spain

Patients with Bell's palsy may undergo early adaptive plasticity changes. These changes could be caused by sensitization of neurons along the trigemino-facial reflex pathway because of repeated inputs from the relatively unprotected cornea. In 70 patients with BP we have recorded the blink reflex responses to electrical stimulation of the supraorbital nerve of both sides. We measured the area of the late responses recorded in the side contralateral to the BP from ipsilateral (R2) and contralateral (R2c) supraorbital nerve stimulation. The results were compared with those obtained in 13 healthy subjects who served as a control group. In order to normalize the interindividual results, we calculated the difference between R2 and R2c (R2-R2c). In control subjects, R2 was usually larger than R2c, with a mean difference of 2788 $\mu V*ms$ (SD=2208 $\mu V*ms$), while in patients, R2c became larger than R2, with a mean R2-R2c difference of -13226 $\mu V*ms$ (SD=1603 $\mu V*ms$). Our results suggest that patients with BP exhibit an enhanced gain of the trigemino-facial reflex to inputs from the affected side. Because of the differences between responses to ipsi- and contralateral stimuli, we conclude that such enhancement occurs at least in part at a premotoneuronal site.

P338
EFFECT OF NEW ANTIRETROVIRAL THERAPEUTIC REGIMENS ON QUANTITATIVE EEG IN HIV-POSITIVE PATIENTS. Michela Mauri, Paola Gambaro, Pierluigi Bertora, Laura Fusi, *Paola Meraviglia, and Alfonso Mangoni. 1st Chair of Neurology, University of Milan; *2nd Dept of Infectious Diseases, Ospedale L. Sacco, Milano, Italy

Central nervous system (CNS) complicances in HIV-infected patients have shown a marked decrease since the introduction in the last two years of therapeutic regimens including protease inhibitors. Quantitative EEG has been shown to be useful as a marker of subclinical neurological damage in HIV infection. In this work the effect of triple-drug regimen (two nucleoside analogues plus one protease inhibitor) on functional alterations of CNS evaluated by quantitative EEG was tested on neurologically asymptomatic HIV-positive patients. Twelve patients (7 men, 5 women, mean age 38.5 yr) without neurological and psychiatric signs or symptoms were included. EEG was recorded at baseline and after 3 and 6 months of treatment. Power spectral analysis was performed for standard EEG frequency bands on 10 minutes of tracing divided into 2.5-sec epochs.. A significant ($p < 0.01$) reduction in relative power of delta and theta bands was seen in 46% of patients after 3 months and in 50% after 6 months. After 3 months 30% of patients also showed a significant shift towards posterior regions of scalp for alpha band relative power. EEG changes were paralleled by a significant ($P < 0.001$) increase of mean CD4+ counts from 188(96 (basal) to 327(110 (3-mo) and 333(93 (6-mo) cells/mm3. These data confirm the effectiveness of triple-drug regimens in improving the neurological status of HIV-infected patients and suggest that a favourable effect in preventing cognitive deterioration may also be seen.

P339
NEUROPHYSIOLOGICAL AND ULTRASOUND FINDINGS IN SURAL NERVE LESIONS FOLLOWING STRIPPING OF THE SMALL SAPHENOUS VEIN. Simonetti S., Bianchi S.*Divisione di Neurologia, Divisione di Radiologia*, E.O. Ospedali Galliera, Genova, Italy

We describe the neurophysiological and ultrasonographycal findings obtained in 2 patients with sural nerve lesions following stripping of the small saphenous vein. In the first case, a US performed through a linear electronic 13 MHz probe showed a nerve section about 10 cm proximal to the right malleolus lateralis and an hypoechoic swelling of the proximal stump possibly due to a terminal bulb neuroma. A sural nerve conduction study performed distally and proximally to the lesion through a near-nerve needle technique, showed absence of responses, indicating a remarkable retro-anterograd axonal degeneration. In the second case, a US study did not show any nerve interruption. Sural nerve conduction study showed absent responses distal to a scar placed behind the lateral malleolus. Nerve stimulation immediately above the scar yield a tiny responses at the sciatic nerve. A subsequent investigation, performed 15 months after the operation, showed absent proximal and distal responses. The sural nerve conduction study with recording even at the sciatic nerve to evaluate a possible retrograde degeneration, and its combination with US study, to our knowledge never been described before, seem able to yield important complementary indications in the management of sural nerve lesions.

P340
A NOVEL METHOD FOR THE ASSESSMENT OF SPINO-THALAMIC CONDUCTION VELOCITY IN HEALTY SUBJECTS. Rossi, M. Serrao, P. Cardinali, L. Parisi, G. Valente, L. Borrello, G. Pozzessere. Istituto di Malattie Nervose e Mentali, II Clinica Neurologica, Università di Roma "La Sapienza", Italy.

Electrophysiological study of the central somatosensory pathways is done classically through somatosensory evoked potential (SEP) by electrical stimulation of the peripheral nerves. This method explores only the large-caliber afferent pathway excluding small-fibers function. The recent development of the carbon dioxide laser SEP (LEPs) may allow an objective exploration of the spino-thalamic tract. LEPs are based on the possibility to evoke a selective activation of cutaneous nociceptors ascending by peripheral A-delta fibers and spinothalamic tracts. At the present time only a cortical evoked response reflecting both central and peripheral functions may be identified. Nevertheless, as for electrical SEP, the separate measurement of central and peripheral pathways should highly refine LEP's diagnostic utility. With regard to A-delta conduction times, recent papers have shown that these data are detectable by means of the cutaneous silent period (CSP).Considering that LEPs latencies are the sum of peripheral and central components, data obtained from CSP (A-delta mediated) may be used to calculate central conduction times of spinothalamic pathways.Aim of this study was to evaluate the conduction velocity of spinothalamic tract (STTCV) by coupling LEPs and CSP techniques. Subjects and Methods. Eight healthy subjects participated to the study. Central conduction times of the spinothalamic tracts (STTCT) were calculated for both upper (u) and lower (l) limbs by mean of the following formulas: STTCTu = LEPu (lt) - CSP (lt); STTCTl = LEPl (lt) - CSP (lt); LEPs=latency of the laser-induce cortical evoked response; CSP(lt)=latency of the cutaneous silent period evoked from the same cutaneous area of the LEPs (dorsum of hands and feet). The conduction velocity of STT between T12 and C7 levels were calculated as follows: STTCV = C7 - T12 distance /STTCTl - STTCTu. Results. STTCV ranged between 10.7 m/sec and 14.3 m/sec according with experimental data..Conclusion. Our preliminary results suggest that the present method may be a reliable diagnostic tool for the assessment of spinothalamic tract functions.

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ELECTRICAL ACTIVITY OF THE HUMAN BRAIN AFTER TRANSCRANIAL STIMULATION. S. Nassetti, A. Priori, S. Maestrini, F. Babiloni, F. Cincotti e P.M. Rossini.Laboratorio di Neurofisiologia, IRCCS "Centro S.Giovanni di Dio-Fatebenefratelli" Brescia, ITALY

This study assessed whether single Transcranial Magnetic Stimulation (sTMS) and repetitive TMS (rTMS) produce after-effects on the human EEG.Five healthy volunteers were studied with EEG recording and TMS. Subjects received at 95% of resting motor threshold intensity either single magnetic stimuli, or single rTMS trains (17 Hz, 1 sec), or sham TMS. The EEG epochs of 30 and 28 sec pre- and post-stimulus respectively were spectrally analyzed for power in the different frequency bands.We observed no qualitative EEG changes before and after both forms of TMS. In contrast, in all the experiments in the central areas bilaterally sTMS elicited the decrement of relative power in the 6-9 Hz band whilst rTMS produced the increase in the 6-12 Hz band. Sham TMS produced a pattern of EEG changes different from that evoked by both rTMS and sTMS.We conclude that sTMS and rTMS elicits significant and specific quantitative EEG after-effects, probably by acting over different cortical mechanisms.

Cerebrovascular disorders

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FREQUENCY AND CAUSES OF STROKE RECURRENCE IN THE PROVINCE OF TERUEL, SPAIN. A FIVE-YEAR PERIOD ANALYSIS (1994-1998). PJ Modrego, MA Pina, M.Mar Fraj, N Llorens. Hospitals of Alcañiz & Teruel, Spain

Recurrent strokes occur most frequently in the early period after the first stroke.. Identification of the causes of recurrence and its treatment may play an essential role in the prevention of further strokes. The aim of our work is to analyse the frequency and causes of stroke recurrence in a five-year period.In this retrospective study we reviewed the clinical records and database of our hospitals and found a total of 1108 patients admitted because of primary stroke. Only the patients with recurrent stroke were selected for a comprehensive analysis. We retrieved 135 patients with recurrent stroke: 94 were thrombotic, 31 cardioembolic and 10 haemorrhagic. The mean age of them was 74 years (sd:8). The most frequent type of recurrence was large vessel atherothrombotic stroke followed by the cardioembolic ones. The major contributing risk factors were hypertension and atrial fibrillation. The fatality rate was higher and the functional prognosis worse in cases of early recurrence. There were more recurrences of thrombotic stroke in patients taking low doses of aspirin or derivatives than in the group taking ticlopidin. In the cases of cardioembolic strokes, the fear to anticoagulation in elderly patients resulted in devastating embolisms. In our opinion a less restricted use of anticoagulants and ticlopidin may help to prevent more recurrences. In many patients, despite the appropriate treatment, stroke recurrence was an unavoidable consequence.

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APC-RESISTANCE AND STROKE - AN UNUSUAL CASE REPORT. W.Schmaus, T.Stelzl, W.Hupfer, and K.A.Fluegel, Abteilung fuer Neurologie und Klinische Neurophysiologie, Staedtisches Krankenhaus Muenchen-Bogenhausen, Germany

Activated protein C (APC) limits clot formation by proteolytic inactivation of factors Va and VIIIa. The recently described phenomenon of APC resistance is associated with the most common hereditary defect predisposing to venous thromboembolism. More than 90 per cent of cases of APC resistance are caused by a point mutation in the factor V gene (factor V Leiden) leading to a poor anticoagulant response to APC in the plasma of such patients. However the role of this parameter in arterial thrombosis causing stroke is disputed. Here we report the case of a 37-year-old male who was delivered to our hospital with an acute complex oculomotor disturbance and a slight dysarthria without further neurologic symptoms. Cranial magnetic resonance imaging (MRI) showed an ischemic infarction in the left medial thalamus. The usual diagnostic investigations failed to show any abnormalities, besides smoking there were no vascular risk factors. However in a transesophageal echocardiogram an open foramen ovale and a possible thrombus in the right atrium could be detected just as a reduced APC sensitivity ratio and a heterozygous factor V Leiden mutation in the further laboratory investigations. Therefore paradoxical cardial embolism was suggested and the patient treated with anticoagulants. This is a rare case of a combination of heterozygous factor V mutation and stroke, and it will be discussed in relation to the current literature.

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IMPAIRMENT OF CEREBROVASCULAR REACTIVITY IN MIDDLE-AGED PATIENTS WITH DIABETES MELLITUS. Mankovsky B.*, Karasevich N.***Institute of Endocrinology; **Institute of Gerontology, Kiev, Ukraine.

Diabetes mellitus is associated with high incidence of stroke. However, the reasons for this predisposition remain not fully understood. Disturbances of cerebrovascular reactivity (CVR) may underlie higher incidence of cerebrovascular accidents in diabetic patients. Therefore, we studied CVR in 18 diabetic patients (aged 52.9±1.67 years) and 10 control sub-

jects (aged 52.6±1.43 years) using transcranial dopplerography. CVR was assessed by calculation of increment of blood flow velocity by left and right middle cerebral arteries (MCA) after maximal voluntary breathhold. We found that basal MCA flow velocity at both sides did not differ between two groups. However, it was statistical trend toward lower increment of flow velocity in patients with diabetes compared to controls - 21.2±4.4% vs. 27.3±4.3% by left MCA and 18.4±4.0% vs. 26.2±4.1% by right MCA, in those with diabetes and control subjects, respectively, p=0.1. Furthermore, in 7 out of 18 diabetic patients (38.9%) it was asymmetry of blood flow increase (difference was more than 10 sm/sec between arteries). In 39% of diabetics CVR was blunted as an increase of flow velocity was less than 10 sm/sec. We may speculate that revealed trend toward impairment of CVR could contribute to higher incidence of stroke in middle-aged patients with diabetes mellitus and assessment of CVR by transcranial dopplerography could be of use for selection of diabetic patients with high risk of stroke.

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TYPE III COLLAGEN DEFICIENCY IN SACCULAR INTRACRANIAL ANEURYSMS:DEFECT IN GENE REGULATION?JSP van den Berg, MD, [1,3], G Pals, PhD,[2], M Limburg, MD[1]. 1 Department of Neurology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands. 2 Department of Human Genetics, Vrije Universiteit, Amsterdam. 3 Department of Neurology, University of Nijmegen, University Hospital Nijmegen, Nijmegen, The Netherlands.

Background To determine if the type III collagen deficiency in patients with saccular intracranial aneurysms (SIAs) is due to a defect in gene regulation. One of the heritable factors possibly involved in the pathogenesis of SIAs is a reduced production of type III collagen demonstrated earlier by protein studies. Methods We analysed the type III collagen gene in a group of 41 consecutive patients with a SIA of whom 6 patients had shown a reduced production of type III collagen in cultured diploid fibroblasts from a skin biopsy. Results No mutations could be demonstrated in the COL3A1 gene, especially not in the globular N- and C-terminal regions. No differences were found between 41 patients and 41 controls in allele frequencies of a DNA tandem repeat polymorphism located in the COL3A1 gene. Conclusions The COL3A1 gene is not directly involved in the pathogenesis of most of SIAs. The repeatedly found reduced type III collagen production in cultured fibroblasts in some patients with a SIA is not explained by the present study, and needs further exploration for instance for posttranslational modifications.

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MRI AND MR ANGIOGRAPHY IN EVALUATION OF SYMPTOMATIC AND ASYMPTOMATIC INTRACRANIAL UNRUPTURED ANEURYSMS: I. Ivanovic, R. Semnic, K. Koprivsek, M. Lucic, M. Prvulovic. Imaging Diagnostic Center, Sremska Kamenica Yugoslavia.

Purpose: to assess the role of MRI/MRA in precise evaluation of unruptured intracranial aneurysms regarding its location, size, number and shape.Materials and methods: Retrospective study of 42 patients, age 30-60, with aneurysms revealed on MRI using standard brain protocol was done. Anerysms were particulary observed after application of three-dimensional time of flight (3D TOF) MR angiography.Results: Unruptured aneurysms were asymptomatic in 45% of our patients. In cases which were clinically significant, following symptoms were MRI confirmed: compression of optic nerve or chiasm 4.8%, isolate or complete third nerve palsy (ptosis, diplopia, pupilary dilatation) in 14.2%, and compression of brainstem in 11.9% patients. Aneurysm site were observed at: ACI 28.5 %, ACM 28.5%, anterior communicant artery 21.5%, vertebral artery 9.5%, ACP 4.7%, ACC 4.7%, posterior communicant artery 2.4%. Giant aneurysms were found in 4.8%. According to aneurysm shape, saccular were observed in 76.2% and fusiform in 19%. Aneurysms with MRI signs of partial thrombosis were present in 48%. Neck of aneurysm was detected in 19% of cases only. Conclusion: The advances in MRI and MRA have produced powerful tools in revealing precise architecture of intracranial aneurisms.

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TISSUE PLASMINOGEN ACTIVATOR EXPRESSION AND ACTIVITY IN EXPERIMENTAL FOCAL CEREBRAL ISCHEMIA.TK Pfefferkorn, B Stauffer, C Zimmermann, G Bueltemeier, M Liebetrau, GF Hamann.Department of Neurology, Klinikum Grosshadern, LMU Muenchen, Germany

Background: Plasmin not only dissolves fibrin but also leads to degradation of extracellular matrix (ECM) proteins with consecutive extravasation of blood components. To elucidate the role of the plasminogen plasmin system in secondary hemorrhage after brain infarction we investigated tPA expression and activity in experimental focal cerebral ischemia.Methods: We used a nylon thread rat model to induce focal ischemia by temporary middle cerebral artery occlusion (3 hours) followed by a variable period of reperfusion (3, 9, 24 hours). Infarct area and tPA expression were detected by immunohistochemistry. PA activity was evaluated by zymography (plasmin mediated lysis of a caseine overlay containing plasminogen).Results: Infarct areas increased significantly with reperfusion time (46.3+/–20.6 vs. 64.4+/–6.2 vs. 74.9+/–6.6 percent of total basal ganglia area after 3, 9, and 24 hours respectively). Generally, tPA was mainly expressed in the precapillary arterioles with additional background staining in infarcted areas. Concerning PA activity there was close overlapping between areas of infarction and areas of zymographic lysis.Discussion: After MCAO and reperfusion in rats we found a strong correlation between reperfusion time and infarct size. In infarct areas tPA expression and PA activity were increased. Previous investigations have shown degradation of ECM proteins in areas of infarction. Our findings support a role of tPA in the degradation of ECM components in focal ischemia and reperfusion.

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FLOW QUANTIFICATION IN EXTRA-INTRACRANIAL HIGH-FLOW BYPASS WITH MR-ANGIOGRAPHY. LMP Ramos, CAJ Broere, TW Polder, CAF Tulleken. Departments of Radiology and Neurosurgery, University Hospital Utrecht, The Netherlands

Purpose: To qualify and quantify flow in an extra-intracranial (EC-IC) high-flow bypass.Materials: Group 1: four patients with an EC-IC bypass between superficial temporal artery (STA) and internal carotid artery (ICA), because of severe stenosis in the ICA. Group 2: five patients with an EC-IC bypass between external carotid artery (ECA) and ICA, because of haemodynamic hemispheral TIA's (n=1), giant aneurysms (n=2), traumatic aneurysm (n=1) or inoperable skull base tumour (n=1).Methods: The nonocclusive Excimer? laser-assisted anastomosis technique was utilized for high-flow revascularisation. Postoperative MRI-MRA was carried out on a 0.5 Tesla whole body imager(Gyroscan?, Philips). 2-D phase-contrast angiography (2D-PCA) was performed with cardiac triggering, and without cardiac triggering. Quantification of flow (QF) was performed in a perpendicular plane to the external part of the bypass on the 2D-PCA images. Reproducibility was estimated using repeated measurements without cardiac triggering. Digital subtraction angiography (DSA) was performed in both groups as a control.Results: Comparison of QF between patients with an STA-ICA or an ECA-ICA bypass showed no significant difference (patient group I: mean 147±22 ml/min; patient group II: mean 186± 36 ml/min; Mann-Whitney p= 0.41). Comparison of QF with or without cardiac triggering in both patient groups, revealed no significant difference was found (Mann-Whitney p=0,73). Repeated measurements without cardiac triggering in 2 patients varied between 110 (7,8) ml/min (SD) and 130 (10.2) ml/min (SD). Conclusion: No significant difference in flow was found between patients with an STA-ICA or an ECA-ICA high-flow bypass.

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STROKE SUBTYPE, FUNCTIONAL OUTCOME AND AGING IN CHRONIC STROKE PATIENTS. Yutaka Hirata, MD, Kazuo Suzuki, MD. Department of Neurology and Epidemiology, Research Institute for Brain and Blood Vessels, Akita, Japan

Objective: To document functional outcome and possible factors influencing outcome. Subject and method: A total of 2,971 stroke survivals older than thirty years were inquired. Stroke subtype was diagnosed by using computed tomography. We analyzed stroke subtype, age and functional outcome using the Rankin scale. Results: Subjects were 1,851 male and 1,120 female patients. They consisted of 1,654 cases of brain infarction (BI), 689 cases of brain hemorrhage (BH), and 628 cases of subarachnoid hemorrhage (SAH). Functional outcome of the whole cases was as follows: independent 44.7%, mildly dependent 25.0%, moderately dependent 21.0%, totally dependent 8.0%, and death 1.8%. For BI survival cases, that was 44.9%, 26.3%, 21.2%, and 7.5%, respectively. For BH survival cases, that was 30.0%, 30.9%, 28.6%, and 10.4%, respectively. For SAH survival cases, that was 63.5%, 17.1%, 12,0%, and 7.4%, respectively, showing significantly increased rate of independent cases. A Cox proportional hazard model revealed no relationship between stroke subtype and frequency of totally dependent cases, which strongly correlated with age. Conclusion: Frequency of totally dependent cases had not correlated to

any subtype of stroke, but strongly correlated with age; this could be a great help for strategy to ameliorate long-term prognosis of stroke patients.

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IS THERE A PARTICULAR SITE OF CEREBRAL ANEURYSM LEADING TO POORER COGNITIVE PROGNOSIS IN SUBARACHNOID HAEMORRHAGE? Élia Baeta*, C. Vilela#, M. Cunha e Sá# *Neurology Department, # Neurosurgery Dep.Hospital Garcia de Orta - Almada - PORTUGAL

Most authors argue that patients who suffered a subarachnoid haemorrhage (SAH) following rupture of intracranial aneurysm of the anterior communicating artery (AcomA) perform worse than patients do with ruptured aneurysm located elsewhere. Nevertheless others relate cognitive defects to SAH, itself. The debate is maintained due to some methodological problems namely miscellany of aetiologies and extreme selection of cases. In order to clarify this issue we evaluated 32 patients with SAH following rupture of intracranial aneurysm, more than one year after delivery from hospital. Fifteen patients had AcomA aneurysms. They were submitted to a neuropsychological battery including the following tests: Wechsler Memory, Trail Making A and B, Stroop Test, Toulouse Pieron attention test, Benton Line Orientation Test, Raven Matrices, Language Battery of Lisbon, Token Test, verbal fluency, praxic skills and calculation. They were also asked about professional state and independence level. Data were analysed by means of statistical methods. Results point out that: 1) Patients with SAH following rupture intracranial aneurysm of the AcomA do not have poorer performance on cognitive tests, than patients with SAH secondarily to rupture of intracranial aneurysms located elsewhere. 2) Cognitive deficits are not related to functionality level neither with professional situation; 3) Those patients who suffered neurologic complications, during the acute period following SHA, are more prone to neuropsychological deficit.

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STROKE IN PATIENTS WITH DIABETES: RESULTS IN ZARAGOZA, SPAIN. S. Santos, LF. Pascual, J. López del Val, C. Tejero, E. Mostacero, C. Rios.Service of Neurology.University Clinical Hospital of Zaragoza. Spain

Purpose: Previous studies have demostrated that stroke in diabetic patients is different from in nondiabetic patients in several aspects. The aim of this study is to determine in our community-based stroke population how diabetes influences in prognosis, severity and mortality.Methods: This study include 435 acute stroke patients admitted in a 1-year period. All patients were evaluated and divided into two groups: patients without diabetes and patients with known diabetes. We analyzed age, sex, neurological deficit, mortality, risk factors, functional outcome, type of stroke. The Student's t test was used for the comparison of continuous data and the chi-test was used for noncontinuous data.Results: The diabetic stroke patient was younger than the nondiabetic (p=0.008) and had hypertension more frequently (p=0.002). Initial severity (Canadian scale) was increased in diabetic patients (p=0.05) as well as 7-day functional discapacity (Rankin scale; p=0.05). Mortality and type of stroke were comparable between the two groups. Small and lacunar infarcts seems to be similar in patients with and without diabets. Diabetic patients with infarction were younger than nondiabetic patients (p=0.014). Conclusions: Diabetes influences stroke in several aspects: in age, initial severity and functional outcome. The diabetic stroke patient is younger and recovery is slower but mortality is not increased perhaps because we must also consider admission glucose levels.

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THE STUDY OF LARGE CEREBRAL INFARCTS ASSOCIATED WITH ATRIAL FIBRILLATIONS-Authors: Dragan Marjanovic, Milan Savic -Hospital for cerebrovascular disorders "Sveti Sava", Belgrade, SR Yugoslavia

Atrial fibrillation (AF) is one of main risk factors for cerebral infarcts. The mechanism by which AF produces large brain infarcts could be embolisation of main cerebral vessels.Objective: Among 37 patients with large brain infarcts and AF dominate lesions in territory of middle cerebral artery(MCA), posterior cerebral artery (PCA) and anterior cerebral artery (ACA) in that order which is in strong correlation with middle diameter(MD) of their proximal parts.Method: Study includes 37 patients,17 males and 20 females, aged 49-84 years. They developed a frank neurological deficit and passed trough routine physical and neurological examination, electrocardiography and CT of brain.Results: In this group of patients CT revealed large supratentorial infarcts localized as follows: in 24 patients infarcts were in territory of MCA(64,86%),11 in territory of PCA(29,73%) and 2 in ACA territory(5,41%).Among MCA infarcts 18 (75%) were on left side while among infarcts in PCA territory 8 (72,72%) were on the right and infarcts in ACA territory on the right.Conclusion: Assuming embolic mechanism of cerebral infarcts we conclude that MD of MCA,PCA and ACA strongly correlates with localization of brain infarcts. According to anatomical data MCA MD= 3,0-3,9mm, PCA MD = 2,4mm, ACA MD= 2,0-2,6mm. This means there is highest risk for arteries with widest MD at their origin to be occluded by embolus coming from heart.

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EFFECTS OF HYPOXIA, REOXYGENATION AND TUMOR NECROSIS FACTOR (TNF)-α ON THE SECRETION OF MATRIX METALLOPROTEINASE (MMP)-2 BY HUMAN ENDOTHELIAL CELLS. Shapiro S, Lahat N, Finkelstein D, Bitterman H, Miller A. Lady Davis Carmel Medical Center and Technion, Israel Institute of Technology, Haifa, Israel.

Recent evidence from certain autoimmune diseases has shown ischemic processes to be important secondary pathological phenomena. Products of inflammation, cytokines and endogenous matrix degrading enzymes (MMPs) play a complex role in the hypoxic process. Our aim was to study the effects of hypoxia/reoxygenation and TNFα, a key inflammatory mediator, on the secretion of MMP2, a collagenase which is consitutively expressed by endothelial cells. Methods Cultured human endothelial cells (EAHy936) were subjected to hypoxia (P02 25-35 mgH92) for 6-48 hours followed by rexoygenation for 24 hours, with or without the addition of TNFα. Activity of secreted MMPs was evaluated by gelatin zymography. The relative density of digested protein was evaluated by denistometry and western blotting was performed to verify the identity of the MMP. Results: Endothelial cells constitutively secreted active MMP2 (66kDa) which was inhibited by short term hypoxia (6-12 h) and normalized by prolonged hypoxia or reoxygenation. TNFα added to normoxic endothelium did not affect active MMP2 but induced a dose dependent elevation of MMP2 zymogen form (72kDa). Short hypoxia inhibited the TNFα-induced 72kDa MMP2, while reoxygenation obliterated this inhibition. Prolonged hypoxia combined with TNFα resulted in a pronounced decrease of both forms of MMP2 which was not restored by reoxygenation. Conclusion Hypoxia or inflammation (as portrayed by TNFα) per se, only temporarily enhanced or inhibited MMP2 secretion. The combination of hypoxia and TNFα lead to irreversible suppressive effects on MMP2 activity, possibly perturbing MMP2 dependent endothelial functions involving physiological matrix modulation.

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MEASUREMENT OF HUMAN BRAIN TEMPERATURE USING PROTON MAGNETIC RESONANSE SPECTROSCOPY-B. Mihara, H. Takayama, M. Kobayashi, [1]S.Suga and [2]S.Gomi. Mihara Memorial Hospital, Gumma, 1 Keio University, Tokyo, 2 Aoyama Gakuin University, Tokyo, Japan

BACKGROUND: The effectiveness of moderate brain hypothermic therapy for severe brain injury has been reported. Recently it is shown that temperature-dependent chemical shifts in the magnetic resonance frequency of water could be utilized to determine absolute brain temperature in the living animals. This study was aimed to develop the technique for measuring human brain temperature using proton magnetic resonance spectroscopy([1]H-MRS). METHODS: All experiments were performed on a 1.5T Siemens MAGNETOM Vision. (1) In vitro calibration data was acquired from phantom containing choline, creatine and N-acetyl-aspartate(NAA), over the temperature from 32 to 40°C. Non-1120-Suppressed MR spectras of the phantom were obtained and chemical shifts between water and NAA(Δppm) at each temperature were evaluated. (2) Healthy volunteers, non-neurologic patients with fever acute stroke patients and patients under brain hypothermic therapy were enrolled in this study. The Δppms were measured in the occipital cortex and deep brain structures. The tympanic membrane temperature(TMT) was also monitored during the study. RESULTS: (1) The relationship between the temperature-induced Δppm and the phantom temperature (0.0098XΔppm- 2.7288). (2) The values of calculated brain temperature of the deep brain structure was not identical to the TMT. CONCLUSIONS: It is suggested that the non-invasive measurements of human brain temperature using [1]H-MRS should

be a potential strategy for managing patients with severe brain injury, especially during brain hypothermic therapy

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A PROSPECTIVE STUDY OF SERUM HOMOCYSTEINE AND RISK OF VASCULAR EVENTS AFTER STROKE. T. Del Ser, R. Barba, V. Seijas,C.López-Manglano, M. Pondal, J. Domingo. Hospital Severo-Ochoa. Leganés. Spain.

OBJECTIVE: Moderate hyperhomocysteinemia is an independent risk factor for stroke. The aim of this study was to determine whether hyperhomocysteinemia would be also a risk factor for vascular events after stroke.METHODS: We prospectively followed with a standard clinical protocol 101 stroke patients (90 ischemic, 11 haemorrhagic; age >65 years) from the Hospital Severo-Ochoa Registry of Stroke. We determined serum homocysteine three months after the stroke. Vascular events (venous thrombosis, stroke recurrence, coronary or peripheral arterial disease) were identified during the 36 months follow up. We used Kaplan-Meier analysis to determine the cumulative proportion of patients with homocysteine above or below percentile 75 who survived free of vascular events, and Cox models to estimate the relative risk of vascular events.RESULTS: Serum homocysteine was higher in patients with a vascular event (27.3 versus 20.5 µmol/L; OR 1,1 p=0.04). The cumulative proportion of patients without any vascular event was 53.6% in the group with homocysteine over 75 percentile and 74,4% in the other group, (log rank test 6,5; p=0.01). The relative risk of vascular event associated with high homocysteine was 2,7 (IC 95% 1,2-6,1; p=0,01) after adjusting for demographic factors, hypertension, diabetes and cardiac diseases.CONCLUSIONS: Hyperhomocysteinemia may be a significant independent risk factor for vascular events after stroke. This finding might have therapeutic relevance in the secondary prevention of vascular diseases.

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THE INFLUENCE OF MK-801 AND CGP-43487 ON SEIZURE SUSCEPTIBILITY IN MICE EXPOSED TO LEVINE MODEL OF BRAIN OLIGEMIAHYPOXIA. Rejdak R.[1], Rejdak K.[1], Sieklucka-Dziuba M.[2], Kleinrok Z.[1]. 1-Department of Pharmacology, Medical University in Lublin; 2-Department of Hygiene, Medical University in Lublin

Seizures are relatively common sequela of stroke. A non-competitive NNIDA antagonist MK-801 and competitive NNIDA antagonist CGP-43487 may be regarded as a model seizure-preventing drugs. The aim of the study was to examine the effects of both drugs on seizure susceptibility of mice exposed to oligemic-hypoxic insult. METHODS: Levine model of rat brain oligemia-hvpoxia, was adapted to mice (right carotid artery occlusion + hypoxia). 7 days after surgery pharmacological treatments were given. Treatment groups consisted of placebo, MK-801 (0.2 mg/kg i.p.) and CGP-43487 (4 mg/kg i.p.). Drugs were administered 30 min before induction of seizures with bicuculline (2.5 mg/k-g s.c). Seizures were 1, classified as mycoclonic, clonic and tonic convulsions. Additionally, 7 days after exposure to Levine procedure GABA content in brain tissue was measured. RESULTS: Levine mice displayed increased frequency of myoclonic and generalised clonic/tonic seizures. The treatment with CG-P-43487 modestly diminished the frequency of myoclonic and clonic seizures, but it did not influence the generalised tonic seizure activity. MK-801 strongly diminished clonic/tonic seizure susceptibility. Biochemical analysis of GABA content in brain.. tissue of animals exposed to Levine model showed a. very significant decrease in ipsilateral hemisphere to the occlusion and also moderate decline in contralateral one. CONCLUSION: Our data suggest the potential usefulness of NM13A receptors antagonists as a therapeutic agents for treating brain damage induced by cerebral ischemia and hypoxia.

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CONSTRICTIVE-STENOTIC ARTERIOPATHY COURSE PECULARITIES IN PATIENTS WITH SPONTANEOUS CEREBRAL HAEMORRHAGES IN CONNECTION WITH HAEMORRHAGIC SOURCE LOCATION. Volodymyr A. Golyk, Ludmila A.Dzyak, C. Dnipropetrovsk, Ukraine

Constrictive-stenotic arteriopathy (CSA) appears after cerebral haemorrhages & serves as negative prognostic factor worsen the outcome due to secondary developed ischaemic deterioration of brain. CSA peculiarities according to transcranial dopplerography (TCD) study & its correlation with haemorrhage source location were evaluated in such patients. Materials & methods: 120 patients composed 3 groups: I - 50 (subarachnoid haemorrhages), II - 30 (intraventricular haemorrhages), III - 40 (pure intracerebral haemorrhages). Computerised tomography & lumbar puncture verified diagnosis (the latter was negative according to macro- & microscopic investigation in III group). All patients were admitted on 0-3rd day of haemorrhage, TCD was performed on the day of admission, day 4, 9, 13, 15, 20 after ictus. All persons underwent angiographic evaluation for pathology source disclosing (I group - arterial aneurysms (AA) 48, not disclosed (nd)- 2 patients; II group - AA - 10, vascular malformations (VM) - 17, nd - 3, III group- AA-20, VM - 16, nd - 4) followed by operation. Its timing was established according to Hunt-Hess scale. Results: In I group CSA was developed in all patients: first signs appeared on days 3-4 - 35 persons, day 9 - 10, day 13 & further - 5; II group - 8, 14, 8 patients; III group - 1, 8, 6 consequently & not developed in 25. Distribution of CSA was correlated with SAH severity according to Fisher scale. Ischaemical complications due to CSA developed in: I group - 10 patients (severe -2, mild - 4, transient - 4), II group 11 (severe - 4, mild - 2, transient - 5), III - 3 (severe). Conclusions: correlation between haemorrhage source location & CSA expression with following ischaemic deterioration were revealed.

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FACTORS INFLUENCING ACCESS TO REHABILITATION TREATMENT AFTER STROKE: RESULTS FROM A REPRESENTATIVE, POPULATION-BASED STROKE REGISTER IN GERMANY Bernhard Neundoerfer, Peter L Kolominsky-Rabas, Peter U Heuschmann,Unit for Stroke Research and Public Health Medicine, Dep. of Neurology, Friedrich-Alexander University Erlangen-Nuremberg, Germany

Background: Population-based representative data about frequency of rehabilitation treatment after stroke and the factors predicting access to rehabilitation are lacking.Methods: The ERLANGEN STROKE PROJECT (ESPRO) is a ongoing community-based survey of outcome of first-ever-in-a- lifetime-stroke (FELS) in a German community. The total study population is 101.450, 15.364 (15.1%) inhabitans are aged > 65 years. Several overlapping sources of information are used to ensure ascertainment of hospitalized and non-hospitalized cases. CCT was performed in 94% of the study patients. All identified patients were followed up at time- intervalls at 3 and 12 months after stroke.Results: In a two-years period 354 consecutive patients with FELS were identified and followed up for 12 months. 35% (n=90) of all hospitalized stroke patients had access to rehabilitation treatment after FELS. 76% (n=68) of these subgroup were admitted to rehabilitation without any time delay.In the univariate analyses younger aged people ($p < 0.001$), men ($p < 0.01$) and pre-stroke independent patients ($p < 0.01$) were more often treated in a rehabilitation unit. Frequency of rehabilitation treatment was high in the severe and midly disabled group of stroke patients and low in the very severe, moderate and non disabled group (p=0.15). No influence could be demonstrated for the diagnosis and the numbers of risk factors.In the multivariate model the variables severity of stroke ($p < 0.002$), age ($p < 0.005$) and pre-stroke patterns of care ($p < 0.02$) were identified as the only independent predictors for access to rehabilitation treatment.Conclusion: In our population-based sample there was evidence, that access to rehabilitation facilities should not only be provided to younger patients, but should focuse on older age groups as well as on patients with pre-stroke dependancy. As the number of elderly comorbid patients in Europe will increase in the future decades access criteria to rehabilitation treatment should be refined to provide the necessary care for this increasing group of stroke patients.

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SIRIRAJ ACUTE STROKE UNIT: THE STROKE PARADIGM OF THAILAND. Niphon Poungvarin MD,FRCP, FRCP(Glasg), FRCP(Edin), Vorapun Senanarong MD,Naraporn Prayoonwiwat MD, Arkhom Arayawichanont MD. Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok 10700,Thailand.

It is well established that the management of stroke in the stroke unit has been an excellent results. Siriraj Acute Stroke Unit has been established in Thailand since May 1997, and it is the only unit in the country. It composes of 11 beds with fully trained stroke team including nurses, physiotherapist, radiologists and neurologists. Methods: We analyzed 363 patients from the total of 363 admitted cases during the last 18 months, using SPSS 7.0 The main criteria of admission were stroke patients who did not need respirator, and who had Glasgow Coma Scale over 11/15. Results: Three hundred and sixty three stroke patients were admitted at Siriraj acute stroke unit.180 percents (49.59 per cent) were female, mean age was

63.11 ± 13.84 years old. (range 19-94 yrs) 89.26 per cent of them had CT/MRI brain scan either before or on the arrival at the stroke unit.Seventy six point five eight percent of the patients had cerebral infarction, 17.36 per cent had cerebralhaemorrhage and 3.96 per cent had transient ischaemic attack. Risk factors of stroke were as the following: 57.58 per cent had hypertension, 30.58 per cent had diabetes mellitus 23.33 per cent had underlying heart disease either ischaemic heart disease, valvular heart disease, or cardiac arrhythmia. 13.22 per cent had history of current alcoholic drinkers, 33.88 per cent had hyperlipidaemia. Mortality rate in this stroke unit was only 2.2 per cent (8 from 363). Conclusion: Mortality rate of acute stroke patients being managed at general medical ward at our hospital was about twenty five percents. Thus Siriraj Acute Stroke Unit has given patients a better chance of survival.

P360
IN-HOSPITAL MORTALITY AND LENGTH OF STAY FOR STROKE PATIENTS IN PIEMONTE, ITALY.M. Leone, G. Ciccone, C. Varrasi, F Monaco, Novara, Torino, Italy.

Background: geographical variations in clinical practice and outcomes for stroke have been observed, but no information is available for Italy. Objective: to compare in-hospital mortality and length of stay in all hospitals of a well-defined area (Piemonte Region in north-western Italy, population 4,4 millions).Methods: all patients discharged in the year 1996 from all the hospitals of the Region were collected. Patients were eligible if they were coded with one of the following International Classification of Diseases, Ninth Revision principal diagnosis codes: 430 (subarachnoid hemorrhage), 431 (cerebral hemorrhage) and 434 (ischemic stroke).Results: we found 6902 admissions: 471 had the code 430, 1363 the code 431, and 5068 the code 434. We excluded rehabilitation hospitals and hospitals with less than 10 admissions. The mean length of stay varied between 5.1 and 22.1 days for the code 430; 9.3 and 26.4 days for the code 431; and 9.3 and 26.4 days for the code 434. In-hospital mortality was 22% for code 430, 32% for code 431 and 17% for code 434. In-hospital mortality varied among hospitals: from 6 to 20% for code 430, from 13 to 42% for code 431 and from 6 to 39% for code 434.Conclusions: the use of administrative data to assess the quality of the assistance has been questioned; however the validity of the discharge codes has improved in recent years in Italy. Our study showed a large variability of both length of stay and in-hospital mortality.

P361
TIME COURSE OF CEREBROVASCULAR RESERVE IN CRITICAL CAROTID STENOSIS. S. Hallmeyer*, G. Gahn*, R.H. Ackerman§, G. Hahn*, S. Schellong#, D.M. Ockert+, H. Reichmann*Departments of *Neurology/ #Angiology/ +Vascular Surgery, University of Dresden, Germany; §Neurovascular Lab, Massachusetts General Hospital, Harvard Medical School, Boston, USA

Objective: To evaluate the time course of cerebrovascular reserve (CVR) findings in normal stroke-age patients and in patients with carotid stenosis. Methods: Simultaneous bilateral TCD recordings of middle cerebral artery (MCA) signals were compared in 30 patients (mean age 66.0(10.6 yrs) with symptomatic unilateral critical carotid stenosis (>90% lumen diameter reduction) and 27 age matched normal controls (67.3(9.3). CVR was calculated as %change in MCA mean blood flow velocity during sequential trials of breath-holding. We measured the time intervall between beginning of breath-holding and reaching the peak blood flow velocity. All patients had CVR testing before and after CEA. Results: For the normal controls the peak velocities were reached on the both sides after 28.6±8.7 sec (mean time difference 0.006(0.7 sec) after beginning of breath-holding. The patients with carotid stenosis reached the peak velocity on the side of severe stenosis after 33.6(11.8 sec, on the normal side after 31..5(11.6 sec (mean difference 2.0(2.6 sec). After CEA the time interval was 30.2(8.9 sec on the normal and 30.3(9.0 on the operated side, the mean difference was 0.1(0.5 sec. The differences between the delay before and after surgery are significant at a "p"-value.0001 (Paired-samples T-Test). Conclusion: Prolonged transition time of systemic CO2 causes delayed CVR on the side of critical carotid stenosis presumably because of longer travel distance of blood through collateral path-ways. This finding suggests a local dilatational response of cerebral vessels to increase in systemic PaCO2.

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CEREBROVASCULAR DISEASE: EPIDEMIOLOGICAL UPDATE OF RISK FACTORS [RF] Gandolfo C., Saggese J., Povedano G.. Churruca-Visca Hospital. Argentina.

Cerebrovascular risk factors remained unquestionnable for at least the last decade. In order to update our epidemiological information we reviewed data from stroke inpatients.We searched antecedents of hypertension, cardiopathy, diabetes, alcoholism, smoking and snoring. We classified the patients based on CT findings in haemorraghic [n:43] [13.2%] and ischaemic [n:283] [86.8] Infarcts were subclassified in deep infarct (n:188) and cortical stroke (n:95).From 326 new stroke events, 142 were women [43.6%] with a mean age of 69.96 +/– 11.39 years significantly different from men {mean age 65.65 +/– 11.09 years).Hypertension and cardiac disease were more common in cortical stroke ($p < 0.02$). Smoking, enolism ($p < 0.001$) diabetes and snoring (p 0.05) were associated to earlier presentation of deep ischaemia and hypertension and cardiopathy to later one ($p < 0.05$).Regarding gender, we found no differences in RF of haemorrhagic, while ischaemic male patients showed significantly more enolism ($p < 0.001$), tabaquism ($p < 0.001$) and snoring ($p < 0.03$). Mean age for deep lesions was 64.97 years for men and 71.63 for women ($p < 0.001$).Female with deep lesions showed significatively more snoring than cortical ($p=0.039$).We think that pharmacological treatment of hypertension or cardiopathy may delay the appearence of stroke, essentially deep or multi-infarct ischaemia. Lack of therapeutical measures for smoking, snoring or enolism, keep them as real risk factors, determining an earlier stroke presentation Female had lower incidence of the latter, and consequently deep infarctions occur later.

P363
CLINICAL PREDICTORS OF CENTRAL POST STROKE PAIN IN PATIENTS WITH LATERAL MEDULLARY INFARCTION.S Fitzek[1,2], C Fitzek[4], U Baumgärtner[3], W Magerl[3], PP Urban[2], RD Treede[3], P Stoeter[4], HC Hopf[2]. 1-Department of Neurology, University of Jena, 2-Department of Neurology, 3-Institute of Physiology and Pathophysiology and 4Institut of Neuroradiology, University of Mainz, Germany

Patients and methods: Clinical findings, frequency of post stroke pain, high resolution MRI, blink reflex, and quantitative sensory testing of pressure and thermal sensation thresholds were investigated in 12 patients with medullary infarction. Results: Of the 12 patients with medullary infarction, 8 (67%) developed central poststroke pain within days to 24 month after acute infarction. The pain syndrom mostly was constant and affected the ipsilateral peri-orbital region alone (3 patients) or in combination with the contralateral limbs (3 patients), but did not in all cases request therapy. Ipsilateral sensory deficit was found in all and abnormal blink reflex in 5 of 6 patients with facial pain but in none of those without. Facial pain correlated significantly with MRI lesions in the lower parts of the medulla and with contact of the lesion with the trigemial spinal tract and nucleus (TSTN). Although there was one patient who had a small lesion projecting on the spinothalamic tract (ST) and developed a contralateral pain sydrom of limbs only we found no statistical correlation between pain syndromes and contact of lesions with ST. Conclusions: Ipsilateral sensory deficit and abnormal blinkreflex revealed a highly specific (100/100 %) and sensitive (100/83%) finding for chronic central pain of the face. The findings support the theory that chronic central pain of the face after medullary stroke is caused by lesions of the lower parts of TSTN.

P364
FLOW CYTOMETRY ANALYSIS OF PLATELET ACTIVATION MARKERS IN PATIENTS WITH REVERSIBLE ISCHEMIC NEUROLOGIC DEFICIT (RIND) AND COMPLETED STROKE (CS) Ewa Beliniak-Legie, Zbigniew Stelmasiak, Urszula Chyrehel, Department of Neurology, Medical Academy, Lublin, Poland

Platelet activation seems to play a critical role in a number of vascular diseases including stroke. The aim of our study was whole-blood flow cytometry evaluation of platelet activation markers: P-selectin (CD62), glycoprotein-53 (CD63) in vivo in patients with reversible ischemic neurologic deficit (RIND) and completed stroke (CS) We investigated 23 patients with RIND (13 men and 10 women in mean age 66,5) and 27 patients with CS (16 men and 11 women in mean age 69). Parameters of platelet activation were measured on the 1st, 3rd and 7th day after stroke onset. Comparisons were made with 20 control patients matched in age.. Compared to the controls (1,6±0,7%) the patients with CS showed higher 1 expression of CD62 on the 1st (3,1±1,6%), 3d (4,4±2,3%) and 7th (3,9±2,3%) day after stroke onset ($p < 0,05$). Increase of CD62 expression between the 1st and the 3rd day was also statistically significant ($p < 0,05$). Compared to the controls (1,5±0,6%) the patients with CS had also higher expression of CD63 on the 1st (1,9±0,7%), 3rd (2,2±0,6%) day after stroke onset ($p < 0,05$). Compared to the controls the patients with RIND had

higher expression of CD63 (1,7±0,4%) and CD62 (2,1±0,9) on the 1st day after stroke onset. Compared to patients with RIND patients with CS had higher expression of CD62 in all days after stroke onset. The differences were statistically significant ($p < 0,05$).Elevated expression of CD62 and CD63 indicate platelet activation during the acute phase of ischemic stroke especially in patients with CS.

P365
MICROEMBOLIC SIGNALS AFTER PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY WITH AND WITHOUT STENTING IN THE CAROTID ARTERY TERRITORY - A PROSPECTIVE MULTIGATE-DOPPLER STUDY B.G.H. Schoser, MD; I. Nowack; A. Thie, MD. Departments of Neurology University of Hamburg, and *Itzehoe Hospital, Germany

Stenting of carotid arteries is a technique in evolution to improve results of percutaneous transluminal angioplasty (PTA). Evaluation of ultrasonic changes of microembolic signals (MES) after carotid PTA using stent techniques is not settled yet. Therefore, we prospectively studied the effect of stenting of carotid artery on peri- and postinterventional cerebral MES. Methods Ten patients undergoing carotid PTA for symptomatic high-grade carotid artery stenosis with (n= 5) and without (n= 5) stenting were studied. Multigate Transcranial Doppler serial recordings from the ipsilateral and contralateral middle cerebral arteries were performed during the first 90 postinterventional days.Results A total of 123 MES were found in 37 of 78 monitorings (47.4%). MES counts on the side of PTA were significantly higher periinterventionally (n=91) than at 90-day follow-up (n=10). In the contralateral carotid arteries, a postinterventional reduction of MES counts could be recorded. Postinterventionally within the first 30 hours, an increase of MES counts in 2 of 5 patients with, and in 2 of 5 patients without stenting was recorded. Thereafter, no differences of postinterventional MES counts were noted in either group.Conclusion After a transient increase of MES within the first 30 hours post-PTA, there is a significant MES reduction regardless of stenting.

P366
SEASONAL PATTERN OF ONSET IN SUBGROUPS OF PATIENTS WITH INTRACEREBRAL HEMORRHAGE.S. Passero, F. Reale, G. Ciacci, E. Zei-Istituto di Clinica delle Malattie Nervose e Mentali, Università di Siena, Italy

Intracerebral hemorrhage (ICH) occur more frequently during the winter months compared with other seasons. The seasonal blood pressure variations have been considered a possible explanation for this pattern of onset. The aim of this study was to analyze the seasonal variations in occurrence of ICH and to determine whether or not the presence of subgroups with specific clinical characteristic would exhibit different pattern. The study population consisted of 1002 patients with non traumatic ICH. Patients were grouped according to the etiology of the ICH: 576 patients had hypertensive ICH; 193 patients had secondary ICH; 56 patients had cerebral amyloid angiopathy related ICH, and 177 patients had ICH of undetermined origin. In the whole population the distribution of ICH across the four seasons showed a clear seasonal pattern. The higher number of ICH occurred in winter and the lowest in summer with a winter/summer ratio of 1.44. Analysis of subgroups showed that this seasonal pattern was significant only in patients with hypertensive ICH (winter/summer ratio of 1.57). These results demonstrated that marked differences in seasonal patterns of ICH onset occur in subgroups of patients with specific clinical characteristic and that the pattern observed in a given total population reflects the contributions of these subgroups.

P367
NEUROEXCITATORY AMINOACIDS IN JUGULAR AND ANTECUBITAL VENOUS BLOOD IN STROKE. RELATIONSHIP WITH CLINICAL EVOLUTION.JJ.Muñoz-Torrero, R.Soler, E.Díez-Tejedor, A.Hernanz*, A.Frank, P.Barreiro. Neurology Department.Stroke Unit. Biochemistry Department*. University Hospital La Paz. Autonoma University of Madrid, Spain.

Both serum and CSF neuroexitatory aminoacids levels have been pointed out as markers of ischemic-induced neuronal damage. We analyse their levels in blood from both internal yugular and antecubital veins and search for a relationship with clinical evolution of stroke.Methods: Inclusion criteria: age 50-85, cortical brain infarction, previous functional independence and non-commatous state. We evaluated Canadian-Stroke-Scale score at 24 hours (CSS-1), 1 week (CSS-2) and 90 days (CSS-3) and Barthel-Scale score at 1 week and 3 months. We took out samples from each patient´s internal yugular and antecubital veins within the first 24 hours after the onset of the stroke. Glutamate, aspartate, taurine and glycine levels were measured. We searched for correlation between them and clinical scores using Pearson´s r test.Results: 15 patients were included. None of the antecubital levels showed correlation with any score. There were correlation between glutamate yugular levels and CSS-2. The differences between yugular and antecubital glutamate levels reached significant negative correlation with all of the clinical scores.Conclusions: The difference between yugular and antecubital veins glutamate levels reached correlation with any scale score measured along the stroke evolution. It seems to be more important in predicting the clinical outcome than the absolute values. It could represent a better aproximation to the glutamate liberated in the infarction and the ischemic-induced neuronal damage.

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ORPINGTON PROGNOSTIC SCALE: ITS USE IN PREDICTING OUTCOME AFTER ISCHEMIC STROKE. S Pittock*, D Meldrum**, O Hardiman*.Departments of Neurology* and Rehabilitation**, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland.

The Orpington prognostic score (OPS) which incorporates measures of motor deficit, proprioception, balance and cognition has previously been shown to be a useful prognostic indicator at two weeks post stroke in the elderly stroke patient. We studied 126 patients prospectively with acute ischaemic stroke admitted through casualty in a Dublin city hospital over a nine month period. Stroke subtypes were clinically classified using the Oxford Community Stroke Project method. Patients were assessed at 48 hours, two weeks and six months with the OPS, European Stroke Scale, Barthel index, Rivermead Motor assessment and Rankin score. Grip Strength, Swallow and Incontinence were also assessed. Premorbid Barthel and Rankin scores were obtained. We found that the OPS measured at two weeks was a good indicator of outcome (as measured by the above scales) at six months.Abnormal swallow and incontinence were present in 30% and 35% of patients respectively at 48 hours and these were also shown to have prognostic significance.In conclusion the use of the OPS and assessment of swallow and incontinence are clinically useful methods of predicting outcome of patients with stroke.

P369
STROKE ETIOLOGY IN YOUNG ADULTS. Cristina Tiu*, Sandrine Canaple **, Alain Rosa***Department of Neurology, Universitary Hospital Bucharest,Romania-** Department of Neurology, Hopital Nord, CHU Amiens, France

The authors present a retrospective study, performed during 9 months. 3960 patients were hospitalised from which 472 (11%) were diagnosed having a stroke (including transient attacks). 32 patients (6,77%) from all the stroke cases were aged between 21-45 years and were included in this study. Sex distribution: 17 women (53,12%) and 15 men (46,88%). The diagnosis included 27 cases of stroke in the carotid teritory and 5 cases of stroke in the vertebrobasilar teritory. The investigations performed for almost all pacients included cerebral computed tomography, magnetic resonance +/– magnetic resonance angiography (or arteriography), extracranial Doppler ultrasound, transthoracic and transoesophagian echocardiography, laboratory exams for glucidic and lipidic metabolism, immunology and prethrombotic states. The results were: arterial dissection 7 cases, paradoxical emboli 2 cases, undetermined etiology 10 cases. In 13 cases the patients had multiple etiological factors which have a low risk of stroke when isolated, but a much higher one when they are associated (patent foramen ovale, oral contraceptive, carency of protein S, elevated homocisteinemy a.s.o.). The authors comment the results by comparison with data from literature and underline the importance of a complete search of the etiology of stroke in order to find the appropiate treatment and improve outcome.

P370
ISCHAEMIC STROKE IN YOUNG PATIENTS. Vohánka S., Jura R., Brno, Czech Republic

Between 1994 and 1998, 38 young patients ((45 years) with ischaemic stroke were admitted to the Department of Neurology in Brno: 22 men and 16 women, with an average age of 33.5 (18- 45) years. Stroke was classi-

fied as completed in 6 cases; 7 patients sustained minor strokes, 13 prolonged transient ischaemic attacks, and 12 persons transient ischaemic attacks only. Two patients died. Decompressive craniectomy was performed on two patients; 1 patient survived with left hemiplegia, the other died. One further patient died. The cause of death in both cases was raised intracranial pressure due to malignant brain swelling.Relevant risk factors are cigarette-smoking, high blood pressure, diabetes mellitus, alcohol consumption, high blood lipids, high fibrinogen level and other types of hypercoagulation. At least one risk factor was present in 35 persons, the median number of risk factors being two.A cardiac source of the embolism was proven in 5 patients; atherosclerotic carotid vessel lesions or stenosis were found in 9 cases. Only one patient had no risk factor or other explanation for the ischaemic event. These results show that the causes of ischaemic stroke in young people are the same as in the elderly: atherosclerosis, arterial hypertension and cardioembolism.

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FAMILIAR PROTEIN C DEFICIENCY AND CEREBRAL VEIN THROMBOSIS.F. Villani*, L. Chiapparini^, D. Croci°*Epilepsy Center, ^Div. of Neuroradiology, °Div. of Clinical Chemistry, Istituto Nazionale Neurologico "C. Besta", Milano - Italy

Objective - Protein C is a vitamin K-dependent plasma protein with a well known anticoagulant function. We describe one patient with an hereditary protein C deficiency who developed a cerebral-vein thrombosis one week after an upper respiratory tract infection.Case report - A 25-years-old man, university student, developed on august 13 1998 an intense headache followed by a generalized seizure. One week before this episode he had a febrile pharingitis, treated with amoxicilline. In the emergency room the patient appeared mildly confused and dysartric with no fever or meningeal signs. Full blood count showed mild leukocytosis with slight neutrophilia. LP revealed a mild CSF protein increase with normal cells and glucose; serological investigations for common encephalitis agents performed on plasma and CSF were all negative. A CT scan revealed hypodensity and local hemorrhages, in the left lateral temporal and occipital lobes. MRI showed a large non-homogeneous area of signal hyperintensity on T2-w.i. in the left temporal and occipital lobes, due to a venous infarction; MR-angiography revealed absence of flow in the left transverse sinus and in the left jugular vein. During the hospitalization he did not have new seizures; confusion and headache resolved rapidly. Three months later he developed complex partial seizures, well controlled by carbamazepine.Four months after the acute episode a complete coagulation screening revealed a protein C deficiency (functional 49%, immunological 52%). The same defect was present in the mother.Conclusion - We conclude that in this patient a cerebral venous infarction may be due to an impairment of the protein C pathway induced by the interaction between inherited and acquired factors (infection).

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POSTPARTUM DISSECTION OF THE CAROTID ARTERY WITH FIBROMUSCULAR DYSPLASIA. A. Collier-Geulette, R. Denays, T. Lambert, D. Chochrad, T. Ledent-Centre Hospitalier Etterbeek - Ixelles-Brussels, Belgium

The risk of cerebral infarction is increased during the puerperium.We report the case of a 39 year old woman who was admitted with a complete left hemiplegia of sudden onset, ten days after a normal delivery. A severe right pulsatile headache had appeared three days before. Two previous pregnancies were uneventful but she complained of repeated migraines since several years. Her mother presented a first reversible stroke with hemicrania at the age of forty-five and later developed severe hypertension, epilepsy and multiple cerebral infarcts. The examination at the admission revealed a slightly confused woman with a complete left hemiplegia and a right palpebral ptosis. The diagnosis of probable right carotid dissection was proposed.Cerebral CT scan was normal. The MRI revealed a hypersignal in the right caudate and lenticular nucleus (T2 spin echo). The angio-MRI showed a thrombus in a long segment of the right internal carotid artery on day two.She was treated with heparin and an almost complete recovery was observec after two days. On arteriography on day 17, multifocal lesions of fibromuscular dysplasia were found in both carotid arteries, right renal and left mammary artery.We will discuss the possible mecanisms of stroke complicating pregnancy in fibromuscular dysplasia.

P373
UTILITY OF CEREBROSPINAL FLUID EXAMINATION IN STROKE PATIENTS UNDER 45 YEARS. R Soler, JJ Muñoz-Torrero, P. Barreiro, E Díez-Tejedor. Department of Neurology. Stroke Unit. Hospital Universitario La Paz. Universidad Autónoma de Madrid. Spain.

Background. In patients under 45 years and stroke of unknown cause usually is recommended to perform a lumbar puncture (LP) to study cerebrospinal fluid (CSF). We want to analyze its diagnostic profitability in these patients. Patients and methods.. In order to evaluate the value of CSF in the diagnosis of stroke in young adults, we analyzed our stroke data bank from January 1991-April 1998. LP was indicated when no evident cause for stroke was present. We selected the patiens in this age-period reviewing the following aspects of CSF: protein, glucose, number and type of cells, immunochemistry, serology, microbiology, pressure and appearance. We analyzed how many studies were determinant in final ethiological diagnosis.Results. There were 170 patients. 51 CSF studies were made(30%), stroke ethiologic subtype diagnoses were: 7 aterothrombotic, 6 cardioembolic, 14 unusual cause and 24 undetermined cause. 46 out of 51 CSF tests were normal and 5 were pathological: 4 elevated protein contents and 1 elevated pression. None of these 5 had influence on the final ethiological diagnosis, because ethiology was evident, or this was found out by another diagnostic test or no one cause was determined.Conclusion. Our review suggests that maybe the CSF examination has not relevant influence on the ethiological diagnosis in this population. In our study CSF test provided no help to diagnosis. Therefore perhaps only in very special cases it should performe this assessment: suspicion for infection or infiltration meningeal or possible subarachnoid hemorrhage with normal neuroimaging.

P374
BILATERAL VERTEBRAL ARTERY DISSECTION AFTER CHIROPRACTIC MANEUVER. M. Hahn, E. Stolz, J. Kraus, F. Leweke, C. Mellinghoff, W. Dorndorf.Department of Neurology, Justus-Liebig-University Giessen, Germany

Neck manipulation is known as a rare cause of cervical artery dissection. The pathogenic process starts in the vessel with tearing of the tunica intima due to mechanical stress. This may lead to immediate or delayed dissection and subsequently stenosis or occlusion of the vessel. We describe a case of bilateral vertebral artery dissection following a chiropractic maneuver.Immediatly after treatment by an orthopedic surgeon including retroflexion of the neck, a 34 year old woman felt a sharp neck pain. Beginning the next day she experienced vertigo, dizziness and vomiting. One week later computed and magnetic resonance (MR) brain tomography showed a left cerebellar stroke. Ultrasound examination documented a distal stenosis in the right and occlusion signal in the left vertebral artery. MR-angiography confirmed the bilateral vertebral artery dissection. Despite immediate therapeutic anticoagulation with Heparin the patient had another transient ischemic attack with diplopia for 5 minutes and developed a severe incomplete Wallenberg-syndrome 48 hours later. MR-imaging 24 hours after clinical deterioration confirmed an additional left sided stroke in the lateral medulla oblongata. We conclude that chiropractic manipulation carries the risc of cervical, especially vertebral artery dissection. Symptoms may occur with delay even under therapeutic anticoagulation. Because of the possible severe consequences, pre-information of the patient and the risc-benefit-ratio of the treatment has to be evaluated carefully.

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TIME-DEPENDENT CHANGES IN SUPEROXIDE DISMUTASE CATALASE XANTHINE DEHYDROGENASE AND OXIDASE ACTIVITIES AFTER CEREBRAL ISCHEMIA IN THE RAT. Nebahat Tapdemir, Abdurrahman Dermet, Bastra Deniz and Mukadder Atmaca. Departments of Neurology and Physiology University of Dicle School of medicine- Diyarbakyr-Turkey

Time dependent changes in the activities and anti-oxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), and an oxidant enzyme, xanthine oxidase (XO) were measured in male Spraque Dawley rats after the permanent occlusion of middle cerebral artery (MCAO) and both carotid arteries were clamped for 90 min. There were no change in SOD and CAT activities in primary and peri-ischemic area after 3h of reperfusion were as at 24h reperfusion activities of these enzymes decreased significantly. After 48h, the enzymes activities returned to the baseline while at 72 h after ischemia further increase was observed both in primary and peri-ischemic tissue.XO has been proposed as an important source of free radical during ischemia. This enzyme normally exists as a dehydrogenase (XD) and it is converted to XO in some ischemics tissues Therefore, we evaluated the

role of XD and XO as a source of free radicals contributing to cerebral ischemic injury in the rats after the MCAO. In nonischemic brain tissue, 15-23% of the enzyme was in the XO form which increased slightly at 3h of ischemia but after 24 h of ischemia returned to baseline and then remained relatively unchanged over the next 48 and 72 h primary and peri-ischemic tissue. Pretreatment with 100mg allopurinol/kg per day over two days before ischemia prevented changes SOD and CAT activities and attenuated brain edema and lipid peroxidation during 24 h of reperfusion.However, neither the total activity of XO nor that of XD changes in allopurinol treated rats at the all reperfusion period. The results of this study indicated that changes in SOD and catalase activity is time-dependent and also XO is probably not an important source of free radicals in focal cerebral ischemia

Higher functions disorders and dementia

P376
SEMANTIC DEMENTIA: AN AUTONOMOUS SYNDROM. Belliard, V. Leblay, V. Golfier, E. Sartori, G.Edan.Clinique Neurologique, Hôpital Pontchaillou, Rennes, France.

Since its description in 1989, semantic dementia is a well-known syndrom of lobar atrophy. While it is considered as a rare entity, in our opinion many cases are not recognized or considered as progressive aphasia or dementia of the Alzheimer's type. We report our experience of 12 cases.Linguistic impairment, semantic but not phonologic in nature, is the most predominant feature but is always associated with failure of "visual recognition" of the same type concerning objects or persons. Many others cognitive abilities, in particular episodic memory, orientation, perception and visuoconstruction are not concerned. Autonomy is normal for many years.Cognitive signs can be associated with mild behavioural features of the frontal type as self centered behaviour, mental rigidity ... which can occur even early in the course of the disease.The syndrom must be differentiated from progressive aphasia. Since the linguistic disorder is predominent, semantic failure of "visual knowledge" of things and persons is always present, even less obviously. Linguistic impairment is only one but the earlier part of a more general semantic breakdown. It must be differentiated from dementia of the frontal type even if many datas are in favour for considering semantic dementia as the temporal variant of frontotemporal dementia.

P377
CORTICAL ACTIVATION IN MIRROR READING BEFORE AND AFTER TRAINING: AN FMRI-STUDY OF PROCEDURAL LEARNING. K Schmidtke, J Kassubek, CH Lücking, MW Greenlee.Neurological University Clinic, Freiburg, Germany

The aim of this study was to analyze the cortical activation during a perceptual procedural learning task and the changes of this activation that occur between the naive and the trained condition.In 10 normal subjects, BOLD-contrast measurements were performed using T2* weighted Echo Planar Imaging sequences. Imaging involved 12 slices covering the motor and premotor frontal, the parietal and the occipital cortex. Cortical activation was evaluated using the BrainTools software, and the results were superimposed on anatomical 3D MR images. On separate days (naive and trained condition), sequences of plain or mirror-reversed words were presented on a screen. Previously employed stimuli were not repeated. Between experiments, subjects received a one-day training of mirror reading.In the naive condition, mirror reading compared to plain text evoked more significantly increased activation in the superior parietal gyrus, supramarginal and posterior cingulate gyrus, and in the frontal eye fields bilaterally. In the trained condition, these differences of activation were no longer present, except for the supramarginal gyrus. The present findings show that procedural learning leads to a significant decrease of task-related bilateral activation in the superior parietal and posterior cingulate area and in the frontal eye fields. It is suggested that trained subjects directly recognize the transformed letters and thus require less visuo-spatial processing capacity for reading mirror-reversed text.

P378
THE DECLINE OF VERBAL FLUENCY IN ALZHEIMER'S DISEASE. A TWO YEARS FOLLOW-UP-LF. Pascual, S. Santos, T. Fernández, C. Tejero, I. Escalza, I. Navas and F. Morales. Hospital Clinico Universitario, Zaragoza, Spain

Background: Deterioration in the Verbal Fluency characterizes Alzheimer Disease (AD). Recent Memory and Verbal Fluency has been described as most effective in discriminating mildly demented from healthy individuals. Word list generation can be a quick tool for evaluation in AD and to assess treatment efficacy. Goals: To determine the rate of decline of Semantic Verbal Fluency in AD patients not receiving Cholinesterase inhibitors. Methods: We reviewed the data of 100 patients (59 women and 41 men; mean age 70.51± 6.31 years) with probable AD. Only those patients not treated with ACE inhibitors were included. MMSE, Temporal Orientation and Animal naming were recorded at the initial assessment, and at 6, 12, 18 and 24 months. Results: Animal Naming: Initial 6.99±3.43; Second year 4.17±2.64 n=23. Temporal Orientation: Initial 2.26± 1.71; Second Year: 0.97± 1.3, n=23. In the 23 patients with complete data available, the initial Verbal fluency was 8.1±3.1 and the rate of decline was 1.71±1.60 per year (range between -3 and 5.5) c.i. 95% was 0.98-2.44. Conclusion: Verbal Fluency had a decline in the 96% of patients evaluated in the two year period. The rate of decline observed was 1.71 points per year.

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COGNITIVE EVALUATION OF SEVERE DEMENTIA: THE TSI AND BANSS SCALES.I.Appollonio1-2, C.Gori1-2, G.P.Rival, D.Spigal, A.Ferrari1, L.Frattola1-2. 1) "Mons. L.Biraghi" Nursing-home, Cernusco s/N and 2) 5th Neurological Dept., S.Gerardo Hospital, Monza, Italy.

Several new scales have been recently developed for the evaluation of cognitive functions in severe dementia: a) observer-based behavioral/symptomatological instruments and b) performance-based cognitive/functional scales. Aim of the study. We evaluated strengths and limits of these two approaches by applying to the same sample a slightly modified version of a performance-based scale, the Test for Severe Impairment (TSI) (score range: 0-46), and an observer-based scale, the Bedford Alzheimer Nursing Severity Scale (BANSS) (score range: 28-7). Sample. A nursing-home population of 64 oldest old subjects suffering from moderate to severe dementia (CDR range:1-4), defined according to DSM-IV criteria. Mean age was 87.4+6.2 y.o. and mean education was 2.0+4.3 yrs. Results. Both the BANSS, and the TSI were independent from age and education. The BANSS could be computed for all subjects (m=18.8+4.9; range: 8-28), whereas the TSI (and the MMSE) could be applied only to 43 subjects (67.2%). Among the latter, 19 (44.2%) had CDR=3-4; 7 of them had a MMSE between 1 and 5 and 12 (27.9%) had a MMSE=0. The modified TSI was different from 0 in 37/43 subjects (86.0%) with a range 0-36 for those 19 subjects with a CDR=3/4. By ANOVA, the mean scores at the TSI were significantly different between CDR stages 2, 3 and 4; no difference was detectable for stages 1 and 2. The BANSS discriminated only CDR stage 4, but not between CDR stages 3, 2 and 1 (early ceiling effect). Conclusions. The TSI may have some utility in the moderate-to-severe range of dementia, whereas the BANSS seems most useful in the severe-to-very severe stages.

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A TRI-DIMENSIONNAL STUDY OF POINTING AND GRASPING IN NEGLECT PATIENTS.C. Benaim, J.L. Blatt, M. Rousseaux. Services de Rééducation Neurologique et de Neurophysiologie Clinique. CHU Lille, France.

The aim of this study was to analyze the ipsilateral upper limb and head kinematics in patients presenting with spatial neglect, using pointing and grasping to object. Four patients were included and compared to an equivalent number of normal subjects. Head, shoulders, and wrist movements were recorded using a three-dimensional VICON system. Objects to be pointed or grasped were localized in the right or left space of the space facing the subjects. Patients presented with a reduction in the mean wrist velocity (p=.0002), which was more obvious in the leftward direction, reduction in peak velocity (p=.041), and severe drop of the time interval between the peak velocity and the end of the movement (p=.0001). The amplitude and mean velocity of left head movements were comparable in both groups. The analysis of the intersegmental coordination showed that the sequence of activation of corporeal segments was similar in patients and controls: head movement, then shoulders rotation, then upper limb extension. The delay between the beginning of the head and wrist movements was increased in neglect patients. Crossed correlation analysis of head and wrist movements showed reduced correlations in patients (p=.014). In conclusion, we demonstrated a global disorder of intentional movement in patients with spatial neglect, which was similar in grasping and pointing to object, and predominated in the approach phase, which is

associated to important visuo-motor adjustments. The analysis showed desynchronization of head and wrist movements, which could contribute to the impairment in daily life.

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PROPOSITIONAL LEARNING IN PATIENTS WITH FOCUSED FRONTAL, THALAMIC, AND TEMPORAL LESIONS. M. Rousseaux, M. Cabaret, B. Bayle, T. Bernati. Services de Rééducation Neurologique. CHU Lille, France.

Most investigations of amnesic patients have assessed long term memory disorders using classical 'episodic' word list or story learning. Little is known about the ability of these patients to learn either correct or incorrect factual propositions, and about errors that could be observed. This study aimed to investigate this problem in thirty two patients with frontal and cingulate (16 cases), thalamic (13 cases), or bilateral internal temporal injury (3 cases), and 15 normal control subjects. They were presented with 2 lists of 18 propositions: A: correct factual information; B: incorrect information. In each list, 6 semantic links between the subject and the object were categorical, 6 functional, and 6 structural. After presentation of the list, patients were presented with the first words of each proposition (sentence) and asked to recall the last one (ex: the baker makes ?: cakes). Forced choice recognition was assessed after recall. Dependent variables were analyzed using ANOVAs (p=.05), after rank transformation of data. Results. Correct responses were more severely reduced (p=.0001) in temporal, thalamic and frontal patients, in that order. The A list was better recalled than the B list (p=.0004), and the performance was higher for structural than functional and categorical propositions (p=.001). Interactions were not significant. The relative frequency of semantic corrections in the B list was higher (p=.0002) in temporal, frontal and thalamic patients than in controls, in that order. Other effects or interactions were not significant. Semantic errors were more frequent in the A list (p=.008), in functional than categorical and structural propositions (p=.002), but were not influenced by the group. Non responses were more frequent in the B list, and in categorical than structural and functional propositions, but were neither influenced by the group. Furthermore, recognition gave similar results than recall. Discussion. This study showed that patients with temporal injury present with the more severe disorder in propositional learning, and that they also have a greater tendency to correct erroneous propositions. When failing to recover the correct information, these patients as less able than other to inhibit the evocation of a semantic correction, which is associated with the prelesional factual knowledge.

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PERFORMANCE IN A DUAL TASK PARADIGM OF PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY OR VASCULAR PREFRONTAL DAMAGE.M. Leclercq, J. Couillet, N. Marlier, P. Azouvi, Y. Martin, E. Strypstein, M. Rousseaux. Centre Neurologique William Lennox, Ottignies Louvain la Neuve, Belgique, Service de Rééducation Neurologique, Hôpital Raymond Poincaré, Garches, France, Centre de Rééducation l'espoir, Lille-Hellemmes, France, CARA, Bruxelles, Belgique, Service de Rééducation Neurologique, Hôpital Swynghedauw, Lille, France.

The aim of this study was to assess divided attention in patients with traumatic brain injury or anterior cerebral lesion of vascular origin. The study population consisted of 16 traumatic brain injuried (TBI) subjects, 9 patients with ruptured aneurysm of the anterior communicating artery (ACoA) and 25 matched control subjects (CS). Subjects were submitted twice to two types of tasks, first performed in a single way, then dually: simple visual reaction time and random number generation. They were also presented with two digit span tasks, and with semantic and literal evocation tests. Both groups of patients were characterized by severe slowness in reaction time tasks (TBI: $p = 0.0006$; ACoA: $p = 0.022$), that was more significantly increased in the dual-task condition, suggesting an impairment in divided attention. In patients with rupture of ACoA aneurysm, randomness of digit production was reduced, with a significant increase in the Rosenberg randomization quotient (p=0.001), triplets production ($p = 0.0003$) and of the Evans randomization index ($p = 0.0004$); however, the counting tendency was discrete. In the random number generation tasks, performance in TBI patients was not different from that of CS. Furthermore, significant correlations were observed between dependent variables of the experimental task and the span and evocation tasks. In conclusion, this study showed (1) that TBI as well as fontal patients present with a disorder of divided attention, and (2) that this problem is relatively independent from disorders of cognitive control associated with random number generation, as the impairment in divided attention was observed in both groups of patients, when the deficit in number generation was solely observed after severe frontal vascular injury (ACoA aneurysm).

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THE ASTROCYTES IN ALZHEIMER´S DISEASE AND IN AGING: A CORRELATIVE ULTRASTRUCTURAL STUDY.Baloyannis SJ, Costa V, Mihmizos D. 1st Department of Neurology, Aristotelian University, Thessaloniki, Greece

Alzheimer´s disease is the most common cause of dementia in senium and presenium. Although the neuritic plaques and the neurofibrillary tangles have been characterized as the morphological hallmarks of the disease, numerous morphological alterations have also been described, affecting the dendritic arborization of the cortical and subcortical neurons, the synapses, the brain capillaries and the blood brain barrier.In addition the astrocytes as well as the microglial cells in the cortex and the hippocampus may play a role in the disarrangement of the morphological pattern of the neuropial as well as the perivascular space in Alzheimer´s disease. In a large post mortem material including ten Alzheimer´s brains we tried to study in electron microscopy the astrocytes in aging as well as in Alzheimer´s disease, correlating their morphology as well as the neuronal-astrocytic relations. In Alzheimer´s brains the astrocytes form a thick network with their long processes, plenty of glial fibers in the hippocampus and the cortex of the brain hemispheres replacing in some extent, the abbreviated dendritic network of the large pyramidal and polyhedral neurons. In morphometric analysis, the density of the astrocytic processes in Alzheimer´s disease is approximately three times higher than in the normal brains of the same age. The perivascular accumulation of the astrocytes is also higher in Alzheimer´s brains than in controls. The astrocytes in Alzheimer´s brains include, large number of elongated mitochondria, which show marked alterations in their interior structure, in contrast to the mitochondria of the astrocytes in the control brains which were morphologically unremarkable. The astrocytic sheath around the synapses in the brain and the cerebellum is thicker in Alzheimer´s brains than in controls, a fact that is particularly prominent in the cerebellar cortex as well as in the CA1 area of the hippocampus. Some of the astrocytes sheathed unattached dendritic spines or surrounded dendritic terminals of hippocampal neurons in Alzheimer´s brain, a phenomenon that is very unusual in normal control brains.

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PRION DISEASES: SERIAL MAGNETIC RESONANCE SPECTROSCOPIC (MRS) CHANGES.V. Diklic[1], N. Delibasic[1], and S. Al-Sarraj[2], 1-Novi Sad, Yugoslavia, and 2-London, UK.

We describe a family in the northern part of Yugoslavia with familial Creutzfeldt-Jakob disease (CJD) in four members from two generations. MRS was performed in Novi Sad (Magnetom SP63, Siemens, 1.5T), two months, three weeks and one day before death, and the diagnosis was confirmed at the autopsy. Paraffin embedded blocks from different parts of the brain were sent to London where immunocyto-chemistry was performed with monoclonal antiprion antibody (3F4),according to the consensus protocol. During life, MRI revealed only moderate brain atrophy and the hyperintense signal on T2W sequence of the corpora striata, particularly affecting the anterior putamina and both caudate nuclei. MRS performed three weeks before death revealed unspecific decrease of choline (Cho), and moderate decrease of N-acetylaspartate (NAA) in the corpora striata, as a result of myelin degeneration and neuronal loss. MRS performed 18 hours before death revealed that NAA and Cho were almost totally lost in the corticosubcortical region, with much lesser depletion in the basal ganglia, which correlated with the extent of histopathological changes in the same regions, seen at autopsy. Our results with MRS in vivo support the thesis of Graham et al (1993) that cortical neurons are lost relatively late, but rapidly, in the prion disease process.

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APOLIPOPROTEIN E ε4 INFLUENCE THE PROGRESSION OF COGNITIVE DECLINE IN NONDEMENTED SUBJECTS WITH MILD MEMORY/COGNITIVE IMPAIRMENT AND ALZHEIMER´S DISEASE PATIENTS. M.Revilla*, R.Sanchez del Valle*, R.Blesa*. R.Oliva**, J.Peña#, M.Aguilar!, T.Soler*, G.Hernández+, J.M.Sol+, Institut Clínic Malaties Sistema Nerviós-Neurology Service* and Genetic Service** Hospital Clinic & IDIBAPS-University of Barcelona, Centro Geriátrico Municipal(IMAS)#, Hospital Mutua de Terrassa!, Parke Davis Lab.+. Barcelona. Spain.

Apolipoprotein E ε4 (APOEε4) is a genetic marker associated with increased risk of late-onset Alzheimer´s Disease (AD) and earlier age of onset, but the role in the progression of dementia is controversial. Objectives: To determine whether the presence of APOEε4 is associated with more rapidly progressive cognitive decline.Materials and Methods: We examined 273 individuals: 150 normal controls, 53 cases of mild memory/cognitive impairment without dementia (MCI) and 50 Alzheimer´s disease untreated patients. We determined the progression of cognitive impairment at 6-months follow-up related to APOEε4 presence by score differences in dementia scales (ADAS, MMS).Results: Controls: ADAS (ε4(-):-1.5; ε4(+):-0.5), MMS (ε4(-):0.27; (4(+):-0.62). MCI: ADAS (ε4(-):0.21; ε4(+):2.22), MMS (ε4(-):-0.50; ε4(+):-1.94). AD: ADAS (ε4(-): 1.52; ε4(+): 8.03), MMS (ε4(-):-1.41; ε4(+):-2.87). Conclusions: These results indicate that APOEε4 is associated with greater cognitive decline in AD and MCI patients at a given disease duration, estimated by ADAS and MMS scales. APOE status may have prognostic significance in patients with cognitive impairment and a dramatic role in the interpretation of the effect of antidementia drugs in clinical trials.

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READING ABILITY IN ITALIAN PATIENTS WITH ALZHEIMER'S DISEASE. Lucia Paciaroni, Susy Paolini, Patrizia Civerchia, Simona Castellani, Osvaldo Scarpino, Anna Berti*.Neurologia Unit, INRCA, Ancona, * Psychology Department, University of Torino (Italy)

It has been suggested, in population of English native speakers, that reading impairment of patients with moderate Alzheimer's Disease (AD) can show the pattern of surface dyslexia. Some studies, however, questioned this conclusion. The aims of the study was to establish 1) whether AD patients are affected by reading problems and 2) whether the error pattern can be ascribed to surface dyslexia also in Italian native speakers.Nineteen patients (mean age: 75.8 yrs; mean education: 6.8 yrs) meeting the DSM IV criteria for AD and 10 healthy controls (mean age: 75.7 yrs; mean education: 6.7 yrs) were recruited for the study.The assesment included the following tasks: 1- Nonword reading. 2- Reading of word of variable frequency. The stress of the words could be syllabic or lexical. Lexical stress could be regular or irregular. 3- A set of trials aimed to examine the semantic system and the orthographic lexicon. AD patients performed significantly more poorly than controls on word and nonwords reading. More errors occurred on reading of words with irregular lexical stress; the level of accuracy was significantly related to the word frequency.This error pattern characteristic of surface dyslexia indicates that AD patients used a reading strategy which prefers the phonological pathway. The worse performance on nonword reading suggests a partial impairment of the phonological processing too.

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THE DETERIORATION OF PASSIVE STORAGE AND ACTIVE PROCESSING FUNCTIONS IN ALZHEIMER'S DISEASE. Lucia Paciaroni, Veronica Saveriano, Patrizia Civerchia, Simona Castellani, Osvaldo Scarpino, Tomaso Vecchi*Unità di Neurologia, Ospedale Geriatrico, INRCA, Ancona (Italia).*Dipartimento di Psicologia Generale, Università di Padova (Italia)

A selective deterioration of working memory functions has been suggested both to explain the cognitive decay of normal elderly subjects and the deterioration associated with Alzheimer's disease. Recent studies have highlighted that elderly people's limitations could be better interpreted when analysing the specific characteristics of the cognitive process. In particular, it has been shown that passive storage functions are less affected by age than active manipulation processes. In the present study, we adapted a procedure used to investigate age-related modifications, involving both verbal and visuo-spatial material in tasks tapping passive and active functions, to investigate the deterioration associated with Alzheimer's disease. A group of Alzheimer patients in the early stage of the disease were matched to a control group of healthy adults (n=16, mean ages were 70.1 and 69.3, respectively). A one-way ANOVA on each task showed that Alzheimer's patients performed less accurate than the control group in all tasks. However, a mixed design ANOVA with all tasks showed a significant interaction between subject groups and tasks indicating that a minor impairment was associated to passive storage functions while the deficit was maximised in the case of the active processes, regardless of the type of material that was used (verbal or visuo-spatial).

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NEUROLOGICAL EVALUATION OF PATIENTS WITH ALZHEIMER TYPE DEMENTIA. M. Tsolaki, M. Aminta, B. Iakovidou, D. Divanoglou, K. Kapinas, A. Kazis 3rd Neurological Clinic Aristotelian University of Thessaloniki

The aim of this study was to record the common neurological signs observed in patients with Alzheimer Disease (AD) in the various stages of the illness so as to guide the neurologist with one more parameter for the diagnosis. Seventy one patients, 26 men and 45 women, with AD in all stages of the illness who met the DSM-IV criteria for dementia and the NINCDS-ADRDA for AD were examined. Their age ranged from 55-95 years (mean age 69,21) and the results to the usual neuropsychological tests performed in our clinic in the same day of the neurological examination were: MMSE 0-24, CAMCOG 0-65, FRSSD 0-36, GDS 0-5, Hamilton 0-15. The patients were classified in three groups -according to the MMSE (mild dementia MMSE 20-26, moderate 11-19 and severe 0-10). The neurological examination was performed using three scales. The Neurological Evaluation Scale (NES) with 26 items examines in detail some systems like the cerebellar, the hemisphere predominance, the auditory-visual competence, the discriminative sensitivity, the extrapyramidal system, the eyes synkinesia and convergence, the tenacity of glance and the primitive reflexes. The second scale was the Webster simplified scale for the estimation of the extrapyramidal signs and the third was the Scripps Neurological Rating Scale (NRS). The results showed a gradual appearance of neurological signs with the progression of the disease. Statistically significant related with the progression of dementia were primarily the appearance of incontinence and the disturbance of the discriminative sensitivity, then the appearance of primitive reflexes and last some pyramidal signs. There was no statistically significant relation found between cerebellar signs and the progression of AD.

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ABNORMAL EVENT-RELATED EEG SYNCHRONIZATION IN ALZHEIMER DISEASE PATIENTS DURING POST-MOVEMENT PERIOD. Babiloni C.1, Babiloni F.1, Carducci F.1, Cincotti F.1, Maestrini S.2, Priori P.2, Tisei P.2 and Rossini P.M.2,3.1 Ist. di Fisiologia umana, Università "La Sapienza", Roma Italy, 2 IRCCS "S. Giovanni di Dio", Brescia Italy, 3 A.Fa.R. CRCCS- Div. di Neurologia, Osp. FBF Isola Tiberina, Roma Italy.

Event-related electroencephalographic desynchronization/synchronization (ERD/ERS) of alpha and beta rhythms was investigated in normal subjects and age-matched mild Alzheimer Disease patients (AD) performing externally (experimenter cue)-triggered unilateral right index movement (about 10 sec inter-movement interval). Electroencephalographic data were sampled based on 10-20 system electrode montage. Surface Laplacian estimate of the potential reduced head volume conductor effects and annulled electrode reference variations. The working hypothesis was that mild AD is a global brain network disease including processing of sensorimotor information, despite no overt movement disorder. The results showed similar bilateral central-parietal alpha (8-12 Hz) and beta (18-22 Hz) ERD in normals and AD patients, during the movement period. In contrast, lower and longer lasting alpha (8-12 Hz) and beta (15-18 Hz) ERS in AD patients than normals was recognized during the post-movement period (alpha and beta rebound). Decreased alpha and beta rebound in AD patients was more pronounced in the central and parietal areas contralateral to the movement. These results would indicate that in mild AD, motor command running is normal but the post-movement idling of the brain activity is prolonged and reduced in magnitude.

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ASYMMETRIC FRONTO-TEMPORAL DEGENERATION S. Rosso, M. Stevens, G. Roks, R. Ravid, W. Kamphorst, J.C. van Swieten. Department of Neurology, and Epidemiology and Biostatistics, Erasmus University of Rotterdam, The Free University of Amsterdam, and The Dutch Brain Bank, The Netherlands.

Introduction: The clinical manifestations of fronto-temporal dementia (FTD) range from behavioural changes to primary progressive aphasia and semantic dementia. Background: A review of literature reveals asymmetric atrophy in FTD (50% in Pick's disease, and 20% in non-Pick FTD) Aim: Our study investigates demographic data, clinical symptoms and neuropathological findings in 90 patients with FTD in order to assess if specific features of asymmetric FTD can be identified. Results: Asymmetric FTD was found in 25 cases (28%); temporal lobe atrophy predominated in 12 of these (48%). Compulsive behaviour (repetitive, intentional, complex behaviour which is associated with agitation when prevented) was present in 12 (48%) of asymmetric compared to 11 (18%) of symmetric FTD. This percentage was highest in cases of asymmetric temporal atrophy (10 cases, 79%; chi-square0.001). Demographic data and other clin-

ical symptoms were evenly distributed in both groups. Neuropathological examination was performed in 15 patients. The diagnosis Pick's disease was established in 2 cases with asymmetric atrophy and one case with asymmetric ventricular enlargement, whereas non-Pick FTD was found in 12 cases with symmetric atrophy. Conclusions: Patients with the asymmetrical temporal variant of FTD often display compulsive behaviour. Our neuropathological findings support findings in literature that Pick's disease might be correlated with asymmetric FTD.

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DEMENTIA PLUS IN A CALABRIAN FAMILY: A NEW DISEASE?Bruni A-C, De Michele G, Costanzo A,Volpe G, Coppola G, Calabrese I, Castaldo G, Casari A, Ballabio A, Caruso G, Cocozza S and Filla A. (Lamezia Terme, Napoli, Milano)

Background. Fourteen subjects affected by a complex disorder have been identified in a Calabrian family, genealogically reconstructed in a kindred of 674 people. Dominant transmission over four generations is evident; no consanguinity was detected.Aim of the study is to perform clinical and molecular study of this large family.Results.The illness is characterized by a wide range of age at onset (24 -52 years, mean + SD 33.5 +10.0) with prominent psychiatric symptoms as first sign. Tremor, dystonia and dysarthria follow, together with a subcortical dementia. The illness progresses slowly with the appearance of gait ataxia, rigidity, anarthria, myoclonus and generalized epileptic seizures.. Mean age at death is at 57.1 + 6.8.. MRI shows marked supra and infratentorial atrophy. Molecular analysis excluded Huntington's disease, SCA1, SCA2, SCA3, SCA6 and DRPLA. Mutations of PRNP gene were also excluded. Linkage analysis for Frontotemporal dementia linked to chromosome 17 was negative.Conclusion. The phenotype of this family, which includes early onset, prolonged course, subcortical dementia, extrapyramidal and cerebellar features is clearly different from the other types of degenerative dementias. We suggest a new dementing disorder for which a genome wide linkage study should be conducted.

Epilepsy, Encephalopathy, Encephalitis

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PROGRESSIVE MYOCLONUS EPILEPSIA AND MERRF-SYNDROME: TOXIC EFFECTS OF VALPROATE TREATMENT-Sixel-Döring F., Rojas-Mackenzie R., Schumacher S.Neurologische Abteilung Wicker-Klinik Bad Wildungen

Gene-mutation induced structural or metabolic disorders in the brain have been identified as the common denominator in the heterogenous group of progressive myoclonus epilepsias. Myoclonic seizures and dementive development are common features. Treatment with valproatic acid, benzodiazepines or ACTH is currently recommended. MERRF-syndrome (mitochondrial encephalomyopathy and ragged red fibres) has been classified as a clinical entity in this disease type: Maternally inherited point mutations of mitochondrial DNA are responsible for faulty tRNA coding, causing defects in oxidative phosphorylation and protein synthesis. The syndrome clinically presents with progressive myoclonic epilepsia, ataxia, muscle weakness, possible loss of hearing and vision as well as variable dementia, usually beginning in the early twenties.In a 27 year old female with progressive myoclonic epilepsia MERRF-syndrome was diagnosed by histopathologic identification of ragged red fibres. 5 1/2 months after introducing valproatic acid as add-on medication for seizure control, the patient developed a hepatotoxic reaction with fatal outcome.Considering the metabolic pathway for elimination of valproatic acid, an enforced toxicity of this anticonvulsive drug may be supposed especially in functional disorders of mitochondria. Therefore valproate should not be recommended for treatment of progressive myoclonus epilepsia based on MERRF-syndrome or other mitochondrial encephalopathias.

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TREATMENT OF EPILEPSY IN PATIENTS WITH SLEEP APNEA. T. Patzold*, S. Kotterba*, K. Rasche**, G. Schultze-Werninghaus**, J.-P. Malin*-*Department of Neurology, **Department of Internal Medicine, Ruhr-University Bochum

Hypoxemia and sleep deprivation are well-known triggers for seizures in patients with epilepsy. In obstructive sleep apnea syndrome (OSAS) repeated apnea periods are accompanied by progressive oxyhemoglobin desaturation and hypoxia. The apneas are usually followed by arousals or awakenings resulting in severe sleep disruption and sleep deprivation.We report clinical and polysomnographic findings of 4 men with onset of generalized tonic-clonic or complex-partial seizures at the age of 40 - 50 years. Neurological examinations and brain magnetic resonance imaging were normal. On awake EEGs, no epileptiform activity was found. All 4 patients were treated with antiepileptic drugs singly or in combination with maximally tolerated doses, but seizure control was inadequate. Their wives reported loud snoring and cessation of breathing during sleep. Polysomnography revealed a moderate to severe OSAS in all 4 patients with a mean apnoe/hypopnoe index (apneas and hypopneas per hour of sleep) at 42,2. Treatment of the OSAS with nasal continuous positive airway pressure (nCPAP) reduced seizure frequency in all patients. Sleep apnea may exacerbate epilepsy by causing hypoxemia and sleep deprivation. High doses of antiepileptic drugs may even worsen seizure frequency by increasing obstructive apneas. Nasal CPAP is an effective therapy for OSAS and seizure control can be much improved by this treatment. Especially in patients with medically refractory seizures, sleep apnea should be considered as a possible cause of insufficient epilepsy treatment.

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CROSSOVER ANALYSIS OF THE EUROPEAN TRIAL ON THE EFFICACY AND TOLERABILITY OF LEVETIRACETAM (LEV) AS ADD-ON TREATMENT IN PATIENTS WITH REFRACTORY PARTIAL ONSET SEIZURES -Dieter Janz, Berlin - Germany; Pierre Loiseau, Bordeaux - France; Christian Otoul, Edith Bielen and Peter Verdru, UCB S.A. Pharma Sector, Braine-l'Alleud - Belgium.

This trial was a double-blind placebo-controlled, two-period (period A and period B, 12 weeks each) and three-treatment (placebo, LEV1g, LEV2g) crossover study with 324 refractory patients randomized. The study was powered to be analyzed as a parallel group design (period A) or as a crossover. Partial onset seizure frequency was the primary efficacy variable. Responder rate was a secondary efficacy parameter.Results: Lower mean seizure frequencies were obtained for LEV1g and LEV2g compared to placebo; percent reduction of seizure frequency over placebo was 16.9% for LEV1g and 18.5% for LEV2g (p 0.001). A median percentage reduction from baseline of 7.0% was obtained for placebo, 22.9% for LEV1g and 23.9% for LEV2g. Responder rate was 12.2%, 26.2% and 34.3% on placebo, LEV1g and LEV2g respectively. Overall, 10 patients were seizure-free on LEV1g and 10 patients on LEV2g; one of these patients became seizure-free on LEV1g and continued to be seizure-free on placebo. The incidence of adverse events (AEs) was similar between treatment groups. Accidental injury, headache, asthenia, and convulsion were the most commonly reported AEs.Conclusions: The crossover analysis of this study confirms the efficacy of LEV as add-on treatment for refractory partial onset seizures.

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IS THERE A RELATIONSHIP BETWEEN SPECT AND EEG ABNORMALITIES IN SYMPTOMATIC FOCAL EPILEPSY? Paci C, Toma L, Curatola L, Thomas A, D'Andreamatteo G, Melchionda D, Onofrj M.

Ictal and interictal Tc-99m hexamethylpropylene aminoxime (HMPAO) SPECT brain imaging examinations can be useful to establish the correct diagnosis of Focal Epilepsy. The injection of stabilized Tc-99 m HMPAO during an ictal event provides a method to obtain the image of the relative perfusion during the seizure. We studied 75 partial epilepsy patients (45 males and 30 females) aged 20 to 60 years (mean=40) who came to our observation during last two years. Their ages at seizure onset ranged from 10-40 with mean of 25. They were affected by symptomatic focal epilepsy (35 temporal, 15 frontal, 20 occipital, 5 parietal) and treated with antiepileptic drugs.All these patients underwent a detailed neurological examinations, ictal and interictal EEGs, CT scan and SPECT imaging.EEG recordings showed epileptogenic abnormalities characterized by 2.5 Hz spike and wave discharges localized in the same regions of seizure foci evidenced by SPECT inspection.Our results suggest that there is undoubtedly an exact correlation between the lateralization of seizure foci on EEG recordings and the documented perfusional changes areas seen in ictal SPECT examination.

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TEMPORAL CORTICAL DISPLASIA AND EPILEPSY: RESULTS OF SURGERY IN CHILDREN-A. Landi, D. Grioni°, C. Fumagalli*, A.Peretti°, C. DeGrandi*,.E.P.Sganzerla, S.M.Gaini.Institute of Neurosurgery, Clinic of Child Neuropsychiatry*, Service of Neuroradiology*. University of Milano - Ospedale San Gerardo, Monza, Italy.

Cortical displasia may be associated with seizures requiring surgical treatment, because drug resistant. Among the children operated for TLE in our Institution, five presented cortical displasia of the mesial temporal cortex. The children (3M, 2F, aging 8-16 yrs), presented partial complex seizures and were referred to our Institution for presurgical evaluation of epilepsy (PSEE). PSEE protocol consists in: 1) clinical and neuropsychological evaluation; 2) electrophysiology (video-EEG, mapping, sleep and prolonged surface EEG monitoring, Visual and Somatosensory EPs); 3) neuroimaging (MRI in T1 and T2 configuration, volumetric aquisitions), SPECT. In all the patients seizures were severe and frequent, drug resistant, suggesting to arise from left (3) and right (2) temporal lobe. EEG showed unilateral temporal focus and neurimaging revealed uncus-hippocampal cortical dysplasia. Surgery consisted in resection of the amygdalo-hyppocampal complex, parahyppocampal gyrus and temporal neocortex, after intraoperative stereoEEG and electrocorticography. Pathology showed cortical dysplasia of mesial temporal lobe. Follow-up (from 38 to 22 months; mean =29) is 1A in four and 1B in one, according to Engel score. In conclusion: although TLE due to cortical displasia presents with poorer outocome as compared to other lesional TLEs, moreover, precocious surgical treatment of the lesion and of the irritative zone might obtain satisfactory results.

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EPILEPSY AS THE MAIN SYMPTOM OF NEUROCYSTICERCOSIS.Kirstic M, Konstantinovic Lj. Kostic V,Vrbic Wovanovic M, Mitrovic G, Petrovic S. Clinic for Infectious diseases, Nis, Yugoslavia

Human cysticercosis has practically a worldwide distribution.In countries where the prevalence of this disease is high, Neurocysticercosis (NCC) or its sequelae is the major raison for late-onset epilepsy.The neurologic manifestations of cerebral cysticercosis are extremly variable and depend on the age location and number of larval cysts in the nervous system. We analyzed 15 patients with NCC (active and inactive forms), and 73% had partial seizures with or without secondary generalization, that 26,6% patients had generalized seizures only. Epilepsy secondary to NCC has some caracteristics features, among them the high frequency of partial seizures (in 72% of cases). The CT scans showed in 80% patients cysts or calcified granuloms in brain parenchyma where the collagenous reaction is less intense as the cysts are surrounded by glial elements. Gliosis is related to epileptogenic activity due to change in neuronoglia relationship as the astroglia is unable to main a proper balance of electrolites and neurotransinitters.The ventricular cysts was in 20% patients.The high frequency of epilepsy in our patients can be expleined by two facts: the prevalence of parenchimal forms of NCC and the epilepsy in the mast common clinical manifestation of NCC.

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UTILITY OF PLASMA LAMOTRIGINE CONCENTRATIONS. CONCEPT OF THE THERAPEUTIC PLASMA CONCENTRATION RANGE FOR INDIVIDUAL PATIENTS.F. J. E. Vajda, P. Angelis-Stoforidis and M. J. Eadie AO. Centre for Clinical Neuropharmacology Melbourne Australia and University of Queensland, Brisbane, Australia.

The concept of the therapeutic plasma concentration range for established antiepileptic drugs (AED's) has been accepted for many years. For the newly emerging drugs, plasma concentration measurements are not generally recommended, as there is no consensus about a therapeutic range applicable to populations and because of the multiple factors affecting individual patients which make population therapeutic ranges difficult to define. Lamotrigine concentrations were measured by a recently developed HPLC method in 40 patients with a variety of epileptic syndromes in the presence of enzyme inducing drugs and sodium valproate, which affect the metabolism of lamotrigine. The results show a wide scatter of values in these patients, indicating no clear relationship to responsive or non-responsive status to lamotrigine levels. It was noted however, that in the presence of valproate, the mean plasma lamotrigine concentrations was 13.82 (5.89mcg/ml (range 7-27mcg/ml) and in the absence of valproate, it was 4.09 (1.54 mcg/ml (2-7mcg/ml). All patients on valproate were classified clinically as responders (reduction of mean seizure frequency by at least 50% below baseline). In the non-valproate group, 50% of the patients showed a positive clinical response, but the mean plasma concentrations were not statistically different (3.32 (0.97 vs. 4.66 (1.76 mcg/ml ($p = 0.294$)) in the responders and non-responders respectively. The utility of measurements comprised the assessment of compliance, aided the ascertainment of toxicity, identified interactions with concomitant AED's and helped with dose escalation. Serial studies are required to prove whether optimal clinical control and an identifiable plasma concentration remain demonstrable, as these factors appear to be important in the determining of plasma levels in individual patients treated with lamotrigine. The question is raised whether valproate in this group, provides, beyond elevation of lamotrigine levels, a pharmacodynamic effect of improving seizure control.

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SEIZURE CONTROL WITH A SUBTHERAPEUTIC ANTIEPILEPTIC DRUG LEVEL.Gülden Akdal, Baris Baklan, Birsen Keskin, Görsev G Yener.Dokuz Eylül University, School of Medicine, Department of Neurology Izmir, Turkey

We investigated retrospectively the data of patients registered to our epilepsy clinic in between 1991-1998 in order to determine the number of seizure free patients with subtherapeutic antiepileptic drug level. Among 1044 patients, 42 patients were seizure free with a low therapeutic drug level. This group constituted the 17 % of seizure free patients in our epilepsy clinic. There were 25 patients with primary generalized seizure, 7 with complex partial seizure, 5 with secondary generalized and 5 with unclassified type of seizure. Thirty-five patients were on monotherapy and 7 were on polytherapy. We have an clinical impression that there is no need for frequent drug monitoring in a well-stabilized patient. Keeping patients on subtherapeutic drug level could reduce the unacceptable side effects. In addition to this, monitoring of drug levels only when needed, will lower the medical costs.

P401
INTERICTAL EPILEPTIFORM DISCHARGES DIFFERENTIATE BETWEEN MESIAL AND NEOCORTICAL TEMPORAL LOBE EPILEPSY-Soheyl Noachtar[1], Mona Pfänder[1], Stephan Arnold[1], Konrad J. Werhahn[1], Anja Henkel[1], Ilonka Eisensehr, Peter A. Winkler[2]. 1-Dep. of Neurology and 2-Neurosurgery, University of Munich, Munich/Germany,

This study evaluates the interictal epileptiform discharges in a consecutive series of patients with mesial (MTE) and neocortical temporal epilepsy (NTE) considered for resective epilepsy surgery.122 consecutive patients with MTE (n=86) and NTE (n=36) were included in this prospective study. All Patients underwent interictal and ictal EEG-video recordings and high resolution magnetic-resonance imaging (MRI). MTE was defined by MRI criteria for mesial temporal sclerosis (MTS) or post-op histology. NTE was defined by neocortical lesion in MRI and lack of (MTS) The interictal EEG was recorded randomly (2-10 min/ h) and analyzed systematically by 2 readers. Only epileptiform discharges identified by both readers were taken for further analysis. Isopotential maps were drawn for each spike focus. The relative frequency of each spike focus was calculated at 50%, 66%, 80%, 90%, and 100% levels.73% of the MTE and 34% of the NTE patients had more than 50% of their interictal spikes in the mesial temporal region ipsilateral to the seizure onset zone ($p < 0.001$). No MTE patient had more than 50% of the spikes in the ipsilateral neocortical temoral region. We conclude from our results that the predominance of interictal epileptiform discharges helps to differentiate mesial from neocortical temporal lobe epilepsy.

P402
THE ANALYSIS OF THE SEIZURE EVOLUTION HELPS IN THE DIFFERENTIATION BETWEEN FRONTAL AND TEMPORAL LOBE EPILEPSY-Soheyl Noachtar[1], Mona Pfänder[1], Stephan Arnold[1], Konrad J. Werhahn[1], Anja Henkel[1], Ionka Eisensehr, Peter A. Winkler[2], Hans O. Lüders[3]. 1-Dep. of Neurology and 2-Neurosurgery, University of Munich, Munich/Germany, 3-Cleveland Clinic Foundation, Cleveland/Ohio, USA.

This study evaluates the seizure evolution in a consecutive series of patients with frontal (FE) and temporal epilepsy (TE) considered for resective epilepsy surgery. 232 consecutive patients with TE (n=163) and FE (n=69) were included in this prospective study. Patients underwent ictal EEG-video recordings (n=232), MRI (n=230), interictal FDG-PET (n= 148) and ictal ECD-SPECT (n=28). The evolution of 2947 seizures were analyzed.FE patients had more often 3 or more (17%) different seizure evolutions than TE patients (4%) ($p < 0.01$). No TE patient had 4 seizure evolutions. Simple-motor (tonic, clonic, versive) seizures were preceded by other seizure types in 98% of the TE and 62% of the FE patients ($p < 0.01$). Complex-motor seizures (automatisms) were preceded by simple-motor seizures in 48% of the FE, but no TE patient ($p < 0.01$). Clonic seizures were the initial seizure type in 22% (11 of 49) of the FE patients,

but no TE patient ($p <• 0.01$). Although abdominal auras were recorded in 12% and automotor seizures in 26% of the FE patients, the evolution of abdominal aura to automotor seizure was observed in a single FE patient (1,4%) as compared to 50% of the TE patients ($p <• 0.01$). We conclude from our results that the analysis of seizure evolution adds valuable information to the distinction of FE and TE, which is a common issue in the evaluation of patients considered for resective epilepsy surgery.

P403
CHILDREN WITH FOCAL SHARP WAVES - CLINICAL ANALYSIS
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Purpose: to gain insight into the spectrum of clinical characteristics of children with focal sharp waves.Method: 98 children with "rolandic-like" sharp waves were questioned regarding seizures, family history of seizures and learning difficulties; their EEG was analyzed for presence and absence of generalized trait patterns. Children with progressive neurological disorders and mental retardation were excluded.On the basis of neurological and imaging findings the non-idiopathic group was separated.Results: 72 children (73%) had seizures. On the other children EEG was performed for different reasons (headache, learning disorders, psychiatric disorders). Only 26 children (36%) had seizures characteristic exclusively for benign epilepsy with centro-temporal spikes (BECTS). Neonatal seizures, febrile convulsions (FC), generalized tonic-clonic seizures (GTCS), non-BECTS characteristic simple partial seizures and complex partial seizures occurred in other patients solely, or in combination. 41% of children with BECTS, 28% of children with other seizures and 31% of non-epileptic children had additional learning and behavioral problems. Family history for seizures was positive in 19% of the non-epileptic and in 27% of the epileptic patients. Significant number of the whole sample had generalized-trait EEG abnormalities.Conclusion: focal sharp waves in children are not restricted to BECTS or even to epilepsy. They could be associated with learning disabilities, behavioral disturbances, headache and can be asymptomatic.

P404
RECURRENT ABSENCE STATUS EPILEPTICUS-B.Baykan, A. Gökyigit, C. Gürses, M. Eraksoy, University of Istanbul, Medical Faculty, Department of Neurology, Istanbul-Turkey.

Eight cases with more than 2 attacks of absence status epilepticus (ASE) were included in this study. Their ages were between 9 and 83 years and 5 of them were women. The mean age at the first ASE episode was 16.5 years. Before the ASE episode, there was a history of epilepsy in 5 patients. A varying degree of confusion was the main clinical symptom associated with mild motor signs like perioral (1), eyelid (2) or generalized myoclonus (4). On the EEG's which revealed the diagnosis of ASE, the multispike-wave discharges were continuous in 3 patients, whereas in the others there were normal intervals lasting 1-4 seconds. IV Clonazepam used in all cases, showed a dramatic improvement of clinical and/or EEG findings. According to the associated clinical and interictal EEG features classification of the epileptic syndromes was made. Two of them had juvenile myoclonic epilepsy. Two had phantom absences and late onset generalized convulsions, one had perioral myoclonia with absences and 2 had eyelid myoclonia with absences. These are proposed but not yet recognized syndromes by the International League Against Epilepsy. The remaining patient had unclassified idiopathic generalized epilepsy characterized by a recurrent ASE attacks on awakening. Our study shows that ASE can recur and most cases could not be classified according to the known epileptic syndromes.

P405
IS EPILEPTIC ACTIVITY IN RELATION WITH PATTERN OF PERIVENTRICULAR HETEROTOPIC GRAY MATTER - A MRI STUDY. M. A. Lucic, D. Kozic, K. Koprivsek, O. Adjic, R. Semnic, A. Zvezdin, N. Prvulovic-Diagnostic Imaging Center in Sremska Kamenica, Novi Sad, Yugoslavia

Purpose of the study was to determine possible relation between MRI finding of the group I periventricular heterotopic gray matter (HGM), considering the classification proposed by Tampieri D. et al (1), and a clinical presence of epileptic activity in examined patients.Materials and Methods: Twenty six patients with periventricular HGM (group I) revealed by brain MRI examination on 1.5T imager were divided into three groups by type (A, B and C), where the patients with 1-3 nodules of HGM were classified as type A, with 3-6 nodules as type B, and with more than 6 nodules or diffuse subependimal heterotopia as type C, and evaluated for seizure activity. Patients classified as group II (periventricular and subcortical heterotopia with/without cortical dysplasia) and group III (giant forms of HGM with cortical dysplasia) on the basis of MRI examination weren't included in the study.Results: MRI examination revealed 13 patients (50%) with less than 3 periventricular nodules of HGM, who were classified as type A. Six of them had no registered epileptic activity, while 7 had seizures. Eight patients (30.77%) were classified as type B, 7 of whom presented with and 1 without seizures. Five patients (19.23%) all with present epileptic activity, who were classified as group C on the basis of MRI examination showed more than 6 nodules in 4 cases and diffuse subependimal islands of HGM in 1 case.Conclusion: Although epileptic activity was established as a leading clinical sign in the great majority of the examined patients with type B (87.5%) and in all patients with type C periventricular HGM, in the patients with type A it was demonstrated in only 53.84% cases, which is significantly less often in comparison to the two other subgroups. That feature suggests the necessity for further investigation with larger number of the patients. References: 1. Tampieri D, Dubeau F, Leblanc R, Melancon D, Andermann F. Imaging of Heterotopic Gray Matter. In: Guerrini R, Andermann F, Canapicchi R et al (eds) Dysplasias of Cerebral Cortex and Epilepsy. Lippincott-Raven Publishers, Philadelphia 1996:163-8.

P406
ELECTROPHYSIOLOGICAL EVIDENCE FOR TRANSMITTER-ACTIVATED INWARD RECTIFIER K+ CURRENTS IN SOMATA AND DENDRITES OF RAT NEOCORTICAL PYRAMIDAL CELLS.Tomoko Takigawa and Christian Alzheimer-Dept. of Physiology, University of Munich, D-80336 Munich, Germany

Several neuromodulators including adenosine (via A1 receptors), serotonin (via 5HT1A receptors), and GABA (via GABAB receptors) target G protein-activated inwardly rectifying K+ (GIRK) currents to influence the excitability of CNS neurons. A number of active ion conductance have been identified in dendrites of CNS neurons that are thought to play an important role in the local integration of synaptic signals. Although various G protein-coupled receptors are capable of evoking GIRK currents in cell somata in CNS neurons, it is not known whether similar GIRK current responses are present in dendritic compartments. In order to determine the density of GIRK-mediated current in dendritic processes and somata, we performed patch-clamp recordings on acutely isolated dendritic segments and somata of rat neocortical pyramidal cells and measured the current response evoked by adenosine, serotonin, and the GABAB receptor agonist baclofen. In whole-cell condition, hyperpolarizing voltage ramps and elevation of extracellular K+ to 40 mM served to identify inwardly rectifying K+ currents. After application of adenosine (100μM), serotonin (20 μM) and baclofen (20μM), all neuromodulators evoked inwardly rectifying K+ currents both in dendritic segments and cell somata. The neuromodulator-induced currents were completely suppressed by Ba2+ (200 μM). When GIRK conductance was normalized to surface area, we found that all these transmitters evoked significantly larger GIRK conductances in dendrites than in somata. Our data suggest that several neurotransmitters might enhance GIRK currents that modulate the electrical properties of dendrites. In addition to voltage-dependent K+ currents and the hyperpolarization-activated cation current (Ih) of the dendrite, GIRK currents should dampen dendritic excitability and thus play a pivotal role of dendritic signal integration. (Supported by SFB 391.)

P407
ANTI-HU PARANEOPLASTIC ENCEPHALOMYELITIS IN ADULT NEUROBLASTOMA MIMICKING MULTIPLE SCLEROSIS - Stephan Arnold1, Soheyl Noachtar1, Felix Rosenow2, Raymond Voltz1-1Dep. of Neurology, University of Munich, Germany, 2Dep. of Neurology, University of Göttingen, Germany

Paraneoplastic encephalomyelitis may be a rare, but important differential diagnosis of multiple sclerosis. We report on a patient suffering from adult neuroblastoma in whom the clinical signs and symptoms initially suggested the diagnosis of multiple sclerosis. A 23 year-old otherwise healthy patient experienced a first episode of blurred vision of her left eye a year ago, remitting after few weeks. Ophthalmoscopic examination depicted papilledema of the left eye, visually evoked potentials could not be elicited on the left side. A lumbar puncture yielded 31/3 pleocytosis of the spinal fluid and intrathecal production of IgG. Eight months later, she developed

progredient ataxia and dysarthria. Additionally, left-hemispheric focal epileptic seizures occured and led to admission. On examination she revealed an opsoclonus and a cerebellar syndrome. Magnetic resonance imaging (MRI) scans showed cerebellar degeneration as well as cortical and subcortical laminar T2-weighted hyperintensity involving the left insula without gadolinium enhancement. Anti-Hu antibodies were found. Computed tomography (CT) of the abdomen revealed 3 nodular tumours adjacent to the left adrenal gland, which were resected consecutively. Histological analysis of the specimen documented neuroblastoma. Chemtherapy was initiated.This case demonstrates that paraneoplastic encephalomyelitis is a rare, but important differential diagnosis of multiple sclerosis.

P408
REFLEX INDUCED SEIZURES: READING AND MUSICOGENIC EPILEPSY: REPORT OF TWO CASES - Öztekin N, Öztekin MF - SSK Ankara Hospital Department of Neurology Ankara, Turkey

Although the term reflex epilepsy is widely used today, in most of the patients who has reflex induced seizures also occur. Reflex seizures are visually induced seizures, startle epilepsy, seizures that are provoked by motor act or cognitive function and induced by movement or other acts. Here we will present the findings of 2 patients with reflex epilepsy.Case I: A 17 year old student first heard a click voice in his throat while he was in an examination. The voice was present during the act of reading and mental concentration. His EEG revealed epileptic activity compromised of bilateral generalised sharp wave and spikes and rudimentary multiple spike and wave discharges. His cranial MRI was normal and was diagnosed as reading epilepsy. Treatment with valproic acid was started. At his follow up his symptoms and EEG discharges were totaly abolished.Case II: A 23 year old female presented with the complaint of chewing, swallowing and bizarre movements hands detected by family members while listening a certain type of Turkish folkloric music. EEG revealed epileptiform abnormality in both temporal regions. Cranial MRI was normal. Carbamazepine was started and she was recommended not to listen to that type of music. At her follow up she was seizure free and her EEG's were normal.

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COMPARATIVE STUDIES ON THE EFFECTIVENESS AND SAFETY OF NEW GENERATION GABAERGIC ANTI-EPILEPTIC AGENTS VS. DRUGS WITH COMPLEX MECHANISM OF ACTION - Piotr Czapinski, Rafal Motyl. Department of Neurology, Jagiellonian University, Cracow, Poland

Goal: The recently published results of the meta-analysis studying the effectiveness of new generation anti-epileptic agents employed in clinical trials do not indicate clearly whether selectively acting agents or drugs with complex mechanism of action are more efficient. There are no studies which would directly compare the efficacy of these agents in clinical trials. Material and method: The investigation was carried out in 64 patients with drug-resistant epilepsy with partial seizures divided into 4 groups of individuals hitherto unsuccessfully treated for at least 3 months employing vigabatrin (VGB), tiagabine (TGB), topiramate (TPM) or felbamate (FBM) as add-on therapy. Patients on gabaergic drugs (VGB or TGB) received complex agents (TPM or FBM), while patients on TPM or FBM were given VGB or TGB. In each group, 50% of the patients (N=8) received a drug from the contrary group at the standard dose: VGB - 2 000 mg; TPM - 200 mg; FBM - 1 200 mg; TGB - 30 mg. The period over which a new drug was introduced and the presently employed agent was withdrawn was two months. Therapeutic effectiveness was followed up for 3 months. Within this period it was possible to change the dosage of the employed agent so that it reached the maximum tolerated dose. Patients who achieved at least a 50% reduction in the number of seizures were recognized as responders. Records were also kept of the number of individuals excluded from the investigation, regardless of the cause. Results: After a 3-month follow-up, the effectiveness of complex drugs measured by the number of responders was slightly higher than in the group of gabaergic agents (TPM+FBM: VGB+TGB = 19:17). The maximum doses were as follows: VGB - 4 000 mg; TGB - 70 mg; TPM - 700 mg; FBM - 2 400 mg. Exclusion from the study occurred more often in the group receiving TMP+FBM, the chief cause being unacceptable adverse effects (TPM+FBM = 8; VGB+TGB = 5). Conclusions: The present results do not answer the question whether drugs with complex mechanism of activity are more effective. Sometimes, as it seems, the higher effectiveness of a given agent resulting from its complex mechanism of action triggers adverse effects necessitating the termination of the employed therapy.

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DIURNAL AND NOCTURNAL BREATHING IN ALS, A LONGITUDINAL STUDY. Iannaccone S, Zucconi M, Sferrazza B, Golzi V, Canovaro P, bianchi A, Fumagalli A, Smirne S, Ferini-Strambi L. Department of Neurology, IRRCS H S.Raffaele, Milan, Italy.

Aim of this study was the evaluation of respiratory function during wakefulness (Spirometry and arterial blood gases) and sleep (polysomnography) in 21 (12 M, 9 F) Consecutive Amyotrophic Lateral Sclerosis (ALS) patients The presence of respiratory prognostic indicators has been evaluated. Results after 2 years follow-up: respiratory parameters during wake showed a moderate to restrictive pattern in 65%of the patients. Sleep respiratory studies showed the presence of apnoeas in 33% of the patients, the events were both Central and Obstructive, mainly during REM sleep. 8 patients (38%) complained of respiratory failure and 4 (19%) died. Of these 4 patients, 3 showed a decline in Forced Vital Capacity (one had also a severe central sleep apnoea) and 1 showed a severe REM hypoventylation but Forced Vital Capacity > 50% of predicted. In conclusion our data did not reveal the presence of a unique prognostic predictor, but indicated the utility of a comprehensive diurnal and nocturnal evaluation of respiratory parameters.

P411
INFLUENCE OF INTERMITTENT NONINVASIVE NASAL VENTILATION (NNV) ON THE QUALITY OF LIFE IN.PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS). 1-H Schreiber 1-U Wiedemuth-Catrinescu, 1-A Sperfeld, 1-AC Ludolph, 2-KH Wollinsky. 1-University of Ulm, RKU Hospital, Departments of 1-Neurology and 2-Anaesthesiology, D-89081 ULM;

The aim of this longitudinal study is to assess the influence of NNV on the quality of life in patients with advanced ALS. Design: Long-term follow-up of patients with ALS-associated respiratory dysfunction defined by El Escorial criteria and receiving intermittent positive pressure ventilation via individually adapted nasal masks and pressure support devices. Data profile: Examination at entry (baseline) and follow-up every four months. To date, 10 patients (mean age 54.2 yr at baseline) were entered into the study with follow-up periods to 8 months. Assessment parameters include: clinical stage of ALS (Norris Scale), respiratory function (vital capacity, pO2, pCO2, O2-saturation), mood scale according to von Zerssen (BfS), Beck Depression Inventory (BDI), Stanford Sleepiness Scale (SSS), Pittsburgh Sleep Quality Index (PSQI), Visual Analogue Scales for sleep quality (VIS-A, VIS-M), Scale for the assessment of mental and physical fatigue (SAF). Results: Preliminary analysis showed that the total number of clinical complaints had markedly decreased between baseline and follow-up examinations. Subjective feelings of breathlessness occurred in 6 patients at baseline, but only in 2 patients under NNV. Early morning headache was reduced in all patients. A clear benefit was also achieved concerning sleep quality (p 0.03), physical fatigue (p 0.02) and daytime sleepiness (p 0.09). Patients also tended to improve in general mood (BfS, p 0.14) and depressiveness (BDI, $p < 0.13$). Nevertheless, BDI rating remained on a clinically relevant level due to disease progression. The positive effects appeared most pronounced in younger patients and when NNV was administered early in the development of hypoventilation. The respiratory parameters worsened gradually but not on a statistically significant level. This suggests interference between the effects of ventilation and disease progression. Conclusion: This study provides evidence for a relevant benefit in overall quality of life provided by NNV to patients with ALS. This study is being continued and follow-up data will be presented.

P412
DIFFERENTIAL EXPRESSION OF GROUP I METABOTROPIC GLUTAMATE RECEPTORS IN RAT SPINAL CORD SOMATIC AND AUTONOMIC MOTONEURONS. POSSIBLE IMPLICATIONS FOR THE PATHOGENESIS OF AMYOTROPHIC LATERAL SCLEROSIS. Johanna M.H. Anneser[1,2], Gian Domenico Borasio[2], Achim Berthele[1,3], Walter Zieglgänsberger[1], and Thomas R. Tölle[1,3]. 1-Clinical Neuropharmacology, Max-Planck Institute for Psychiatry, Munich, Germany; 2-Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians Universität, Munich, Germany; 3-Department of Neurology, Technical University, Munich, Germany.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive loss of somatic, but not autonomic motoneurons. The reason for this selective vulnerability is unknown. The patho-

genesis of ALS is thought to involve glutamatergic excitotoxic mechanisms. While overactivation of ionotropic glutamate receptors may trigger excitotoxicity, we have previously shown that stimulation of group I metabotropic glutamate receptors (mGluRs) can exert neuroprotective effects on cultured motoneurons.Using in situ hybridization, we found a differential expression of group I mGluRs (mGluR1,5) in rat spinal cord. Autonomic motoneurons from the sacral parasympathetic Onuf's nucleus (SPM) and thoracic sympathetic neurons (TSM), which are spared in ALS, express high levels of mGluR5, while somatic motoneurons (SMN) do not. The percentage of the cell surface covered by silver grains was 10.9(6.3% in SPM, 20.1(4.4% in TSM but only 1.6(1.7% in SMN ($p < 0.005$).In addition, mGluR1 mRNA is found only in smaller somatic motoneurons, which seem to be less vulnerable in ALS. Thus, differential mGluR expression might provide a possible clue to the selective vulnerability of different motoneuronal subpopulations in ALS.

P413
A CROSS-SECTIONAL STUDY ON THE QUALITY OF LIFE OF VENTILATED ALS PATIENTS AND THEIR CAREGIVERS IN GERMANY. Dagmar Kaub-Wittemer[1], Nicole von Steinbüchel[2], Maria Wasner[1] and Gian Domenico Borasio[1]. 1-Department of Neurology, Klinikum Grosshadern, and 2-Institute of Medical Psychology, Ludwig-Maximilians-Universität, Munich, Germany.

Objective: Assessment of demographic data and self-perceived quality of life (QoL) of German patients with amyotrophic lateral sclerosis (ALS) on home mechanical ventilation (HMV) and their primary caregivers.Study design: Two separate cross-sectional questionnaires including validated psychological scales as well as demographic, clinical and social background questions.Results: Data were obtained from 48 patient-caregiver pairs (29 patients with non-invasive ventilation, 19 patients with tracheostomy). 89% of the patients would choose ventilation again, 85% of the caregivers would advise the patients to choose it again. 78% of the caregivers would choose ventilation for themselves in a similar situation.When asked to rate their own QoL on a visual analog scale from 0 (disastrous) to 10 (excellent), 47% of patients gave values (5. 37% of the patients judged their QoL equal to or higher than that of their caregivers. There were no significant QoL differences between non-invasively ventilated patients and patients with tracheostomy.Conclusion: Our preliminary data show that the QoL of ventilated ALS patients in Germany is higher than presumed by many clinicians. The detailed analysis of the questionnaires will hopefully provide insight into specific problem areas that can be targeted in the future to further enhance the QoL of ventilated ALS patients.

P414
ALTERNATIVE RNA POLY(A) SITES IN THE GLUTAMATE TRANSPORTER EAAT2 - A POTENTIAL MECHANISM OF VARIABLE EXPRESSION IN ALS AND NORMAL CONDITIONS. C. Münch, S. Cirovic, C. Herrmann, B. Schwalenstöcker, A. C. Ludolph, T. Meyer-Dept. of Neurology, University of Ulm, Albert-Einstein-Allee 11, D-89081 Ulm.

The glial glutamate transporter EAAT2 is responsible for more than 90% of synaptic glutamate reuptake in the CNS. A substantial reduction of EAAT2 has been identified in the motor cortex and spinal cord of some amyotrophic lateral sclerosis (ALS) patients. Aberrant RNA splicing of the EAAT2 mRNA has recently been suggested as a mechanism for the loss of the protein. Therefore, RNA processing of EAAT2 is of major pathogenetic interest in this disease, but incompletely understood. We studied alternative regulatory sequences of EAAT2 mRNA. Using normal human brain we cloned four novel EAAT2 RNA isoforms that are characterized by distinct 3´-untranslated, regulatory sequences and the use of different polyadenylation/cleavage sites. These changes are of potential importance for the EAAT2 RNA stability and expression. The variable polyadenylation sites show different levels of expression in CNS RNA samples. The study was based on rapid amplification of cDNA ends (3´-RACE), using human brain cDNA (Marathon-Ready cDNA, Clontech) as template. For transcript identification we carried out PCR-cloning techniques (TA cloning) and DNA sequencing (ABI Prism).In conclusion, we identified a novel factor in the highly variable EAAT2 RNA processing, that is of major interest in current research on neurodegeneration.

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THE TERMINAL PHASE OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS. Christian Neudert, Maria Wasner, Gian. Domenico. Borasio. Department of Neurology, Ludwig-Maximilians-University, Munich, Germany.

Most patients suffering from amyotrophic lateral sclerosis (ALS), when questioned after the onset of dyspnea, express fears of "choking to death". At present, only few data concerning the dying phase of ALS patients are available. We therefore performed a structured telephone interview with relatives of 62 patients (25 women, 37 men) of our outpatient clinic who died of ALS.We found that 57 patients (92%) died peacefully, 2 in moderate suffering, 1 in great pain, 2 after a resuscitation attempt. 37 patients (60%) died during sleep, 17 (28%) were fully conscious until shortly before death, while 8 (13%) were comatose. No deaths by choking were reported.Concerning the palliative care in the terminal phase, 13 patients (21%) were on a home ventilator, 12 of them via nasal mask, 1 via tracheostoma, and 2 patients were intubated. 13 patients (21%) had been provided with a percutaneous endoscopic gastrostomy (PEG). In 2 patients the PEG caused an infection and had to be removed. Morphine was administered to 15 patients (24%) in the terminal phase, and 13 (21%) took benzodiazepines. The use of noninvasive home mechanical ventilation, morphine and benzodiazepines was judged to be highly beneficial by both patients and relatives.These data support the hypothesis of a generally peaceful death process in ALS and should be communicated to patients and relatives after the onset of dyspnea to relieve fears of choking.

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HHV-8 SPECIFIC SEQUENCES IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENTS-Sola Patrizia, Bedin Roberta, Merelli Elisa - Clinica Neurologica - Università di Modena - Italy

Human herpesvirus (HHV) 8, a new member of the herpesvirus family, has been found in almost all Kaposi's sarcoma patients, with and without AIDS. As for HHV-6, HHV-8 sequences have been detected in the normal population, and in immunocompromized hosts, including transplant patients, Hodgkin's and non Hodgkin's lymphomas, AIDS-related lymphomas, and in patients with lymphoproliferative diseases. We have recently found by the polymerase chain reaction (PCR), the presence of HHV-8 sequences in autoptic brain specimens of 5 out of 12 multiple sclerosis patients (in the plaques), in 3/8 normal adults, and in 2/7 stillborn children. These findings suggest that, like HHV-6, HHV-8 is strongly neurotropic, besides being lymphotropic. Up to now it is not known if HHV-8 is able to integrate in the human genome and to transactivate other viral and/or retroviral genes, as it has been demonstrated for HHV-6.On the basis of the viral pathogenetic theory of ALS and of the biological properties of HHVs, we have previously searched by the PCR the presence of HHV-6 specific sequences in the peripheral blood mononuclear cells (PBMCs) of 20 ALS patients as well as in 20 controls, with negative results. The aim of the present study is to investigate in the same patients the presence of HHV-8 sequences. Our preliminary data, obtained in 8 ALS patients, indicate the presence of HHV-8 sequences in one these, with a bulbar form of disease, and in no one of the 20 controls.On the basis of the reported association between some ALS (5% of cases) and gammopathies/lymphoproliferative diseases, it will be of interest to gain information on the presence of this strongly lymphotropic virus in all the 20 ALS DNAs.

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AMYOTROPHIC LATERAL SCLEROSIS (ALS) AND CANCER: A STUDY OF 12 PATIENTS. M.C. Vigliani, P. Polo, A. Chiò, L. Mazzini, B. Giometto, D. Schiffer-Dept. of Neuroscience, University of Turin; Dept. of Neurology, University of Padua (Italy)

Objective: We assessed whether patients with ALS associated with cancer clinically differ from typical ALS patients and whether they benefit by oncological treatment. Methods: Patients with definite ALS (according to the El Escorial Criteria) and cancer are described. Their sera were examined for anti-nervous system antibodies by means of immunohistochemistry and Western Blot analysis.Results: The series was composed by 9 males and 3 females (3:1 ratio), with a mean age of 65.3 ((8.9) years; in 8 of them ALS preceded tumor diagnosis by 8.9 ((13) months. Three patients had lung adenocarcinoma, 2 breast and 2 bowel tumor; non Hodgkin's lymphoma, hepatocarcinoma, kidney cancer and mesothelioma were observed in 1 case each. Only four patients were suitable for surgical therapy, two of them worsen during the procedure, the others had no benefit. Two patients did not fare better after chemotherapy and radiotherapy. In all deceased patients (7) death was a consequence of ALS. Median survival was 19 months. Anti-nervous system antibodies were never detected. Conclusions: Our population of pure ALS patients with cancer does not significantly differ from classical ALS population. However, the progression of the neurological syndrome, as indicated by survival, seems to be faster. Up to date we have not observed any response to anticancer therapy.

Multiple Sclerosis

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TREATMENT OF DETRUSOR SPHINCTER DYSSYNERGIA WITH BOTULINUM TOXIN- W.H. Jost, Dept. of Neurology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany

Detrusor Sphincter Dyssynergia (DSD) is very common in neurologic disease, for example in spinal cord injury, multiple sclerosis etc. The symptom is due to a spinal lesion interrupting the bulbospinal pathways bilaterally to the sacral cord. This results in a failure of the sphincter to relax during detrusor contraction. Therapeutic effects are limited and the side effects are troublesome.Until today we have treated 26 patients (17 women, 9 men, 31.6 years on average), 19 patients with MS, 7 patients after spinal cord injury.The injection of the toxin was performed transperineal under EMG control on both sides into the external vesical sphincter. The toxin inhibits presynaptic acetylcholine release in muscular synapses. We inject 5 to 20 units Botox® (Allergan, S.F., USA). A good result, especially decreased post-void residual volumes, was obtained in 15 patients, a moderate improvement of symptoms in 7 patients. As a unwanted side effect we found a transient urinary incontinence, which lasted for 1 to 3 weeks in 6 patients. The action lasts for 4.2 months on average, making reinjections necessary.To our opinion BoTx injections offer a new option in management of DSD, especially in patients with multiple sclerosis and spinal cord injury who cannot perform self catheterisation or do not desire surgery. The dosage of 20 units Botox® seems to be adequate. Controlled studies are warranted.

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A PILOT STUDY OF RILUZOLE IN PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS; EFFECT ON SPINAL CORD ATROPHY ON MRI. N.F. Kalkers[1], E. Bergers[2], R.v Schijndel[3], F. Barkhof[2] and C.H. Polman[1]. 1-Dept. of Neurology, 2-Dept. of Radiology, 3-Dept. of Clinical Physics and Informatics. Free University Hospital Amsterdam, Postbox 7057, 1007MB Amsterdam, The Netherlands.

Introduction Since in multiple sclerosis (MS) disability correlates with axonal loss, protection of axons may have a favourable impact on the course of the disease. Riluzole appears to act through inhibition of glutamate transmission. In this pilot-study, the effects of the neuroprotective agent riluzole are monitored in primary progressive MS patients (PPMS) by measuring the spinal cord atrophy visualized by MRI.Method 13 PPMS were examined at baseline, after 6, 12, 18 and 24 months. Each time a 3D MRI was made (MPRAGE). Riluzole treatment was given from 12 months till 24 (2x50 mg daily). From the MPRAGE data set series of 10 contiguous 3-mm axial slices were reformatted using the center of the C2-C3 disc as the caudal landmark. A blinded observer reformatted all slices twice and the average spinal cord area was used as outcome parameter.Results The coefficient of variation of the repeated measures was 2.2%. During the first year (without riluzole) the mean area of the spinal cord changed from 66.7mm2 to 65.35 mm2 (decline 2.05%). During the second year (under riluzole treatment) spinal cord area changed to 65,24 mm 2 (decline 0.17%).Conclusion Preliminary results from this pilot-study suggest a slowing in the rate of spinal cord atrophy during treatment with riluzole. Given the height of the coefficient of variation, the small sample size and the follow-up of only one year there is a need to obtain data from a large placebo-controlled trial.

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DISTRIBUTED CENTERS OF EXCELLENCE - William Likosky, Santa Clara, California, USA; Jay Rosenberg; Jack Burks; Howard Barkan; Jeff Klingman; Jeffrey Javerbaum; Allan Bernstein, U.S.A.

Multiple Sclerosis [MS] has a varying natural history, and large and variable number of possible associated impairments, making patient management a complex and difficult clinical challenge. The potential care fragmentation and poor communication threaten the quality and comprehensiveness of care. Most MS care is provided in non-specialty neurology clinics where structures to provide care may not be present. We are creating Distributed Centers of Excellence [DCOE] for MS. Organizational elements include multi-specialty MS clinics and MS nurse-coordinators. Programmatic elements include implementation of the appropriate guidelines for ambulatory MS care, and patient and provider completed encounter forms linked to these care guidelines which improve communication among those involved in MS care, increase the completeness and consistency of the recording of pertinent clinical and functional information, and contain important data needed for evaluation of the project's clinical effectiveness. The program databases facilitate evaluation of the degree to which the existing MS care guidelines can be implemented, and of the clinical effectiveness of care provided in accord with the guidelines' recommendations. We evaluate the program's success by measuring, comparing, and reporting indices of adherence to the guidelines' recommendations in project and control sites. The project is being implemented in a staged fashion in selected care sites of The Kaiser-Permanente health care system in Northern and Southern California. This staged implementation will permit a controlled evaluation of the project's clinical effectiveness.

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SERUM AUTOANTIBODY (AUTOAB) OCCURRENCE DURING INTERFERON (IFN) BETA-1A THERAPY FOR MULTIPLE SCLEROSIS(MS). G.Isoardo, B.Ferrero, G. Aimo, L.Giorda, A.Oggero, E.Verdun, A.Ricci, B.Bergamasco, R.Pagni, L.Durelli, Torino, Italy.

Serum autoab may occur during IFN therapy and are frequent in MS patients. We detected the following serum autoab (anti-thyroid (AT) and -acetylcholine receptor (AChR) by IRMA; anti-monosialoganglioside (GM1) and -sulphatide by ELISA; anti-tissutal, ie, anti-nuclear (ANA), α-microsomal (LKM), α-smooth-muscle (SMA), α-mitochondrial (AMA) by indirect immunofluorescence). Autoab were monitored every 3 months during the first year of therapy in 59 MS patients never treated with IFN before participating to Biogen study C94-801-P. Patients were treated with 30 mcg IFN beta-1a im once a week. At baseline autoab were observed in 28 patients(47.4%): 6 AT, 10 anti-tissual (8 ANA, 1 SMA, 1 AMA), 3 anti-AChR, 3 anti-sulphatide, 6 anti-GM1. During IFN therapy autoab titer increased in11 of those patients(39.2%) (4 AT; 2 ANA; 2 anti-AChR; 3 anti-GM1); decreased in 7(25%) (2 AT; 1 ANA;1 anti-AChR; 3 anti-sulphatide); disappeared in 3 (10.7%) (1 SMA; 2 anti-GM1). De novo autoab occurred in further 22 patients(37.2%) (1 AT; 10 anti-GM1; 10 anti-sulphatide; 1 anti-AchR). Autoab frequency in MS patients is particularly high already before IFN therapy. In some patient autoab titer may increase or de novo autoab occur during IFN therapy. The high baseline autoab frequency makes it difficult to correlate the observed changes directly with IFN therapy. The finding of serum autoab during IFN therapy needs, however, to be carefully evaluated in relation to the whole clinical setting. The study was sponsored by Dompe' Biotec, Italy and Biogen,USA.

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CARDIAC REPOLARIZATION ABNORMALITIES IN MULTIPLE SCLEROSIS: CORRELATIONS WITH SPINAL CORD MRI FINDINGS. J. de Seze, T. Stojkovic, M. Ayachi, J.Y Gauvrit, T. Saint-Michel, JP. Pruvo, P. Vermersch - Lille, France

Background: The frequency of autonomic nervous system disturbance is probably underestimated in multiple sclerosis (MS). Recently, ventricular repolarization dysfunctions have been reported in MS and experimental allergic encephalomyelitis (Drouin et al., 1998).Objective: The aim of this study was to confirm previous published data and to correlate cardiac repolarization abnormalities with spinal cord MRI findings (demyelinating lesions and atrophy).Patients and methods: We evaluated R-R, QT and corrected QT (QTc) interval in 50 patients and 15 normal subjects. Sagittal and axial plane MRI was performed in T2-weighted images. Spinal cord area was calculated at C2 level. For this sequence we performed a volume acquired inversion prepared fast spoiled gradient echo acquisition. Results: QT and QTc were significantly increased in MS patients compared with control subjects, especially in progressive forms. QTc was higher than 440ms in 32% of MS patients and none of the controls. QTc abnormalities were not correlated with demyelinating lesions but increase of QT and QTc intervals were correlated with spinal cord atrophy. Conclusion: This study confirms the frequency of prolonged QTc in MS. The high frequency of ventricular repolarization dysfunction is probably more related to axonal loss than to demyelination, as shown at the spinal cord level.

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THE PROFILE OF MATRIX METALLOPROTEINASES (MMPs) AND TISSUE INHIBITORS OF METALLOPROTEINASES (TIMPs) IN MULTIPLE SCLEROSIS.Y. Galboiz, S. Shapiro, N. Lahat, S. Honigman, H. Rawashdeh, A. Kinarty & A. Miller.The Center for Multiple Sclerosis & Immunology Research Unit, Carmel Medical Center, Technion-Israel Institute of Technology, Haifa 34362, Israel.

Objective: Characterization of MMPs' and their endogenous tissue inhibitors TIMPs' profile in peripheral blood from multiple sclerosis (MS) patients. Background: Studies of recent years have demonstrated that gelatinase B (MMP9) and matrilysin, MMP7, are elevated in the cerebrospinal fluid (CSF) of MS patients, and MMPs immunoreactivity is seen in MS lesions. Moreover, MMPs-inhibitors have been reported to suppress disease in experimental animals models of MS. Design/Methods: RT-PCR was performed to evaluate mRNA expression of MMPs (gelatinases, MMP2 and MMP9; matrilysin, MMP7; membrane-type, MT-MMP1), TIMP1 and TIMP2 in peripheral blood leukocytes (PBL) from untreated relapsing-remitting MS patients (n=10) and healthy controls (n=9). Results: No differences were observed in MMP9 and TIMP1 mRNA expression between PBL from MS patients and controls, while a trend towards elevated MMP2 (mean 2 fold higher, MS:controls) and MT-MMP (mean 1.6 fold, MS: controls) mRNA expression was observed. The most relevant findings were the significant elevation demonstrated for MMP7, reduction of TIMP2 and the significant four fold elevation in the MMP2/TIMP2 ratio in MS patients. Conclusion: The present study further elucidates the significance of the delicate balance between MMPs/TIMPs expression which may contribute to the development of CNS autoimmune disease. Further studies of MMPs/TIMPs balance may provide important implications for the development of specific immunological markers for disease activity and contribute to the design of immuno-modulatory agents for the treatment of MS.

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CLINICAL STATUS IN MULTIPLE SCLEROSIS DOES NOT CHANGE WITH THE MENSTRUAL CYCLE. Barbara Giesser, M.D., Ronnie Bergen, M.D., Emmanuel Akporiaye, Ph.D. Arizona Health Sciences Center, Tucson, Arizona, USA

This project sought to corroborate previous reports that neurologic status in women with Multiple Sclerosis (MS) may fluctuate during different phases of the menstrual cycle. Specific goals were to assess symptom variation, quantitative measures of neurologic function, and levels of soluble interleukin-2 receptor (sIL-2r).Materials & Methods: Eight MS patients and 10 healthy control subjects participated, all between the ages of 18-50 with regular menstrual cycles. No subject was taking hormones, corticosteroids, or immunomodulators. Evaluation occurred over three months. MS patients completed a daily questionnaire, which rated severity of seven neurologic symptoms. They were examined at three menstrual cycles phases (menstrual, follicular, luteal) by a neurologist who was blinded to phase. Evaluation consisted of standard neurologic examination. Expanded Disability Status Score (EDSS), Scripps neurologic rating score, ambulation index, 9-hole peg test and Beck depression inventory. At each phase blood was sampled to assay levels of sIL-2r for both subject groups.Results: 1) There was no consistent variation in neurologic symptoms or quantitative measures as a function of phase of menstrual cycle. 2) There was no consistent variation in levels of sIL-2r as a function of menstrual cycle phase. Controls tended to have higher levels than MS patients, and levels tended to be higher during menses, and lowest during follicular phase for both groups, but without statistical significance. Supported by PPO565, NMSS

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THE EFFECT OF HIGH-DOSE METHYLPREDNISOLONE ON THE MAGNETIZATION TRANSFER RATIO IN PATIENTS WITH ACUTE RELAPSE OF MULTIPLE SCLEROSIS.C. Lukas, B. Bellenberg2, D. Pöhlau3, J. Schaffstein1, O. Köster1 - Depts. of Neurology and Radiology1, St. Josef-Hospital, University of Bochum; Entwicklungs- und Forschungszentrum für MikroTherapie2 (EFMT) Bochum, Germany

The aim of this MRI study is to examine the effect of high-dose steroids on the magnetization transfer ratio (MTR) of enhancing lesions and of normal appearing white matter (NAWM) in patients with an acute relapse of multiple sclerosis (MS). Preliminary results of six patients are presented..Methods:Six patients with an acute relapse of clinically definite relapsing remitting MS were studied. Pretreatment brain MRIs were compared with studies obtained one week after treatment with methylprednisolone (500mg/d) for 5 days. A control group consisting of six healthy volunteers with no treatment was also studied. All MRIs were performed with the same technique considering careful positioning on a 1..5T Magnetom Vision before and after treatment. MTRs of these lesions were calculated by using the equation (Mo-Ms)/Mo. Results: The control group had a mean MTR of the NAWM of 37.72% (±1.3). After one week no significant changes were found in this group. In patients with MS a mean MTR of 35.10% (±2.45) was measured before treatment. MTRs obtained in this group were statistically lower than corresponding values in control subjects. After treatment a mean MTR of 36.71% ((0.64) was measured. Fourteen enhancing lesions were found in 4 patients. The mean MTR of these lesions was 22.84 (±4.85) before and 22.25 (±4.52) after treatment.Conclusion: In this preliminary study the treatment with high-dose steroids shows no effect on the MTRs of enhancing lesions. In NAWM a tendency of increased MTR values is visible after treatment. This effect must be confirmed by further examinations of patients.

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RISKS FACTORS FOR MULTIPLE SCLEROSIS DISEASE PROGRESSION. P.K. Coyle, Stony Brook, NY, USA

Introduction: Multiple Sclerosis (MS) is divided into relapsing and progressive subtypes. Progressive MS is more severe, and is associated with worse prognosis, greater disability, poorer quality of life, and higher health care costs. Natural history studies indicate that up to 75% of untreated relapsing patients develop secondary progressive M.S. The ability to identify patients at high risk for progression would allow proactive therapeutic strategies.Methods: Review of data from the PRISMS trial of interferon β1a (IFN1a)-Rebif for active relapsing MS, and from the recent MS literature. Results: Secondary progressive MS is the major progressive subtype (30% of all patients). Clinical and laboratory markers can identify relapsing patients at risk to become secondary progressive. In the PRISMS study 17% of active relapsing MS patients had a Kurtzke Expanded Disability Status Scale of greater than 3.5. Compared to the other patients they had a significantly longer disease duration, higher ambulation index and neurologic rating scale, and greater median burden of disease on brain magnetic resonance imaging (MRI). During the two year natural history (placebo group) followup these patients did worse on multiple parameters evaluating relapses and progression, neurologic examination, and hospitalizations. In this more severe relapsing MS group, the optimal disease modifying therapy response required high dose IFNβ1a (132μg, or 36 MIU per week). A review of the literature indicates that other risk factors for progression are male gender; disease duration of 5 to 15 years, increasing relapse rate; polyregional relapses with incomplete recovery; and suboptimal therapeutic response to glucocorticoids and disease modifying therapies. In addition to increased burden of disease, other MRI risk factors are periventricular, posterior fossa, and spinal cord lesions; confluent lesions; increased axon damage and tissue loss; increasing burden of disease out or proportion to contrast lesion activity; myelin disruption independent of blood brain barrier damage; and decreased recovery from lesions. There is suggestive data for a number of other risk factors which encompass immunologic, electrophysiologic, pathologic, cerebrospinal fluid, endocrinologic, and urine parameters. Conclusion: There are specific clinical and laboratory features which can identify relapsing MS patients at risk for progression. Proactive therapeutic strategies for such patients should include high dose IFNβ.

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COMPARATIVE STUDY OF BINDING AND NEUTRALISING ANTIBODIES TO IFN-β IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH IFN-β1a (AVONEX) OR IFN-β1b (BETAFERON). Fernández O, Mayorga C, Luque G, Guerrero G, Guerrero M Blanca M. Neurology Service and Research Laboratory Carlos Haya Hospital, Malaga, Spain

Multiple sclerosis (MS) is an inflammatory-demyelinating disease. Nowadays, IFN-β is an effective treatment in both relapsing-remitting and progressive MS. However, in some patients the therapy is not so effective, this may be due to the production of neutralising antibodies (NAB) which are those that bind directly to the IFN-β cell receptor avoiding the IFN-β biological effect. At present, two types of IFN-β are used in the therapy: IFN-β1a (glycosylated) and IFN-β1b (not glycosylated), these chemical differences can induce a different immunogenic capacity.In order to compare, with the same assay criteria, the different capacity between IFN-β1a and IFN-β1b in the induction of binding and neutralising antibody we studied 26 MS patients treated with IFN-β1a (Avonex) and 28 with IFN-β1b (Betaferon). Binding antibodies were determined by ELISA to IFNβ-1b (Betaferon®) and IFNβ-1a (Avonex®). To detect and quantify the NABs to IFN-β we used a bioassay, measuring the capacity of NABs in blocking the antiviral resistance induced by interferons. Fifty percent of patients treated with IFN-β1b and 30.5% treated with IFN-β1a produced binding antibodies to IFN-β and 25% and 11.5% produced NAB respectively.Theses results demonstrate that the IFN-β1b (Betaferon) molecule is more immunogenic than the IFN-β1a (Avonex). This may be due to the chemical

structure of the IFN-β1b, not glycosylated, that can produce aggregates and enhance this immunogenic capacity.

P428
NO EVIDENCE OF HUMAN HERPESVIRUS 6 BY POLYMERASE CHAIN REACTION IN SERA AND CEREBROSPINAL FLUID SAMPLES OF MULTIPLE SCLEROSIS PATIENTS AND NEUROLOGICAL CONTROLS IN SOUTHERN SPAIN. O Fernández, J Gutiérrez, M Guerrero, MJ Vergara, C Maroto, E de Ramón, G Luque Neurology Department. Complejo Hospitalario Carlos Haya. Malaga (Spain)

The presence of Human Herpesvirus 6 (HHV-6) in cerebrospinal fluid (CSF) and brain lesions has been reported in a proportion of multiple sclerosis (MS) patients. Paired frozen sera and CSF samples of 40 MS patients and 34 neurological controls (cerebral vascular diseases, idiophatic intracraneal hypertension, lateral amyotrophic sclerosis, Gullain-Barré, chronic inflamatory demyelinating polyneuropathy, dementia, neurolues, etc) from Southern Spain were analysed. A comercially available PCR kit (Herplex, Pharma Gen) was used because a high sensitivity level of the assay. All oligonucleotids used for PCR were synthetized by the solid phase triester-method. The sequences of oligonucleotids used in amplification and hibridization have been reported and included a set for the viral DNA polymerase region. The amplicon was detected with ELISA assay. No DNA was found in any CSF o serum samples of MS patients or controls, with the primers used in our samples, and we were unable to confirm the implication of HHV-6 in MS.

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TROPHIC DISTURBANCES IN MULTIPLE SCLEROSIS (MS): SEVERITY IS NOT ONLY RELATED TO DISABILITY - Albrecht H, Meister H, Königbauer V, Erasmus LP, König N Marianne-Strauss-Klinik, Milchberg 21, D- 82335 Berg, Germany

In a prospective study we investigated 301 MS patients in sequence of their admission. Ninety-three out of them had trophic disturbances like livid colouring of the skin, edema, or decubital ulcer, respectively. We used a numerical scale to evaluate the extent and the size of these pathological findings at the legs, dividing them up in three grades: 37 patients showed only slight (grade 1), 19 moderate (grade 2), and 37 severe disturbances (grade 3). The disability was scored using the Kurtzke-EDSS (Neurology 1983, 33:1444-1452): mean EDSS was 6.04 (1.37 (standard deviation) for the first, 6.42 (1.07 for the second, and 6.55 (0.96 for the third grade group. Statistical evaluations (t-test) did not show any significant differences between the EDSS values of the different groups. Therefore we conclude that the extent of trophic disturbances in patients with MS is not only depending on secondary factors like the degree of immobilization, but also on primary effects caused by the disease like failures of the central autonomic regulation.

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EFFECTS OF INTERFERON β-1B ON SOLUBLE INTERCELLULAR ADHESION MOLECULE-1 AND TUMOR NECROSIS FACTOR αIN MULTIPLE SCLEROSIS PATIENTS: A SHORT AND LONG-TERM FOLLOW-UP. Rana Karabudak, Munire Kilinç - Department of Neurology Hacettepe University Hospitals, Ankara, Turkey

Objective: To evaluate the short and long-term effects of INFβ-1b on sICAM-1 and TNFα in multiple sclerosis patients.Methods: Twenty-four (16 female,8 male) definite RRMS patients, ages 23-51, ambulatory with EDSS: 5.5 or less were included.16 patients were given INFβ-1b.8 patients were followed-up as MS controls.Age and sex matched 8 additional non-inflammatory disease (NID) patients were served as controls.Blood was drawn from the two patient groups monthly for six months and once at the end of their 18th month. All patients underwent 2 lumbar punctures ; initially and at sixth month. CSF and matched serum levels of sICAM-1 and TNFα were measured by dual ELISA. Results: - MS patients had high serum levels of sICAM-1. In patients with NID sICAM-1 levels were significantly low (256.8 ± 7ng/ml {mean ± SD}) (p:0.018) compared to both INFβ-1b treated (537.8 ± 2), and un-treated (537.6 ± 2) groups (Kruskal - Wallis VA).- Serum sICAM-1 levels were found to be significantly high after three months of treatment compared to baseline values (578.8 ± ng/ml to 509.7 ± 2ng/ml) p:0.002 (Wilcoxon Matched -Pairs SRT).This increment returned to baseline values by sixth month.Recent follow-up data at 18th month did not show any significant change compared to mean values.CSF values andTNFα sera levels showed insignificant changes during the treatment period; and between the three groups.Conclusion: In this controlled serial analysis our findings suggest that INFβ-1b could exert short-term upregulating effects on sICAM-1 molecules however, no significant influence was observed on TNFα. It seems more likely that these changes are reflecting an ongoing homeostatic mechanism rather than a consequence of inflammatory activity.

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A CROSS SECTIONAL STUDY ON QUALITY OF LIFE OF MULTIPLE SCLEROSIS PATIENTS TREATED WITH BETA INTERFERON. Patti F., Deinite G., Cacopardo M., Lopes R., D'Amico S. and Reggio A.

Objective. To evaluate the effects of beta interferon (β IFN) treatment on quality of life (QOL) of patients with Multiple Sclerosis (PwMS).Background. There is a large amount of literature data showing that β IFN treatment is able to change the natural course of MS, reducing the relapse rate and burden of disease, as measured by Magnetic Resonance Imaging of both brain and spine and also producing important beneficial effects on disability progression. However the main clinical trials on β IFN show poor evidence that QOL of β IFN MS treated patients may be improved. Methods. We designed a cross sectional study on four groups of PwMS. Three groups were treated with βIFN plus megadoses of steroids when relapses occured, while the last group received only steroid treatment for eventual relapses. Thus 108 patients were grouped as follows: one year of β IFN 1b treatment (27); two years of β IFN 1b treatment (27); one year of β IFN 1a treatment (27); untreated patients (27). All patients were evaluated with a multidimensional instrument, including Kurtzke EDSS and a questionnaire of self evaluation, consisting of SF-36, fatigue impacts scale, Tempeelar social checklist, Beck inventory for depression and six visual analogic charts, investigating physical functioning, social functioning and emotional well being.Results. The analysis of data show that β IFN 1a treated patients do better either in physical or social functioning than β IFN 1b treated group. These results are more evident, when compairing β IFN 1a group with one year - β IFN 1b patients. Furthermore, it appears evident that β IFN 1a patients perceive a reduced sensation of fatigue, as measured by FIS. Discussion. Our results, although preliminar, and obtained with a cross sectional study, seem to confirm the favorable effects of β IFN 1a treatment on QOL. By the way, longer periods of β IFN 1b administration don't worse QOL of PwMS.

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INFLUENCE OF CLADRIBINE (2-CDA) TREATMENT ON THE CONCENTRATION OF IMMUNOGLOBULIN A (IGA),IMMUNOGLOBULIN G (IGG) AND IMMUNOGLOBULIN M (IGM) IN THE SERA OF MULTIPLE SCLEROSIS (MS) PATIENTS. Z. Stelmasiak*, J. Ilzecka*, P. Grieb**, B. Dobosz*Department of Neurology, Faculty of Medicine, Lublin, Poland*Medical Research Center in Warsaw, Polish Academy of Sciences**

Immunosupressive treatment with Cladribine (2-CDA) is conformable to the autoimmunological concept of multiple sclerosis. The aim of this study was to investigate the effect of 2-CDA treatment on the concentration of immunoglobulins, the main indicators of humoral immunity, in the sera of MS patients. We studied 30 subjects, 15 MS patients and 15 controls. The immunoglobulins were measured using Mancini's method of radial immunodiffusion before the treatment and after the 1st, 3rd and 6th month of the treatment with 2-CDA. The results were statistically analysed by means of t-Student test. As statistically significant level $p < 0,05$ was taken. Before the treatment the serum concentration of IgA was higher than in the control group (2,51±0,96 g/l), IgM was lower than in the control group (1,50±0,66 g/l), but IgG concentration did not differ from its concentration in the control group (11,54±1,23 g/l). After the 1st month of the treatment the average concentrations of the immunoglobulin were: IgA - 2,67±0,84 g/l, IgG - 12,54±1,73 g/l, IgM - 1,60±0,84 g/l, after 3 months of the treatment: IgA - 2,64±0,88 g/l, IgG - 12,34±1,77 g/l, IgM - 1,58± 0,79 g/l and after 6 months of the treatment: IgA - 2,87±0,84 g/l, IgG - 12,59±2,16 g/l, IgM - 1,40±0,77 g/l. The difference of the concentrations of the immunoglobulins after and before the treatment with 2-CDA was not statistically significant. The administration of 2-CDA does not cause significant change of immunoglobulin concentrations in the sera of MS patients.

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HYPERTROPHIC CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP) AND MULTIPLE SCLERO-

SIS (MS).Huerta M1, Baiges JJ1, Orti A1, Montero J2, Ferrer I3. 1 Dep. of Neurology, Hospital Verge de la Cinta, Tortosa. 2 Dep. of Neurology and 3 Neuropathology, Hospital de Bellvitge, L'Hospitalet de Llobregat, Spain.

Case report: A 41-year-old man complained of slowly progressive unsteadiness with distal pain and paresthesias. Seventeen years earlier he developed left motor and sensory symptoms lasting some weeks, and four years later a left internuclear ophthalmoplegia. Neurologic examination disclosed a distal symmetric sensorimotor polyneuropathy with a marked hypertrophy of the superficial nerve trunks and a right Babinski sign. Nerve conduction studies showed demyelinating features without conduction blocks. Magnetic resonance imaging confirmed demyelinating periventricular and C4 lesions, and showed hypertrophied nerve roots compressing the spinal cord. Cerebrospinal fluid protein level was 680 mg/dl without increased immunoglobulin G synthesis or oligoclonal bands. Sural nerve biopsy revealed onion-bulb formations, loss of axons and marked fibrosis. Familiar study has been negative. Our area is endemic for leprosy but physical examination, skin scrapings, lepromine skin test and sural biopsy ruled out the diagnosis. Clinical and histologic features ruled out Refsum's disease, acromegaly, amyloid neuropathy and neurofibromatosis.Conclusion: Association of CIDP and MS is not unusual. Some patients with CIDP who have clinical or subclinical features of central nervous system involvement suggestive of MS have been reported. Our aim was to describe this case of marked hypertrophic neuropathy, its differential diagnosis and the association of central and peripheral inflammatory demyelinating diseases.

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AUDITORY EVENT-RELATED POTENTIALS (EPR) AND NEUROPSYCHOLOGICAL TESTS IN PATIENTS WITH DEFINITE MULTIPLE SCLEROSIS. 1 Urszula Chyrchel, Ewa Wrzos, Ewa Legiec, Zbigniew Stelmasiak, Department of Neurology, Medical Academy, Lublin, Poland

Cerebral involvement in Multiple Sclerosis (MS) may result not only in sensory and motor symptoms but also in impaired mentation. Cognitive event-related potential (especially P-300) is a neurophysiological test which seems to be the index of cognitive processing time. The latency of P-300 is though to reflect the time taken to conclude that a task-relevant stimulus has been presented (prolonged latency is connected with cognitive impairment).The main goals of this study was to evaluate (using P-300 ERP) cognitive impairment in patients with MS and to find out if the latency of P-300 correlates with results of neuropsychological tests.We studied 35 patients (23 females and 12 males, mean age 36 years) with definite MS using two-tone discrimination task to elicit P-300 ERP and Mini Mental State (MMS) test to evaluate patients' mentation. The latency of P-300 was significantly prolonged in 40% of patients with MS when compared with age and sex matched control group. We found statistically significant correlation between the latency of P300 and results of MMS test (r = 0,45).Cognitive impairment in patients with MS can be detected with both neurophysiological and neuropsychological examinations. Significant association between these two tests suggests that P-300 component of ERP is a useful and reliable test in estimating cognitive state in MS patients.

P435
COMPARATIVE ANALYSIS OF TWO CLINICAL SCALES FOR MULTIPLE SCLEROSIS. REVISION OF 302 CASES. Felipe E, Tilbery C P, Moreira M A, Mendes; M F. From Departament of Neurology, Santa Casa of Sao Paulo, Brazil.

Many neurologic scales have been used in multiple sclerosis, but the authors don't have a consense about the best scale to evaluate the evolution and new relapses. Expanded Disability Status Scale (EDSS) is the most used. The authors analised the performance of two scales: EDSS and Neurologic Rating Scale (NRS), by Sipe et al, in 302 multiple sclerosis patients. The results showed NRS is more sensitive to determine clinical changes than EDSS in 22% of the analised cases. The changes of NRS occurred more in EDSS of 3,0 and 3,5.The authors made comments about these findings and suggest the use of these two scales in multiple sclerosis new treatment trials.

P436
MANUAL DEXTERITY IN NORMAL INDIVIDUALS AND THOSE WITH MULTIPLE SCLEROSIS, BOX AND BLOCK TEST. Mendes M F, Balsimelli S, Barao - Cruz A, Kjantor L, Tilbery C P. Neuropsychological Branch. Neurology Service. Santa Casa de Scio Paulo Medicine School. Sao Paulo, Brazil.

The manual dexterity is normally not assessed in the Standardized neurological examinations in patients with multiple sclerosis (MS) and frequently changes if this function interfers in the daily life. The authors standardized the box and block test of manual dexterity in normal patients and studied the same in patients with MS.Methods: 409 healthy volunteers (male and female) were selected with age 15-70 years old. The box and block test is expressed by the total number of cubes that the patient transported, in a period of one minute, with one of the hands over the partition of a hardwood box. After this, the same test was performed in 42 MS patients.Results: The normal subjects were subdivided in categories according to the age (10 years each), the Sex and the performance on the right and left hand. In the causes with MS there was 61,5% of alterations in the female patients and 51,7% in the male patients.Conclusions: The easily applied box and block test is also a quite easily reproducible instrument to be used in the evaluation of MS patients.

Pain & headache

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ATENOLOL IS EFFECTIVE IN THE PROPHYLACTIC TREATMENT OF MIGRAINE.Bolukbasi O*, Akyol A*, Ozmenoglu M**, Tekten T***Departments of Neurology* and Cardiology***, Medical Faculties of Adnan Menderes University(Aydin) and Department of Neurology, Medical Faculty of Karadeniz Technical University(Trabzon)*, Turkey.

Objective. To assess safety and efficacy of atenolol in the prophylaxis of migraine.Background. Beta-blockers are effective as long term prophylactic treatment of migraine. Reduction of brain catecholaminergic hyperactivity is the current hypotheses of therapeutic window. A selective, hydrophylic beta-blocker; atenolol, with its lower side-effect profile, may be better tolerated than other beta-blockers.Design/Methods In two tertiary care center of neurology, patients with migraine were recruited for a prospective, open label study between January, 1994 and November, 1998. According to International Headache Society Criteria, migraine subtypes, attack frequency/intensity and demographic datas were recorded. Other antimigraneous medications were stopped three weeks before the beginning of the study. Whole of the patients were evaluated with head magnetic resonance imaging and a detailed cardiological work-up. Patients consistent with the study inclusion criteria (95 women and 33 men aging 19 to 54) were started on 50 mg/day atenolol. After the first two weeks, the dose was increased to 100 mg/day. Patients are continued to taking atenolol at least six months and monthly follow-ups were done. Only sumatriptan were allowed to use in the periods of attacks. Changings if any in the frequency/intensity of attacks and tolerability of the drug were assessed. Results/Conclusions. Atenolol was generally well tolerated. The major complaint for discontinue to the study (9) was weight gain. Daytime hypotension were noted (5) but easily improved with the increase of salt in the diet. Overall decrease in the frequency and of attacks was higher than 70 % at the end of the first months and and 89% at sixth months. Effect of decrease in the intensity of attacks were noted even at the end of the first two weeks. Visual symptoms of four patients with retinal migraine were improved excellently with atenolol. It is concluded that atenolol is effective and well-tolerable in prophylaxis of any type of migraine even with visual symptoms

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EFFICACY OF MAGNESIUM, FLUNARAZINE AND AMITRIPTYLINE FOR THE PROPHYLAXIS OF MIGRAINE. Seref DEMIRKAYA, Okay VURAL, Erdal EROGLU, Fatih OZDAG, Yasar KUTUKCU, Zeki GOKCIL, Zeki ODABASI, Kemal HAMAMCIOGLU. Department of Neurology, Gulhane Medical School, TURKEY

Several types of drugs such as propranolol amitriptyline, and flunarazine are used in migraine prophylaxis. Circumstantial evidence points to the possible role of magnesium deficiency in the pathogenesis of migraine and has raised questions about the clinical utility of magnesium as therapeutic regimen in migraine.Objective: To compare the efficacy of magnesium with that of flunarazine and amitriptyline for the prophylaxis of migraine in a prospective, randomized, double-blind, placebo controlled study.Materials and methods: We studied ninety-two patients having had at least three significant headaches per month for the prior year. Their ages ranged from 22 to 54 years (mean 31.2 yrs). Those patients were divided into four

groups. First group, comprising of 24 patients, was given magnesium 296 mg (12 mmol) per day. Second group, comprising of 23 patients, was given flunarazine 10 mg per day. Third group, comprising of 22 patients, was given amitriptyline 10 mg per day. Last group, comprising of 23 patients, was given placebo. All patients were seen monthly during three months.Result: While the monthly frequency of migraine attacks was 4.2± 1.3 at the beginning of the study, it was found as 3.0±1.3, 3.5±2.1, 3.6±1,8, and 3.9±1.4 in magnesium, flunarazine, amitriptyline, and placebo treated patients respectively at the end of the first month. At the third month, it was 1.4±1.8 in magnesium treated group, 1.7±1.4 in flunarazine treated group, 1.9±1.6 in amitriptyline treated group, and 3.8±2.1 in placebo group.Conclusion: Although all the drugs mentioned above are effective in decreasing frequency of the attacks, magnesium has more effect than the others.

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MMPI PROFILES IN CHRONIC HEADACHE AMONG YOUNG GREEK MALES.Triantafyllou, N. Grigoriadis, G. Rizos, I. Demertzis, I. Milonas B' Univ.Department of Neurology, AHEPA Hospital, Thessaloniki, Greece

Evaluation of psychological state and personality structure is though to be of great importance for successful treatment of headache. In addition, there are strong indications for a population of patients that may be subjects to frequent headache. To assess the clinical and personality characteristics of patients with chronic daily headache, 33 young Greek male soldiers (25,5±7,1 year old) were examined and the Minnesota Multiphasic Personality Inventory (MMPI, Greek abbreviated version) was administered. All the patients included in the study had at least a two year history of headache, were not under any prophylactic or other treatment specific for headache and were in the army for at least 1 year. According to the International Headache Society criteria the patients were divided in two groups: 19 patients with Tension Headache (TH) and 14 with Migraine (M). All patients were evaluated within a period of two months. A Mann-Whitney U-test compared each of the 13MMPI scores of both groups of patients, with the mean value of the correspondent scores valid for the general Greek population of this age. Our analysis indicated that patients presented significantly higher scores at the hysteria scale (68,42% of TH and 71,4% of M patients) and the hypochondriasis scale (63,46% of TH and 85,70% of M patients). Only a small percentage of patients had high score in the depression scale (15,78% of TH and 21,42% of M patients). The scores (mean value ± SD) were as following: for hysteria, TH: 19,15±5,17, M:21,5±5,17 vs 13,51±4,25 for the general population and for hypochondriasis, TH:28,15±6,32, M:28,42±13,23, vs 21±4,73 for the general population. Our results further support previous studies where hysteria and hypochondriasis were the main characteristics of chronic headache patients, suffering either from TH or M. An interesting finding in our study is the small score of the depression scale in the majority of patients, since, due to the stressfull environment of the army, the opposite would be expected.

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MIDAS QUESTIONNAIRE: TEST-RETEST RELIABILITY OF THE FIRST ITALIAN FORM.D. D'Amico, A. Ferraris, M. Leone, L. Grazzi, G. Bussone. Neurological Institute "C. Besta", Via Celoria, 11 - 20133 Milan, Italy

The Migraine Disability Assessment Questionnaire (MIDAS) is a recently-developed and validated instrument for assessing the impact of Migraine on everyday life (Sawyer J, Edmeads J, Lipton RB, Stewart WF, Neurology 1998;50:A433-34). It is a simple but reliable test that assesses Migraine-related impairment of all daily activities. We performed this study to evaluate the reliability of the first Italian version of MIDAS, translated at our Headache Centre. We recruited 104 patients suffering from Migraine without aura. They were asked to complete MIDAS form during a consultation, and complete a second identical from at home 21 days later. Pearson's and Spearman's tests were used to assess test-retest reliability.In 67 (78%) of the 87 patients (83%) who completed the study, the disability grades assigned at the second compilation were the same as those assigned at the first test. Pearson's (r = 0.84) and Spearman's (r = 0.76) tests showed good test-retest reliability. The first Italian version of MIDAS is therefore satisfactorily stable, and prepares the way for a definitive Italian adaptation of the questionnaire.

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TREATMENT STRATEGIES IN CHRONIC DAILY HEADACHE WITH DRUG ABUSE. Licia Grazzi, Domenico D'Amico, Massimo Leone, Gennaro Bussone- Neurological Institute "C. Besta", Via Celoria, 11 - 20133 Milan, Italy

Analgesics abuse is a common problem with migraine patients and they always record an increases of frequency and instensity of pain attacks which induce much more use of analgesics. Treatment includes out patient care but often patients require in patients management in order to discontinue use of the analgesics. Pharmacological agents, behavior modifications, psychotherapy, dietary intervention may be necessary to treat the patients. This report shows the results obtained from 2 groups of abusers patients hospitalized for drugs withdrawal and then followed with regular meeting in order to determine the clinical improvement after withdrawal by hospitalizzation. The first group (Group A) was treated by pharmacological and relaxation training combined to biofeedback (BFB). For Group B a behavioral treatment was added to the pharmacological therapy.The purpose was to determine if BFB may reinforce the pharmacologic treatment and favour a faster clinical improvement. The results confirm a significant clinical improvement for both groups as we can see from the Pain Total Index decrease (PTI Group A pre 425(67.3; after 1 month 167(125.4; after 1 year 197.2(124.4 p pre vs 1 month 0.0001; pre vs 1 year p 0.0001; 1 month vs 1 year ns; PTI Group B pre 444.7(95.5; after 1 month 119.6(150.3; after 1 year 256(163.6; pre vs 1 month p 0.0001; pre vs 1 year p >0.0001; 1 month vs 1 year p 0.02). Our data seem to confirm the necessity that abusers have to be hospitalized for the withdrawal before beginning a new pharmacological approach. After the withdrawal there is a significant improvement of the headache condition and a stop of analgesics abuse in both groups. The significant decrease of PTI is probably due to the therapeutical approach, although it does not seem that biofeedback reinforces the clinical efficacy of the hospitalization and of the pharmacological treatment.

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LEFT VAGUS NERVE STIMULATION REDUCES EXPERIMENTAL MECHANICALLY INDUCED PAIN.Kirchner*, F. Birklein*, H. Stefan*, H. Handwerker+*Departments of Neurology and +Physiology, University of Erlangen-Nürnberg, Germany

Electrical stimulation of vagal afferents is known to moderate neural and behavioral responses to different painful stimuli in mammals. To investigate the effect of vagus nerve stimulation (VNS) on pain in humans we evaluated pain to mechanical stimuli in 3 patients who underwent left VNS as a treatment for medically refractary seizures.Mechanically induced pain was studied by applying tonic pressure using a pinch-device (8 Newton). Pain was quantified using a visuell analogue scale with 0 being no pain and 100 being the strongest pain imaginable. Pain rating was performed over 2 minutes of pinching. Patients were tested at three different timepoints: before begin of VNS treatment, at low current stimulation and after several weeks at higher current stimulation. Under stimulation conditions pain was assessed in stimulation on and off time, respectively. As controls 7 healthy volunteers were studied.When tested consecutively during VNS treatment, pain to mechanical stimuli in patients was reduced to 43-100 percent of the baseline value. No difference could be observed between on and off time pain rating. In controls pain rating remained unchanged in three consecutive sessions.Our data suggest that nociception in humans is altered by vagal influences. Since there was no difference in pain rating between on and off stimulation time, antinociception by VNS may rather be mediated by longstanding effects like neural plasticity or changes in transmitters.

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IDIOPATHIC HYPERTROPHIC CRANIAL PACHYMENINGITIS WITH DURAL CALCIFICATIONS. A TEN-YEAR FOLLOW-UP. K. Beauvais, O. De Marco, D. Baudet, T. Dufour, A. Hamlat, G. Edan, J.-F. Pinel. Rennes, France.

The hypertrophic pachymeningitis is a rare entity, quite often idiopathic; headaches, ataxia and cranial nerve palsies are the most common clinical manifestations. We report a new case with a 25 year history, characteristic because of calcifications, thrombosis of superficial venous sinuses and ineffective medical and surgical therapies. This 35-year-old man presented at the age of 10 a subacute episode (headaches, vertigo and vomiting), then a bilateral deafness. Headaches reappeared when he was 22. The CT scan showed diffuse calcifications of meninges, enhanced after injection. Magnetic Resonance Imaging and angiography showed thrombosis of the venous sinuses. Cerebrospino-Fluid and meningeal biopsy were inflammatory. He had papillar oedema (almost stabilized since 1992) and intermit-

tent diplopia, for which he received several therapy tests (steroids, acetazolamide, Non-Steroidal Anti-Inflammatory Agents, lumbo-peritoneal shunt, dura enlargement of the posterior fossa). Deafness was treated by cochlear implant. We discussed the nosographic position of this entity and the therapeutic possibilities, compared with previous literature.

Poster session 3

Clinical neurophysiology

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THE VALUE OF SOMATOSENSORY AND MOTOR EVOKED POTENTIALS IN PRE-CLINICAL SPONDYLOTIC CERVICAL CORD COMPRESSION.Bednarík J +, Kadanka Z +, Vohánka S +, Novotny O +, Surelová D +, Filipovicová D +, Prokes B *.

Previous studies have yielded conflicting data concerning the value of evoked potential parameters in the assessment of clinical relevance of cervical cord compression in clinically "silent" cases. A two-year follow-up prospective electrophysiological and clinical study was performed in patients with pre-clinical spondylotic cervical cord compression. The objective of the study was to assess the value of somatosensory (SEP) and motor evoked potentials (MEP) in the evaluation and prediction of the clinical course. Thirty patients with magnetic resonance signs of spondylotic cervical cord compression but without current clinical signs of myelopathy were evaluated clinically and using SEP and MEP during a 2-year period. Results. SEPs and MEPs documented subclinical involvement of cervical cord in 50% of patients with clinically "silent" spondylotic cervical cord compression. During a 2-year period clinical signs of cervical myelopathy was observed in one-third of patients with entry EP abnormality in comparison with no patient with normal EP tests. Conclusions. Combined SEPs and MEPs proved to be a valuable tool in the assessment of the functional relevancy of subclinical spondylotic cervical cord compression. Normal EP findings predict a favourable 2-year clinical outcome.

P445
THE RELATION BETWEEN THE PROGRESS OF DIABETIC NEUROPATHY AND THE INCIDENCE OF PERIPHERAL NERVE COMPRESSION. Mori I, Hasegawa O, Department of Neurology, Yokohama City University School of medicine, Yokohama, Japan

The incidence of the so-called double crush syndrome was investigated in diabetic neuropathy, where the carpal tunnel syndrome appears frequently. Three hundred and three cases of diabetic neuropathy were examined by means of motor nerve conduction studies and their lower extremity polyneuropathy index (LPNI) was recorded as the mean value of the normal value (of 6 indices) over two nerves. The average of their LPNI was 82.9%. The distal latency ratio (DLR) was determined by comparison of the distal motor latency of the median nerve with that of the ulnar nerve. DLR could represent the conduction delay across the carpal tunnel. The patients' DLR (1.44±0.24) was higher than the normal value (1.29±0.10). About 30% of the diabetics had abnormal DLR values, especially the women whose value was as high as 39%. Among the patients with a very low LPNI (< 70%), 44% had abnormal DLR values, and among those with a moderately low LPNI (from71% to 85%), 28% had abnormal DLR values. This means that patients with advanced diabetic polyneuropathy are likely to have an electrophysiological carpal tunnel syndrome. Consequently, focal nerve damage could be induced by the advanced diabetic polyneuropathy.

P446
CARDIOVASCULAR AUTONOMIC EVALUATION IN NEUROLOGICAL DISEASES BY MEANS OF TIME AND FREQUENCY DOMAIN ANALYSIS. D Linden, RR Diehl, Essen, Germany

The most popular test of autonomic cardiovascular function is the heart rate response to deep breathing (HR_{DB}) which represents a time domain analysis of respiratory-related heart rate oscillations at a frequency of 6 cycles per minute (cpm). The HR_{DB} is a measure of vagal outflow to the heart but depends on breathing characteristics and the associated ABP oscillations. We, therefore, perform spectral analysis of both HR and ABP oscillations and calculate the transfer magnitude from ABP to HR (GAIN = HR/ABP in bpm/mm Hg) which is a corrected measure of vagal outflow. Analogous calculations may be done for the respiratory-related oscillations during normal breathing (~10-15 cpm). Moreover, non-respira tory oscillations in ABP and HR at 5-6 cpm (Mayer waves) give a quanti tative measure of sympathetic vasomotor activity and vagal and sympa thetic cardiomotor activity, respectively. The transfer magnitude of th Mayer waves represents an excellent non-invasive measure of barorefle sensitivity. In idiopathic Parkinson's disease (IPS), for example, thes methods provided evidence that there is no real vagal dysfunction but ab normal breathing leading to reduced heart rate oscillations. In addition, di minished Mayer waves indicated reduced sympathetic activity at the leve of the heart and the vessels. In amyotrophic lateral sclerosis, time domai tests gave normal results. Spectral analysis showed vagal withdrawal dur ing normal breathing and reduced baroreflex sensitivity. We conclude tha spectral analysis provides important pathophysiological information anc therefore, adds considerably to the autonomic evaluation in normal an abnormal conditions.

P447
AN APPLICATION OF LUMBILICAL AND INTEROSSEI RECORDING OF NERVE CONDUCTION STUDIES. Hasegawa O, Matsushita Y Iino M, Matsumoto S, Mori I, Department of Neurology, Yokohama City University School of Medicine, Yokohama, Japan

Lumbilical (L) and interossei (I) recording is known to be a simple an sensitive method in detecting the existence of carpal tunnel syndrome Nevertheless, by this method not only compound muscle action potential (CMAPs) from L and I, but also sensory nerve action potential (SNAP from the digital nerve (N) can be recorded. These characteristics enable u to evaluate median and ulnar neuropathies. Sixteen healthy individuals, 1 patients with carpal tunnel syndrome, 3 patients with ulnar neuropathy a the elbow, 6 polyneuropathy and 3 amyotrophic lateral sclerosis patient were examined using this method. Stimulations were given at 9 cm proxi mal to the recording electrode. In patients with carpal tunnel syndrom prolonged latency difference (L-I), and reduction in N amplitude were ob served. Ulnar neuropathy patients presented decreased latency differenc (L-I). Every polyneuropathy patient demonstrated prolonged latency to L I and N, reduced amplitude in N. Patients with amyotrophic lateral sclero sis demonstrated reduction in CMAP amplitude from L and I. Amplitud of SNAP (N) (normal value; 7514V) was larger than those by conven tional antidromic or orthodromic sensory nerve conduction studies. Thi lumbilical and interossei recording, as it was designed to detect carpal tun nel syndrome, is useful in evaluating various types of neuropathies.

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SERIAL RECORDINGS OF NERVE CONDUCTION STUDIES IN VASCULITIC NEUROPATHY-Hasegawa O, Iino M, Matsumoto S, Kurita R, Mori I, Department of Neurology, Yokohama City University School of Medicine, Yokohama, Japan

Most of the multiple mononeuropathies are caused by vasculitis, in whicl main pathologic change is an axonal degeneration. In nerve conductior studies reduced amplitude of compound muscle action potential (CMAP and sensory nerve action potential (SNAP) with slight conduction slowing in selected nerves is a characteristic feature. We observed these findings ir 8 patients with vasculitic neuropathy. Progression of Wallerian degenera tion was serially evaluated in one patient; CMAP amplitude decreased ear lier than SNAP amplitude. In two patients an existence of conductior block at the tender point was demonstrated. These conduction blocks were resolved in several months. In the recovery period from axonal degenera tion delayed responses with extremely high stimulus threshold were noted which were supposed to be originated from regenerating fibers. These de layed responses were gradually normalized in their stimulus threshold anc conduction velocity, which raised the amplitude of CMAP. In the devel opment of Wallerian degeneration neuromuscular junction stops working first after the cessation of axonal flow. This is the reason why CMAP am plitude decreases earlier than SNAP amplitude. Conduction block may be caused by damaged sodium channel around the node of Ranvier. Regener ating fibers present slow conduction and high stimulus threshold, which were gradually normalized in a few years. We can observe these findings in patients with vasculitic neuropathies.

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ANKLE JERK, GASTROCNEMIUS-SOLEUS H-REFLEX AND ELECTRONIC ANKLE T-REFLEX CHANGE IN DIABETIC PATIENTS. Dae-Seong Kim and Kyu-Hyun Park. Department of Neurology, Pusan National University Hospital, Pusan, Korea

The ankle jerk abnormality is the most earliest objective sign in diabetics. However, the clinical grading of the ankle jerk is not objective because it is dependent to the examiner's subjective judgement. For the objective quantitation of the ankle jerk, both ankle T-reflex (ATR) and gastrocnemius-soleus H-reflex(GSHR) test can be used. However, their roles and relations in representing the status of the ankle jerk had not been studied in detail. The authors studied the ankle jerk, ATR and GSHR in 204 legs of 102 patients with diabetes mellitus and the results were analysed. Among the 114 legs with absent ankle jerk, the ATR and GSHR was obtainable in 22 and 29 legs respectively, revealing higher sensitivity of these tests in recording the minute reflex contraction of gastrocnemius muscle than clinical testing. However, on the other hands, the ATR and GSHR was defined as abnormal in 5 and 17 cases respectively among those with clinically normal ankle jerk. In revealing the reflex abnormality, the GSHR was more sensitive than ATR. In 8 cases, the GSHR was not obtained even though the ankle jerk was elicitable, while ATR was obtained in all.. Thus, GSHR seemed more sensitive than ATR in revealing subclinical abnormality of the ankle reflex arc, while the ATR is more reliable indicator of ankle jerk status itself.

P450
LONG-TERM CHANGES IN MOTOR CORTEX ORGANISATION AFTER SUBCORTICAL STROKE.M Bymes, GW Thickbroom, BA Phillips, S Wilson, F L Mastaglia. Australian Neuromuscular Research Institute, Queen Elizabeth II Medical Centre, Nedlands 6009, Australia

We have previously shown changes in the topography of the motor projection to the hand in the first 4 wks after a subcortical stroke. In this study we used transcranial magnetic stimulation to investigate the long-term changes in the motor cortex in 7 patients (4M, 3F; age 17-64 yrs) with longstanding (6 mths-15 yrs) subcortical ischaemic lesions (internal capsule 5; striato-capsular 1; corona radiata 1) who had substantial or complete motor recovery. A motor evoked potential (MEP) was recorded from the abductor pollicis brevis (APB) muscle of the affected hand in all subjects but the motor threshold was increased on the side of the lesion in 4 subjects. The MEP amplitude was lower in the affected than the unaffected hand in 5 subjects (27-75%) and higher in 2 (216-267%). Corticospinal conduction times were normal in all subjects. Maps of the corticomotor projection to the affected APB were displaced in 6 subjects: 3 medio-laterally (interside difference 7-23mms cf 3 mms in normal controls); 3 anteriorly (15-21mms cf 7mms in controls). The findings indicate that there are persisting changes in motor cortex excitability and organisation after recovery of conduction in the corticospinal pathway. The map shifts suggest a process of reorganisation in the motor and premotor cortex which may have a role in the recovery of motor function after subcortical stroke.

P451
COGNITIVE EVOKED POTENTIALS VEP P-300 IN INDIVIDUALS EXPOSED TO LEAD-Vrca A, Restek N, Zagreb, Croatia

Cognitive evoked potentials VEP P-300 were determined in three groups of subjects exposed to lead. The first group consisted of 19 workers with long-term exposure to low concentrations of lead in dust during the manufacture of lead paint. The second group consisted of 11 workers with long-term exposure to high concentrations of lead in the working environment during the manufacture of car batteries and lead glass. The third group consisted of five people subacutely accidentally poisoned by consumption of homeopathic lead preparations intended for the treatment of bronchial asthma. The results of the investigation indicated that the latencies of the P-300 waves in each of the above groups were statistically significantly different from relevant laboratory standards and that in the first two groups latency and amplitude of the cognitive wave VEP-300 did not significantly depend on intensity but rather on the length of exposure. The level of exposure to lead was calculated by repeated determination of ALAD, EP and lead in peripheral blood.

P452
LEUKOARAIOSIS PROGRESSION AND VASCULAR RISK FACTORS. E Vicenzini, M Altieri, S Di Legge, D Tombari, C Mostardini, M Calabresi, V Di Piero, GL Lenzi.Dept. Neurological Sciences, Univ. of Rome, Italy.

Factors involved in the development of leukoaraiosis are still controversial. In a 3 years follow-up study of a cohort of 17 (60±6 yrs) healthy controls and 53 (63±9 yrs) chronic non-demented cerebrovascular patients we investigated the time-course of leukoaraiosis. MRI was performed at baseline and at follow-up. Leukoaraiosis was classified according to Fazekas' semi-quantitative scale, ranging from 0 to 3. An increase of at least one point was considered as a worsening; we therefore considered as exclusion criterion a leukoaraiosis score of 3. Subjects were divided into two groups, according to the leukoaraiosis score: a) those that did not show MRI changes (11 controls, 42 stroke patients); b) those that showed a worsening of the leukoaraiosis score (6 controls, 11 stroke patients). Among all the putative risk factors for leukoaraiosis, a significant difference between the two groups was observed only for alcohol consumption at follow-up ($p<0.04$). The percentage of alcohol retainers rose from 49% observed at baseline to 75% in those who did not show a leukoaraiosis development and/or progression, while no difference in the percentage of alcohol retainers was found in the group of those with a worsening of leukoaraiosis. These data may suggest that alcohol consumption retention might represent a protective factor for the development and/or worsening of white matter MRI abnormalities.

P453
SHORT-TERM OUTCOME IN "OLDEST-OLD" STROKE PATIENTS. M Altieri, V Di Piero, E Vicenzini, D Tombari, C Mostardini, S Di Legge, D Tombari, G Bruti, GL Lenzi. Dept. Neurological Sciences, Univ. of Rome, Italy.

We investigated predictive factors for short-term outcome in people over 75 years of age. One-hundred eleven elderly (>75 yrs) cerebrovascular patients consecutively admitted to our clinic were enrolled. The study protocol included: clinical and neurological examination, routine blood tests, EKG, neck vessels duplex-scanning, transcranial doppler, brain CT or MRI. Clinical diagnosis was classified according to Bamford criteria and scored by Unified Stroke Scale (USS). Disablement was defined as a score of 3 or higher on the Rankin Scale (RS). Out of the 111 patients (age 81.6± 4.75 yrs, range 75-97 yrs), 56 presented with a disabling stroke (RS≥3) and 17 died within the first month. The significant independent predictors of a disabling stroke were: age hypertension, level of consciousness and low USS score at admission, presence of a middle cerebral artery infarction and haemorrhagic transformation of the lesion. A logistic regression analysis showed that disability was mainly related to USS score at entry, the diagnosis of TACI, and age. These data shows that neurological presentation at admission is the main predictor of short-term stroke outcome in the oldest old. In addition in our cohort of stroke patients, age per se is an independent predictor of outcome.

P454
THE EFFECT OF FATIGUE ON AUTONOMIC AND COGNITIVE FUNCTIONS IN PHYSICIANS. Y. Balash, C.Klein, B.Mildorf Bar Zvi, L.Pollak, J.M. Rabey, Zerifin, Israel

Background: The effect of fatigue on the performance in physicians on duty has not been sufficiently studied. Aims: To evaluate the effect of fatigue on autonomic functions and cognition in physicians after duty for 24 hours. Methods: We examined weight, changes of pulse rate and blood pressure (BP) to load (10 or 20 squats in women and men, respectively), subjective fatigue symptoms (Japan Society for Occupation Health Scale; JSOHS), calculation, and Raven's color progressive matrices tests (CPMT), P300 - potentials (50 target tones among 250 non target ones), and ability to fix gaze on a specific point during the P300 registration in 10 healthy physicians before and after night duty. Results: After duty weight decreased by 0,65 kg ($p=0.013$), and pulse rate was slowed by 14 beats/min ($p=0.03$). BP did not changed. Emotional symptoms and general languishment (according to JSOHS characterizations) worsened ($p=0.02$ and $p=0.03$, respectively). Mean P300 latencies were prolonged (333.2 ms vs. 318 ms; $p=0.003$) while increased mistakes in gaze fixation were scored. Calculation tasks and CPMT before and after duty did not changed. The increasing of P300 latencies correlated negatively with the amount of mistakes in CPMT before and after duty (Pearson coefficients 0.778 and 0.801, respectively). Conclusions: Although P300 latencies seem to be a good physiological marker of fatigue, they do not necessarily correlate with some cognitive functions (calculation, visual recognition).

P455
NOVEL ELECTROCHEMICAL FREE RADICAL DETECTION FOR DETERMINATION OF REAL TIME SUPEROXIDE AND NITRIC OXIDE LOCAL CONCENTRATIONS IN NEUROLOGICAL IN VIVO

MODELS-SJ Read, AA Parsons, AJ Hunter-Neurosciences Research, Smithkline Beecham Pharmaceuticals, New Frontiers Science Park, Harlow, Essex, UK.

Pathophysiological variations in nitric oxide levels are accompanied by a dynamic interplay with superoxide (Stamler 1994). This study describes electrochemical in vivo nitric oxide and superoxide detection techniques in the cortex of craniotomised, anaesthetised, rats (n=3). Measurement of superoxide comprised the immobilisation of cytochrome c to a gold electrode using a thiol linker (3,3'-dithiobis(sulphosuccinimidylpropionate). Superoxide detection is achieved by monitoring cytochrome c re-oxidation current at +100mV (versus a Ag/AgCl reference electrode) (Manning et al., 1998). The sensor electrode and reference electrodes were placed above the cortex surface in an aqueous layer. Electrochemical NO measurement used Model NO-501, NO monitoring device, Inter Medical (UK) (Read et al., 1997). Increasing cortical NO levels by systemic infusion of the NO donor glyceryl trinitrate at 2 µg/kg/min i.v. for 30min increased local NO to 141 + 13 % of baseline. NO levels remained elevated above baseline for a further 30min until the conclusion of the experiment at which time point nitric oxide levels were 110 + 8% of baseline. In all animals, superoxide levels were inversely related with nitric oxide levels. Infusion of GTN induced a supression of superoxide levels below baseline which was associated with increasing nitric oxide levels to 48 + 14% of baseline. Superoxide concentrations remained depressed to completion of the experiment, at which time point levels were 63 + 15% of baseline. These studies demonstrate that electrochemical NO and superoxide detection techniques are readily applicable to in vivo neurological models. Manning et al., (1998) Free Rad. Bio. Med. (24) 1304-1309.Read et al., (1997) Neurosci. Letts. (232) 127-30.Stamler (1994) Cell (78) 931-36.

P456
THE EFFECT OF THE POSTURE AND THE POSTURAL FIXATION IN REPETITIVE NERVE STIMULATION TEST.Mori I, Hasegawa O, Department of Neurology, Yokohama City University School of Medicine, Yokohama, Japan

Repetitive nerve stimulation (RNS) test is recognized as being useful in the diagnosis of myasthenia gravis. Normal twenty median nerves were stimulated with 120% of supramaximal intensity. Compound muscle action potential (CMAP) was recorded with the electrode on the abductor pollicis brevis. In a single stimulus the amplitude of CMAP in the passive and voluntary flexion position of the thumb were increased by 8% and 34% compared with that of the middle-position. Nevertheless, the negative potential areas (NPA) of CMAP slightly decreased by 2% and 5%, because of the briefer duration by 10% and 30%. In RNS test the size of the first 4 CMAPs in the free condition was compared with in the fixed by the examiner's hand. With 10 and 20/sec stimulation, NPA decreased by 5% and 12% by the comparison of the fourth value with the first, though the amplitude increased by 9% and 24%. In the fixed with 20/sec stimulation, the increase of amplitude diminished to 18% and the decrease of NPA diminished to 4%.. Incremental response at high rate stimulation was a classical clinical findings, however, in our study against the literature, NPA decreased while the amplitude increased, which may relate to the briefer duration. Consequently, besides synchronization, the position change increasing the elasticity of muscle could play a role in the incremental response. The effect of fixation demonstrated this suggestion.

P457
QUANTITATIVE EEG (EEGQ) IN HEAD TRAUMA. Saggese J., Gandolfo C., Povedano G. Churruca Hospital. Buenos Aires, Argentina

Traumatic injury to the brain is a significant health problem and the most common cause of traumatic death and disability. Even minor head injury can lead to significant disability preventing patients to return to their jobs. In order to determine EEGq sensitivity to detect disturbances in patients with postraumatic complaints we design a a clinical-neurophysiological prospective study.We evaluated 26 patients (9 females mean age 45.6 ± 24.54years and 17 males mean age 38.54 ± 14.95 years, p: ns) through a short questionnaire about complaints features, CT scan, MRI and EEGq.We asked for headache, depression, hypomnesia, dizziness, seizures and mood disturbances. We also considered head trauma side and its evolution time.In EEGq, relative power for alpha, theta, delta and faster frequencies (beta 1 + beta 2) in F3 F4, P3 P4, O1 O2, T1 T2, T3 T4 and T5 T6 leads were analized.We found that depression was significantly associated to higher Delta rhythms in F3 (p=0.02) and mood disturbances to lower alpha rhythms in O2 (p=0.03)Hypomnesia was related to Delta and Theta increase and Alpha decrease in T4, T6, O2 y F4 (p=0.001).Regarding trauma side, right side injuries were related to Alpha power diminution in P4 (p=0.03) and Delta power raise in T4 (p=0.03) and T6 (p=0.01), but not with CT scan findings.Our results suggest that EEGq is a usefull tool offering a biologic measurement to redeem postraumatic complaints from it current subjectivity.

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NEUROPHYSIOLOGICAL EVALUATION OF THE ACOUSTIC SYSTEM AFTER DIAGNOSTIC LUMBAR PUNCTURE. Papathanasopoulos P (1), Flabouriari K (1), Tsintzos S (2), Papapetropoulos Th (1), Papadeas E (2). Neurological Clinic (1) and Otoryngology Head and Neck Clinic (2), University of Patras, Greece.

The aim of this study is to examine probable hearing impairment after diagnostic lumbal puncture (LP).50 patents who unterwent lumbar puncture for neurological causes have been included in our study.All patients have been examined with audiogram and brainstem auditory evoked potentials (BAEPs) before LP.10 out of 50 patients wno reveiled subclinical episodes of tinnit~us after LP were examined 1 day after LP and one month later Witn audiogram and BAEPs. 7 out of 10 patients revealed hearing impairement in low and median frequencies (5 out of 10 in both sides and 2 out of 10 unilaterally). 3 out of 10 in one month follow up had normal audiogram, 2 out of 10 had remarcable recovery and 2 out of 10 showed no change. The BAEPs had normal latencies in waves 1,III and V but 5 out of 10 had inter-ear difference prolongation more than 0,4msec for wave 1 latencies one clay after LP.At conclusion after LP 1-3% reveal temporary hearing loss because of problems in the endolemphatic flow(patent cochlear aqueduct allows loss of perilymphatic fluid into the cerebrospinal space.)

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REINNERVATION AFTER TRAUMATIC PERIPHERAL NERVE LESIONS IN UPPER LIMBS-AN ELECTROPHYSIOLOGICAL STUDY. Schlotter, B[1]; Dunkel, S[1]; Walter, M.C[1]; Stützle, H[2]; Stock,W [2]; Müller-Felber, W[1] - [1]Friedrich-Baur-Institut, Neurologie.[2]Handchirurgie und Plastische Chirurgie, LMU München

The aim of this study was to investigate the electrophysiological outcome after surgery of traumatic peripheral nerve lesions in upper limbs. Electrophysiological investigations of motoric and sensory nerves were done after a period of max. 8 years. years. Nerve conduction velocity (NCV), distal latency (DL) and amplitude were determined. In all cases the damaged nerve was compared to the intact opposite side. Half of the patients underwent needle-electromyography (EMG). Up to now 37 patients are included (mean age 41 years, range 4 - 73 years). In only two patients an interponate of the N. suralis was implanted, all others received a primary nerve suture.First results show normal NCV in only 15 % of the patients. There is an elongation of DL in 77 % of motoric nerves and in 65 % of sensory nerves. NCV is decreased in 89 % of motoric nerves even proximal to the lesion-site and in 93 % of the sensory nerves. Amplitudes are reduced significantly with an accentuation in sensory nerves. The EMG revealed spontaneous activity in 3 out of 30 nerves (time after surgery 2.2 – 5.3 years). Maximal voluntary contraction revealed neurogenic configurated motor action potentials resulting in a reduced interference pattern in about 83.3 % of the examined muscles. EMG was normal in 4 patients.

P460
A STEADY-STATE RESETTING INDUCED BY TRANSCRANIAL MAGNETIC STIMULATION IN SECONDARY Orthostatic Tremor. B.Legros[1], F.Setta[2], J.Jacquy[3], E.Godaux[4], M.Manto[1]Neurologie, Hôpital Erasme, Bruxelles, [3]CHU-Charleroi, [4]Neurosciences Department, University of Mons, Belgium-[2]Clinica Neurologica II, Universita La Sapienza, Roma-Italy

Orthostatic tremor (OT) is characterized by high frequency burst firing in weight-bearing muscles. In primary orthostatic tremor, transcranial magnetic stimulation (TMS) does not reset tremor. We investigated effects of TMS in OT associated with cerebellar cortical atrophy (CCA). Three patients (1 man, 2 women; age: 49, 62, 64) exhibited a pancerebellar syndrome associated with pancerebellar atrophy on MRI. Surface EMG recordings showed OT with 14 Hz, 15 Hz and 14Hz frequency, respectively. TMS was applied using angled figure-eight coil for lower limbs, which was positioned over vertex. Quadriceps EMG activity was recorded. Resetting index was evaluated according to method described by Lee and

Stein (Ann.Neurol.1981;10:523-531). Stimulus delay after EMG burst was 25%, 30%, 40%, 50%, and 60% of average cycle length. Differences in timing (d1,d2,d3,d4,d5) between measured bursts and predicted bursts for each of five bursts after TMS were calculated. Relations between stimulus delay and differences in timing (d1 to d5) was calculated by linear regression analysis. To distinguish transient resetting from steady-state resetting, ratios of regression line slope obtained for d1 was divided by regression line slope obtained for d5 ($I^{st}/5^{th}$ ratio). Regression analysis demonstrated that relations between stimulus delay and differences in timing were linear with average slope of 0.72, which is in favor of resetting of tremor. $1^{st}/5^{th}$ ratio was 1.07, suggestive of steady-state resetting. In conclusion, there is steady-state resetting in OT associated with CCA, indicating an important role of motor cortex in pathophysiology of this tremor.

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GALVANIC VESTIBULAR STIMULATION IN FMRI: DIFFERENTIATION OF VESTIBULAR, AUDITORY, AND NOCICEPTIVE CORTEX AREAS. S. Bense[1], Th. Stephan[1], T. A. Yousry[2], Th. Brandt[1], and M. Dieterich[1]. Departments of [1]Neurology and [2]Neuroradiology, Klinikum Grosshadern, Ludwig-Maximilians-University Munich, Germany

In a previous fMRI feasibility study using FLASH sequences galvanic stimulation of the mastoids activated three different sensory systems in the insula-thalamic region: the vestibular, the auditory and the nociceptive systems. The aim of this study was to locate the vestibular effects of galvanic stimulation and differentiate these activation areas from those of the auditory and nociceptive systems when examining the whole brain. Six right-handed volunteers were examined during galvanic vestibular stimulation with fMRI using an EPI sequence (Siemens Vision 1.5T) as well as under two control conditions: (1) nociceptive (electric stimulation at the C5/C6 level of the neck) and (2) auditory stimulation. Voxels above a Z-score of 3.00 were considered significant (SPM96 software). Galvanic stimulation caused significant activation of the parietal cortex (BA 40) and the prefrontal cortex (BA 46), the anterior insula (adjacent to the inferior frontal gyrus), the posterior insula (PIVC), the thalamus, the medial parieto-occipital visual area (BA 19/37; MT/MST), and areas corresponding to the medial frontal gyrus (BA 6, 9). Moreover, the vestibular galvanic stimulus activated the caudate nucleus, putamen, midbrain, and the medial part of the insula. Acoustic stimulation led to a broad activation in the transverse temporal gyrus, postero-laterally to the vestibular activation in the posterior insula or a small activation in a region of intersection between the vestibular and the auditory areas located at the posterior border of the insula. When comparing galvanic versus nociceptive stimulation, a remainder of activity was located in the anterior insula, partly in the medial insula, the posterior insula, as well as in the parietal lobe (ocular motor areas MT/MST and parietal eye field). Thus, "pure" galvanic vestibular stimulation elicited activation in the anterior, medial, and posterior parts of the insula (including the human homologue of the parieto-insular vestibular cortex), the motion-sensitive area MT/MST, and areas in the parietal cortex. These could be clearly differentiated from activation areas induced by nociceptive and acoustic stimulation.

Cerebrovascular disorders

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CAROTID STENTING: OUR EXPERIENCE. Pappadà G, Marina R, Fiori L, Sganzerla EP, Gaini SM, Frattola L.Monza- ITALY

The way to treat carotid stenosis is up to now controversial. A conclusion has not still reached about the indication for treatment of moderate stenosis and a further discussion begins about a new kind of procedure. Biocompatibility of materials and vascular navigation allow endovascular approach to carotid plaque. Endovascular technology has improved rapidly in the recent years from PTA (percutaneous transluminal angioplasty) alone, then PTA plus Palmaz stent and, finally, with the positioning of a self-expanding stent. In literature, restenosis, radiation arteritis, FMD and stenosis at the origin of common carotid, subclavian and vertebral artery are believed as absolute indication to endovascular treatment. Other situations, such as contralateral thrombosis, high bifurcation, short and thick neck, serious systemic diseases (BPCO or renal insufficiency), intimal dissection or ulcerated plaque may be considered for stenting too. A retrospective, not controlled, analysis of 2591 cases treated with Palmaz or Wallstent, showed a perioperative stroke/death rate of 5.8%. During the two last years we performed 25 endovascular procedures in 25 patients. Before angiography, all patients underwent echo-color-Doppler evaluation to study the morphology of the plaque. Indications to stenting were restenosis, ulcerated plaque without haemodynamic effect and common carotid and subclavian artery origin. We observed transient neurological complication in 2 patients; no case of stroke or death occurred. We believe that much must be still done before comprehending the indication of this procedure.

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CEREBRAL VENOUS THROMBOSIS AND PROTHROMBIN GENE G20210A MUTATION. Verdelho A*, Ferro JM*, Palmeiro A**, Antunes C***Neurology Department, Hospital Santa Maria, Lisboa **Hematology Lab., Coimbra University Hospital, Coimbra Portugal

Background: The prothrombin gene variant G20210A has been described as a risk factor for deep vein thrombosis. More recently, this mutation has been associated with cerebral venous thrombosis, although all reported cases had other concomitant risk factors. Case reports: We describe a 33 years old woman, with no previous vascular nor thrombotic risk factors, who was admitted with drowsiness and bilateral focal signs. MRI showed thrombosis of superior longitudinal, lateral and sigmoid rigth sinus.The father had deep venous thrombosis 3 years before. One year later, the 29-year-old sister of the proband, developed massive deep venous thrombosis, when she was 8 months pregnant. Laboratory investigations showed elevated anticardiolipin antibodies titer in the proband. Prothrombin activity was in the normal range in the 3 patients. Prothrombin gene mutation G 20210A was detected in the 3 patients. Factor V Leiden and other prothrombotic conditions were negative in all cases.Discussion: This familiar cases of cerebral and deep venous thrombosis confirm the role of prothrombin gene mutation G 20210A as predisposing factor for these patologies.As the presence of more than one thrombofilic factor (in the reported case, prothrombin G20210A mutation and anticardiolipin antibodies) increases the likehood of a thrombotic event, it is recomended to screening for thrombotic genetic conditions, even when other vascular risks are present, and vice versa.

P464
THE ROLE OF DIFFERENT CASPASES IN THE RAT MODEL OF FOCAL CEREBRAL ISCHAEMIA.Krupinski J, Marti E, Lopez E, Ferrer I; Barcelona, Spain

Introduction.Apoptotic cascade requires activation of caspase cysteine proteinase family. Contribution of different caspases to cell death after ischaemic injury is not fully understood. Methods. Focal ischaemia was induced in rats by electrocautery of the proximal branch of the MCA following modified method initially described by Tamura. Animals were left for 0,30 min, 1,4, 8,12,24,48hrs and 4 days after the MCA occlusion. Antibodies to caspases (C-1,C-2,C-3, C-6,C-8) were purchased from Santa Cruz Lab. Results. There was increased immunoreactivity ipsilaterally in the areas corresponding to infarct and surrounding penumbra. Furthermore within 12 hours there was enhanced immunoreactivity within corpus callosum which persisted for 48 hours. The peak of immunoreactivity was between 12 and 24 hours for most of the caspases. In the contralateral hemisphere and in SHAM operated animals there was only weak staining for C-3 and C-8. C-1 immunoreactivity was very strong in the infarcted area in both neurones, astrocytes and microglia, and in penumbra mainly neurones were stained. C-2 immunoreactivity appeared in the affected areas at 12 h and continued at 4 days post-surgery. C-3 was more widely distributed than other caspases and staining was very selective for neurones in the infarcted areas and for microglia within penumbra. C-6 immunoreactivity was limited to neurones and some glial cells in the selected areas. There was generally less staining for C-8, but neurones within penumbra and infarct were strongly stained. Conclusions. This is the first study to compare caspase immunoreactivity at different time-points following brain ischaemia. Unlikely reported in previous studies caspases are differentially regulated after ischaemia and other caspases like C-6 and C-8 should be considered when planning therapeutical strategies.

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HOMOCYSTINURIA AND DEEP CEREBRAL VENOUS THROMBOSIS. A. Callén, A. Martínez-Yélamos, M. Jato, F. Rubio. Department of Neurology. C.S.U.Bellvitge. Barcelona. Spain

Introduction Homocystinuria is an inborn error of metabolism generally caused by a diminished activity of the cystathionine -synthase. It's an independent risk factor for vascular disease. Coincidence of homocystinuria and deep cerebral venous thrombosis (DCVT) is an uncommon associa-

tion. We present a patient with homocystinuria disclosed after DCVT.Case report.A 26 years-old female with headache, vomiting, severely withdrawn, right eye ptosis, left side hemiparesis and left Babinski's sign was admitted to our hospital. Her history was scoliosis, mental retardation, ectopia lentis and consanguineous parents. Physical examination demonstrated: dolichostenomelia, high-arched narrow palate, flat feet, arachnodactyly and skin hypopigmentation. Results The CT scan showed bithalamic hypodensities. MRI confirmed thrombosis of the internal cerebral veins and the vein of Galen, consistent with the diagnosis of DCVT. Plasma levels of homocysteine were elevated (138 µmol/l-normal < 9 µmol/l-), what is diagnostic for homocystinuria. We initiated intravenous heparin and later oral anticoagulants, pyridoxine and folate were introduced. Three months later homocysteine maintained at the same levels and 6 gr/day of betaine were added. Cystathionine -synthase activity in cultured fibroblast was 0, and it explained the lack of response to vitamin treatment. Conclusions Homocystinuria is a predisposing condition for DCVT. This is an uncommon association: only one similar case was reported. This is the first case of homocystinuria diagnosed secundary to DCVT We suggest that homocystinuria should be considered as a differential diagnosis when DCVT is present.

P466
MEDULLARY INFARCTIONS: CLINICAL AND MRI- TOPOGRAPHIC CORRELATION. Aref H., Ismail I., El-Nahas N., Hamido T. (Cairo, Egypt)

Several medullary stroke syndromes have been described, however, only the medial medullary and lateral medullary syndromes have gained acceptance. In the past, autopsy was the only way to study these syndromes. With the advent of new neuroimaging modalities especially MRI, clinico-topographic correlation in different medullary infarctions became possible.In this work we employed a standard protocol of MRI and MRA using Magnetom Vision 1.5 tesla (Siemens), to study eleven consecutive patients with medullary infarctions. Two levels were studied, one at the upper medulla at the level of the inferior olivary nucleus and the other at the lower medulla at the level of the pyramidal decussation. The infarctions among our patients showed the following topographic patterns: 2 medial medullary infarctions (MMI), 2 lateral medullary infarcations (LMI), 2 hemimedullary infarctions (HMI), 1 dorsolateral, 2 dorsal and 2 midlateral infarctions. The diversity of clinical picture was quite evident among cases with the same topographic pattern of infarction, which agrees with previous studies.Two of our patients were presented separately as case reports since they had unusual presentation of two rare types of infarcts. One case of MMI with pure motor stroke sparing the face and the other of HMI with failure of spontaneous breathing (Ondine's curse), with ipsilateral bulbar palsy and hemiparesis despite being fully conscious.

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DONEPEZIL FOR THE COGNITIVE SYMPTOMS OF MILD AD AND THE CONSEQUENCES ON CAREGIVER STRESS. Bernard Laurent, Michele Puel, Colette Fabrigoule, Jacques Touchon, Philippe Robert, Florence Lebert, Sylvia Goni, Bruno Dubois, Saint-Etienne, France.

Objectives: To evaluate the effects of donepezil on attention and memory cueing processes, often the first cognitive functions to be impaired in mild AD, and any associated consequences on caregiver stress. Methods: A 12-week, randomized, double-blind, parallel-group study involving 318 patients with mild AD (MMSE scores 18-26), of whom 66% received donepezil and the remainder placebo. Patient's visual memory and verbal fluency were measured at baseline and Weeks 8 and 12 using the Benton and modified Isaac tests, respectively.. Caregivers were evaluated at baseline and Week 12, using the abridged Relative Stress Scale (aRSS) on which change from baseline scores of –4 to +4 were possible. Results: At endpoint, the differences in the least-squares mean change from baseline scores of the actively-treated and placebo groups on the Isaac and Benton scales were 1.904 ($p < 0.001$) and 0.562 ($p < 0.05$) points, respectively, indicating improvement in visual memory and verbal fluency. At Week 12, the total mean change score from baseline on the aRSS was –0.506 for the caregivers of the donepezil-treated patients (significantly less stress), and 1.649 for the caregivers of the placebo group (significantly more stress; $p < 0.01$ for drug versus placebo in both cases). Conclusions: Donepezil administration over a 12-week period improves the cognitive symptoms of patients with mild AD, with an attendant reduction in the stress experienced by their caregivers.

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QUANTITATIVE MRI IN CADASIL: DISABILITY AND COGNITIVE PERFORMANCE CORRELATE WITH TOTAL LESION LOAD ON T1- AND T2/PD-WEIGHTED SEQUENCES. Dichgans M., MD (1), Filippi M., MD (2), Brüning R., MD (3), Iannucci G., MD (2), Minicucci L. PhD (2), Gasser T., MD (1), Yousry T. A., MD (5); (1) Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians-University, D-81377 Munich, (Germany); (2) Neuroimaging Research Unit, Department of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, 20132 Milan (Italy); (3) Institute for Diagnostic Radiology, and (4) Department of Neuroradiology, Klinikum Grosshadern, Ludwig-Maximilians-University, D-81377 Munich, (Germany).

CADASIL is an increasingly recognized hereditary form of small vessel disease caused by Notch3 mutations. MRI abnormalities have been found both in asymptomatic and symptomatic CADASIL individuals. We performed quantitative measurements on cerebral MRI in 64 CADASIL individuals. MRI lesions were quantified using a semi-automated segmentation technique based on local thresholds. MRI total lesion volume was significantly correlated with disability (Rankin scale) both on T1- and proton density (PD)-weighted images. There was a significant inverse correlation between total lesion volume and overall cognitive performance as determined by the Mini-Mental State Examination (MMSE). Age but not sex was correlated with lesion load both on T1- and PD-weighted images. There was no detectable influence of the Notch3 genotype on quantitative MRI variables. Longitudinal studies are now warranted to investigate whether quantitative MRI may be used as an adjunct outcome measure in future therapeutic trials in CADASIL.

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DIFFUSION-WEIGHTED IMAGING OF PATIENTS WITH RECENT CEREBRAL ISCHEMIA: A COMPARISON WITH CONVENTIONAL AND CONTRAST-ENHANCED MRI.Augustin M, MD (1, 2), Bammer R, Ph.D. (1, 2), Simbrunner J, MD, Ph.D. (2),Stollberger R, Ph.D. (1, 2), Hartung HP, MD (1), and Fazekas F, MD (1, 2).Department of Neurology (1), MR-Institute (2), Karl-Franzens University, Graz, Austria.

Purpose - Diffusion-weighted imaging (DWI) depicts signal alterations from focal ischemic damage rapidly and may help to delineate recent cerebral ischemia even beyond the acute phase. We attempted to determine this contribution in comparison to conventional and contrast enhanced (CE) MRI.Methods – Navigated DWI with interleaved echo planar imaging was performed in a consecutive series of 57 patients (mean age 66 +/- 14 years) after suspected recent cerebral ischemia. Time between ictus and MRI ranged from 1 -21 days (mean 6.8 +/- 5 days). 0.1 mmol/kg Gadolinium-DTPA was administered in 29 patients.Results - DWI clearly delineated recent ischemic damage in 43 (75.4%) patients versus 35 (63.2%) with lesions identified or suspected on conventional T2w-series. Adding evidence for lesion multiplicity or clinically unrelated recent lesions DWI provided information not accessible with T2 in 17 patients. Recent ischemic lesions were also more often seen by DWI than on CE-scans (20 versus 13 patients). Diagnostic contribution of DWI was more likely in the first week of stroke and in patients with small lesions or pre-existing ischemic damage. False negative DWI occurred in three patients.Conclusion - Ischemic damage is better shown on DWI than on conventional and contrast- enhanced MRI not only in the acute phase but throughout the first week after stroke onset. Imaging protocols for subacute cerebral ischemic lesions should include DWI.

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FREQUENCY AND LOCATION OF MRI DETECTED MICROBLEEDS (MB) IN PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE.G.Roob, A.Lechner, R.Schmidt, E.Flooh, H.P. Hartung, and F.Fazekas - Department of Neurology and MR Institute, Karl-Franzens University Graz, Austria

Background and goals: Hemosiderin sensitive MRI sequences have been shown to detect clinically silent microbleeds (MB) in patients with spontaneous intracerebral hemorrhage (ICH) and in small patient groups their location appeared suggestive of specific types of small vessel disease such as cerebral amyloid angiopathy. We now attempted to confirm specific patterns of MB distribution in a larger clinical series.Methods: We obtained gradient echo T2* - weighted scans on a 1.5T MR system in 109 consecutive patients with ICH. They were 50 women and 61 men in an age range of 22 to 91 years (mean 64.6 yrs.) Results: MB were seen in 59 (53%) patients and ranged in number from 1 to 90 lesions (median 2).. Most often MB were seen in various parts of the brain and their location was cortico-subcortical in 43 patients, in the deep white matter in 12, the basal ganglia and thalami in 41, in the brainstem in 24 and in the cerebel-

lum in 23 patients, respectively. MB were associated with significantly higher rates ($p < 0.005$) of extensive white matter hyperintensities, lacunes, old bleeds and with hypertension. These relations were independent of MB distribution. However, there was a trend for a regional association between MB and the site of the clinically apparent hematoma.Conclusion: MB can be detected in more than half of patients with ICH. Their wide distribution does not allow to identify specific patterns so that they appear to be quite universal markers of various types of bleeding prone microangiopathy.

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NEUROLOGICAL COMPLICATIONS IN PATIENTS WITH IMMUNE-MEDIATED HEPARIN-INDUCED'- THROMBOCYTOPENIA. C. Pohl, MD; U. Harbrecht*, MD; A. Greinacher**, MD; P. Harifland*, XM; T. Klockgether MD

Objective: To evaluate neurological complications in patients with immune-mediated heparininduced thrombocytopenia (HIT) with respect to incidence, clinical characteristics, diagnosis and therapy. Methods: 105 consecutive patients with immune-mediated HIT were studied retrospectively over a period of 10 years for the occurrence of neurological complications. Diagnosis of HIT was based on established clinical criteria and confirmed by detection of heparin-induced antibodies using functional and immunological tests.Results: Ten of the 105 patients (9,5%) presented with neurological complications, six of them suffered from ischemic cerebrovascular events, three from cerebral vein thrombosis and one had a transient confusional state during high-dose heparin administration. No patient suffered from primary intracerebral hemorrhage. Relative mortality of the group was 50% and was significantly higher (Chi square $p < 0.01$) than in HIT without associated neurological complications (12%). In three patients neurological complications preceded thrombocytopenia. There was a high coincidence of HITassociated cerebral ischemia with other thrombotic manifestations in arteries and veins (80%).Conclusion: Neurological complications in patients with HIT are relatively rare, however associated with high a comorbidity and mortality. HIT-associated neurological complications present with a wide spectrum of clinical symptoms due to cerebrovascular ischemia, cerebral vein thrombosis and acute reactions to high-dose heparin administration. HIT should always be considered in patients developing cerebrovascular thrombosis and unexplained cognitive disturbances during heparin administration even in case of normal platelet count. Diagnosis of HIT requires immediate cessation of heparin treatment and anticoagulation using the currently most satisfactory therapeutic alternatives danaparoid or r- hirudin.

P472
ECHO CONTRAST AGENTS IN EXTRA- AND TRANSCRANIAL COLOR-CODED DUPLEX ULTRASONOGRAPHY OF THE POSTERIOR CIRCULATION. Bartels Eva, Depart-ment of Neurology, Hospital Bogenhausen, Munich, Germany.

The purpose of this study is to present the diagnostic utility of echo contrast agents (CA) in the evaluation of the vertebrobasilar system with extra- and transcranial color-coded duplex ultrasono-graphy (DU). Methods: 36 patients (mean age 63 years) with verteb-robasilar ischemia were examined with a color-coded imaging system (Acuson 128 XP 10). For the CA study 2.5 mg Levovist (300 mg/ml) was administered. In 30 pat. the results were controlled with MRA, in 6 pat. with DSA. Results: Contrast enhanced DU revealed hypo-plasia of the vertebral artery (VA) in 8, proximal stenosis (ST) of the VA in 5, intracranial ST of the VA in 4, proximal occlusion of the VA in 5, distal occlusion of the VA in 4, dissection of the VA in 2, ST of the basilar artery (BA) in 3, dissection of the BA in 1 and no pathological findings in 4 pat.. Using CA agents BA could be imaged deeper than by native DU (9.6 cm ± 1.4 cm). Conclusion: Echocontrast agents increase the diagnostic utility of the DU in patients with vertebrobasilar ischemia.

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EARLY DETERMINANTS OF LONG-TERM PROGNOSIS IN DIFFERENT CLINICAL STROKE SYNDROMES. A. Slowik, A. Szczudlik, U. Wyrwicz-Petkow, K. Kasprzyk, W. Turaj, J. Pera, T. Dziedzic. Department of Neurology, Jagiellonian University, Krakow, Poland

Objective: To determine early predictors of one year survival in different clinical stroke syndromes: TACS (total anterior circulation syndrome), PACS (partial anterior circulation syndrome), LACS (lacunar syndrome) and POCS (posterior circulation syndrome). Design/Methods: From January 1994 through January 1997, a consecutive cohort of patients with a CT and/or autopsy verified stroke was enrolled into the study. The following data were collected within 48 hours after stroke onset: patient characteristics, risk factors, comorbidities, complications, and stroke severity as measured by the Scandinavian Stroke Scale (SSS). Patients were followed up every three months for a year or until death. Mortality rates in TACS, PACS, LACS and POCS were estimated by the Kaplan-Meier method. Cox proportional hazards regression was used to assess predictors of mortality in different clinical syndromes.Results: 804 patients were enrolled with the following characteristics: mean age: 69.512.4 years, 47.9% male, 81% first stroke. At admission TACS was diagnosed in 15.5% of patients, PACS in 44.5%, LACS in 28.1% and POCS in 11.8% of patients. Survival rates in patients with TACS were: 64 % at 30 day, 47 % at three months and 37 % at one year, in patients PACS: 80%, 69% and 60% respectively, in patients with LACS: 86%, 79% and 73% respectively and in patients with POCS: 61%, 59% and 53% respectively. Multivariate analysis showed that in patients with TACS independent predictors of death within a year after stroke were: age (hazard ratio=1.05[1.02-1.07], p=00.05), fasting glucose above 6.8 mmol/l (HR=2.23 [1.99-2.47], $p < 0.05$), white blood cells count (HR=1.00008 [1.00003-1.0001], $p < 0.05$), and body temperature above 37.5 deg. C (HR=2.65 [2.06-3.24], $p < 0.05$); in patients with PACS: age (hazard ratio=1.05[1.03-1.07], $p < 0.05$), fasting glucose above 6.8 mmol/l (HR=2.02 [1.65-2.39], $p < 0.05$), and body temperature above 37.5 deg. C. (HR=1.70 [1.30-2.10], $p < 0.05$); in patients with LACS: age (hazard ratio=1.05[1.02-1.08], $p < 0.05$), fasting glucose above 6.8 mmol/l, (HR=2.61 [2.13-3.09], $p < 0.05$), white blood cells count (HR=1.0001 [1.00002-1.0002], $p < 0.05$) and in patients with POCS: fasting glucose >7.8 mmol/l (hazard ratio=4.2 [3.83-1.45], $p < 0.05$) and white blood cells count (HR=1.0001 [1.00009-1.00013], $p < 0.05$). Conclusion: Patients with TACS, PACS, LACS and POCS have different short- and long-term prognosis, but similar prognostic predictors.

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LIPOPROTEIN (A) IN STROKE: RELATION TO THE CLINICAL COURSE AND OUTCOME. A. Szczudlik, M. Rudzinska, A. Slowik, W. Turaj, U. Wyrwicz-Petkow, K. Kasprzyk, T. Dziedzic, J. Pera. Department of Neurology, Jagiellonian University, Kraków, Poland

High serum Lp(a) level is a risk factor for myocardial infarction and ischaemic stroke. The aim of the study was to evaluate a relation between serum Lp(a) levels and clinical course and outcome in ischaemic stroke patients.Material and Methods: Consecutive ischaemic stroke patients admitted within 24 hours after stroke onset and age- and sex-matched control subjects without stroke entered the study. The following data were collected: patient characteristics, risk factors, clinical stroke classification, presumed aetiology, comorbidities, complications, stroke severity as measured by the Scandinavian Stroke Scale (SSS) as well as Lp(a) serum levels determined on the first or second day of stroke. Three months after stroke blood sampling for Lp(a) was repeated in 62 (68%) survivors. Patients were followed up for three months or until death.Results: 104 patients with acute stroke were enrolled with the following characteristics: mean age, 71.9+ 10,2 years, 47.6% female. Patients were subdivided according to a clinical stroke classification: TACI (11%), PACI (48%), LACI (31%) or POCI (4%) and classified as having cardioembolic (26%), large vessels disease (46%), small vessels disease (24%) and undetermined cause stroke aetiology (4%). There were no significant differences in median Lp(a) values between stroke patients and control subjects: 8,3 (3,4-22,3) mg/dl vs. 6,35(3,6-15,5) mg/dl. Increased Lp(a) levels (>=30 mg/dl) in acute stroke patients was found in 18.3% of stroke patients and in 15.0% of controls. Patients with increased Lp(a) levels had significantly more frequent history of myocardial infarcts prior to stroke than patients with normal Lp(a) levels and control group (36.8%vs. 7.1% vs. 8.6%, respectively, $p < 0.05$) and atrial fibrillation (47.2% vs. 21.2% vs. 4.3%,respectively, $p < 0.05$). Increased Lp(a) level was also related to the clinical diagnosis of TACI ($p < 0.05$). No relation was found between Lp(a) levels and presumed cause of stroke, CT findings, stroke severity and 30-, 90-day mortality. Lp(a) serum levels assessed in acute phase of stroke and three months later did not differ significantly: 8,3 (3,6-21,1) vs. 7,65 (3,0-23,1) mg/dl, respectively. The distribution of Lp(a) values in patients in acute, chronic phase of stroke and control subjects were similar. Conclusions: The study supported the view that increased Lp(a) in stroke patients was associated with the cardiovascular risk profile (history of myocardial infarction and atrial fibrillation), occurred more frequently in patients with TACI, but not influenced stroke prognosis.

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THE ROLE OF MAGNESIUM (Mg) A NATURAL CALCIUM (Ca) ANTAGONISTS IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE. (CLINICAL STUDY). Galeas Th.*, Kontos T., Exarchos P.,Tegos N., Galea B. B'Internal Medicine Clinic, General Hospital of Trikala Medical student of University of Thessaloniki**GREECE

The purpose of the work is to show the contribution of Mg-a natural Ca antagonist in the treatment of ischaemic stroke.Patiens-Method Material of the study were all the cases with the indication of acute ischaemic stroke admitted in the Internal Medicine Clinics of the General Hospital of Trikala, during a period of one year. 510 patients, male and female, aged 72,26+/-10,91 were hospitalized, of whom 70 died,aged 78,82+/-8,75.We separated the patients in two groups,one of 233 patiens aged 71,25+/-10,95 who received Mg intravenously (1850 mg of magnesium. L-aspartate-HCI equivalent to Mg^{++} 15 mEq or 7,5 mmol or 183 mg) daily, and the other 277 patiens aged 73,27+/-10,87 who received placebo. Criteria of the therapeutic results were peasured by the Medical Research Council (MRC) Scale and the Mini Mental State Examination (MMSE) Scale.Braine CT was necessary (penumbra).The x^2 method was used for the statistical analysis.The recommendations of the Helsinki declaration were also followed.Result 75% of the patients who received Mg (175) and 50% of the patiens of the patients with placebo (166) survived up to the 30th and 90th days in an improved condition. X^2 =5,19 0,025P0,01.In conclusion magnesium, a calcium antagonist should be administered in the treatment of the acute ischaemic stroke as it improves the clinical and laboratory picture of the patients.

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DIFFUSION-WEIGHTED MRI IN THE MONITORING OF CHOLESTEROL CRYSTAL EMBOLIC SYNDROME. F. Perin-Dureau, X. Vandamme, C. Oppenheim, C. Dupel, F. Koskas, Y Samson and G. Rancurel. Service Urgences Cérébrovasculaires, Service de Chirurgie Vasculaire, Hôpital Pitié-Salpêtrière, Paris, France.

A 54-year-old man was admitted for recurrent strokes for eight months (three sudden hemiparesis, left and right, with satisfying recovery). In-between, insidious alterations of cognitive status and daily life activities were noticed, despite treatment. On admission, patient was severely disabled. Others clinical findings were remarkably normal. He had an history of cigarettes and alcohol abuse, and of untreated arterial hypertension. After each stroke, paraclinical findings were the followings: severe leucoaraiosis and multiple small hypodensities on CT, congruent hypersignals on T2-weighted-MRI, strongly suggesting a lacunar state. 24-hour-EKG, supra-aortic US, transthoracic cardiac US, routine laboratories examinations were all normal, except elevated ESR and left ventricular hypertrophy. He was treated by atenolol and acetylsalicylic acid. In our unit, diffusion-weighted MRI (DWI) showed multiple small area of decreased diffusion coefficient in subcortical and deep regions of both hemispheres and cerebellum. Cerebral arteriography was normal. Transesophageal echocardiography showed multiple profound ulcerated atheromatous plaques and spontaneous intravascular echographic contrast in the aortic arch. Retina examination showed cholesterol crystal emboli. Simvastatine and colchicine were added to treatment. No sudden event was noticed during the 6-months follow-up, but his neurological status continue to worsen seriously and progressively, and serial DWI regularly showed new asymptomatic cerebral lesions. Surgical treatment of the embolic source was subsequently decided.

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FLAIR AND DIFFUSION-WEIGHTED MR SEQUENCES FOR THE DISTINCTION BETWEEN ISCHEMIC STROKE AND STROKE-LIKE EPISODES.D. Somme, S. Crozier, C. Oppenheim*, X. Vandamme, D. Dormont*, Y. Samson, C. Marsault* and G. Rancurel. Service Urgences Cérébrovasculaires, *Service de Neuroradiologie. Hôpital Salpétrière, Paris, France.

Even in stroke centers, distinction between stroke and stroke-like episodes may be difficult in about 20% of emergent admissions. Indeed, CT-scan may be insufficient for diagnosis of sudden neurological deficit. In these cases, new magnetic resonance (MR) sequences may improve accuracy of diagnosis while reducing the amount of other required investigations. The contribution of Diffusion-Weighted Imaging (DWI) and Fluid Attenuated Inversion Recovery (FLAIR) in the diagnosis of stroke will be illustrated by 2 observations. The first patient is a 43 years-old woman who suddenly experienced a left hemiparesis. CT-scan performed at 48 hours, demonstrated a right corona radiata hypodensity consistent with a deep middle cerebral artery infarction. However, the stroke hypothesis was ruled out by DWI which failed to show bright signal areas. FLAIR showed multiple hypersignals in the white matter, suggesting an inflammatory demyelinating disease. The second patient, a 54 years-old man who experienced five episodes of right upper and lower limb sensitivo-motor deficits and dysarthria lasting 1 or 2 minutes. These deficits were associated with major anxiety. CT scan at 24 hours was normal, but DWI/FLAIR imaging showed a left thalamus hypersignal consistent with a recent infarction. These observations demonstrate that DWI/FLAIR imaging can be useful for the initial management of patients with atypical neurological focal deficit.

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CONFABULATIONS IN PICTURE NAMING TASK: A COMPARISON OF SUBCORTICAL ISCHEMIC VASCULAR DEMENTIA (s-IVD) PATIENTS TO THOSE WITH ALZHEIMER'S DISEASE (AD). A.P.Cannatà, M.Alberoni, E.Farina and C.Mariani.Neurorehabilitation Unit, "S. Maria Nascente" IRCCS, "Don C.Gnocchi" Foundation, University of Milan

Data on performance in naming tasks of patients with s-IVD are up to now only sparse, while a significant impairment has been consistently reported in patients with more broadly defined 'vascular' dementia and in patients with AD.We compared the performance in a 36-items picture naming task, using a comprehensive classification of error types, of three groups of subjects: 19 patients with s-IVD (mean age 72.88.1 years); 19 AD patients (mean age69.58.9 years) and 13 age-matched normal controls entered the study. Naming errors were classified into 6 main categories: visual errors, ambigous errors, semantic errors, non-responses, perseverations and unrelated errors. All experimental subjects were also tested with an extensive neuropsychological battery exploring frontal lobe functions.Dementia groups were not statistically different in terms of age, level of education, gender, Mini Mental State Examination and Hamilton Depression Rating Scale. Performance in the naming task of both dementia groups was significantly impaired in comparison with controls ($F=20.5$ $p < 0.001$). s-IVD patients commited more unrelated ($F=10.7$ $p < 0.0001$) and perseverative errors than AD ($F=13.7$ $p < 0.0001$), while semantic related errors were present both in AD and s-IVD. s-IVD patients were also more severely impaired than AD in several frontal lobe tasks.Unrelated and perseverative errors appear to be typical of s-IVD and related to severity of frontal lobe deficits.Unrelated answers represent a bizzare naming impairment, that we hypothesize to be a form of confabulatory behaviour due to frontal lobe dysfunction, presumably attributable to a lack of response inhibition.

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STROKE UNITS MAKE THE DIFFERENCE IN BRAIN HAEMORRHAGE. B.Fuentes, E.Diez-Tejedor, M.Lara, P. Barreiro.Dept Neurology. Stroke Unit. University Hospital La Paz. UAM. Madrid. Spain.

Background: The efficacy of stroke units (SU) has been amply demonstrated, especially in ischaemic stroke. We assess the repercussion of SU in parenquimatous brain haemorrhage. Methods: We compared the outcome of three homogeneous samples of patients suffering from parenquimatous brain haemorrhage (stroke data base) during the year before (1994) and after (1995 and 1996) the establishment of SU in our Department. Before 1994 patients were attended by a Sroke Team. We analysed length of stay, mortality, functional state (Rankin Scale) and destiny at hospital discharge. Statistics: t-student, Chi-square.Results: 151 patients were studied: 48 (1994), 46 (1996) and 57 (1996), (10,1% of total stroke in-patients). We found a reduction in length of stay from 25,1 26 to 11,28 and 14,1 9 (p 0,01). Functional state at discharge improved (Rankin 2 vs 3; p 0,01). There was an increment in the proportion of patients able to live in home (up to 63%; ns) and in discharge to rehabilitation wards (up to 28%; $p < 0,05$) with a reduction in discharge to nursing homes (from 22,9% to 10,3%; $p < 0,05$). There was a saving in acute stroke care costs (32,2-57,3%).Conclusions: The specific management in SU determine a best outcome in parenquimatous brain haemorrhage with a reduction in length of stay, an improve in functional state and a significant increment in patients able to go home and to rehabilitate.

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CEREBRAL INFARCTION DUE TO SEPTIC EMBOLISM SECONDARY TO ASPERGILLUS AORTITIS. G. Suárez, B. Fuentes, [1]R. Sánchez, A. Frank, [1]M. Gutiérrez, E. Díez Tejedor. Department of Neu-

rology. Stroke Unit. [1]Dept. of Neuropathology. University Hospital La Paz. UAM. Madrid. Spain.

Introduction and objectives: Cerebral infarction secondary to aspergillus arteritis or septic embolism is an exceptional finding. We present a case of multiple systemic embolism and cerebral infarction secondary to aspergillus aortitis.Patient/methods: An 65-years-old male with hypertension, hyperglycaemia and myocardial infarction and aorto-coronary bypass surgery in 1995, that suffers cerebral infarction in middle right cerebral artery territory and right cubital artery embolism in June 1997. In July 1997 he presents abrupt increase of his left hemiparesia and left central facial paresia. Laboratory tests, CT and echocardiogram were performed. He died eight days later, with a febrile syndrome.Results: Hemogram: leucocytes 34.700 /uL (86,5% N; 4,8% L). Cranial CT: cerebral infarction in middle right cerebral artery territory. Transthoracic Echocardiogram: moderate left ventricular hypertrophy and slight inferior hypokinesis. Transesophageal Echocardiogram: without changes. Arteriography: complete thrombosis of left internal carotid in their start. Necropsy: Parietal aortic aspergillosis with generalized septic embolism (cerebral, renal, pancreatic,...). Cerebral infarction in middle right cerebral artery territory and thrombosis of left carotid siphon with aspergillus arteritis.Conclusions: Aspergillosis is an exceptional cause of cerebral infarction and their diagnosis is very difficult, being habitually found at necropsy. Nevertheless, it should be considered in cases of cerebral infarction in patients with heart surgery history.

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BALLOON OCCLUSION OF INTRACRANIAL ANEURYSMS: LONG-TERM FOLLOW-UP. GV McDonnell, M Elliott, T Baird, E Murtagh, K Bell, CS McKinstry. Belfast, Northern Ireland.

Objective: To assess the long-term outcome of endovascular treatment of intracranial aneurysms with detachable balloons. Background: Surgical clipping or coil embolisation of cerebral aneurysms is not always possible and intravascular balloon occlusion may be appropriate. There are few reports of the long-term sequelae with this technique and no studies incorporating follow-up transcranial doppler data. Methods: 12 patients have undergone endovascular balloon occlusion of an internal carotid artery (ICA) aneurysm using a silicone detachable balloon. Consent was sought for full clinical evaluation, lateral skull X-ray (SXR), carotid duplex ultrasound and transcranial doppler (TCD) ultrasound studies (Logidop 4 TCD machine; Scimed, Bristol, UK). Results: All 12 (age 25-72 years) were alive 7 months-7 years post-occlusion. Each consented to full assessment. Two had developed strokes, one within 24 hours of the procedure and the second a delayed event at 2 months. One had a residual minimal hemiparesis and the other, a moderate hemiparesis. The remaining 10 were stable or improved on their pre-operative state. Lateral SXR revealed continued inflation of balloons in 11/12 cases. TCD indicated occlusion of the target ICA in all instances. Intracranial crossover flow in the anterior communicating artery was indicated by flow reversal in the ipsilateral anterior cerebral artery (ACA) and increased flow velocities in the contralateral ACA in all patients. Conclusions: This study of a small cohort of patients suggests that intravascular balloon occlusion has been a relatively safe, effective treatment for ICA aneurysms. The TCD data indicates the persistence of an excellent collateral crossover circulation in all treated cases.

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THE EFFECT OF PSYCHOLINGUISTIC THERAPY ON RECOVERY FROM APHASIA.Zeki Gokcil, Oguz Tanridag, Seyhan Ovgu, Erdal Eroglu, Okay Vural. Department Of Neurology, Gulhane Medical School, Turkey

Recovery from aphasia has been reported to be affected by many factors. Although there has been a common belief that greatest improvement occurs in the first 3-6 months, recovery rates and profiles in different types of aphasia have been controversial. Current approaches to treatment of aphasia include psycholinguistic therapy, cognitive neurorehabilitation, and pharmacotherapy. Psycholinguistics is the study of relationship, between linguistic behavior and psychological processes thought to underlie it.We present 20 patients (5 women and 15 men whose ages from 21 to 70 years) who have been rehabilitated by psycholinguistic therapist. 16 patients had CVD, 4 craniocerebral trauma. All patients underwent stimulation of retrieval of linguistic defect, characteristic of aphasia, by using paragraph and naming, memory and attention. The patients were evaluated by using Gulhane Aphasia Test (GAT) and cranial CT and/or MRI evaluation. 5 patients had nonfluent, 5 fluent, and 10 global aphasia. Language evaluation were performed periodically in all patients. The mean follow-up periods were 41 months. The initial scores of global, nonfluent, and fluent aphasia were found 5.1%, 34.5%, and 38.8%, respectively. After rehabilitation, the last scores of aphasic patients were found 58.2%, 77%, and 68.2%, respectively.In conclusion, psycholinguistic therapy appears to have a positive effect on the recovery of aphasia in patients receiving intensive language therapy.

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VERBAL FLUENCY AND SEMANTIC CLUSTERING IN ALZHEIMER'S DISEASE (AD).S.Pomati, E.Imbornone, P.Venco, N.Del Grosso Destreri, A.P.Cannatà, E.Farina, M.Alberoni and C.Mariani.IRCCS Don Gnocchi Foundation, Neurorehabilitation Unit, University of Milan

In order to detect differences in the ability to access and organize semantic knowledge in patients with AD and healthy subjects, we analyzed performance in a verbal fluency test for animals with a new scoring procedure. We rated amplitude of the semantic store for animals calculating total number of items evoked within 60 seconds and number of semantic categories (domestic vs wild animals, birds, insects and fishes). The ability to organize semantic knowledge was rated calculating a series of semantic clustering parameters.63 patients with probable AD and 34 age and education matched controls entered the study. 11 AD showed very mild (CDR 0.5), 41 mild (CDR 1) and 11 moderate (CDR 2) dementia.AD differed from controls in ratings of semantic storage and organization ($p < 0.001$). Profile of performance of patients with very mild, mild and moderate dementia differed in terms of number of categories ($p < 0.0001$),number of clusters ($p < 0.0001$), clustered items ($p < 0.0001$) and total number of items ($p < 0.0001$). MMSE score significantly correlated ($r > 0.5$) with total number of items, clustered items and clusters.Our data confirm the existence and relevance of semantic memory impairment even in the early stages of AD. In mild AD the impairment is mainly in accessing and organizing semantic knowledge; only in the course of the disease would a storage impairment ensue.

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FUNCTIONAL LIVING SKILLS ASSESSMENT: A STANDARDIZED INSTRUMENT BUILT TO MONITOR ACTIVITIES OF DAILY LIVING IN DEMENTED PATIENTS: PRELIMINARY DATA. E.Farina, R.Fioravanti, L.Chiavari, E.Imbornone, S.Pomati, G.Pinardi, M.Alberoni, and C.Mariani. IRCCS Don Gnocchi Foundation, Neurorehabilitation Unit, University of Milan

This study illustrates preliminary data from the Functional Living Skills Assessment (FLSA), a standardized battery built to evaluate performances in everyday life activities in demented patients The FLSA is an echological instrument, useful to assess abilities hardly revealed by formal neuropsychological testing.Nineteen patients with probable Alzheimer's Disease (AD) (mean age: 74.2 ± 6.9 years, range 63-83) in different stages of the disease (mean MMSE=20.6 ± 3.7, range 15-26) entered the study. The FLSA explores and scores the patients' abilities in the following areas: resources; consumer skills; public transportation; time management; money management; leisure; telephone skills; self-care, health and safety awareness.A good correlation was found ($r=.55$, $p<.05$) between MMSE score and total FLSA score. Total FLSA score significantly differed in patients with very mild (CDR=0.5), mild (CDR=1) and moderate (CDR=2) dementia ($p<.0002$). Analysis of the profile of performance of AD patients grouped according to CDR rating showed a preservation of self-care, time management and leisure also in moderately demented patients, despite a fall in consumer skills and use of public transportation and resources. These preliminary data demonstrate that the FLSA can represent a useful tool for monitoring the progression of dementing illnesses. Furthermore it can also prove a useful instrument for evaluating, beyond formal neuropsychological testing, the impact on everyday life of cognitive rehabilitation or of pharmacological intervention.

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DYGRAPHIA IN ALZHEIMER'S DISEASE (AD): PATTERN OF PERFORMANCE OF MILDLY TO MODERATELY DEMENTED PATIENTS. N.Del Grosso Destreri, E.Imbornone, M.Alberoni, E.Farina, P.Venco, P.Nichelli, and C. Mariani.IRCCS Don Gnocchi Foundation, Neurorehabilitation Unit, Universities of Milan and Modena

Lexical and peripheral dysgraphia is often reported in AD, both in spontaneous writing and under dictation. In order to control for word frequency

and spelling regularity, we tested a group of italian patients with a standardized battery for writing under dictation of 150 words with regular, partially regular and ambiguous spelling. Transparent grapheme to phoneme correspondence of Italian words allows to distinguish between 'expected' errors (due to misapplication of orthographic rules in words with partially regular and ambiguous spelling) and 'unexpected' errors (due to omission, substitution or interposition of letters both in regular and irregular words). 28 patients with probable AD with mild to moderate dementia (mean age: 72.6 ± 47.6 years; mean MMSE=20.11 ± 3.73) entered the study. Their performance was compared to that of 16 healthy age and education matched controls.AD patients were significantly more inaccurate than controls only in words with partially regular and ambiguous spelling (F=4.63, p=.037; F=7.27, p=0.010). For all classes of stimuli, performance of AD patients was significantly different from controls in terms of 'unexpected' errors (F= 10.01, p<0.003) but not for 'expected' errors.The number of 'unexpected' errors for words with regular, partially regular or ambiguous spelling was the trait that best differentiated AD patients from healthy controls (Xsquare= 13.1, p=0.0003) suggesting that, at least for languages with transparent orthography, this pattern of errors may represent a sensible marker of dementia.

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CONCURRENCE OF MUTATION IN THE PRESENILINE-1 (PS-1) GENE WITH APOLIPOPROTEIN (APOE) GENOTYPE 4,4 IN TWO SISTERS.B. Yagüe; A. Frank; J. Aldudo*; M.A. Santana; E. Díez-Tejedor; P. Barreiro.Department of Neurology - Hospital Universitario "La Paz" and * Department of Molecular Genetics "Severo Ochoa" -Universidad Autónoma de Madrid- SPAIN

Introduction: The 4 allele of the APOE gene seems to be one of the most important genetic factors in developing late-onset esporadic Alzheimer's disease (AD). The highest risk occurs in its homozygous form. Mutations in the PS-1 gene are associated with the development of early-onset familial AD. It is exceptional, that both (APOE 4,4 and PS-1 mutation) occur together.Patiens/Methods: We describe clinical data of two sisters with a low school level, aged 64 and 68 years respectively, both with PS-1 mutation and APOE 4,4 genotype. A family history of early-onset dementia, psychiatric disease and Huntington's disease was present.Results: The neuropsychological examination confirmed in the younger patient a severe dementia syndrome of 4 years of evolution, with a Mini-mental test of 6/30, whereas the older sister kept her cognitive functions preserved, with a Mini-mental test of 23/30, being independent for daily activities and without any dementia syndrome.Conclusions: These results indicate that neither the homozygous form of APOE ε4, nor the presence of a mutation of PS-1 gene, are absolutely decisive factors for early onset dementia.

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APOLIPOPROTEIN E (APOE) GENOTYPE AND CLINICAL OUTCOME IN ALZHEIMER´S DISEASE (AD). M.A. Santana; B. Fuentes; P. Barreiro; E. Díez-Tejedor; A. Frank. Dep. Neurology – University Hospital "La Paz" - Universidad Autónoma de Madrid- SPAIN. On behalf the investigators who participate at the Multicenter Study: SB202026

Introduction and objetives: ε4 allele of APOE is a well recognized susceptibility factor for developing AD, but its influence on clinical outcome is not well-known. Cognitive and non cognitive subscales of the Alzheimer´s Disease Assesment Scale (ADAS-Cog and ADAS-non Cog), as well as Mental State Examination (MSE), are used as efficacy measures in a lot of AD clinical trials. Our main objetive was to investigate if APOE-4 genotype determines a worser outcome in AD.Patiens/Methods: A series of 76 AD patients (age: 72.5 ± 5.7 years) who participated in a Multicenter Clinical Trial in 19 Hospitals in Spain between 1996-1998 were studied. APOE genotype was undertaken after signed consent. Clinical outcome was analyzed during a six month follow-up period using ADAS-Cog, ADAS-Non Cog, and MSE scores at baseline and at final visit. Chi-square and Student's t tests were used for statistics.Results: 43 patients beared one or two APOE ε4 alleles (Group 1), whereas 33 patients did not (Group 2). Cognitive function showed a significant decline along the follow-up period in the whole series, however, no differences were found between Group 1 and Group 2 in MSE, ADAS-Cog and ADAS-non Cog scores at basal and at final visit.Conclusions: These results indicate that APOE-4 genotype does not condicionate a worser clinical outcome of the cognitive decline in AD.

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HEREDITARY SPASTIC PARAPARESIS AND PSYCHOSIS. Paul Mc Monagle and Michael Hutchinson. Dept of Neurology, St Vincent's Hospital, Dublin, Ireland.

Background:Hereditary Spastic Paraparesis (HSP) is clinically and genetically heterogeneous condition with slowly progressive spastic weakness of the lower limbs the most prominent feature. Reports of higher function disorders associated with the condition have received little attention and are mainly confined to mental retardation, dementia and hypomania.Purpose:We describe the finding of psychosis with HSP in 5 families with the condition. Methods:As part of an ongoing survey of HSP in Ireland all family members were examined by two neurologists and an assessment of cognitive function was performed using either the mini mental state examination (MMSE) or the Cambridge Cognitive examination (CAMCOG). Results:Seven individuals from five families were found to have psychosis in association with HSP, cognitive impairment was a common feature. Four had schizophrenia, two had a schizo-affective disorder and one had psychotic depression. Families with autosomal dominant 'pure' HSP, HSP with cognitive impairment and Kjellin's syndrome were represented. Age at onset was early (< 35 years of age) in four pedigrees.Conclusions:Psychosis in association with HSP should not be assumed to be a chance finding and may represent multi-system involvement in the condition.

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DEMENTIA WITH LEWY BODIES AS A DIFFERENTIAL DIAGNOSIS OF CREUTZFELDT-JAKOB-DISEASE. Henriette J. Tschampa[1], MD; Manuela Neumann[2], MD; Inga Zerr[1], MD; Karsten Henkel[1], MD; Walter Schulz-Schaeffer[2], MD; Hans A. Kretzschmar[2], MD and Sigrid Poser[1], MD.[1]Department of Neurology and [2] Institute of Neuropathology, University of Göttingen, Germany

The most frequent clinical differential diagnosis of Creutzfeldt-Jakob-Disease (CJD) is Alzheimer's dementia. In general Dementia with Lewy bodies (DLB) is often found in autopsy without having been diagnosed clinically. In a neuropathological series of patients (N=104) suspected of having CJD and in whom this diagnosis was ruled out, the most frequent cause of dementia following Alzheimer's disease was DLB (N=14). We present clinical features of 5 DLB-patients who had been seen prospectively by our CJD-surveillance unit. They are classified according to international diagnostic criteria.One patient met the diagnostic criteria for probable CJD (dementia, extrapyramidal signs, myoclonus and typical EEG-findings). In the cerebrospinal fluid (CSF) the protein 14-3-3 was not detectable and the neuron specific enolase was normal. This patient fulfilled the criteria of possible DLB (dementia and visual hallucinations). Three patients had dementia, extrapyramidal signs and myoclonus without specific EEG- or CSF-findings. They were classified as possible CJD. Presenting with parkinsonism and either visual hallucinations or fluctuations or both, they fulfilled the criteria for probable DLB. One patient did not meet criteria for CJD nor DLB.In patients suspected of having CJD, DLB must be considered if they present with extrapyramidal signs, myoclonus and even CJD-typical EEG-findings but when CSF-testing is negative.

P490
SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) IN 19 PATIENTS WITH CREUTZFELDT-JAKOB DISEASE.Karsten Henkel*, Johannes Meller**, Inga Zerr*, Walter Schulz-Schaeffer***, Andreas Schroeter*, Henriette J. Tschampa*, Hans A. Kretzschmar***, Wolfgang Becker**, Sigrid Poser* *Department of Neurology, **Department of Nuclear Medicine and ***Department of Neuropathology, University of Goettingen, Germany

In several dementing diseases typical deficits of cerebral perfusion, detected by SPECT, were described, e.g. bilateral hypoperfusion of the temporal and parietal lobe in Alzheimer´s disease. There are only single case reports about pathological SPECT in Creutzfeldt-Jakob disease (CJD). The aim of this study is to determine the frequency of pathological findings in a greater number of patients and the possibility of establishing typical patterns of hypoperfusion.The ^{99m}Tc-HMPAO- or ^{99m}Tc-ECD-SPECT images of 19 patients with definite or probable CJD were sampled and rated by two of the authors blinded to the diagnosis.In 17 cases (89%) an abnormal SPECT was found. In three patients the hypoperfusion was frontal bilateral or in the adjacent temporal and parietal lobes. Five cases showed widespread temporo- and/or parieto-occipital deficits of perfusion. In eight cases the tracer-uptake was reduced either over one whole hemisphere partly combined with the cerebellum or from frontal to occipital lobes bilaterally. In one patient SPECT showed bi-temporo-parietal and left-thalamic hypoperfusion. The majority of patients had widespread reduction in cerebral perfusion including the occipital lobes, the cerebellum or one whole hemisphere. These results are usually not found in Alzheimer´s disease and most of the other differential diagnoses of CJD.

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MAGNETIC RESONANCE IMAGING (MRI) IN CREUTZFELDT-JAKOB DISEASE.Schröter A*, Zerr I*, Henkel K*, Tschampa H*, Finkenstaedt M, Poser S**Dept. of Neurology, University of Göttingen, Germany

Creutzfeldt-Jakob disease (CJD) is a transmissible brain disease with an incidence of 1 case per million per year and a fatal outcome. It is characterized by a rapidly progressive dementia with a duration shorter than two years, myoclonus, ataxia, extrapyramidal and pyramidal disturbances and akinetic mutism, typical EEG and detection of protein 14-3-3 in the cerebrospinal fluid. Definitive diagnosis is made by neuropathological examination.Until now, magnetic resonance tomography plays only a minor role in the diagnosis of CJD. In literature there are only a few case reports describing bilateral symmetric hyperintense abnormalities in the basal ganglia like caudate nucleus and putamen on T2-weighted MR images. Bilateral, symmetrically increased signal intensity in the basal ganglia on T2- and proton-density-weighted MRI were reported previously in 23 of 29 patients with CJD (79%). We now studied a large number of 157 patients with sporadic CJD and 56 cases with dementia. These patients were initially referred to the CJD unit as suspected cases, but other diagnoses were made in the follow-up. MRI scans were rated by one of the authors (MF) blinded to the diagnosis. 106 of 157 patients (67%) show such hyperintense abnormalities in MRI, whereas in the control group 52 of 56 other cases do not show these abnormalities. The abnormal high signals in basal ganglia were best seen using diffusion-weighted images and were present in all patients studied so far. In conclusion, these results indicate that MRI is a useful, valuable tool for the clinical diagnosis of CJD, like the EEG or cerebrospinal fluid.

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POSITRON EMISSION TOMOGRAPHY IN ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA AT INITIAL DIAGNOSIS. P. Santens, J. De Bleecker, P. Goethals, K. Strijckmans, I. Lemahieu, G. Slegers, R. Dierckx, J. De Reuck - Dept. of Neurology and Nuclear Medicine, University and University Hospital Gent, Belgium.

Objectives: To characterize the differences in regional cerebral uptake of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) in probable Alzheimer's disease (AD) and frontotemporal dementia (FTD) at the time of initial differential diagnostic workup. To compare visual analysis with semiquantitative analysis based on different reference regions. Methods: Fourteen patients (AD n = 8, FTD n = 6) were included. Conventional PET studies with bolus injections of FDG were performed. Visual analysis was performed by a blinded reader. Twenty-three ROI's were determined and normalized using the visual cortex, cerebellar and sensorimotor cortex activity. Non-parametric tests and correlation analysis were performed. Results: Visual analysis confirmed earlier findings, including prevalent asymmetric patterns in both groups. Only normalization to the sensorimotor cortex confirmed the visual analysis and added to differential diagnosis. There were no differences in medial temporal lobe activity between both groups. There was no correlation of medial temporal lobe activity with dementia severity. Conclusions: Heterogeneous patterns of FDG uptake exist at initial diagosis of FTD and AD. Parietal involvement is highly discriminative between both groups. Semiquantitative analysis is highly dependent on the choice of the reference regions. The sensorimotor cortex seems to be the most reliable reference region.

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APOLIPOPROTEIN E ε4 IS ASSOCIATED WITH MEMORY DECLINE IN COGNITIVELY IMPAIRED ELDERLY: THE LASA STUDY. M.G. Dik (1,2), C. Jonker (1,2), L.M. Bouter (1), P. Eikelenboom (2), G.J. van Kamp (3), D.J.H. Deeg (1,2).Amsterdam, the Netherlands

It is well-known that the Apolipoprotein E ε4 allele (ApoE4) increases the risk of developing Alzheimer's Disease (AD). It might be expected that ε4 carriers will decline cognitively at a faster rate. The aim of this study was to investigate the effect of ApoE4 on memory decline in a population-based elderly sample. The study sample, selected from the Longitudinal Aging Study Amsterdam (LASA), consisted of 1243 subjects (62-85 years) with Mini Mental State Examination (MMSE) scores 21-30 and known ApoE phenotypes. Memory performance was measured with an abbreviated Auditory Verbal Learning Test (AVLT) and repeated after three years (N=854). Memory decline was defined as three or more points decline on Immediate Recall, based on the AVLT. Logistic regression analyses showed that ApoE4 was a risk factor of memory decline in older subjects (75-85 years) with baseline cognitive impairment (MMSE 21-26) (OR adjusted for age, sex, education and baseline recall score 4.46, 95% CI 1.44 – 13.77). No significant association was found in 62-74 year old subjects. ApoE4 did not affect the rate of decline among subjects with normal cognition (MMSE 27-30). These findings suggest that ApoE4 determines memory decline in the preclinical symptomatic stage of AD. The results do not support the hypothesis that the risk of ApoE4 on AD decreases with increasing age.

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AGE-ASSOCIATED MEMORY IMPAIRMENT AND RISK OF FURTHER DEMENTIA. Alexander Tsiskaridze, Roman Shakarishvili, Marina Janelidze, Tamara Vashadze, Sarajishvili Institute of Neurology, Tbilisi, Georgia

Background and Purpose: The term "aged-associated memory impairment" (AAMI) was coined to characterize some lowering of cognitive functions in elderly persons, which is not sufficient enough to establish the diagnosis of dementia. However, there are controversies in opinions on whether this condition could be considered as a phenomenon of normal aging or a preclinical stage of dementing illness. The aim of the present study was to reveal factors that may contribute to the further development of dementia in persons with AAMI.Methods and Results: A cohort of 47 elderly persons with AAMI was followed-up for 3 years. Twenty-two of them (47%) had reached an end-point that was defined as the Mini-Mental State Examination Score < 24 and fulfilling the Diagnostic and Statistical Manual -III Edition (revised) criterion for dementia. Using Cox proportional hazards model adjusted for age and sex, the following factors at baseline were associated with higher Relative Risk (RR) of reaching the end-point: (1) low education level of the patient (RR = 1.8, 95% Confidence Interval (CI) = 1.2-4.8); (2) extensive brain atrophy (RR = 2.5, 95% CI = 1.4-4.7) and (3) presence of multiple infarctions (RR = 2.7, 95% CI = 1.9-4.0) on the computed tomography and magnetic-resonance imaging.Conclusion: Although AAMI frequently is considered to be a phenomenon of normal aging, its association with some factors such as low education level of the patient and the presence of structural changes in the brain (atrophy and multiple infarctions) should be regarded as a predictor of the development of dementia on follow-up.

P495
ARE THE HALLUCINATIONS OF IDIOPATHIC PARKINSON'S DISEASE (PD) NECESSARILY ASSOCIATED WITH PROGRESSIVE INTELLECTUAL IMPAIRMENT? Graham JM, Grünewald RA, Sagar HJ. Sheffield, UK.

Drug-induced hallucinations in patients with PD are frequently associated with cognitive impairment. Our recent study confirmed this relationship for hallucinations that first occurred after five years disease duration (late-onset) but found no association for hallucinations of early-onset (Graham et al, 1997). This study was designed to investigate the progression, over time, of cognitive performance in patients with hallucinations relative to matched patients who had never hallucinated. Measures of motor disability, cognition and affect were completed by 54 patients with PD, and repeated at a mean interval of 2.7 years later (range: 1.2 to 4.7 years). Patients with early-onset hallucinations showed no difference from matched controls in rate of progression of cognitive deficits (composite cognitive score (CCS), t=0.04, p=0.97), affective (Beck Depression Inventory (BDI), t=0.57, p=0.57) or motor disability (Unified Parkinson's Disease Rating Scale (UPDRS), t=0.39, p=0.70). Patients with late-onset hallucinations had a similar rate of progression of motor disability to the matched controls (UPDRS, t=0.11, p=0.91) but showed greater deterioration in both cognition (CCS, t=2.56, p=0.02) and affect (BDI, t=2.24, p=0.03). Over the time period studied, early-onset hallucinations, unlike late-onset hallucinations, were not specifically associated with progressive intellectual impairment. Hallucinations in PD are probably mediated by heterogeneous neuropathological processes which may benefit from different clinical management strategies.

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MAGNETIC RESONANCE IMAGING (MRI) IN THE DIAGNOSIS OF FRONTOTEMPORAL DEMENTIA (FTD). M. Savoiardo, M.Grisoli, M.G. Bruzzone, L.D'Incerti, F. Tagliavini, O. Bugiani. Milano (ITALY)

A consensus statement on the clinical diagnostic criteria for FTD only requests demonstration of asymmetrical frontotemporal atrophy from struc-

tural imaging studies (Neary et al. Neurology 1998). We reviewed the MRI findings of 13 patients with FTD to establish in detail the value of atrophic changes and signal abnormalities. The clinical criteria on which the diagnosis had been made matched with the criteria of the consensus statement. In 1 case the diagnosis was confirmed by autopsy and in 2 cases by DNA analysis. All MRI examinations included coronal T1 and axial and coronal proton density (PD) and T2-weighted sequences. All the cases presented marked or very severe atrophy of the frontal and temporal lobes, with "knife-edge" thinning of the cerebral convolutions, asymmetrical in 9. Atrophy also involved the basal ganglia, particularly the heads of the caudate nuclei, resulting in a severe dilatation of the frontal horns of the lateral ventricles. Atrophy of the medial part of the cerebral peduncles resulting in enlargement of the interpeduncular cystern was also observed. PD and T2-weighted images demonstrated high signal intensity in the atrophic frontal and temporal lobes fading in the posterior regions, leaving unaffected the optic radiations. No differences were found between proven and clinically diagnosed cases.The MRI pattern of abnormalities here described corresponds to the pathological changes involving the frontotemporal cortex, the underlying white matter, basal ganglia and the frontopontine tracts. It is a constant and distinctive feature of FTD and may be used as an adjunctive diagnostic criterion.

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β-AMYLOID PEPTIDES INDUCE THE PRODUCTION OF MCP-1 IN CULTURED HUMAN ASTROCYTES.Prat E, Meda L, Galimberti D, Ardolino G, Agazzi P,Tadeo S, Baron PL, Scarpini E, Conti G, Scarlato G. Institute of Neurology, Dino Ferrari Center, University of Milan, IRCCS Ospedale Maggiore, Milan - Italy

There is a strong evidence that senile plaques (SP) in Alzheimer disease (AD) are sites of chronic inflammatory response. In addition to β-amyloid (Aβ), SP are associated with reactive microglial cells and astrocytes, which are sources of locally produced cytokines, complement components and proteolitic enzymes. Previous findings in vitro support a model in which microglia are activated at the initial stage of Aβ deposition and the associated cytokine expression exacerbates further Aβ production or processing and induce neurodegeneration as well. In this study, we examined whether human astrocytes stimulated with Aβ peptides express the monocyte chemotactic protein (MCP-1), which is a proinflammatory cytokine that is known to stimulate chemotaxis of peripheral blood monocytes and to modulate several monocyte responses. We demonstrate that upon incubation with Aβ-[1-42] and Aβ-[25-35] the human astrocytoma cell line U-373MG accumulates MCP-1 mRNA and produces significant amount of MCP-1 in cell free supernatants. Even though no data are currently available on the expression of MCP-1 within the brain during AD, the release of MCP-1 by astrocytes in response to Aβ might account for microglia recruiment and plaque maturation. This finding adds further insights into the spectrum of proinflammatory functions modulated by Aβ, wich might be involved in the pathogenesis of AD.

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STIMULATION OF SECRETORY PROCESSING OF AMYLOID PRECURSOR PROTEIN BY INSULIN THROUGH A GLUCOSE-INDEPENDENT PATHWAY. M. Racchi[1] M. Sironi[2], D. Solano[2], S.B. Solerte[3], and S. Govoni[1] 1Institute of Pharmacology University of Pavia, 2Institute of Pharmacological Sciences, University of Milano, 3Department of internal Medicine, Geriatrics and Gerontology Clinic, University of Pavia

Several biochemical evidences suggest the involvement of energy metabolic defects and increased oxidative stress during brain aging or in neurodegenerative diseases such as Alzheimer's Disease. An impaired glucose metabolism has been observed in parietal temporal and cortex of AD patients. Insulin is the principal hormone controlling glucose uptake, in addition it modifies the expression or activity of a variety of enzymes and transport systems in nearly all cells. Secretory cleavage of amyloid precursor protein (APP) is regulated by a complex cellular mechanism. Among other, receptors that possess an intrinsic tyrosin kinase activity, such as EGF and NGF receptors, can stimulate sAPP release. We studied the effect on APP metabolism of insulin, in a cellular model (neuroblastoma SH-SY5Y), that express endogenously insulin receptors. Insulin treatment elicited a significant increase in sAPP. The release was concentration-dependent reaching a maximum at 1μM. The amount of sAPP released in the medium was about 2.5 folds of basal release. The insulin mediated release was independent from the presence of glucose in the medium and was abolished by genistein, a specific inhibitors of tyrosin protein kinase. Moreover we show that the release is dependent from activation of phosphatidyl inositol 3 kinase (PI3K) since simultaneous treatment with insulin and wortmanin or LY294002, specific inhibitors of PI3K, block the insulin mediated sAPP release.

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ICTAL ASYSTOLY AND APNEA ASSOCIATED WITH FOCAL EPILEPSY- Eisensehr, S Noachtar, HO Lüders-Department of Neurology, Ludwig-Maximilians-University Munich, GERMANY,Department of Neurology, The Cleveland Clinic Foundation, Cleveland U.S.A.

We report on patients whose focal epileptic seizures were associated with either asystoly or apnea. Case 1: A 30-year-old woman with aura continua and epilepsia partialis continua probably caused by viral encephalitis. Ictal EEG showed recurrent right temporal seizure patterns associated with acustic aura and absence seizures. Right temporal seizure pattern occured 17 times during sleep and once in the wake state with intervals of about 30 minutes. All seizures were associated with central sleep apneas and O_2-desaturations (minimum: 80%, baseline: 94%) without any other ictal symptoms.Case 2: This 58-year-old woman has had right mesial temporal lobe epilepsy due to mesial temporal sclerosis. Ictal EEG showed a right temporal seizure pattern which was followed by cardial asystoly of 23 seconds duration 77 seconds after EEG seizure onset.Our patients demonstrate central apnea and asystoly as clinical correlates of focal epileptic seizures. The incidence of vegetative disturbance associated with epileptic seizures such as breathing and heart rate abnormalities will most probably be higher than expected if polygraphic recordings were performed. Ictal apnea and asystoly may be the underlying causes of sudden unexplained death in epilepsy patients.

P500

RIGHT NEGLECT-DYSLEXIA (RND) IN ENGLISH AND HEBREW AFTER POSTERIOR LEFT HEMISPHERIC LESION: CHARACTERISTICS AND EFFECTS OF READING DIRECTIONALITY-Y. Kaufman[1]., N. Silberman[2], A. Katz[2], E. Wertman[2], Department of Neurology Hadassah University Hospital[1] and Neurobehavioural Unit, Herzog Hospital[2], Jerusalem, Israel.

Objective: To investigate features of RND after a posterior left hemispheric lesion in both English and Hebrew. Background: Neglect-dyslexia is characterized by visual reading errors which reflect the neglect of parts of words. RND after left hemispheric lesions was only rarely reported. The comparison of RND features in both languages might enable to define the attentional component and the deficient level of orthographic processing in RND. Methods: We compared reading skills in a 62 year-old right-handed man, with a left occipital hemorrhage with 5 controls, using batteries of high and low frequency English and Hebrew, each containing 400 words. Results: RND errors were found in 9.2% of words. Two types of errors were detected to the right of the neglect point: pure and combined. The distribution of pure and combined neglect errors differed significantly among the different batteries. The average number of letters in the neglected segment right of the neglect point was greater in high frequency English than in Hebrew (p=0.01). No dimensionality or hemifield effects were found. CONCLUSIONS: RND after left occipital lesion seems to cause 2 types of neglect errors. Reading directionality effected distribution of these types, but not of total RND errors. RND, in our case, seems to be more of a representational-central rather than perceptual-peripheral mechanism.

P501

FATAL FAMILIAL INSOMNIA: DESCRIPTION OF THE FIRST SPANISH FAMILY. Polo JM, Tabernero C, Muñoz R, Sevillano MD, Berciano J, Cabello A, Báez B, Ricoy JR, Carpizo R, Figols J, Cuadrado N, Clavería LE. Santander, Segovia and Madrid, Spain.

Fatal familial insomnia (FFI) is a hereditary prion disease associated with a mutation in the prion protein gene (PRNP). We report the clinical, neuropathologic and molecular features of the first FFI Spanish family. A 40-year-old woman and her 48-year-old brother presented in 1995 and 1997 respectively with depressive thoughts. The subsequent clinical course was uniform, including impairment of sleep, confusion, ataxia, dysarthria, weight loss and dysautonomia. EEG background activity became progressively slow, polysomnographic studies showing absence of electrophysiological patterns of sleep with a decrease of the total sleep time. CT and MRI were normal. The patients died 9 and 7 months after the disease onset. Histologic examination revealed a marked degeneration in the anterior

ventral and mediodorsal thalamic nuclei. Both patients were found to carry the mutation D178N with a homozygous pattern (met/met) at codon 129. Twenty years before, the mother (age 47) had presented a very similar and also fatal clinical picture, at that time thought to be Creutzfeldt-Jakob disease. Autopsy was not performed. As more FFI families are reported, it has been more and more evident an inconstant genotype-phenotype correlation; but in the family here described, the clasical FFI phenotype was associated with homozygosity for methionine at codon 129 of the PRNP.

P502
NON CONVULSIVE STATUS EPILEPTICUS INDUCED BY SERTRALINE. G Castelnovo, B Biolsi, P Labauge.Service de Neurologie, CHU Caremeau, Av Pr Debre. 30029 Nimes. Cedex 4. France

Background. Non convulsive status epilepticus (NCSE) is defined by prolonged loss of awareness with epileptiform activity on electroencephalogram. Main causes are infectious diseases, electroconvulsive therapy and benzodiazepines withdraw. We report an observation of a patient who presented NCSE provocated by sertraline intake.Objective. To report an observation of non-convulsive status epilepticus induced by sertraline intake.Results. A 68-year-old woman without any past medical condition was treated by amitriptiline since 1996 for a chronic depression. Because of the worsing depression, amitriptiline therapy was progressively reduced and substitued by sertraline. When the dose of 200 mg per day was reached, the patient became confuse. Neurological examination did not show any abnormalities except for confusion. In pecular, no myoclonic contractions were observed. EEG objectived generalized sharp and slow waves predominating in the frontal lobes. Standard biological analysis, lumbar puncture and brain MRI were normal. Sertraline was withdrawn and diazepam was administered intravenously. Confusion progressively disappeared and EEG became normal. Conclusions. Precipitating factors of NCES included infectious diseases, inadequate anticonvulsant medication and benzodiazepine withdrawl. In addition, it could be provocated by antidepressant drugs intake. This is the first report of NCES induced by sertraline intake.

General neurology

P503
AQUIRED NEUROMYOTONIA AND SENSORIMOTOR NEUROPATHY – A COMBINATION OF PARANEOPLASTIC SYNDROMS IN A PATIENT WITH HODGKIN´S DISEASE. Lahrmann H, Drlicek M, Hitzenberger P, Lindner K,Urbanits S, Grisold W. Ludwig Boltzmann Institut für Neuroonokologie, Kaiser Franz Josef Spital, A-1100 Wien, Austria

Paraneoplastic neurological syndroms are rare in patients with Hodgkin´s lymphoma.Objective: We report a patient with Hodgkin´s disease, neuromyotonia.and sensomotory neuropathy.Patient and methods: In a 58 year old woman Hodgkin lymphoma was diagnosed 30 years ago. She received radiotherapy and ABVD-chemotherapy. She was in complete remission when she noticed tingling sensations in both upper extremities and gait disturbance a year ago. Her speech became increasingly unarticulated. About 2 months ago she noticed difficulties in relaxing her muscles after handgrip. Oncologically there were no signs of recurrence of Hodgkin`s disease.Results: Clinical examination revealed dysarthria without other cranial nerves involved, normal muscle power, decreased deep tendon reflexes, normal plantar responses, hypesthesia in a stockinglike pattern in both lower extremities and gait ataxia. Muscle tone of hand muscles was increased and opening of hand grip slow. Motor and sensory nerve studies demonstrated axonal neuropathy, confirmed by sural nerve biopsy. Electromyography revealed spontaneous pseudomyotonic discharges at rest and a massive increase of discharges upon voluntary contraction. Muscle action potentials were of normal shape and duration. Magnetic resonance imaging showed no signs of cerebellar atrophy. Routine blood samples and CSF were normal. No specific autoantibodies were detected in serum and CSF.Conclusions: The combined occurrence of neuromyotonia and neuropathy in a patient with Hodgkin`s lymphoma in remission has not been reported up till now. Carbamacepin treatment, without additional immunosuppression, was effective and stiffness and gait difficulties improved within days. Also the dysarthric speech returned to normal, suggesting that bulbar muscles had been affected by neuromyotonia.

P504
PERIPHERAL NEUROPATHICS BY ANTINEOPLASTIC CHEMIOTHERAPICS. G. Campo, V. Bombace, P. Suriano, T. Trubia, A. Papalia, E.A.Corso. Clinica Neurologica – Università degli Studi di Catania – Policlinico

Less than a fifth of patients treated with antineoplastic chemiotherapics shows such important peripheral neurological damages to impose modifications or even interruptions in antineoplastic treatments. The authors have driven an analysis of antineoplastic medicines and of their commonly used associations in chemiotherapy. They have valued neurological toxicity, made a list of actual therapeutic drugs used to reduce neurological damages, particularly they have estimated preventive uses of medicines able to protect neurological cells from damages provoked by antiblastic drugs. Medicine used in reducing neurological damages is AMIFOSTINE (WR-2721, S-2 [3-AminoPropylamino]-EthylPhosphorothioic Acid). First results in research seem to show that therapy interruptions come less often in those patients receiving AMIFOSTINE before undergoing chemiotherapic treatment than in control groups, while percentages of reactions to antiblastic therapy are equal in both groups, as a result that AMIFOSTINE selectively protects normal tissues. The authors think that using medicines able to protect neurological cells during antiblastic therapy is extremely important because, when neurological damage appears, the only effective therapeutic treatment is modification in posology of the type of used medicine till complete suspension of therapy.

P505
LAMBERT-EATON SYNDROME: DESCRIPTION AND DIAGNOSIS OF A PARANEOPLASTIC AFFECTION ALLOWING AN EXTREMELY FAST DIAGNOSIS OF MICROCITOME. G. Campo, T. Trubia, P. Suriano, V. Bombace, A. Papalia, E.A. Corso. Clinica Neurologica – Università degli Studi di Catania – Policlinico.

Lambert-Eaton syndrome (LEMS), also called miasteniform syndrome due to some aspects that make it to be apparently similar to miasteny, consists in alterations of neuro-muscular transmission characterised by smaller delivery of acetilcoline from motor nerve endings.Commonly it is a paraneoplastic disease as a result that in more than 50% of cases it is associated to small cells lung carcinome or microcitome.The authors describe clinical aspects, differential diagnosis with miasteny, the importance of presence of anti voltage-dependent calcium channels specific anti-bodies (anti VOCCs anti-bodies).

P506
MYASTHENIA GRAVIS AFTER THYMECTOMY FOR CLEAR-CELL THYMIC CARCINOMA. Clio Spanaki, John Drossitis* and Minas Tzagournissakis. Depts of Neurology and *Thoracic Surgery, University Hospital, Crete, Greece

Thymectomy may improve the symptoms of myasthenia gravis (MG). However, there are cases where MG has been developed after excision of thymomas in previously non-symptomatic subjects. Here in, we report a case of post-thymomectomy MG for a rare form of thymic carcinoma.A 58-year-old man with vague chest pain underwent a routine chest X-ray and was found to have an anterior mediastinal shadow. Clinical and laboratory investigations were normal. CT and MRI showed the mass in the anterior mediastinum with no evidence of invasion. The tumor was fully resected via median sternotomy. Postoperative complementary radiation therapy was instituted. Macroscopically, the tumor had a lobulated surface and a tan-yellow color. Microscopically, the tumor was mostly composed of cells with clear cytoplasm and bland nuclear features in a lobular or sheet-like arrangement. This histologic form of thymic tumor is extremely rare with only 13 previously reported cases, and it behaves as a high grade carcinoma. Two months after the operation the patient presented eyelid ptosis, diplopia, dysphagia and weakness of the head. EMG and AchR antibodies were positive for myasthenia gravis. Pyridostigmine produced little to no improvement and immunosuppresive treatment with prednisolone was started with complete remission of the symptoms. This is the first report that relates myasthenia gravis to the clear-cell thymic carcinoma. The possible pathogenetic mechanisms of post-thymomectomy myasthenia gravis are discussed.

P507
ACUTE BRAINSTEM ENCEPHALITIS AND POLYNEUROPATHY AS A POST-INFECTIOUS SYNDROME.Volonté MA, Amadio S, Martinelli V, Poggi A, Grimaldi LME, Comi GC, Canal N.Scientific Institute Ospedale San Raffaele - Milan

The Bickerstaff's brainstem encephalitis (BBE) and the Miller-Fisher syndrome (MSF) may show an overlapping of clinical, pathological and immunological features. Either the BBE and the MFS were reported as a consequence of an anti-GQ1b antibody reaction to Campylobacter Jejuni. We describe two patients with symptoms and signs consistent with a brainstem encephalitis associated with a polyneuropathy, developed after a febrile illness.The first case is a 14-year-old girl who, three weeks after a febrile illness with slight respiratory involvement, developed distal limb paresthesias, dysarthria, dysphagia; abnormal smooth pursuit ocular movements, cerebellar and right pyramidal signs were detected. High titers of serum anti-Mycoplasma IgM antibodies and mild CSF pleocytosis were found. Brain MRI showed a brainstem lesion. EMG demonstrated a mixed axonal and demyelinating polyneuropathy. She completely recovered after two weeks.The second patient, a 65-year-old man, five days after a febrile illness had an acute onset of drowsiness, ophtalmoparesis, nystagmus, cerebellar dysmetria, absence of ankle reflexes, followed by respiratory failure and coma. Pleocytosis and increased CSF proteins were found. MRI detected lesions in the brainstem, internal capsula and corpus callosum. EMG demonstrated a severe polyneuropathy. Six months later the patient did not still recover. Both patients had no anti-GQ1b antibodies.The association of a brainstem encephalitis and a peripheral neuropathy in our patients may suggest an immuno-mediated reaction against common components of oligodendrocytes and Schwann's cells, not related to anti-GQ1b antibodies.

P508
A DIFFERENTIAL DIAGNOSIS BETWEEN PRIMARY ANGIITIS OF CENTRAL NERVOUS SYSTEM (PACNS) AND MULTIPLE SCLEROSIS (MS).Martinelli V., Rodegher M., Volontè M.A., Colombo B., Del Carro U., Magnani G., Campi A., Canal N. and Comi G. Department of Neuroscience H San Raffaele, Milan, Italy

Background: Primary angiitis of Central Nervous System (PACNS) represents a puzzling (although rare) differential diagnosis with MS, because of the lack of systemic features and since the clincal involvement is limited to CNS with dissemination in time and space of lesions. Abnormal cerebral angiography is usually considered a major criterium for PACNS diagnosis even if it may be sometimes normal since the most consistent pathology is in small arteries and arterioles.Patients: We describe clinical and paraclinical findings of 6 patients (4 M and 2 F, age 18-48 years, duration of disease 1-3 years) with a normal cerebral angiography, who had had a previous diagnosis of MS and a final diagnosis of PACNS.Results: General laboratory parameters and acute-phase reactants were normal in all patients. CSF had a mild pleocytosis and/or elevated protein levels in 3 patients; Oligoclonal Bands were positive in 2 patients. One or more Evoked Potentials were abnormal in 5 patients. In all patiens cerebral MRI had multiple abnormal areas, most of which showed enhancement at Gd injection. Cerebral biopsy performed in 2 patients documented a small vessel vasculitis.Steroid therapy induced a rapid and dramatic decrease of the number of enhancing lesions as well as a significant clinical improvement. Chronic steroid resulted in a persistent suppression of the disease activity (mean follow-up 3.1 years).Conclusions: The enhancement of most of MRI lesions during a clinically active phase of the disease, not at presentation, is the most important non-invasive criterium for PACNS diagnosis.

P509
PHOBIC POSTURAL VERTIGO: INCREASED BODY SWAY ACTIVITY WITHOUT BALANCE IMPAIRMENT.Veronika Schlamp, Siegbert Krafczyk, Marianne Dieterich, Thomas Brandt.Department of Neurology, University of Munich, Marchioninistr. 15, D-81366 Munich

Patients with phobic postural vertigo (PPV) typically show a dissociation between subjective postural instability and objectively maintained balance skills in routine clinical testing. In a previous posturographic study on patients with PPV, body sway activity was found to be increased in the higher frequency range (3.5-8Hz). This subsequent study tested whether the increase in body sway activity impairs postural balance or not. In 16 patients with PPV (mean age: 33) and 15 normal subjects (mean age: 42) lateral body sway was analyzed for two standing positions on a foam rubber padded platform: a) normal upright stance, b) tandem stance (one foot directly behind the other), and each with the eyes open or closed. At normal upright stance (eyes open or closed) patients showed an increase of lateral sway path values and of lateral body sway activity between 3.5 and 8Hz. The same held for tandem stance with the eyes open. However, in the most difficult balance task, tandem stance with the eyes closed, lateral body sway activity ($p=0.66$) and sway path values ($p=0.91$) did not differ between patients and normals. Thus, objective balance skills were not impaired in patients with PPV. We suggest that increased body sway activity reflects a common postural strategy in which anti-gravity muscles are coactivated. This strategy adopted by normal subjects in demanding balance tasks, is inadequately applied by patients with PPV at normal upright stance.

P510
SEVERE FALCIPARUM MALARIA RESULTING IN NEUROLOGIC SEQUELAE IN ADULTS.Roze.E[1], Thiebaut.MM[2], Mazevet.D[1], Bricaire.F[2], Caumes. E[2]; Department of Neurologic Rehabilitation[1], Department of infectious and tropical diseases[2], Pitié-Salpétrière hospital, Paris, France.

Malaria persists as a leading cause of suffering and death world-wide. Severe forms of the disease are the consequence of plasmodium falciparum infection in non-immune hosts. Severe malaria in adults is commonly supposed either to result rapidly in death or to be cured without referable sequelae though current reports have emphasised that neurologic sequelae could be witnessed in few cases. We reviewed the experience with malaria at an infectious department in a large teaching hospital in Paris from 1989 to 1998 focusing on the patients with a diagnosis of falciparum malaria who experienced neurologic sequelae on discharge. We describe herein six imported-cases of severe malaria in adults resulting in neurologic sequelae. The most striking findings were neuropsychological disorder -particularly memory impairment- on clinical examination and diffuse white matter damage on MRI examination. Only half of the patients made a full recovery within six months. Issues on epidemiology, pathophysiology, clinical and MRI aspects and management are discussed. Literature on this purpose is also reviewed.

P511
DIFFERENT PATTERNS OF PERIPHERAL NEUROPATHY FOLLOWING BONE MARROW AND ORGAN TRANSPLANTATION. A Blancher, P. Chemouilli, C. Lacroix, D. Adams, G. Said - Service de Neurologie, CHU de Bicêtre, Univ. Paris-Sud, 94275 Le Kremlin Bicêtre, France.

The pathophysiology of peripheral neuropathy that occurs after tissue transplantation is unclear. In order to learn more on post transplantation neuropathy (PTN) we reviewed the clinicopathological data of 12 patients who manifested a severe polyneuropathy between 1 and 36 months after organ transplantation. Patients 1 & 2 received a kidney, Patients 3-7, a liver; Patients 8-11 had an autologous bone marrow and Patient 12 a lung transplantation. Patients 1-4 & 6 developed a subacute sensory-motor deficit affecting all four limbs; patient 9, a sensory and patients 5 & 8 a sensory and motor deficit restricted to the lower limbs, while four patients (7, 10-12) manifested a multifocal neuropathy. Two patients (Pts 1 & 2), both after kidney transplantation, had a chronic demyelinating polyneuropathy; the others had severe axonal lesions, associated in patients 5 and 7 with endoneurial inflammatory infiltrates. *Toxoplasma gondii* were found in patient's 5 nerve specimen. Three patients died shortly after the onset of the neuropathy: Patient 9 of a progressive multifocal leukoencephalitis; patient 7 of a brain abscess, patient 10 of the sensory-motor deficit. The other patients recovered, with sequelae in some. Patients 1, 5-8 & 12 were treated for cytomegalovirus infection, but CMV were not present in the nerve specimens. Multiorgan failure occurred in patients 1, 3 & 6. Patients 8 & 10 had a graft vs host reaction. Patients 6 & 12 were treated with tacrolimus, a potentially neurotoxic immunosuppressive drug, which does not actually seem to be responsible for neuropathy in our patients. We conclude that PTN mainly occurs in severely infected patients or in the course of a graft vs host reaction.

P512
IMAGE GUIDED ENDOSCOPIC THIRD VENTRICULOSTOMY. Broggi G*, Dones* I, Ferroli* P, Franzini* A, Servello* D, Duca° S-
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Third ventriculostomy (IIIVS) has become an increasingly popular procedure. This is mainly due to the improvement in fiberoptics and endoscopic instruments available for neurosurgery. Considerable experience has been accrued with image guidance systems and evidence of clinical benefits in open surgery as well as accuracy in frameless stereotactic surgery has been aknowledged.Between october 1997 and october 1998, 17 patients (12 females, 5 males; 12-82 year-old; mean age 43) underwent image-assisted

(EasyGuide, Philips Medical System) endoscopic (neuroendoscope NMT Cordis 7FC-R06E) IIIVS for hydrocephalus (H) at the Istituto Nazionale Neurologico "C.Besta" of Milano. In 14/17 cases IIIVS was the first surgical treatment of H, in 3/17 it was performed following shunt malfunctioning. Diagnosis was congenital acqueductal stenosis in 8/17 patients, post surgical H in 3/17 and idiopathic H in 6/17 cases. In eight patients there were signs of chronic intracranial hypertension, in two symptoms of acute intracranial hypertension and seven presented with the classical clinical picture of chronic normal pressure hydrocephalus (NPH). There was no mortality and no long term morbidity. Complete symptoms relief was observed in 13/17 cases, marked improvement of gait in 2/17 (idiopathic NPH) and two patients remained unchanged (NPH). Gated phase contrast Cine-MR showed the patency of IIIVS in all but one patient.In conclusion our experience shows that IIIVS is a reliable, safe and successful method to treat H of different etiologies and that neuronavigation systems are useful in assisting this procedure.

P513
LAFORA-LIKE INCLUSION BODIES IN A CASE OF PROGRESSIVE MYOCLONIC ATAXIA ASSOCIATED WITH COELIAC DISEASE-Erdem Tüzün*, Candan Gürses*, Nesimi Büyükbabani**, Betül Baykan*, Aysen Gökyigit*-*Department of Neurology, Istanbul Faculty of Medicine, University of Istanbul-**Department of Pathology, Istanbul Faculty of Medicine, University of Istanbul, Turkey

We report Lafora-like inclusion bodies in a patient of progressive myoclonic ataxia associated with coeliac disease and discuss the possible associations between two different pathological conditions.A 27-year old woman presented with slowly progressing myoclonic jerks of all limbs, dysarthria and ataxia. She defined four complex partial seizures. Family history was unremarkable, there was no parental consanguinity and previous school performance was normal. Neurologic examination revealed dysarthria, lateral gaze nystagmus, generalised hyperreflexia, wide-based gait, action myoclonus activated by walking or being touched and actional tongue myoclonus. Neuropsychological examination showed evidence of minimal deterioration in frontal lobe tasks, Mini Mental State examination score was 29 and total IQ was 70, however the patient denied any intellectual decline and her daily life activities were not affected. Light microscopy examination of axilla skin biopsy specimen showed PAS-positive and diastase resistant intracellular inclusion bodies in the apocrine sweat gland cells. Endoscopic duodenal biopsy examination demonstrated subtotal villous atrophy with a chronic cell infiltration in lamina propria.The presence of Lafora-like bodies and coeliac disease may be purely coincidental but there may also be a common mechanism for both pathologies. This clinical constellation (myoclonus, ataxia, rare seizures, Lafora-like bodies without prominent dementia, lack of clearly progressive course, coeliac disease) may be a new clinical entity and presence of Lafora-like inclusion bodies and malabsorption due to coexistent coeliac disease may somehow contribute to the unknown aetiology of Lafora's disease.

P514
IDIOPATHIC DURAL HERNIATION OF THE SPINAL CORD OR "SYNDROME DE LA MOELLE EN MANIVELLE" Bouhour F., Pageot N., Grimaud J., Moreau Th., Setiey A., Bascoulergue Y., Fischer G., Confavreux Ch. Hôpital Neurologique, Lyon, France.

The idiopathic dural herniation of the spinal cord, without any spinal trauma, is an uncommon aetiology of adult Brown-Sequard syndrome. We report two cases of Brown-Sequard syndrome at the dorsal level with a slowly progressive course. On the dorsal CT myelography and MRI, the spinal cord appeared focally atrophic and tethered antero-laterally on axial slices, with an aspect of "moelle en manivelle" on sagittal slices. In the two cases, the surgery allowed to release the spinal cord herniation and to close the dura mater fissure. Post-operative outcome was good, with clinical stabilisation in one case and gait improvement in the other. The interest of this rare anatomo-clinical syndrome is threefold: clinical presentation is characterised by a slowly progressive Brown-Sequard syndrome; radiological aspect, based on CT myelography and MRI, is a typical pattern; surgical treatment usually allows to stop the clinical progression.

P515
THE "WET SOCK": HERALDING SIGN OF SOLITARY SCHWANNOMA OF THE SCIATIC NERVE. Agnetti V, Maioli MA, Murrighile MR, Ortu R, Piras C, Sechi GP. Neurological Clinic, University of Sassari, Sassari, Italy

Schwannomas of the sciatic nerve and its main branches are rare. They usually present as a mass and/or pain in the thigh or in a dermatomal stripe down the leg. Autonomic dysfunctions are not reported as presenting signs of peripheral schwannomas. We observed two cases of schwannoma of the sciatic nerve in which hyperhidrosis of the foot was the earliest sign of the tumor. Case 1 - A 49-year-old man with a ten years history of pressure provoked shooting pain at his left medial calf radiating into the medial malleolus complained of his heel bathed in sweat ever since. Only recently occasional spontaneous pain occurred. Case 2 - A 59-year-old man had been complaining for one year of severe pain in the l ateral popliteal side of his right leg exacerbated by local pressure with irradiation to his ankle, foot and lateral three toes. Two months before pain onset he had noticed a great discomfort for persisting profuse sweating that drove him to repeated foot washing throughout the day. In the two cases sonography and MR documented a tumor in the tibial portion and in the main trunk of the sciatic nerve, respectively. The complaint of "wet sock" reported by both patients as result of circumscribed unilateral hyperhidrosis of the foot deserves attention and seems a good sign to be recorded and kept in mind by neurologists facing up to peripheral nerve injuries.

P516
DETAILED MR ANATOMY OF THE HYPOGLOSSAL NERVE. I. Yousry, G. Fesl, M.Wiesmann, T. A. Yousry-Department of Neuroradiology, Ludwig-Maximilians University, Munich, Germany

Purpose The hypoglossal nerve (NXII) is one of the smallest cranial nerves (diameter 1.3-1.5 mm). The cisternal course of NXII has not been investiagted by magnetic resonance imaging (MRI) yet. We wanted to assess the anatomic relationship of NXII using the three dimensional Fourier transformation constructive interfearence in steady state (3DFT CISS) sequence. Materials We examined 10 volunteers (20 nerves), using the 3DFT-CISS sequence. NXII was evaluated with repect to its identification, number of roots, cisternal course and presence of a nerve-vessel-contact. The length of the subarachnoid space accompanying the nerve into the hypoglossal canal was measured.Results We detected a total of 51 nerve roots. Fifty roots revealed a relationship with the vertebral artery: 44 roots passed posteriorly (27 with contact) and 5 anteriorly (4 with contact). Seventeen roots revealed a relationship with the posterior inferior cerebellar artery: 14 roots passed anteriorly (10 with contact) and 2 (without contact) posteriorly. An evagination of the subarachnoid space into the hypoglossal canal was identified in 16 sides, in one of them 2 evaginations were detected. The length of the evagination varied: in $8 \leq$ 1mm, in 5 between 1 and 3mm and in $4 \geq$ 3mm. Conclusion: The roots of NXII, their anatomical course and their neurovascular relationship can be reliably assessed using the 3DFT-CISS sequence.

P517
FUNCTIONAL NEUROIMAGING OF A COGNITIVE MODEL FOR APRAXIA. P. Peigneux°, M. Van der Linden‡, F. Collette‡, G. Garraux°, Luxen°, G. Franck°, E. Salmon°-°Cyclotron Research Centre, ‡Neuropsychology Department, Liege University; Belgium

The neural basis of a cognitive modelling of limb apraxia (Rothi et al., 1997; adapted by Peigneux and Van der Linden, 1998) was investigated with positron emission tomography. Twelve scans were obtained using oxygen-15 labelled water in 3D mode in 6 healthy subjects, during the practice of four tasks: imitation of meaningful (IMS) and meaningless (IMNS) gestures, pantomime to command (COS) and functional association decision (AF; i.e. to decide if an object may be used for the same tool function as another object). Gestures to perform with the right limb were digital as well as manual, the latter implying positioning the whole limb in the extrapersonal space (e.g., to hitchhike). Statistical parametric mapping (SPM96) demonstrated that the visual processing of gestures activated significantly the lateral occipito-temporal junction (Brodmann area [BA] 19/37), which replicates the findings of a previous study (Peigneux et al., 1998). Moreover, the postcentral regions (BA 2/7/40) were found to be bilaterally involved in the mental transformations of the body required during IMNS condition. Finally, a more widely distributed brain network, including mainly the frontal inferior (BA 45) gyrus in association to the middle temporal gyrus (BA 37) and the superior parietal lobule (BA 7) might support the output praxicon (i.e., the evocation of the visuo-kinaesthetic engrams of meaningful gestures), which calls for further studies.

P518
CLINICAL RELEVANCE OF NEURON SPECIFIC ENOLASE IN CEREBROSPINAL FLUID AND SERUM IN NEUROLOGICAL DIS-

EASES. B.W. Walther*, H.-J. Kühn**, A.Wagner** - *Department of Neurology, Klinikum Erfurt, Germany-**Department of Neurology, University Leipzig, Germany

Introduction Neuron specific enolase (NSE) is a cytoplasmatic protein localized mainly in neurons. The enzyme could be a useful biomarker for diseases with a neuronal loss. Until now the determination of NSE in cerebrospinal fluid (CSF) and serum is established in the diagnostic of Creutzfeld-Jacob-disease (CJD) only. Method Using an enzyme-immunoassay NSE was determined in 503 CSF/serum pairs of 362 neurological patients. Out of this population we selected retrospectively 107 patients (61 female, 45 male, aged 6-83 years) as control group. CSF/serum NSE of cerebrovascular disorders (72 patients), inflammatory diseases (83), degenerative disorders (32), tumors (6), trauma (5), polyneuropathia (13), epilepsias (18) and others (13) were determined. The course of serum NSE values following cerebral hypoxia (20) was analysed, furthermore serum NSE in Wilson disease (55). Results We did not found an age or gender relation of NSE concentration in CSF or serum. The re-ference values for NSE in CSF were 0-25 ng/ml. In serum we propose normal values 0-20 ng/ml, borderline pathologic values 20-30 ng/ml, pathologic values >30 ng/ml. Within 3 days after ische-mic stroke simultaneous pathologic CSF and serum NSE values showed a poor outcome (Glasgow outcome scale, GOS 1/2) whereas normal values correlated with a good one. Pathologic NSE values in CSF were found in acute/subacute inflammation of central nervous system (CNS) as a marker for a severe course. All patients with a Glasgow coma scale 5 points and pathologic CSF/NSE within 14 days after cerebral hypoxia had a poor outcome (GOS 1). The NSE peak was reached faster (after 2.1 days) in patients with GOS 1. Conclusion Reference values for NSE in CSF and serum were defined. In addition to CJD NSE can give prognostic information in cerebrovascular diseases, but the simultaneous determination in CSF and serum is needed. In inflammatory CNS diseases CSF NSE is of poor benefit. In other diseases with neuronal loss like degenerative or chronic inflammatory no pathologic values were noted.

P519
FUNCTIONAL NEUROANATOMY OF EMOTIONAL FACE RECOGNITION-Gorno Tempini ML[1], Pradelli S[1], Serafini M[3], Pagnoni G[2], Nichelli PF[1] Clinica Neurologica[1] and Dipartimento di Scienze Biomediche[2] Universita' di Modena, Azienda Policlinico Modena[3], Italy.

While observations on patients with selective brain damage and neuroimaging studies have provided evidence of functional segregation of emotional faces processing in the human brain, it is still unclear which regions are critical for explicit recognition. We used functional Magnetic Resonance Imaging to investigate the neural correlates of explicit and implicit processing of happiness and disgust.Ten subjects were presented happy, disgusted or neutral faces while EPI images were acquired using a 1.5Tesla GE MRI system. The design was a 2X2 factorial: type of task (gender decision versus explicit emotion discrimination) and type of emotion (disgusted, neutral and happy faces). The control condition was a feature detection on scrambled stimuli. Data were analyzed using SPM97.All face conditions activated a network of cortical (bilateral temporo-occipital, left(L) parietal, bilateral dorsolateral prefrontal) and subcortical regions (Lamigdala, putamen and thalamus). The prefrontal regions (BA46/47/10) were more active for explicit recognition. No areas were specific for implicit processing nor for disgusted or happy faces, but an interaction was found in the L anterior amigdala, which was selectively activated by explicit recognition of disgusted faces.This study demonstrates involvement of a common network of areas activated by both happy and disgusted emotional faces. The network can be modulated by the nature of the task or by the interaction between task and type of emotion.

P520
RANDOMIZED COMPARATIVE PLACEBO-CONTROLLED ASSESSMENT OF INTRAVENOUS VALPROIC ACID EFFECTIVENESS AND SAFETY IN PATIENTS WITH ACUTE MIGRAINE-Piotr Czapinski, Rafal Motyl. Department of Neurology, Jagiellonian University, Cracow, Poland

Goal: Studies carried out to-date indicate that valproic acid (VPA) is effective in migraine prevention. Communications on controlling acute migraine attacks by administration of VPA are scarce. So far only oral VPA has been investigated and assessed. No intravenous form of VPA has been evaluated in comparison to placebo. Material and method: Randomized placebo-controlled studies included 25 patients (18 women and 7 men) who had reported to the Department in the course of an acute migraine attack, with or without aura, within 6 hours after the onset. They were administered either valproic acid as 5-minute intravenous injections at the dose of 15 mg/kg of body weight, or 0.9% NaCl according to the same protocol. Within a 4-hour follow-up period the following parameters were assessed: degree of headache, intensity degree of migraine accompanying symptoms, degree of the patient's disability, safety of drug administration measured as the number of adverse effects, and the effect of the drug on vital and biochemical parameters. The evaluation also included the number of recurrent migraine attacks measured as the development of a recurrent moderate or severe headache after the original pain had decreased or subsided within 2-24 hours after VPA administration. Results: Out of 13 patients treated with VPA, ten showed a decrease or subsidence of pain, in contrast to four patients out of 12 in the placebo group. In eight of the former patients a significant improvement in pain intensity was noted within 2 hours after VPA administration. Recurrent migraine occurred in two patients from both groups. Five patients from the VPA group developed such adverse effects as dizziness, stomachache and burning sensation at the site of injection. These phenomena were mild or moderate and did not require any intervention. Adverse effects were noted in six patients from the placebo group. VPA was found to exert no effect on vital and biochemical parameters. Conclusions: A statistically significant difference was noted in the studies of VPA effectiveness in controlling acute migraine in comparison to placebo. At the same time the agent was proven to be well tolerated. It seems that valproic acid may become an alternative to sumatriptan derivatives or ergotamine in controlling migraine attacks in some patients. Investigations performed in a larger group of patients are necessary to confirm the conclusion.

P521
HEREDITARY SPASTIC PARAPLEGIA WITH ATROPHY OF THE CORPUS CALLOSUM: REPORT OF AN ITALIAN PATIENT. Cricchi F[1], Spadaro M[1], Pierelli F[2], Bianco F[1], Fortini D[1], Damiano M[1], Corigliano D[1], Amabile A[1], Casali C-[1] Istituto di Clinica delle Malattie Nervose e Mentali, Università "La Sapienza", Rome, Italy-[2] IRCCS Istituto Neurologico Mediterraneo "NEUROMED", Pozzilli, (IS), Italy

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of disorders characterized by insidiously progressive spastic weakness in the legs. They are classified into pure and complicated forms, with autosomal dominant, recessive and X-linked inheritance. We describe a 25 year-old woman, born to unrelated healthy parents, after unremarkable pregnancy and delivery. She developed normally until age 20 when she started having slowly progressing difficulties in walking. Neurological examination showed mild weakness in her legs, marked spasticity, extremely brisk reflexes, and bilateral Babiski sign. No sensory, cerebellar, and cranial nerve impairment were found. Visual acuity and hearing are normal. She only complains of slight urinary urgency. She is mentally normal. Serum tests and B12 were normal; anti HTLV and antiGM antibodies were negative. Brain MRI showed marked atrophy of the corpus callosum and frontal cortex. Spinal cord MRI was normal as well as EMG. HSP with atrophy of the corpus callosum is regarded as a complicated form of HSP, because moderate to severe mental impairment is often present. It has been reported in less than 20 patients and is considered typical of Japan. Our patient is remarkable because of her different racial background and the occurrence of an extremely thin corpus callosum in a "pure" form of HSP. Whether this represents a different disorder from the Japanese form is difficult to judge. The extent of the involvement of the transcallosal fibers in HSP is probably often underestimated, and MRI is a relatively recent technique not always performed when the diagnosis of HSP is obvious. However it is important to delineate different syndromes because they might be associated to different molecular abnormalities and course and, ultimately, future therapeutic approaches.

History of neurology

P522
NEUROLOGY IN THE WRITINGS OF AVICENNA AND EARLY ISLAMIC BELIEFS - Bolukbasi O*, Turgut M-Departments of Neurology* and Neurosurgery, Medical Faculty of Adnan Menderes University, Aydin, Turkey.

Objective. To describe the concepts about neurological problems in the works of Avicenna and the hadiths of the Prophet Mohammed.Background. Great Turkic philosopher and scientist Avicenna(Ibn Sina) was an outstanding medical writer through dark ages and European Renaiscence.

He wrote a gigantic medical tome " Canon de Medicina "and made enormous contribution to the medical scholarship. Three centuries before of Avicenna, Prophet Muhammad founded the Islam and gave some medical advises including neurological remedies to the believers. Design/Methods We examined neurological matters in the writings of Avicenna and hadiths resources (advises of the Prophet). Results/Conclusions. The most interesting difference in medical thinking of Avicenna was seeing medicine as a natural matter. In his Canon he had described the medicine as "... is the science by which the dispositions of the human body are kown so that whatever is necessary is removed or healed by it, in order that health should be preserved or if absent, restored "... He described pupil functions, meningitis, nerve suturing, apoplexy and gave many interesting observation about sleep and epilepsy. He was the founder of child psychiatry, also. In his medicine, "demons" or other supernatural powers had no role in the repertoire of causes of diseases. Muhammad introduced a lot of novelty into medicine and contrary to the " peater naturam " medical practice of the Christian Church, his medical advises were logical and regional. Neverthless, he advocated consanguineous marriages and occult mystical acts to some problems like epilepsy and stroke. Until University Reform of Turkey in 1933, people practiced (as folk medicine) remedies of hadiths in place of positivist scientists like Avicenna and their followers. These religious folk remedies still have a sense to some undereducated people of Turkey

Multiple sclerosis

P523
SERUM AND CEREBROSPINAL FLUID ANGIOTENSIN-CONVERTING ENZYME ACTIVITY IN MULTIPLE SCLEROSIS. D. Ferriby[1], T. Stojkovic[1], J. De Seze[1], A. Racadot[2], P. Vermersch[1].Department of Neurology[1], Biochemical laboratory[2]. CHRU Lille France.

The interest of angiotensin-converting enzyme (ACE) in multiple sclerosis (MS) have been recently suggested by Constantinescu et al (Arch. Neurol., 1997).OBJECTIVE: The aim of this study was to confirm the frequency of high serum and cerebrospinal fluid (CSF) ACE level in MS patients. We also studied the correlations between ACE activity and clinical outcome or prognosis.PATIENTS and METHODS: We prospectively studied 50 patients with clinically or radiologically definite MS (first group), 30 patients with other neurological diseases (second group), and 15 healthy controls. ACE activity was measured in serum and CSF using a spectrophotometric assay. Results were correlated with the occurence of relapse and with clinical parameters (EDSS score). RESULTS: High level of ACE in serum was found only in 3 patients (6%) of the first group, in 2 of the second (6.6 %), and none in controls. Only 1 (2%) of the MS patients had elevation in CSF, non observed in serum. High level was correlated with relapses, but not with disability.CONCLUSION: This study showed that ACE activity is not a good marker of activity and prognosis in MS.

P524
CLADRIBINE EFFECTIVE IN MULTIPLE SCLEROSIS.G Katsamakis, D Stefoski, K Karlin, FA Davis.Chicago, USA

To retard or arrest secondary progressive multiple sclerosis (MS), we administered cladribine in 63 patients who failed to benefit from one or a combination of standard treatments. Cladribine, a purine nucleoside analog with selective toxicity toward lymphocytes, has been successful in the treatment of MS both clinically and on MRI in a few studies, with good safety and tolerability, although a few others demonstrated no benefit. The paucity of published data prompts this report of our clinical experience.Adapting from the model of Sipe et al, we administered four to six courses of cladribine 700 mg/kg over five days IV or SC at 4 to 6 week intervals. Patients with more rapid progression received concomitant daily methylprednisolone 1500 mg IV with one or more courses. The main outcome measure was comparison of post-treatment to pre-treatment functional scores. Patients' subjective outcome assessments were also recorded.Sixty-two patients received cladribine over an average of 5 months. One patient died after the 3rd course of cladribine from graft-versus-host disease due to a non-irradiated blood transfusion. Side effects included transient leukopenia, thrombocytopenia, hepatic enzyme elevations and one case of cutaneous zoster. On average followup examinations of 14 months, 44 (69%) patients benefitted, 21 (33%) improved and 23 (36%) stabilized, using a previously published functional assessment scale. Subjectively, 41 (65%) patients benefitted, 23 (36%) reported reduced symptoms and 18 (29%) stabilized. We conclude that cladribine is effective in MS.

P525
MATRIX METALLOPROTEINASES AND TISSUE INHIBITORS OF METALLOPROTEINASES IN RELAPSING-REMITTING AND CHRONIC-PROGRESSIVE MULTIPLE SCLEROSIS.Verena Leussink, Christian Ramp, *Guido Stoll, Andreas Weishaupt, Klaus V. Toyka, Ralf Gold. Departments of Neurology, University of Wuerzburg, *University of Duesseldorf, Germany

There is evidence that matrix metalloproteinases (MMPs) and their natural inhibitors are involved in the pathogenesis of inflammatory demyelinating disorders of the central nervous system. As yet there are only few data available on the expression of MMPs, tissue inhibitors of metalloproteinases (TIMPs) and soluble vascular cell adhesion molecule-1 (sVCAM-1) in body fluids in relation to the subtypes of multiple sclerosis and disease activity.We measured concentrations of MMP-1, MMP-2, MMP-3, MMP-9, TIMP-1 and TIMP-2 and sVCAM-1 by ELISA in serum or plasma(MMP-9) and CSF from patients with acute relapsing-remitting MS (RRMS, n=14), stable RRMS (n=9), secondary chronic-progressive MS (SPMS, n=14), and primary chronic-progressive MS (PPMS, n=16). Patients with non-inflammatory neurological diseases (NIND, n=32), inflammatory neurological diseases (IND, n=7) and meningitis (n=7) served as controls. In all patients higher concentrations of MMPs and TIMPs were observed in blood with the exception of TIMP-2, where higher levels were detected in CSF than in blood. In patients with SPMS, TIMP-2 was decreased in serum (meanSD: 56 ± 15ng/ml, $p < 0.05$), but tended to be increased in CSF (115 ± 60ng/ml, p=0.1) in comparison to NIND (serum 69 ± 17ng/ml, CSF 85 ± 29ng/ml). In acute RRMS, the ratio of TIMP-1 / MMP-9 was decreased in CSF (103 in RRMS vs. 170 in NIND, $p < 0.05$), obviously due to upregulation of MMP-9 and downregulation of TIMP-1. In PPMS, the ratio of TIMP-1 / MMP-2 in serum was increased (2.0 vs. 0.9 in NIND, $p < 0.05$). sVCAM-1 was slightly elevated in CSF of patients with PPMS (12 ± 3ng/ml vs. 9 ± 4ng/ml in NIND, $p < 0.05$). Our findings suggest a complex regulation of MMP-2, MMP-9, TIMP-1 and TIMP-2 activity in CSF and blood in different subtypes of MS. Further investigations on the balance between MMPs and TIMPs are necessary in future.
Supported by: University research funds

P526
A LONGITUDINAL ^{1}H-MR SPECTROSCOPY STUDY OF NAWM IN PATIENTS WITH CLINICALLY ISOLATED SYNDROMES SUGGESTIVE OF MS. PA Brex, GJM Parker, GJ Barker, CA Davie, GT Plant, DH Miller. NMR Research Unit, Institute of Neurology, London, UK.

Widespread axonal damage can be detected in the normal appearing white matter (NAWM) of patients with established multiple sclerosis (MS) using ^{1}H-MR Spectroscopy to measure N-acetyl aspartate (NAA) concentration, a neuronal marker. The stage in the disease when this occurs has not yet been determined. Recent histopathological studies suggest axonal loss may be an early feature.We studied 33 patients within 6 months of their presentation with a clinically isolated syndrome (27 optic neuritis, 4 brainstem and 1 spinal cord syndrome). A significant proportion of these patients are likely to be at the very earliest clinical stages of MS. Single voxel spectra (1.5T GE scanner, TR 3000ms, TE 30ms, PROBE, PRESS) were acquired from NAWM in the posterior parietal or centrum semiovale regions of the brain. We also studied 21 age and sex matched controls. Eighteen of the patients and 9 controls were restudied nine months later. There were no significant differences between NAA in the patient and control NAWM at baseline (patients: 7.5mM, controls: 7.8mM; p=0.3). After follow up there were no significant changes in NAA in either group.This technique has proven to be a reproducible measure of NAA concentration. The absence of a detectable change in NAA in these patients suggests that significant axonal damage has not yet occurred in the NAWM. Continued follow-up is necessary to determine the timing of this event.

P527
PAROXYSMAL ATTACKS IN MULTIPLE SCLEROSIS. Tüzün E, Akman-Demir G,Eraksoy M.Department of Neurology, Istanbul Medical Faculty, University of Istanbul, Turkey

Paroxysmal attacks in multiple sclerosis (MS) have been reported extensively and ephaptic transmission of demyelinated neurons is the presumed mechanism of this phenomenon. We evaluated retrospectively, clinical and neuroradiological findings of patients who developed any paroxysmal attacks during the course of their disease.Sixty (41 women, 19 men) out of 1624 cases followed at the MS unit of our institution between 1987-1998, experienced paroxysmal symptoms. 57 had clinically or laboratory sup-

ported definite or probable MS, 1 possible MS, 1 neuro-Behçet's disease and 1 Devic's syndrome. Paroxysmal attacks were the presenting symptoms in 18 cases. In the remaining 42 cases they occurred 6 months to 27 years after the initial symptoms. Patients reported paroxysmal tonic seizures (27 cases), dysarthria and ataxia (14 cases), diplopia (13 cases), numbness (8 cases), hemiparesis (2 cases). Five of these cases had more than one type of attacks. 42 cases had cranial MRI examination and 33 of these (79%) had lesions which might be related with their symptoms. Paroxysmal attacks are rare but quite typical and much disturbing phenomena which may be seen in the course of MS. They are rather easily handled in the clinical practice and therefore their recognition is important both in the diagnosis of MS and management of the patients.

P528
CORRELATION BETWEEN MAGNETIC RESONANCE IMAGING OF THE OPTIC NERVE, VISUAL EVOKED POTENTIALS AND VISUAL PSYCHOPHYSICS. A SERIAL STUDY IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS. Weatherby JM[1], Davies MB[1], Lai MH[1], Williams R[1], Haq N[1], Foster DH[2], Hawkins CP[1] [1]Keele MS - Research Group, Stoke-on-Trent. [2]Aston University, UK.

In multiple sclerosis (MS), interferon-beta may exert its effect on inflammatory processes. This hypothesis was investigated in 20 patients with secondary progressive disease enrolled in a trial of beta-interferon-1a. Short T1 inversion recovery sequences (STIRS) of the anterior visual pathway, pattern reversed visual evoked potentials (VEP) and visual psychophysical measurements were performed at enrollment and at three years. Psychophysical thresholds were obtained at isoluminance for 0.25 cyc/deg, 1cyc/deg, and 4cyc/deg gratings, presented to preferentially stimulate the magnocellular or parvocellular pathways. At baseline, correlation was found between P100 latency and optic nerve total lesion load (r=0.34, p=0.01) and P100 and psychophysical threshold (magnocellular- 0.25cyc/deg r=0.34 p=0.02; 1cyc/deg r=0.64 p=0.000002; 4cyc/deg r=0.36 p= 0.014; parvocellular- 0.25cyc/deg r= 0.48 p=0.0007; 1cyc/deg r=0.58 p= 0.00003 4cyc/deg r=0.48 p=0.001). After three years a significant improvement in lesion load (p=0.03) occurred and a trend for improvement in contrast thresholds associated with the magnocellular pathways was identified (0.25cyc/deg p=0.005; 1cyc/deg p=0.2, 4cyc/deg p=0.006). A non-significant numerical worsening in P100 latencies was noted. Changes within these parameters did not show correlation. This study suggests that improvement of psychophysical measures and anterior visual pathway lesion load may occur independently of the VEP and that improvement in psychophysical thresholds may reflect release of conduction block in demyelinated fibres.

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SERIAL IMAGING STUDY OF THE OPTIC NERVE IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS. S.J.M.Weatherby, M.B. Davies, N. Haq, R. Williams, C.P. Hawkins. Keele Multiple Sclerosis Research Group. Stoke-on-Trent. UK.

The visual pathway is frequently involved in Multiple Sclerosis (MS). However, relatively little is known about the long-term dynamics of optic nerve lesions and therefore six-monthly magnetic resonance imaging (MRI) of the anterior visual pathway was performed in a group of 26 patients with secondary progressive MS enrolled in a trial of beta-interferon 1a. Images were acquired using a 0.5T scanner using a STIR sequence (TR 1400/TI 140/TE 25ms); twelve contiguous 4mm coronal slices and interslice gap 1mm. Sequential images were obtained from the optic disc to the chiasm. Two observers (SW and NH) agreed lesion identification. The area of involved optic nerve was delineated using a manual outlining technique.82% (43/52) of the optic nerves showed abnormality during the study, involving anterior orbit (42%), posterior orbit (31%), optic canal (24%) and prechiasmal region (3%). The average area of affected optic nerve was 9.2mm^2 per slice. The total number of involved slices was 371 (188 right eye, 183 left). 24% of these were new optic nerve lesions and in 45% of cases persisted for two or more consecutive scans. In 36% of slices abnormality subsequently resolved. We conclude that involvement of the optic nerve in patients with secondary progressive multiple sclerosis enrolled in the said treatment trial is a dynamic process with significant fluctuation of lesions seen on magnetic resonance imaging.

P530
MICROGLIA CAN PROMOTE MATURE OLIGODENDROCYTE SURVIVAL. RS Nicholas, DAS Compston, MG Wing-University of Cambridge, Neurology Unit, Addenbrookes' Hospital, Hills Road, Cambridge, CB2 2QQ, UK.

Background: We have previously demonstrated that microglia can promote both the differentiation and survival of stressed oligodendrocyte progenitor cells (OPC's) through a mechanism involving the release of platelet-derived growth factor (PDGF) and modulation of the PDGF signalling pathway. Here we show that microglial supernatants have a separate survival effect for mature oligodendrocytes. Materials and Methods: Rat mixed glial cultures were used to derive both microglia and oligodendrocytes. The effect of microglial conditioned supernatants on mature oligodendrocyte survival and apoptosis after 48 hours in culture was then studied.Results: Microglial supernatants enhanced mature oligodendrocyte survival due to an anti-apoptotic effect on mature oligodendrocytes, which was independent of microglial activation. This effect was not dependent on PDGF but was related to the presence of insulin-like and ciliary neurotrophic factors. Insulin-like growth factor 1 (IGF-1), implicated in oligodendrocyte survival, is produced by activated microglia. However an insulin bioassay confirmed that insulin-like activity within our cultures was not modified by microglial activation. Antibody blockade confirmed that IGF-2 was responsible. Enhanced survival was specific for oligodendrocytes since microglial-derived supernatants had contrasting effects on astrocytes and neurons. Conclusions: Together with the detrimental effect that microglial activation has on OPC's these experiments strengthens the case for therapeutic intervention in diseases such as Multiple Sclerosis targeted at microglia.

P531
IS THE RESPONSE TO COPOLYMER-1 THERAPY RELATED TO HLA ALLELES?V Brescia Morra[1], R Lanzillo[1], G Coppola[1], M Coppola[1], V Lombari[2], G Pirozzi[2], E Pace[3], ML Lombardi[2], G Orefice[1], C Fusco[3], [1]Dpt. Neurological Sciences, [2]Oncologia Sperimentale, INT, [3]SIT, ARN "A. Cardarelli", Naples, Italy,

In vitro and in vivo Experimental Allergic Encephalomyelitis (EAE) and RR-MS studies suggest that mechanism of Copolymer-1 (Cop-1) activity involves its binding to MHC class II molecules as an initial step. The aim of the present study was to study the relationship between HLA alleles and response to Cop-1 therapy. Twenty-nine RR-MS patients, with baseline EDSS ranging from 1.5 to 6 and at least two relapses in the prior two years received Cop-1 for one year. Clinical outcome was assessed according to following criteria: treatment failure was declared in patients with two or more disabling exacerbations and/or EDSS increase of one point or more (non-responder); good clinical outcome was defined as decrease of disability and absence of relapses (responder); patients characterized by one exacerbation and/or steadiness or slight worsening of disability, were considered as intermediate. As described for other ethnic groups, a significant increase of DRB1*1501 frequency was found (27.5%, $p < 0.001$). Comparing the DRB1*1501 frequency and response to Cop-1 therapy in the three groups of patients, we found the highest DRB1*1501 frequency in the responder group (55.6%; p=0.05), whereas no DRB1*1501 positive patient was in the non-responder group; only 20% of patients of the intermediate group had the same allele. These results, although slightly significant, suggest a relationship between presence of DRB1*1501 and response to Cop-1 therapy in RR-MS and need confirmation from a longer follow-up and greater series.

P532
INTERFERON-γ INDUCIBLE PROTEIN-10 IS INCREASED IN THE CEREBROSPINAL FLUID OF PATIENTS WITH MULTIPLE SCLEROSIS.Prat E., Baron PL., Meda L., Scarpini E., Conti G., Galimberti D.,Ardolino G.,Agazzi P.,Tadeo C. S., Bussini S., Scarlato G. Institute of Neurology, Dino Ferrari Center, University of Milan, IRCCS Ospedale Maggiore, Milan - Italy

Chemokines are low molecular weight chemotactic cytokines that have been shown to play an important role in early inflammatory events such as perivascular transmigration and accumulation of leukocytes at the sites of tissue damage. Interferon-γ (IFN-γ)-inducible protein-10 (IP-10), a newly discovered cytokine of chemokine family, appears to target specifically activated T lymphocytes and it is produced by monocytes, lymphocytes and endothelial cells in response to IFNγ. In the present study, IP-10 levels were determined by radioimmunoassay (RIA) in the cerebrospinal fluid (CSF) and in the serum from 14 patients with clinically definite relapsing remitting multiple sclerosis (MS) and from 12 control patients with non-inflammatory neurological diseases. We showed that the concentration of IP-10 in CSF was significantly elevated in MS (469 pg/ml) compared with control samples (272 pg/ml) (p=0.0002). Low or undetectable levels of IP-10 were found in serum of both MS and control pa-

tients. These data, together with the previous finding of transient burst of IP-10 expression at the onset of experimental autoimmune encephalomyelitis (EAE), point out the possible involvement of IP-10 in phagocyte recruitment during MS in relapse.

P533
CYTOKINE BALANCE, METALLOPROTEINASES AND GLIAL CELLS: INFß 1A* DECREASES THE CAPACITY FOR TNFα TO INDUCE MMP-9 AND MMP-3 EXPRESSION IN HUMAN ASTROCYTES. Gignoux L, Confavreux C, Chalon A, Malcus C, Belin MF, Giraudon P (Hôpital de l'Antiquaille & U433 INSERM, 69372 Lyon France)

Metalloproteinases (MMPs), a family of endopeptidases secreted by neural cells, have been associated with neurological diseases including multiple sclerosis (MS). Overexpression MMP-9, -3 and -7 have been found in the cerebrospinal fluid and lesions within the central nervous system (CNS) of MS patients. They are thought to open the brain-blood barrier thus facilitating T-cell infiltration and inflammation, to cleave myelin componants and to be involved in the maturation of cytokines. MMP activity is controlled by natural inhibitors, TIMPs and expression regulated by cytokines. Since elevated pro-inflammatory cytokines is a characteristic feature in MS, we hypothesise that a dysbalance between pro- and anti-inflammatory cytokines may lead to a dysbalance in MMP/TIMP ratio. This may result in excessive MMP secretion by glial cells hence in neural cell impairment. To assess this idea, the effect of various cytokines on the expression of MMPs and TIMPs was evaluated on a human glial celle line (Dev) by using zymography (enzyme activity) and RT-PCR (mRNA expression). Pro-inflammatory cytokines (IL1α, IFNγ et TNFα) were shown to induce MMP-9 and MMP-3 secretion in glial cells while anti-inflammatory (IL4, IL10, IFNß1a*) remained without any effect. Co-treatment with TNFα and IL4, IL10 or IFNß1a* revealed a clear inhibition by anti-inflammatory cytokines of the inductive effect of TNFα on Mmp-9 and MMP-3. Moreover, treatment with IL10 potentiated the effect of IFNß1a*. This study indicates that an inflammatory environment within the CNS may result in excessive secretion of MMP-9 and MMP-3 and suggests a beneficial effect for IFNß1a* at this level. (*IFNß1a Rebif® Serono)

P534
"USE OF COPAXONE® IN FRANCE THROUGH THE "ATU" (TEMPORARY AUTHORISATION FOR USE) BEFORE REGISTRATION" Moreau T (Department of Neurology, Hôpital de la Croix-Rousse, Lyon, France) and Heinzlef O (Department of Neurology, Hôpital Tenon, Paris, Fance)

COPAXONE® has proved to be effective in reducing both the relapse rate in relapsing-remitting forms of multiple sclerosis[1] and the MRI activity of the disease[2].Thus, COPAXONE® is now marketed in several countries including the USA, Canada and Israel. Waiting for this approval in France, on request of the neurologists, the French Medical Authorities may grant an "ATU".The "ATU" is a specific procedure settled by the French Medical Agency (FMA) in order to allow the prescription of a drug of interest before its Marketing Authorisation, under the full responsibility of the physician. The COPAXONE® "ATU" has been approved at the end of 1997 for contraindications or side effects to the prescription of interferons.The objective of this "ATU" is to analyse data concerning compliance and tolerance in order to assess, beside the specific use within clinical trials, the first French prescriptions in a practical situation.Data are collected first at the beginning of the treatment and then every three months, and documented in a specific database by a Clinical Research Assistant. 53 patients have been included so far. From the analysis of the initial visit documented data for 35 patients, we have 26 women and 9 men, mean age: 38.7 (23-56), who have begun the treatment all over the country. Their characteristics are in terms of illness duration: mean 8.3 years; initial EDSS: mean 3.3 (0-7) and indications: depressive syndrome, transaminases elevation, local or general allergic reactions, epilepsy... 12 patients were previously treated with Avonex®, 17 with Betaferon®, 4 with Imurel®. We can emphasize that the mean EDSS of these patients is rather low, which corresponds to a mildly disabled population. The present total exposure to COPAXONE® through this "ATU" is around 5000 days of treatment. The adverse events reported are mainly local site injection reactions.(1) KP Johnson and al. Neurology, 1998; 50: 701-708.(2) Internal report. In press.

P535
EFFECTS OF ANAPSOS IN THE TREATMENT OF MULTIPLE SCLEROSIS (MS) PATIENTS: De Castro, P (*);Carreño, MM (*); Sempere, JM (^ $); (*) Department of Neurology. University of Navarra. (^) Division of Immunology. University of Alicante. ($) Scientific Department of ASAC Ph Int A.I.E, Alicante..

INTRODUCTION: Anapsos is a medicine registered in Spain and other countries, obtained from the rhyzome of the fern Polypodium leucotomos. Several studies show an ability of the product tomodulate production of proinflammatory cytokines as well as expression of certain differentiation antigens (CD) of the immune system.AIMS: To analyse the effect of Anapsos on lymphocyte subsets from MS patients, and to compare it with that produced by other treatments.PATIENTS AND METHODS: Whole blood lymphocyte subsets of 46 non-treated patients and 38 treated patients (10 with Anapsos, 13 with azathioprine and 15 with natural interferon) were analysed by Flow Cytometry (Epics XL; Coulter), according to the most appropiate combination of monoclonal antibodies in each case.RESULTS. Anapsos vs.no treatment, significantly increased the CD4+CD29+(88.2 * 2.2 vs.82.1* 7.2,p=0.01) and CD4+CD29+CD45RA-(62.8* 12.4 vs.53.5* 11.5,p=0.03) subsets, and showed a trend to increase the CD4+CD29+CD45RA-/CD4+CD29+CD45RA+ rate (3.02* 2 vs.1.9* 1.5p=0.06) and to diminish CD4+CD29+CD45RA+(27.6* 12.3 vs.34.02* 9.9,p=007) subset. Azathioprine also increased the CD4+CD29+CD45RA-(60.9* 11.9, p=0.04) subset. On the contrary, interferon decreased the CD4+CD29+CD45RA-(45.3* 7.9,p=0.01) and CD4+CD29+CD45RO+ subsets, and increased the CD4+CD29+CD45RO- subset.CONCLUSIONS An effect of Anapsos on different lymphocyte subsets has been shown, these results suggesting a possible benefit of the product in the treatment of MS patients.

P536
METABOLIC AND MAGNETIC RESONANCE IMAGING FEATURES IN MULTIPLE SCLEROSIS PLAQUES. Simone IL, Tortorella C, Giannini P, Federico F, Lucivero V, Bellacosa A, Livrea P - Bari-Italy

Background T1 hypointensity seems to be related to axonal damage, but as suggested by histopathological data the hypointensity may be affected by different factors and the axonal loss may be an early event in plaque evolution.Objective. To correlate metabolic and imaging patterns in Multiple Sclerosis (MS) plaques. Patients and Methods: Fifty clinically definite MS patients were evaluated. MRI included: PD, T2 (TR/TE: 2200/20-80 msec), pre and post contrast T1 (TR/TE: 600/15 msec) weighted SE scans. 1H-MR spectroscopy was performed on 63 localized plaques (SE sequence, TE: 135 msec) (Magnetom Siemens 1.5 T). Thirty-six plaques were Gd enhancing (Gd+) (27 hypointense and 9 isointense on pre contrast T1-weighted scans) and 27 Gd unenhancing (Gd-) (22 T1 hypo and 5 isointense). Twenty-two healthy subjects were used as control group (NC). Results: The Gd+ plaques showed: 1) presence of lactate with higher frequency (38%) than Gd- plaques (18%). 2) significant increase of Choline/Creatine (Cho/Cr) ratio both in T1 iso (p= 0.04) and hypointense (p= 0.001) than in NC. 3) no differences in N-acetyl Aspartate (NAA)/Cr mean. Nevertheless, 44% of T1 iso and 33% of T1 hypointense plaques showed NAA/Cr values lower than 10th centile of NC. The Gd- plaques, both iso (p= 0.02) and hypointense in T1 (p= 0.001), showed a significant decrease of NAA/Cr ratio than NC. Frequency of pathological values of NAA/Cr (40% in T1 iso and 50% in hypointense) did not differed from that reported in Gd+ plaques. Conclusions: Our study indicate that demyelination is an early process in active plaques. Axonal damage is a typical event of inactive plaques, but it is already detectable in the acute phase and both in T1 hypo and isointense plaques.

P537
PREDICTIVE FACTOR OF MULTIPLE SCLEROSIS (MS) COURSE: AGE AT ONSET. Liguori M., Tortorella C., Lepore V., Carrara D., Livrea P. and Simone I.L. - University of Bari - Bari - Italy

Introduction/Background: Retrospective analysis on MS population showed that the occurrence of the disease before the age of 15 yrs. (early onset MS - EOMS) was often misdiagnosed. Aim of the study: to identify prognostic categories in a controlled MS population subdivided by age at onset of the disease in EOMS and AOMS (MS in adult life > 15 yrs.) groups. Materials/methods: Eighty-hundred-eighty-eight MS patients (62 EOMS and 826 AOMS) followed at the Department of Neurol - University of Bari, have been submitted to a retrospective comparison (Chi-square; Mann-Withney U-test) of their clinical and demographic data (EDMUS database). A survival model (Kaplan-Meyer by SAS package) was performed to assess the prognostic values of several variables (sex, age at onset) associated with outcomes (time to reach EDSS 4 and EDSS 6); sta-

tistical differences were tested by Log-rank and Wilcoxon. Results: Sex ratio was 1.95 in EOMS and 1.8 in AOMS. The disease course was relapsing remitting in 84% of EOMS patients compared to 70.4% of AOMS ($p= 0.03$); no EOMS patients had a chronic progressive course. In EOMS an higher mean interval between the first and the second clinical attack ($p= 0.007$) and a lower progression index (EDSS/disease duration; $p < 0.001$) were found in comparison to AOMS group, suggesting a more benign course of the disease with early onset. In AOMS time intervals to reach EDSS 4 and EDSS 6 were shorter than those observed in EOMS ($p= 0.0001$ and $p < 0.0027$). When stratified by sex, these significances were confirmed in the female ($p= 0.003$ and $p < 0.02$), whereas no differences was observed in male groups. Conclusions: These data indicate different prognostic value assumed by the age of onset in MS and confirm a more benign course in EOMS.

P538
IN VIVO β-IFN1B TREATMENT IN MS PATIENTS DECREASES TRANSMIGRATION OF PBMNCS THROUGH ENDOTHELIUM. Corsini E., Gelati M., Dufour A., La Mantia L., Milanese C., Nespolo A., Salmaggi A. Ist. Nazionale Neurol."C.Besta", Milan, Italy

Since the development of mononuclear cells infiltrates is a crucial step in Multiple Sclerosis pathology, a drug able to reduce PBMNCs extravasation through the BBB could be beneficial in MS course. β-IFN-1b decreases clinical exacerbations in relapsing-remitting MS and reduces the number of active lesions at MRI, but its mechanism(s) of action in MS are still under investigation. An in vitro study has shown that β-IFN-1b inhibits transmigration of lymphocytes across fibronectin monolayers, decreasing MMP-9 production by lymphocytes (Stuve, 1997). Moreover, inhibitors of matrix metalloproteinase have proved effective in the treatment of MS models (Liedtke, 1998). It has also been demonstrated that soluble adhesion molecules, such as sVCAM-1 and sICAM-1 increase in sera after β-IFN treatment.We evaluated the transmigration of PBMNCs from 7 RR MS patients through endothelial cells (HUVECs) monolayers, before (T0) and after 3 (T3) and 6 (T6) months of β-IFN-1b treatment. We also quantified serum sPECAM-1, a molecule crucial in transmigration phenomena and assessed MMP-9 in the sera and in the supernates of MS patients' monocytes, collected at the same time points. Transmigration ability and MMP-9 and sPECAM-1 levels were also studied in 7 healthy controls.In MS patients, the absolute numbers of transmigrated cells decreased, although not significantly, after β-IFN-1b treatment. We also observed a marked decrease in MMP-9 levels, both in sera and in monocyte' supernates, while sPECAM-1 did not change. Our data seem to suggest that in our transmigration model, with endothelium monolayers, in vivo β-IFN can reduce PBMNCs transmigration by decreasing their MMP-9 production.

P539
INTERFERON BETA TREATMENT IN RELAPSING-REMITTING MULTIPLE SCLEROSIS. THE FIRST POST-MARKETING STUDY IN LOMBARDIA (ITALY)Milanese C, La Mantia L, Palumbo R and the MS Centers of the Lombardia. Istituto Nazionale Neurologico C. Besta, Milano, Italy

We report the first post-marketing study in Italy on clinical efficacy and tolerability of IFN1b and 1a, in the early post-approval period, collecting.the clinical experience of the MS Centers of the Lombardia (Italy). Baseline and follow up data were collected by an ad hoc schedule from 20/22 centers, identified on the basis of the published list.The patients treated with IFN 1b and IFN 1a have been considered separately.At 30 June 1998, 317 patients have been treated with IFN 1b and 156 with IFN 1 a. The baseline clinical data of the patients were similar, among Centers, which have included patients with low disability and high relapse frequency, according to pre-defined criteria.Relapse rate markedly decreased in both groups, from 1.76 to 0.61 and 0.62 at 1 and 2 years in IFN beta 1b, and from 1.6 to 0.4 at 1 year for IFN beta1a- group. At 1 year the probability to be relapse freedom and of progression of disability were similar in both groups. 65 IFN 1b and 5 IFN 1a stopped therapy, most fo them for treatment failure or side effects. Our data confirm IFN beta is effective in reducing relapse frequency. The impact of drop out on the observed results will be discussed

P540
COMPARATIVE EVALUATION OF NEUROPSYCHIATRIC CHANGES IN RELAPSING REMITTING MULTIPLE SCLEROSIS (RR MS) PATIENTS DURING TREATMENT WITH INTERFERON BETA 1B OR AZATHIOPRINE: A CONTROLLED STUDY. Palumbo R*, Fontanillas L*, Salmaggi A*, La Mantia L*, Mendozzi L + and Milanese C*. *Istituto Nazionale Neurologico "C. Besta", Milan - Italy.+ IRCCS Fondazione Don Gnocchi, Milan - Italy

Mood disorders have been reported in patients treated with Interferon beta 1b (IFN 1b); however, the neuropsychiatric effects of IFN are probably more complex. In this study we followed prospectively RR MS patients treated with IFN beta 1b for 1 year, with administration of a questionnaire based on DSM IV definitions for affective disorders, acute delirious syndromes, neurotic disturbances, obsessive compulsive disorders, psychosomatic diseases and disturbances in eating conduit. The questionnaire was administered every three months together with Beck Depression Inventory and Hamilton Depression Rating Scale. Patients receiving no active tretament or azathioprine (AZA), were similarly monitored as control groups. During IFN beta therapy the following disorders occurred: insomnia (3); irritability (2) panic disorders (2 patients). Frank depressive episodes occurred in two individuals. Only one case of reactive depression occurred in AZA group. Pre-existing depression did not worsen untreated patients (3/12); post -partum depression occurred in one patient. No shifts occurred in Hamilton scores in all the groups. These data suggest that IFN beta 1b therapy may induce a wider spectrum of neuropsychiatric disorders, than suggested by previous studies.

P541
COMPARATIVE EVALUATION OF CLINICAL EFFICACY AND QUALITY OF LIFE IN RELAPSING REMITTING MULTIPLE SCLEROSIS PATIENTS TREATED WITH AZATHIOPRINE OR INTERFERON BETA 1B: A CONTROLLED STUDY. Salmaggi A *, Palumbo R*, La Mantia L*, Caputo D + and Milanese C** Istituto Nazionale Neurologico "C. Besta", Milan -Italy. + IRCCS Fondazione Don Gnocchi, Milan -Italy

Interferon beta 1b (IFN beta1b) and Azathioprine (AZA) are effective in reducing relapse frequency in relapsing remitting multiple sclerosis (RR MS). No comparative study is available on concomitantly followed groups of patients with the same inclusion criteria.Moreover, the impact of these therapies on the quality of life (QoL) has not been evaluated.In this prospective study, RR MS patients fulfilling the requirements for IFNbeta1b treatment were allocated either to IFNbeta1b or to AZA therapy and followed every 3 months with neurological evaluation and QoL assessment (SF-36). A third group of patients with similar features, declining active treatment, was followed concomitantly. 33 patients entered the study: 11 have been assigned to IFN, 10 to AZA and 12 to no active treatment. Pre-treatment features showed a lower relapse frequency in untreated and a longer disease duration in IFN -treated patients. After 1 year relapse frequency decreased both in IFN and aza-treated patients, while it unchanged in untreated patients. EDSS was stable in all the 3 groups.QoL scores at 12 months did not show worsening in any item in the 3 groups.The results stress the comparable clinical efficacy of IFNbeta1b and AZA in the short-term

P542
A PROSPECTIVE OPEN ECONOMIC & CLINICAL TRIAL IN RELAPSING-REMITTING (RR) MULTIPLE SCLEROSIS (MS) IN SWITZERLAND: PRELIMINARY RESULTS. Schluep M*, Solida A*, Banz K**, Venetz W***. *Dept. of Neurology, CHUV, Lausanne; **Outcomes international, Basel; ***DataGen, Füllinsdorf, Switzerland.

To test the hypothesis that the use of health care resources increases with progression of disability (EDSS), 302 RR MS patients were included in an open, prospective, economic and clinical trial that is still currently running. Patients were receiving interferon- 1a (Rebif®) 22 g weekly. We present here the economical intermediate results at one year (183 patients). Results: total indirect costs (patients' productivity loss; 79% of total costs) clearly outweighed total direct cost (DC) (in- and outpatient treatments respectively 32%, 36% DC, rehabilitation, 20% DC, physiotherapy 11% DC, auxiliary services 1% DC). Although a considerable variation in costs between patients with equal EDSS score was found, this study indicates a strong correlation between average per-patient direct costs as well as indirect costs per year and the EDSS score. This correlation was also evident for each direct cost component. Conclusions: RR MS is associated with tremendous direct and particularly indirect costs, with a correlation between disability, treatment costs and productivity loss.Co-investigators: Albanese A, Bogousslavsky J (Lausanne); Buettner UW (Aarau); Chof-

flon M (Geneva); Hess K (Zurich); Kappos L (Basel); Ludin HP (St Gallen); Vaney C (Montana).

P543
COMBINED TREATMENT WITH CORTICOSTEROIDS AND MOCLOBEMIDE NORMALIZES HYPOTHALAMO-PITUITARY-ADRENAL AXIS DYSREGULATION IN RELAPSING-REMITTING MULTIPLE SCLEROSIS. T. Kümpfel, F. Then Bergh, A. Grasser, C. Trenkwalder, F. Holsboer. Max-Planck-Insitut fuer Psychiatrie, Neurology, D-80804 Muenchen, Germany

Hypothalamo-pituitary-adrenal (HPA) axis hyperresponse, reflecting diminished corticosteroid receptor function, has been described in multiple sclerosis (MS). It probably influences the immune response, but its clinical significance is not clear. Similar HPA dysregulation occurs in depression and is reversible upon successful antidepressant treatment.30 patients with definite MS (17 females, age 37.6 ± 2.0 years, EDSS 2.0-7.0, acute relapse (RR) in 20, chronic progression in 10) were included in a randomized, double-blind trial and were treated with placebo (n=13) or 300mg moclobemide (reversible MAO-A inhibitor, n=17) for 12 weeks. All received oral fluocortolone, tapered over the first four weeks. Effects were evaluated clinically and using the combined dexamethasone-CRH-test, at 0, 4 and 12 weeks.Baseline HPA activity correlated significantly with clinical course. Treatment effect was therefore evaluated for patient subgroups separately. In 20 patients with RR-MS, baseline neuroendocrine parameters were comparable for treatment groups. HPA system hyperresponse was maintained in the steroid-alone group (n=12, area under the curve for cortisol, AUC-Cort, 193.0 ± 61.2, 192.2 ± 80.6 and 188.2 ± 79.2 arbitrary units, meanSEM). Moclobemide co-treatment in contrast resulted in normalization of the HPA axis response (n=8, AUC-Cort, 213.8 ± 76.8, 90.8 ± 25.7, and 106.8 ± 59.5). (AUC-Cort in healthy controls studied previously, 113.4 ± 14.1). The change in EDSS was comparable for both groups. While corticosteroids alone have no effect, moclobemide combined with corticosteroids helps normalize the HPA response in relapsing-remitting MS.

Peripheral neuropathy

P544
FACIAL PALSY AFTER INTRAVENOUS IMMUNOGLOBULIN IN MILLER FISHER SYNDROME: A CLINICAL REPORT OF 3 CASES. Lebrun C*, Boucraut J°, Bourg V*, Chatel M* (*) Service de Neurologie. Hôpital Pasteur, 30 voie romaine, NICE, FRANCE (°) Laboratoire d'immunopathologie. Hôpital La Timone. 27 bd J Moulin Marseille, France.

The presence of serum IgG antibodies to GQ1b ganglioside have been reported in the acute phase of Miller Fisher Syndrome (MFS), as in Guillain-Barré syndrome (GBS) with ophthalmoplegia or Bickerstaff's brainstem encephalitis, raising the question of an autoimmune mechanism in the pathogenesis of the paresis of extraocular muscles. Facial palsy (FP) may ensue during MFS (47.5%). Chida et al reported 2 cases of bilateral facial palsy during immunoadsorption plamapheresis in MFS raising the problem of the pathogenesis of this relapse.PATIENTS: We describe 3 similar unusual cases (2 men, 1 woman:35; 47; 60 years) of Miller Fisher Syndrome (MFS) treated with intravenous immunoglobulin (IVIg) who developed FP after the end of the treatment. RESULTS: The reported 3 patients had facial palsy after IVIg infusion, while MFS symptoms started to improve. All of them had a complete recovery within 2 months, including FP. They had high level of IgG anti-GQ1b antibodies in serum and CSF and 1 patient was positive for Campylobacter jejuni. A direct and negative relationship between relapse and treatment need to be raised.CONCLUSION: Development of facial palsy following onset of improvement are mostly observed in GBS during treatment with IVIg but not in MFS. It suggests that the pathological process continues to develop at new sites in the peripheral nervous system in waves, with one site improving while another worsening. This complication has not been reported with IVIg either in polyradiculopathy or other IVIg indications but needs to be considered. Three causes can be discussed: this association can be a particular form of relapsing polyradiculopathy, a new complication of IVIg, or the consequence of a common mechanism of treatments with anti-GQ1b antibody clearance by circulating immune complexs and complement activation.

P545
EFFICACY OF SUBCUTANEOUS INTERFERON BETA 1A (IFN-B1A) IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) PATIENTS Radziwill, Th. Kuntzer, AA Steck Basle and Lausanne, Switzerland

Objective: To study whether IFN-B1a is an effective treatment for CIDP in patients who show no remission after treatment with intravenous immunoglobulins (IVIg).Backgrounds: The short-term benefit of oral prednisone, plasma exchange (PE) and IVIg have been proved in controlled trials. It is possible to keep most CIDP patients in remission by repeating treatments despite inconvenience and expense. Few observations suggest that IFN-B1a might represent an adjunctive therapy in CIDP.Methods: 4 primary CIDP patients who received no previous treatment with prednisone, PE and IVIg in the last 2 months were treated with IFN-B1a 12.0 MIU three times a week for 24 weeks. Neurological examination with quantitative assessment and EMG were carried out repetitively.Results: One patient improved with the IFN-B1a treatment alone with a follow-up of 45 weeks and 3 patients showed no sufficient benefit and were treated with the combination of IFN-B1a and IVIg, one after 3 weeks (relapse) and 2 after 24 weeks. The IFN-B1a treatment alone showed no significant change of the different scores whereas the combination therapy showed significant improvement of the NDS motor weakness subscore ($p = 0.0339$), the timed 10 m-walk ($p = 0.0339$) and of the Hammersmith score ($p = 0.0339$). There was no change of the EMG parameters.Conclusions: Our patients did not benefit from a monotherapy by IFN-B1a, but the combination therapy IFN-B1a and IVIg in 3 patients showed a significant improvement of the different motor scores. More studies are needed to confirm these results.

P546
CARPAL TUNNEL SYNDROME IN PREGNANCY: Turgut F*, Turgut M**, Bolukbasi O****, Baskaya V*- Department of Gynecology and Obstetrics*, Aydin Maternity Hospital; Departments of Neurology*** and Neurosurgery**, Medical Faculty of Adnan Menderes University, Aydin, Turkey.

Objective. To estimate both the incidence of carpal tunnel syndrome (CTS) in pregnant woman and its relationship with possible factors and to determine its natural history after delivery.Design/Methods A cohort of 2364 pregnant woman, aged 15-48 years, who had suffered from CTS during pregnancy, and delivered at Aydin Maternity Hospital was selected. Results. Follow-up showed that CTS at 6 and 12 months post partum was reported by 11% and 4% of the woman, respectively. The difference in prevalence of CTS between young woman and older ones was statistically significant (p 0.05). The history of diabetes mellitus and infant birth weight were similar in the two groups. There was no difference in the number of previous pregnancies between woman with CTS and without CTS during pregnancies ($p > 0.05$).Conclusions. These results indicate that, in most pregnant patients with CTS, the symptoms are present in both hands and are first noted during the third trimester. The majority of patients with CTS obtain spontaneous relief in the immediate postpartum period.

P547
INTRAMEDULLARY MYELOPATHY CAUSED BY SUBACUTE COMBINED.DEGENERATION, CASE REPORT. S. Hennecken, A. Schogel, W. Hupfer, K. A- Flugel,Neurologische Abteilung, Stadt. Krankenhaus Munchen-Bogenhausen, Germany.

We report the MRI findings of an intramedullary myelopathy in a patient with subacute combined degeneration with normal serum Vitamin BI 2 concentration: A 66 year old woman with a month history of numbness in the tips of her fingers and toes progressing to both arms, legs and the chest up to Th 3-4. Clinical examination at this time showed an ataxia in gait, Lhermitte and Romberg's positive, vibration sense reduced, while distal joint position and reflexes were normal. Plantar response bilateral negative. Laboratory studies showed a hyperchromic macrocytosis without anaemia, Vit.B12 and folate concentration were normal. MRI showed a definite swelling Of the upper cervical cord extending from C2-6 without contrast enhancement Magnetic evoked responses were PrOlOnged, wheras analysis of CSF and peripheral nerve conduction studies were normal Due to the differential diagnosis of a myelitis the patient was initially treated with steroids, but clinical symptoms and MRI showed no improve~.Schilling test showing a lack of intrinsic factor and atrophic gastritis led to the diagnosis of subacute combined degenerations Under the following hydroxycobalamin therapy clinical symptom and macrocytosis resolved, MIU six month follow up was normal. Conclusion: The differential diagnosis of an intramedullary myelopathy includes a subacute combined degeneration of the spinal cord due to Vit.1312 deficiency. Even in case of normal Vit.B 12 concentration or no haematological abnormalities a Schilling test and Vit.B12 substitution may be considered

P548
IS THERE ANY DIFFERENCE IN OUTCOME OF SURGERY FOR PATIENTS AFFECTED BY A MORE SEVERE CARPAL TUNNEL SYNDROME?.Capone L, Schönhuber R, Pentore R, Balsam M°*, Amoroso P*, Luchetti R°-San Marino (RSM)°, Modena* and Bolzano (ITALY)

Background: Carpal tunnel syndrome (CTS) is the most frequent entrapment neuropathy. A preoperative neurophysiological evaluation is always recommended to confirm the diagnosis and to assess severity of the nerve damage. Aim of the study: To evaluate if CTS severity affects the outcome of surgery. Materials: All the 243 CTS patients operated by the same surgeon (LR) between 1991-1993 were retrospectively surveyed by telephonical interview using a questionnaire specific for CTS (Levine, 1993) and the generic SF-36. Results were correlated with the severity of the nerve damage, assessed by the preoperative neurophysiological evaluation. Results: Of the 126 responders, for 93 (74%) a neurophysiological evaluation before surgery was available. Their CTS were classified for severity into 5 groups: 7 were negative; 12 minimal; 13 mild; 31 moderate; 30 severe. The mean score of 1.5 (maximum possible: 5) at Levine's questionnaire showed a good overall outcome. No statistically significant differences were found for each severity group at the specific and generic questionnaires. Conclusions: Preoperative CTS severity does not seem to affect the outcome of surgery. A wider prospective study, including also extremely severe CTS, is needed to confirm these data.

P549
OPHTALMOPLEGIA, FACIAL DIPLEGIA AND AREFLEXIA WITHOUT SERUM ANTI-GQ1b ANTIBODIES: AN ATYPICAL MILLER-FISHER SYNDROME. Capone L, Schönhuber R, Pentore R - Bolzano (ITALY)

A clinical syndrome comprising ophtalmoplegia, ataxia, areflexia, with or without bulbar and facial involvement, is considered as a variant of Guillain-Barré syndrome, called Miller-Fisher syndrome (MFS). The very close association between MFS and serum anti-GQ1b antibodies has been previously reported.Case report: A 40- year-old man complaining diplopia was admitted. All tendon jerks were absent. Limb strength and sensitivity were not decreased. He complained a subjective balance disturbance, without clinical cerebellar signs. After 7 days he developed complete ophtalmoplegia and facial diplegia. Routine blood and urinalysis were unremarkable, serum anti-GQ1b antibodies were absent. Albuminocytologic dissociation was found in the CSF. At neurophysiological evaluation motor and sensory nerve conduction studies were normal; blink reflex showed increased R1 and R2 latencies following right trigeminal stimulation and increased R2' latency following left trigeminal stimulation. Magnetic resonance imaging of the brain was normal. He was treated with intravenous immunoglobulins (0.4 g pro Kg/die) for 5 days. During therapy there was a good recovery of facial movements. At a follow-up after 3 weeks he had recovered only the vertical gaze. Tendon jerks were slightly impaired. After 3 months ocular movements were almost normal. Comment: Based on clinical feature and evolution, albuminocytologic dissociation in the CSF and blink reflex abnormalities, we considered this syndrome as an "atypical MSF", although anti-GQ1b antibodies were not detectable in serum.

P550
PROXIMAL DIABETIC NEUROPATHY - IMMUNOTHERAPEUTIC POSSIBILITIES.A.Barada, M.Reljanovic, Z.Milicevic, N.Car, S.Ljubic, Z.Metelko - Vuk Vrhovac Institute, Zagreb, Croatia

A prospective study was undertaken to investigate the effect of immunomodulating (human immunoglobulin intravenously (IVIG)) and immunosuppression therapy (prednisone with azathioprine p.o.) in patients with subacute PDN, characterized by pronounced pain in the upper legs, atrophy of upper legs muscles, loss of predominantly pelvifemoral muscle strength as well as a marked reduction in femoral nerve motor conduction velocity (FNCV). Fifteen type II diabetic patients (mean age 64.8 yrs., duration of diabetes 10 yrs., duration of PDN 4.9 months, HbA1c 7.47 %) were included in the study. The patients were randomised; 9 patients received prednisone (1 mg/kg) and azathioprine (100 mg) whereas 6 patients received IVIG (2.0 g/kg). Response to treatment was evaluated using visual analogue scale for pain (VAS), muscle strength manual test (MMT) after 4,8,12,24 weeks and FNCV was measured at 12 and 24 weeks. Both therapies were found te be beneficial. Improvement was found for pain (baseline vs. follow-up VAS Z= 3.3, p=0.0001) muscle strength (baseline vs. follow-up MMT Z= 3.3,p=0.0001) and FNCV (baseline vs. follow-up Z=3.2, p=0.0015). The most pronounced improvement occurred in the first 4 weeks. Immunosuppression caused greater improvement in FNCV after 3 months as well as VAS after 2 months, compared to immunomodulation but the difference was not statistically significant. Our results indicate an efficacy of immunotherapy in subacute proximal diabetic neuropathy. Further studies are neccessary to evaluate possible difference in long term outcomes between the therapies.

P551
REGENERATION THROUGH INTERCHANGE SCIATIC NERVE GRAFTS BETWEEN NORMAL AND STREPTOZOTOCIN-DIABETIC LEWIS RATS - Zhi-Jie Luo, R.H.M.King and P.K.Thomas, London, UK

Nerve regeneration is known to be defective both in human and experimental diabetes mellitus. This contributes to the clinical deficits in human diabetic sensory polyneuropathy. It is not established whether this is because of an unfavourable microenvironment in diabetic nerve, including the Schwann cells and extracellular connective tissue matrix, or whether it is related to a reduction in the regenerative capacity of diabetic axons. In this study we have examined regeneration through interchange grafts between normal and syngeneic Lewis rats with the following combinations: grafts from normal animals into normals; normals into diabetics; diabetics into normals; diabetics into diabetics. The results have been analysed histologically by examination of transverse sections through the grafts and the distal stump immediately distal to the distal suture line. Preliminary analysis suggests that there is a deficit in regeneration related to a reduction in the regenerative capacity of axons in diabetic animals rather than a defect in the microenvironment of the nerve trunk.Supported by the Juvenile Diabetic Foundation International.

P552
MOLECULAR CLONING OF TROPIC 1808 PROTEIN, A NOVEL FACTOR INDUCED BY NERVE INJURY. Xaiosong Gu[1], P.K. Thomas[2], Xiangling Tan[1], R.H.M. King[2], Ding Fei[1], Gao Zheng[1], Fan Ming[1], J.M. Cooper[2] and A.H.V. Schapira[2].[1]Nantong, PR China, and [2]London, UK.

We have previously shown that an 18kDa protein produced by the distal stump of rat sciatic nerves possesses a strong chemotropic influence on outgrowing neurites from explanted neonatal dorsal root ganglia in tissue culture. In order to identify its gene we established a cDNA library for the distal stump of rat sciatic nerve using the bacterial host strains Y1090 and LE392. Molecular cloning of the neurotropic substance which we have termed Tropic 1808 was undertaken. A monoclonal antibody to Tropic 1808 was established by the hybridoma technique and immunoscreening of a large number of recombinant plaques was performed. The cDNA inserts from the bacteriophage DNA was removed by digestion with EcoR1 and subcloned into the EcoR1 site of a pUC18 vector. Five clones of appropriate size were chosen and their nucleotide sequences analysed. One predicted a 33kDa protein which we have named Tropic 1808 gene (GeneBank AF078811). Using immunoaffinity chromatography, the eluate fraction from a Tropic 1808 monoclonal antibody column was detected by native PAGE. This appeared in the 18kDa position, but was situated at the site of a 32kDa band on SDS-PAGE. In situ hybridization demonstrated that Tropic 1808 mRNA was specifically expressed in Schwann cells in the distal stump of the transected rat sciatic nerve but was not detected in normal nerve. In a search of nonredundant nucleotide and amino acid database no homology with other cDNA or proteins was detected. **Supported by the National Science Foundation of China, grant 39425006.**

P553
PERINEURIOSIS: DIFFERENT PATTERNS OF PERINEURIAL OVERGROWTH IN FOCAL AND MULTIFOCAL NEUROPATHIES. P.K. Thomas, J.M. Workman, R.H.M. King, London, UK

The rare disorder focal hypertrophic neurofibrosis or perineurioma is now well recognized. It consists of a monofocal neuropathy in which the salient histological feature is the presence of multiple concentric cellular arrangements surrounding single or small numbers of myelinated or unmyelinated axons. The appearances resemble those of classic onion bulbs but the concentrically-arranged cells are of perineurial type and not Schwann cells. We have identified a second form of perineurial overgrowth in a patient with a cryptogenic multifocal neuropathy associated with optic neuropathy. The peripheral nerve histology is characterized by exhuberant and ir-

regular intrafascicular extensions of perineurium. These produce endoneurial compartmentation but do not duplicate the pseudohypertrophic pattern of focal hypertrophic neurofibrosis. The perineurial cells show multiple small protrusions that contain mitochondria. The perineurium surrounding the fascicles tends to be attenuated but otherwise shows normal morphological features including the presence of tight junctions. There has been discussion as to whether focal hypertrophic neurofibrosis represents a neoplastic process or is the consequence of recurrent trauma, or whether it is secondary to defective perineurial barrier function. Recent studies raise the possibility that these examples of perineurial overgrowth could be due to abnormalities of intercellular signalling.

P554
MULTIFOCAL MOTOR AND SENSORY DEMYELINATING NEUROPATHY (MMSDN): A PROBABLE DISTINCT CONDITION FROM MULTIFOCAL MOTOR NEUROPATHY (MMN). Osvaldo JM Nascimento, Marcos RG de Freitas, and Myriam Hahn. Rio de Janeiro, Brazil.

MMN is characterized by pure motor mononeuropathy multiplex (MM), persistent multifocal motor conduction block (CB), lack of steroid therapy response, and by strong association with anti-GM1 antibody. MMSDN is a demyelinating motor and sensory MM, that responds well to steroid treatment. We have examined 10 patients (6 male and 4 female) with a mean age of 39.4 years (21-62) presenting a progressive mixed motor and sensory MM. Other causes of MM were ruled out. Anti-GM1 antibody was negative in all cases. The most common symptoms were related with neuropathy involving the upper extremities (7 cases). Motor and sensory neurological deficits were characteristically asymmetrical in all patients. Spinal fluid protein was elevated in 6. Nerve conduction studies showed evidences of demyelination with CB in all cases. A sensory nerve biopsy (sural: 7 cases; ulnar: 2; radial: 1) disclosed decreased density of myelinated fibers (7 cases), active demyelination (6 cases), remyelination (9 cases), and inflammation (4 cases / one with tomacula). All patients improved with steroids. Our cases of MMSDN have features that are distinct from the described cases of MMN. We suppose that these two disorders are clinically different, and probably have different immunologic characteristics. We also believe that MMSDN represent a clinical variant of chronic inflammatory demyelinating polyneuropathy (CIDP).

P555
POLYGLUCOSAN BODIES AND LONG EVOLUTION SENSORY-MOTOR POLYNEUROPATHY. Marcos RG 'de Freitas, Osvaldo JM Nascimento, José MG Barreiros and Myrian D Hahn. Niterói, Rio de Janeiro, Brazil.

Polyglucosan body (PGB) is a hyaline structure PAS-positive, occasionally seen in myelinated axons in some chronic axonal polyneuropathy (CAPN). When in large numbers the possibility of polyglucosan bodies polyneuropathy (PGBPN) should be verified. We have examined a Jewish lady at 54 who complained about paresthesias in lower limbs since she was 20. She progressively felt difficulty to walk. She had distal atrophy of the legs with feet drop, hyperactive knee jerks, reduced ankle jerks and decreased vibration in the feet. The EMG revealed axonal polyneuropathy. The DNA test for duplication and mutation in chromosome 17 was negatif. The retinal angiography showed several drusen and the skull MRI was normal Other causes of CAPN were excluded. The sural nerve biopsy showed moderate loss of myelinated fibers, axonal regeneration and several PGB.The presence of PGB in sural nerve biopsy can be considered uncommon. Our patient presented a chronic axonal sensory-motor polyneuropathy and mild pyramidal signs. The presence of drusen of the optic disc and a large number of PGB in nerve biopsy suggest that the CAPN of our patient is part of the spectrum of this rare disease (PGBPN), characterised by the accumulation of these corpuscles.

P556
UPREGULATION OF TUMOR NECROSIS FACTOR RECEPTOR I AND II IN MOUSE SCIATIC NERVE AFTER CHRONIC CONSTRICTIVE INJURY. A. George and C. Sommer. Neurologische Universitätsklinik Würzburg, Germany.

Pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF) may contribute to the development of neuropathic pain. In chronic constrictive injury (CCI) of the sciatic nerve, an animal model of painful mononeuropathy with incomplete nerve lesion, antibody studies suggested that TNF mediated hyperalgesia is dependent on the TNF receptor 1 (TNFR1). Here, we investigated local protein levels of TNF and its receptors (TNFR1 and 2) after CCI by enzyme-linked-immunoassay (Elisa) and immunohistochemistry. In female C57BL/6-mice one sciatic nerve was loosly constricted by three ligatures, a sham-operation was performed contralaterally. Sciatic nerves were removed on day 0, 0.5, 1, 3, 7 and 14 post lesion (n=12 per timepoint), pooled and homogenized. Levels of TNF, TNFR1 and TNFR2 were measured in supernatants by Elisa after assay validation for nerve tissue. We observed an early and transient increase of TNF in lesioned nerves (on day 0.5, 1, 3) followed by a longer-lasting receptor upregulation: Already detectable in uninjured nerves, TNFR1 increased slightly on day 3 (38 vs. 24 pg/mg protein; CCI vs. sham-operation). In contrast, the inducible TNFR2 was found elevated already 12 hours post injury (152 vs. 85 pg/mg protein), with a further increase on day 3 (243 vs. 85 pg/mg protein). These results suggest that treatment directed at the TNF receptors might be useful in patients with neuropathic pain. *Funding: DFG, SFB 353.*

P557
ANTICIPATION IN PROXIMAL MYOTONIC MYOPATHY. C Schneider[1], T. Grimm[2], C.R. Mueller[2], W. Kress[2], C.D. Reimers[3], K. Reiners[1], H.-M. Meinck[4], P. Broich[5], B. Mueller-Myhsok[6], A.S. Gonschorek[7], K.V. Toyka[1], K. Ricker[1] Departments of Neurology Universities of Wuerzburg[1], Goettingen[3], Heidelberg[4], Bonn[5], and Magdeburg[7], Department of Human Genetics[2], Wuerzburg, Bernhard Nocht Institute for Tropical Medicine, Hamburg[6], Germany

Background: Proximal myotonic myopathy (PROMM) is an autosomal dominantly inherited disorder similar to but distinct from myotonic dystrophy (DM). In DM, anticipation is associated with an unstable trinucleotide repeat expansion. The mutation in PROMM has not been identified, although recently a gene locus could be linked to chromosome 3q. Methods: We investigated 80 families with PROMM. CTG repeat expansion on chromosome 19q was excluded by DNA analysis. Nine families were tested for linkage to chromosome 3q using DNA markers D3S1541 and D3S1589. Analysis of anticipation was based on the age at disease onset. Anticipation was assumed if the offspring had first symptoms earlier in life than the parent. Results: In 63 of the 80 families subsequent generations were affected. In 73 of 78 living pairs, and in 60 of 69 pairs with a deceased parent anticipation was shown. In living parent-offspring pairs a mean age of onset interval of almost two decades was found. A similar degree of anticipation was found in the eight of nine families already identified with linkage to chromosome 3q. Conclusion: The results of our study show that anticipation is a feature of PROMM including families with linkage to chromosome 3.

P558
CHARACTERISTICS OF MILDLY AFFECTED PATIENTS WITH GUILLAIN-BARRE SYNDROME (GBS). Van Koningsveld R.[1], van Doorn P.A.[1], Schmitz P.I.M.[1], van der Meché F.G.A.[1].Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands.

Purpose For purpose of treatment and understanding pathofysiological mechanisms it is important to study the complete spectrum of a disease. Knowledge of GBS however mostly arises from the more severely affected patients participating in treatment trials. Patients and methods 436 GBS patients from an epidemiological survey were evaluated. Clinical characteristics of mildly affected patients, defined as being able to walk unaided at nadir (functional grading score [f-score < 3) were compared with data on severely affected patients (f-score ≥ 3). Results 28% of the patients was mildly affected, 72% severely. In the mild group more patients with age under 50 years were found ($p < 0.001$). Additionally men were more frequently mildly affected than women (p=0.001). 70% in both groups reported a clinically preceding infection. Serological evidence of infections with Campylobacter jejuni, CMV, EBV and Mycoplasma pneumoniae was found in 25% in the mild group versus 42% in the severely affected patients (p=0.02). Conclusions 28% of GBS patients are still able to walk unaided at nadir. These patients are more frequently younger (< 50 years) and of male gender. A difference in preceding infectious agents seems to be related with the severity of the disease.

P559
THE DENSITY OF SYMPATHETIC, BUT NOT OF AFFERENT C-FIBERS DIFFERS IN SURAL NERVE BIOPSIES BETWEEN PATIENTS WITH AND WITHOUT NEUROPATHIC PAIN. A.Bickel, M.Butz, M.Schmelz*, H.Grehl, B.Neundörfer. Neurologische Klinik mit

Poliklinik und #Institut für Physiologie I, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91054 Erlangen, Germany.

Objective: Associations between pathological changes in specific classes of peripheral nerve fibers and pain have been suggested, but no clear morphological correlates are known. Aim of our study was to analyze, whether there are histopathological differences between patients with and without pain concerning small fiber density in sural nerve biopsies.Methods: Subgroups of unmyelinated nerve fibers were analyzed in sural nerve biopsies from 27 patients (13 with, 14 without pain) by immunocytochemistry. Markers against Substance P and Calcitonin-gene-related-peptide were used for detecting afferent, against Tyrosin-hydroxylase (TH) and VIP for detecting autonomic nerve fibers. Results were compared to the total nerve fiber density, detected with a panneuronal marker against PGP9.5 (protein-gene-product 9.5). Clinical tests of small fiber function (temperature thresholds, pain thresholds, quantitative sudomotor-axon-reflex-testing and histamine flare reaction) were performed before taking the biopsy.Results: Both patient groups did not differ in age, duration of illness, clinical parameters or results of tests of c-fiber-function. Furthermore there were no differences concerning the density of afferent fibers. In contrast, the amount of TH-positive sympathetic nerve fibers was significantly higher in the patient group with pain (p=0.0004).Conclusions: The higher density of sympathetic nerve fibers in patients with painful neuropathy supports the theory, that the sympathetic nervous system may play an important role in the generation of neuropathic pain.

P560
A CASE-CONTROL STUDY OF ANTI-GANGLIOSIDE AND ANTI-CAMPYLOBACTER JEJUNI ANTIBODIES IN GUILLAIN BARRE' SYNDROME IN WESTERN LOMBARDIA.Carpo M, Bersano A, Allaria S, Citterio A, Nobile-Orazio E for the GBS study group, Milan and Pavia, Italy.

We implemented a case-control study of Guillain-Barré syndrome (GBS) in western Lombardia from 1996 to 1998 to evaluate the frequency of anti-ganglioside and anti-Campylobacter jejuni (CJ) antibodies. Two age-, sex- and residence-matched controls were recruited for each patient in neurological (NC) and surgical ward (NNC) respectively. 46 acute GBS (39 of which retested after 3 weeks), 43 NC and 41 NNC sera were collected and tested by ELISA for anti-GM1 IgG, IgA and IgM, and for anti-GD1a, -GD1b, -GM2, -GQ1b, -CJ IgG and IgM. Anti-GM1 IgG and IgM were found in 6% and 15%, respectively, of acute GBS and 15% and 4% respectively, of convalescent GBS while anti-GM1 IgA were found in a similar proportion of GBS and controls. There was no correlation between anti-GM1 IgM in the acute and anti-GM1 IgG in convalescent sera. Anti-GQ1b IgG were found in 12% of acute and 35% of convalescent GBS. Anti-CJ IgG were only found in 7% of acute GBS sera. While anti-GM1 IgM congruously decreased in GBS during recovery, anti-GQ1b and -GM1 IgG were more frequent in convalescent than acute GBS and did not follow an antecedent rise of anti-GM1 IgM possibly indicating a secondary immune response to GM1.

P561
MALIGNANT HISTIOCYTOSIS AS A CAUSE OF SEVERE MENINGORADICULITIS. REPORT OF A CASE. Adams D, Lacroix C, Rerat K, Vantelon JM, David P, Hayat M, Said G. Paris, France

Malignant histiocytosis is an uncommon systemic disorder with progressive invasion by morphologically atypical histiocytes which may primarily affects the nervous system. We report a case of malignant histiocytosis restricted to spinal roots and leptomeninges. A 32 year old man was referred for lightning pains in lower limbs and progressive walking difficulties of 3 months duration which were related to meningoradiculitis. Successive CSF analysis showed a lymphocytic meningitis with decreasing glucose content. No malignant cell could be found. On examination, he had a severe paraparesia and hypesthesia in a stocking distribution, with tendon reflex abolished in the lower limbs. General examination was normal. Lumbar MRI showed hypertrophic lumbar roots with nodular contrast-enhancement. CSF showed polyclonal lymphocytic meningitis with aglycorrhachia. Surgical biopsy of a sensory thoracic root showed a malignant histiocytic infiltration. Total body CT scan, skeletal scintigraphy and bone marrow biopsy were normal. Regression of meningitis and improvement of neurological condition occurred after intrathecal chemotherapy. The course was marked by relapses of radicular pains in the lower limbs requiring intrathecal chemotherapy and oral corticosteroids. Walking difficulties fluctuated and trigeminal pain occurred. CSF was haemorrhagic with haemophagocytic histiocytes. MRI of nevraxis showed contrast-enhanced masses in trigeminal's cave, epiphysis, and temporal horn, and a tumour of the cauda equina. Systemic chemotherapy followed by autologous stem-cell transplantation improved neurological manifestations and normalised CSF initially. Walking disability, refractory pains and meningitis reappeared. Patient underwent radiotherapy of the lumbar roots but died suddenly 20 months from the onset.

P562
ASSESSING GRIP STRENGTH IN HEALTHY INDIVIDUALS AND PATIENTS WITH IMMUNE-MEDIATED POLYNEUROPATHIES. Martina ISJ[1], Schmitz PIM[1], Samijn JPA[1], Toyka KV[2], van der Meché FGA[1], van Doorn PA[1], for the Inflammatory Neuropathy Cause and Treatment (INCAT) group; [1]Rotterdam, The Netherlands; [2]Würzburg, Germany.

To provide clinically useful grip strength reference values for the Vigorimeter (VM) and to examine its reliability, validity and responsiveness in patients with immune-mediated polyneuropathies. The VM was applied in 530 healthy controls and 113 patients who experienced Guillain-Barré syndrome (GBS) in the past, currently have a clinically stable chronic inflammatory demyelinating polyneuropathy (CIDP) or a polyneuropathy associated with a gammopathy of undetermined significance. Also, 10 patients with recently diagnosed GBS or CIDP and changing clinical conditions were examined longitudinally (longitudinal-group). Additionally, a disability sumscore (DSS) was assessed in all patients. In the healthy controls, there was a significant relation between grip strength, age and gender. Maximum grip strength was observed between 20-40 years. Clinically useful reference grip strength values were calculated depending primarily on age and sex. In addition, hand-circumference in men proved to be the best indicator of grip strength of all personal variables tested. Good inter-/intra-observer reliabilities (R=0.95-0.97; $p < 0.0001$), significant validity (correlation VM and DSS: r=-0.53-0.74; $p < 0.0002$) and high standardised response mean scores (>0.8) as a measure of responsiveness were demonstrated. This study provides clinically useful grip strength reference values and good clinimetric properties for the easily applicable hand-held Vigorimeter. The results emphasise the value of the Vigorimeter in monitoring clinical changes over time in patients with GBS and CIDP.

P563
FATIGUE IN IMMUNE-MEDIATED POLYNEUROPATHIES: AN UNDER-RECOGNISED ENTITY. Martina ISJ, Schmitz PIM, Samijn JPA, van der Meché FGA, van Doorn PA, for the Inflammatory Neuropathy Cause and Treatment (INCAT) group; Rotterdam, The Netherlands.

To determine the severity of fatigue and clinimetric properties of the Fatigue Severity Scale (FSS) in patients with immune-mediated polyneuropathies. FSS was assessed in 113 patients who experienced Guillain-Barré syndrome in the past, currently have a chronic inflammatory demyelinating polyradiculoneuropathy or a polyneuropathy associated with a monoclonal gammopathy of undetermined significance, and in 113 age/sex matched healthy controls. Data on 4 additional scales (MRC sumscore, functional grading scale, sensory sumscore, Medical Outcome Study 36-items health status [SF-36]) were obtained in the patients. SF-36 was also assessed in 59 controls. 'Severe' fatigue (FSS values95^{th} percentile in controls) was present in 80% of the patients. Fatigue was not significantly related to general strength, sensory deficits, functional grading and duration of symptoms. Even patients with normal strength or sensation reported 'severe' fatigue in 81-86%. Eighty percent of patients (controls: 12%) reported their fatigue being among the three most disabling symptoms. In the patients group, quality of life scores were significantly lower compared with controls and partially related to FSS scores. Good internal consistency, validity and reliability were obtained for the FSS. In conclusion, fatigue is a prominent complaint with significant impact on health status in patients with immune-mediated polyneuropathies. Future studies should focus on understanding and managing this disabling symptom. The FSS seems appropriate for assessing fatigue in these patients, since good clinimetric properties were demonstrated.

P564
SENSORY AND MOTOR NEUROPATHY WITH MULTIPLE NERVE CONDUCTION BLOCK AND CRANIAL NERVE INVOLVEMENT - A CASE REPORT. Kayser, D. Heuss, S. Probst-Cousin, B. Neundoerfer-Dept. of Neurology, University of Erlangen, Germany

Multifocal motor neuropathy (MMN) is characterized by focal demyelination of peripheral motor neurons, showing multiple sites of motor conduc-

tion block in nerve conduction studies. GM-1 antibodies may be present. Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic demyelinating disease involving both motor and sensory nerve fibres of peripheral nerves. Treatment of choice in both diseases is intravenous infusion of immunoglobulins.We are presenting a 62 year old patient with right-sided palsy and atrophy of the tongue, palatoplegia on the left, proximal more than distal muscle weakness of both arms and legs, atrophies of his right upper arm and both thighs. Also he presented with predominantly distal hypaesthesia and hypalgesia of all fingers and both feet. Muscle reflexes were present only on the left arm and the patellar tendon reflex on the left. No plantar reflexes.Nerve conduction velocity showed slowed nerve conduction velocity of motor and sensory nerves. nerve conduction blocks on both arms and the left leg were present.GM-1-antibodies were negative. CSF-laboratory findings were unrevealing. Muscle biopsy showed neurogenic atrophy. The patient improved with intravenous immunoglobulins.Because of the clinical symptoms and the results of diagnostic investigations we consider this case – although mild sensory disturbances are present – an interesting case within the spectrum of systemic motor neuropathies.

P565
THE RYDEL-SEIFFER GRADUATED TUNING FORK: RELIABILITY AND RESPONSIVENESS EVALUATION IN PATIENTS WITH IMMUNE-MEDIATED POLYNEUROPATHIES. Martina ISJ, Schmitz PIM, van der Meché FGA, van Doorn PA, for the Inflammatory Neuropathy Cause and Treatment (INCAT) group; Rotterdam, The Netherlands.

The aims of the current study were to investigate the reliability and responsiveness of the graduated Rydel-Seiffer tuning fork in patients with immune-mediated polyneuropathies. Its validation has already been demonstrated. The tuning fork was applied in 113 patients who experienced Guillain-Barré syndrome (GBS) in the past, currently have a stable clinical condition of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or a polyneuropathy associated with a gammopathy of undetermined significance. Additionally, this instrument was longitudinally utilised in 10 patients with recently diagnosed GBS or CIDP and changing clinical conditions. The measures were done in triplicate at 4 locations in the arms and legs each. The values were compared with the recently published vibration threshold normal values and scored as normal or abnormal. A functional grading score (f-score) was also longitudinally assessed. Good inter-/intra-observer agreements (weighted kappa[2]=0.67-0.98) were demonstrated. Predominantly high standardised response mean scores (>0.8) were obtained in the longitudinal group of patients, indicating good responsiveness of the tuning fork. The f-score correlated well with the vibration scores (r=0.58-0.72; $p \leq 0.0002$). In conclusion, good reliability and responsiveness are demonstrated for the Rydel-Seiffer tuning fork in patients with immune-mediated polyneuropathies. The results provide further evidence.for incorporation of this easily applicable pocket size instrument in routine neurological examination, particularly for the evaluation of the vibration sense in patients with polyneuropathies.

Poster Session 4

Clinical neurophysiology

P566
CALORIC STIMULATION IN PATIENTS WITH BILATERAL VESTIBULAR FAILURE (A PET STUDY). S. Bense[1], M. Dieterich[1], P. Bartenstein[2], M. Schwaiger[2], and Th. Brandt[1]. Departments of [1]Neurology, Ludwig-Maximilians-University Munich, and [2]Nuclear Medicine, Technical University Munich, Germany

In an earlier PET study we showed that caloric irrigation in healthy volunteers elicits bilateral activation of the vestibular cortex (parieto-insular vestibular cortex and retroinsular regions) but causes a highly significant deactivation of the entire striate visual cortex (BA 17, 18, 19) Wenzel et al., Brain, 1996. Our hypothesis that activation of the vestibular cortex leads to a simultaneous deactivation of the visual cortex was proven in a further study involving patients with bilateral vestibular failure (BVF). Three right-handed patients (2 males, 1 female) with BVF were examined in a Siemens 951 R/31 PET scanner using a O-15 water-bolus technique during vestibular stimulation, i. e., caloric irrigation of the right or left ear with 100 ml water at 44°C. Prior to statistical subtraction analysis, data were realigned, spatially normalized, and smoothed using the SPM96 software package (The Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Differences between control and activation images, averaged within each subject, were expressed as voxel-by-voxel t-statistical values (Z-scores). None of the patients showed any activation (or deactivation) of the visual cortex following caloric ear irrigation. This finding supports the view that the preservation of vestibular function is a necessary prerequisite for the inhibitory interaction between the visual and the vestibular cortices.

P567
THE EXTEROCEPTIVE SUPPRESSION OF MASSETER MUSCLE IN INFERIOR ALVEOLAR NERVE LESIONS. Ceriani F., Poloni M., Scarpelli M.*, Stromhenger A.* - Cl. Neurologica III and *Cl. Odontoiatrica – Univ. di Milano – Osp. San Paolo – ITALY

Peripherally induced exteroceptive suppression is a negative motor phenomena that can be elicited in masticatory muscles of normal subjects with electrical stimulation of skin areas innervated by trigeminal nerve: two periods of transient electromyographic (EMG) suppression are recorded with early (ES1) and late (ES2) onset. In our study we have investigated 11 patients with suspected lesion of the inferior alveolar nerve due to surgical dental treatment in the mandibular region. Clinically these patients usually complain of sensory loss confined to the gum, labial and chin areas of the same side associated with persistent paresthesias and pain sensation of different degree. Exteroceptive suppression to non-painful electric stimuli (25 mA) applied to the skin below the inferior lip during sustained voluntary contraction of the masseter muscle has been investigated, recording from surface adhesive electrodes. Mean latency times and duration of both ES1 and ES2 were calculated on 10 consecutive stimuli delivered at 0.2 Hz. All the patients showed abnormalities of the EMG suppression periods when the affected side was stimulated: in 6 cases either ES1 or ES2 were absent, while the others showed increased latency of the suppression (ES1 and/or ES2) with shorter duration. These results emphasize the value of the exteroceptive suppression as a diagnostic tool for the assessment of the integrity of afferent trigeminal pathways.

P568
MYOTONIA IN PROXIMAL MYOTONIC MYOPATHY (PROMM): AN ELECTROPHYSIOLOGIC APPROACH. Sterlicchio*, V. Sansone, S. Radice, GR Naji*, G. Meola. Dept. Neurology and Neurophsyiology Service*, Univ. Milan - San Donato Hospital, Milan - Italy

Background: Previous studies have suggested that the myotonia of proximal myotonic myopathy (PROMM) is provoked by heat and diminished by cold, but precise electrophysiological criteria have not been established. Objective: The aim of our study was to further characterize the electrophysiological features of the myotonia in PROMM. Materials and Methods: 20 patients with PROMM were subjected toneedle EMG recording at baseline, after a standard exercise test, after repetitive stimulation at 3 and 5Hz, after cooling the skin temperature to 30°C and after heating to 37°C. The results were compared to patients with myotonic dystrophy (n = 20), patients with myotonia congenita (n = 20), patients with sodium channelopathies (n = 10). Results: In PROMM we observed: (1) no decremental response following exercise and repetitive stimulation; (2) insensitivity of myotonia to cooling. In one patient myotonia was apparent only after heating; (3) motor unit potentials were only rarely reduced in amplitude and duration. Conclusions: The myotonia in PROMM is often detectable in a few muscles, is usually proximal, may be inconsistent, mild and insensitive to heating or cooling. Our data suggest that the myotonia in PROMM may have a different physiologic basis than traditional myotonic syndromes.

P569
POWER SPECTRA AND INITIAL REAGIBILITY AS PROGNOSTIC ELECTRENCEPHALOGRAPHIC PREDICTORS IN PATIENTS WITH HYPOXIC BRAIN DAMAGE. D. H. Meinecke; M. Schröder; F. Behse; Berlin-Germany

Objective: To study the importance of quantitive EEG analysis and initial reagibility (IR) in the prognostic evaluation of patients with hypoxic encephalopathy. Methods: We examined 60 consecutive patients after cardiopulmonary resuscitation who were comatose for more than 8 hours. Clinical and neurophysiological examination (digital EEG with acustic, visual, and somatosensory stimulation; somatosensory evoked potentials) was performed during the first day of coma. Qualitative (sensory reagibility, dominant frequencies) and quantitative (power spectra) EEG analysis

are compared to somatosensory evoked potentials and to the outcome after 6 month. Results: 72% of the patients died (40% from brain death, 60% from extracerebral complications), 22% had a good recovery, and 6% remained in a vegetative state. Initial reagibility in the qualitive EEG analysis proved to be a reliable prognostic predictor as 94% of the patients whith initial IR awakened from coma while in the group with initial lost only IR 42% of the patients awakened. The predictive importance of IR was independant from predominante frequencies both in the qualitative and quantitative EEG analysis. Further, the absolute and relative power in the δ-range correlated with outcome. Conclusion: Evaluation of IR and power spectra analysis permit a more reliable prediction of outcome after hypoxic brain damage than clinical examination, qualitative EEG analysis and SEP alone.

P570
AFTER-EFFECTS OF MUSCLE FATIGUE ON SPINAL INHIBITORY INTERNEURONES. Alessandra Pesenti*, Alberto Priori* §, Alberto Cappellari*, Guglielmo Scarlato* & Sergio Barbieri*. Clinica Neurologica, IRCCS Ospedale Maggiore-Policlinico, Milano* & IRCCS Centro San Giovanni di Dio–Fatebenefratelli, Brescia§, Italy.

The reflex action of muscle afferents on spinal motoneurones is critically dependent on muscle's immediate previous history of contraction. To assess whether previous muscle activation influences also spinal inhibitory interneurones, we studied the after-effects of muscle contraction on reciprocal inhibition (RI) between antagonist muscles. We conducted 10 experiments (6 human subjects) with the ethical committee approval. Subjects were instructed to grip as strong and as long as possible a spring-hand grip with their dominant hand. RI was studied at rest before and after (0.75 ± 1 min) contraction by conditioning the test H-reflex elicited in forearm flexor muscles (FAFMs) by median-nerve stimulation at the elbow. Conditioning stimuli were delivered at motor threshold to the radial-nerve in the spiral groove at the intervals of 0 and 20 ms before median-nerve test stimulation. The Mmax and the Hmax were also measured. After a sustained fatiguing contraction of FAFMs (3.2 ± 0.6 min) [mean ± SEM] the Mmax and the Hmax were substantially unchanged. In contrast, RI was markedly reduced both at the 0 ms interval (before 48.9 ± 5%; after 65.5 ± 9.3%) and at the 20 ms interval (before 55.3 ± 4.7%; after 78.9 ± 6.3%). RI was restored after ~40 min of rest. Our data show that muscle fatigue produces after-effects reducing the action of spinal inhibitory interneurones, which might contribute to the resumption of maximum motor output.

P571
THE ADDITIONAL DIAGNOSTIC VALUE OF EMG IN LUMBAR RADICULOPATHY. Ernest J Wouda, Jan AL Vanneste, Christoph S van der Reyden, D Martin Laman, Sint Lucas Andreas Ziekenhuis, Amsterdam, the Netherlands.

The diagnosis of lumbar radiculopathy (LR) can remain uncertain after clinical and CT or MRI assessment. Neurophysiological assessment is commonly used as the next diagnostic step, although the value of electromyography (EMG) for increasing the diagnostic accuracy of LR is unknown. Methods. A prospective study on the diagnostic value of EMG in patients with presumed neurogenic leg pain was carried out. The diagnosis (reference test) of LR was based on combined clinical and CT data expressed as a global clin/CT score, with three categories of probability: improbable/possible/probable LR. EMG and nerve conduction studies (NCS) with blinding to the clin/CT score were carried out according to a pre-established protocol. The results were ranked into the same three categories of diagnostic probability according to pre-established criteria. Thereafter, the diagnostic accuracy of EMG/NCS was assessed. Results. Data of 119 adult patients were analysed. The global clin/CT scores were used as reference test in 95 patients (44 probable LR + improbable LR). The sensitivity of EMG ranged between 41-73%, the corresponding specificity between 84-69% and the predictive accuracy between 64-70%, depending on the strictness of EMG/CNS diagnostic criteria for LR. In the group of 24 patients with "possible" LR on the clin/CT score, additional EMG/NCS did not result in increasing the diagnostic accuracy or a different clinical management. Conclusion. The additional diagnostic value of EMG in patients with an equivocal clinical LR is very limited.

P572
INTRACORTICAL INHIBITION IN PATIENTS WITH HEMISPHERIC STROKE Kunesch E., Kaschner I., Stefan K., Benecke R, Classen J. Dep. of Neurology, University of Rostock, FRG

Following stroke a sustained impairment of intracortical inhibition (ICI) might put the motor cortex at an increased excitotoxic risk to undergo delayed neuronal damage. Identification of patients with persistently deficient ICI might open the way toward new interventional pharmacological therapies. Transcranial magnetic stimulation (TMS) was applied in 11 patients who had suffered an acute hemispheric stroke at least 2 days before testing to investigate whether ICI was impaired. Using standard protocols, various parameters of cortical excitability (resting motor threshold, RMT; paired-pulse inhibition, and -facilitation, PPI and PPF; cortical stimulation induced silent period, CSSP; amplitude ratio cortically/peripherally evoked potential, %MEP) were assessed in the ipsilesional and contralesional hemispheres recording from the appropriate abductor pollicis brevis (APB) muscles. In 7 patients intracortical PPI or PPF could be studied. At an interstimulus interval (ISI) of 3ms the magnitude of the conditioned response was similar for the affected (68+/-37% of control amplitude) and for the non-affected APB (63+/-31%; n.s.). At an ISI of 13ms PPF was also similar on both sides (affected: 156+/-29%; non-affected: 139+/-50%; n.s.). RMT was increased in 5, %MEP was reduced in 9, and CSSP was increased in all 11 patients (affected: 318+/-215ms; non-affected 133+/-27ms, means+/- S.D.; $p < 0.05$). Thus, $GABA_A$-receptor mediated inhibition (PPI) was unaltered and $GABA_B$-receptor mediated inhibition (CSSP) was increased as compared to the intact hemisphere. These findings do not provide evidence for a persistently impaired ICI on the affected hemisphere in subacute stroke patients. Rather, increased $GABA_B$-receptor mediated inhibition might represent a protective neuronal mechanism.

P573
MEDIAN NERVE AND POSTERIOR NERVE SOMATOSENSORY EVOKED POTENTIALS IN HUNTINGTON'S DISEASE JM Paquet, JC Turpin. CHU Reims. France.

The age at onset of Huntington's disease (HD) is correlated with the number of CAG triplets repeats. But the phenotypic expression of Huntington's disease is heterogeneous. The aim of our study is to determine if somatosensory evoked potentials are helpful in the early diagnosis and in the evaluation of the progression of symptoms of Huntington's disease. The scalp somatosensory evoked potentials (SEP) of 18 Huntington's disease patients were studied: N20 in the upper limbs and P40 in the lower limbs. The diagnosis of HD was based on family history, clinical examination and molecular biology. The mean age of the patients was 40.3 years (20-72). One patient had no sign of HD (presymptomatic diagnosis). The 17 other patients were classified in 5 stages according the Shoulson's classification, stage 1: 6 patients, stage 2: 4 patients, stage 3: 4 patients and stage 5: 3 patients. The SEP were recorded in the department of neurology of REIMS between 1996 and january 1999. In 17 symptomatic patients, SEP were abnormal. No response were recorded (P40 and N20) in 2 cases, the patients were in stage 1 and stage 3 of the disease. Absence of P40 and low amplitude of N20 was recorded in 7 cases and low amplitude of P40 or N20 in 8 cases. The presymptomatic patient's SEP were normal. There was no correlations between abnormal SEP and the stage of HD. The conclusion is that the SEP can be useful in the diagnosis of HD, even in the early stage of the disease, but not in the evaluation of the progression of symptoms.

Cerebrovascular disorders

P574

SIMULTANEOUS CEREBELLAR INFARCTION IN YOUNG MONOZYGOTIC TWINS WITH PATENT FORAMEN OVALE. S. Paganoni, S. Corti, S. Strazzer, M.P. Perini, S. Tadeo, Y. Torrente, N. Bresolin, G. Scarlato, Milano, Italy.

Cerebral ischemia in young adults represents 3% of all cerebral infarcts; in approximately half of these patients a clear underlying cause is not found despite extensive investigation. Twins and familial aggregation studies support a role for genetic factors in the pathogenesis of stroke with a nearly fivefold increase in the prevalence of stroke among monozygotic twins compared with dizygotic pairs. We describe the first report of simultaneous cerebellar strokes in young monozygotic twins. The episodes were clinically similar: they experienced sudden onset of dysarthria, dysmetria and upper limb hypotonia. Brain MRI showed, in both patients, a low density area in their cerebellar hemispheres. Cerebral angiography showed no sign of arterial dissection. Carotid ultrasonographic investigations were negative. The patients had no signs of cardiological disease; ECGs and transthoracic echocardiography were normal. Also cerebrospinal fluid and

VEPs were normal. Our patients at transesophageal echocardiography showed patent foramen ovale. The doppler ultrasound of the middle cerebral arteries detected microembolic signals during Valsalva manovre. Patent foramen ovale has been associated with cryptogenetic stroke in several studies. A high frequency of posterior circulatory stroke in patients with patent foramen ovale and atrial septal aneurysm has been reported. The role of genetics in this condition has not been assessed. Patent foramen ovale is confirmed as a possible risk factor in all young patients, particularly in posterior circulatory strokes.

P575
TRANSIENT APHASIA WITH HEADACHE AND CSF LYMPHOCYTOSIS: WHAT'S ABOUT DIFFUSION MRI ? Caroline Roos*, Livia Zagame*, Sonia Alamowitch*, Antoine Khalil**, Etienne Roullet*. *Neurology, **Radiology, Tenon hospital, Paris, France.

The aetiology of the syndrome of transient headache with neurologic deficits and CSF lymphocytosis (HaNDL), (Berg M.J and Williams L.S; Neurology 1995;45:1648-1654.) remains unkown. Conventional neuroimaging is generally normal; in some cases, non specific abnormalities such as focal areas of decreased uptake in SPECT or small high signal on T2-weighted MRI are reported. Case report: A 31 years old man presented with a global aphasia of sudden onset, which lasted for 18 hours. He had no history of migraine, but he suffered from moderate bifrontal headache without nausea or vomiting for 7 days, which became more severe at the onset of aphasia, and lasted for 10 days. CSF analysis showed 43 nucleated cells (96% lymphocytes), normal protein and no oligoclonal bands. Extensive general and infectious work-up was negative. T1- and T2-weighted MRI performed within 24 hours after the onset was normal, but the diffusion sequences showed a high signal intensity in the splenium of the corpus callosum, which resolved in 8 days. Cerebral angiography (day 8) was normal, but resulted in severe confusion for 10 hours. Clinical recovery was complete. Conclusion: This is the first report of diffusion MRI abnormalities in HaNDL. The transient MRI pattern and the lack of clinico-radiologic correlations suggest a diffuse or multifocal process of ischemic origin.

P576
STROKE IN ASSOCIATION WITH CANNABIS ABUSE IN A YOUNG MAN. Nègre C., Mary J., Faillie X., Arnoud B. Department of Neurology, Hopital Maréchal Joffre, Perpignan, France.

A 17 -year -old man with a six month of cannabis abuse présented an ictal right hemiparesis with dysarthry. The early XRay scan was normal.The MRI scan show an infarct in the profund left sylvian territory. The cerebral artériography did not reveal any vascular cerebral or cervical lesion. Cannabis abusè was the only risk factor for the cerebrovascular disease. Diverses effects of the cannabis are listed, either neuroprotective effects or vascular effects as significant increase of cerebral blood flow. So stroke appears as paradoxical and vascular spasm may be a mechanism.

P577
DIAGNOSTIC WORK UP OF PATIENTS WITH CEREBRAL ISCHEMIA. DOES TRANSCRANIAL DOPPLER SONOGRAPHY (TCD) HAS AN IMPORTANT ROLE?.Th. Arida. N. Artemis, D.Karacostas, C.Vadicolias, 1. Milonas. B' Univ. Department of Neurology, AHEPA Hospital, Thessaloniki, Greece

Objective: Evaluate the utility of TCD as part of noninvasive cerebrovascular assessment in patients with ischemic cerebrovascular events. Methods: Between January 1998-December 1998, 149 patients (pts) were referred for ultrasonographic evaluation of extracranial and intracranial circulation. Routine examination included color-coded doppler sonography of carotid and vertebral arteries and TCD. Interpretation of > 50% stenosis in the extracranial circulation was based according to our standarized validation criteria. A cuttof point of 80cm/sec (mean flow velocity) for the anterior circulation and 70cm/sec for the posterior circulation were used for indentification of intracranial stenosis. Results: 6 pts were excluded of the study because of inadequate temporal window. A total of 143 pts were examined (107 males, 36 females). The mean age was 62,3±6,48. 25% of them had completed stroke and 51,75% had transient ischemic attacks. According to the findings: 27,27% had extracranial arterial stenosis (extracranial carotid artery: 42, extracranial vertebral artery: 6), 25,17% had intracranial arterial stenosis (middle cerebral artery: 18, intracranial internal carotid artery: 2, posterior cerebral artery: 2, basilar artery: 7, distal vertebral artery: 13) and 6,29% had both intracranial and extracranial stenosis. Totally 31,46% of the pts would have been remained undiagnosed if TCD examination was not performed. Conclusion: Our results suggest that TCD examination must be included in the standard diagnostic evaluation of patients with ischemic cerebrovascular events.

P578
POWER DOPPLER IMAGING VERSUS COLOR DOPPLER FLOW IMAGING IN THE EVALUATION OF INTRACRANIAL VERTEBRO-BASILAR SYSTEM IN NORMAL SUBJECTS. Th. Arida, N. Artemis, 1. Milonas. B' Univ. Department of Neurology, AHEPA Hospital, Thessaloniki, Greece

Power Doppler Imaging (PDI) is an ultrasound method based on the display of the integrated power of the doppler signal. This study was undertaken in order to evaluate the utility of the method in the assessment of intracranial vertebrobasilar (V/B) system. Methods: The intracranial V/B system was examined in 35 healthy individuals (mean age+SD:5±15) by using PDI technique. All subjects were also examined with Color Doppler Flow Imaging (CDFI). Results: The intracranial part of vertebral arteries (VA4) and the V/B junction was displayed adequated by CDFI in 82,8% and by PDI in 74,8% of subjects. Combining both methods visualization of VA4 was obtained in 88,57%. Indentification and imaging of the right or left posterior cerebellar arteries was better with PDI than with CDFI (PDI:20/35, CDFI:15/35). PDI was also superior in visualization of basilar artery (BA) (PDI: 33/35, CDFI: 27/35). In all patients the course of BA was demonstrated better by PDI that with CDFI. In 6 subjects only PDI was effective to demonstrate a curved course of BA. With both methods the mean depth of depiction of BA was 90±5mm. The EM maximum depth was 103mm but it was obtained only in 3 subjects. Conclusion: Our results suggest that: 1)Combination of both methods improved the depiction of VA4 segment. 2) PDI offers better visualization of BA. 3) Top of the basilar artery remains a blind spot for both PDI and CDFI.

P579
ICAM-1 LEVELS AND CEREBROVASCULAR RISK FACTORS IN ACUTE STROKE. Pierluigi Bertora, Davide Mantica, Giovanni Alberti, Michela Colombo, Alfonso Mangoni. 1st Chair of Neurology, University of Milan, Italy

The blood levels of the adhesion molecule ICAM-1 are indicative of endothelial activation and may play a role in atherogenesis. We measured soluble ICAM-1 (sICAM-1) in serum of 14 patients (5 men, 9 women, aged 48-92 yr) within 24 hours from the onset of acute cerebrovascular accident (ischemic stroke in 11, TIA in 3) and in 19 age-matched control subjects without acute cerebrovascular disease. A trend towards higher sICAM-1 levels was found in patients with ischemic stroke than in those with TIA (p=0.07). sICAM-1 was higher in patients with ischemic stroke than in controls without cerebrovascular risk factors (CRFs)(227 ± 100 vs 118 ± 50 ng/mL, P=0.01), but not significantly different from controls with one or more CRFs. sICAM-1 levels were higher in patients with diabetes mellitus than in nondiabetics (350 ± 146 vs 186 ± 70 ng/mL, $p < 0.02$); no relationship with other CRFs was seen. A strong correlation (r=0.74, p= 0.002) was found between sICAM-1 and erythrocyte sedimentation rate in patients. Control subjects showed higher sICAM-1 levels according to the presence of one (P=0.008) or more (P=0.04) CRFs. We found no relationship between sICAM-1 levels and neurological damage evaluated by National Institute of Health Stroke Scale (NIHSS), but improvement over the next 7 days of NIHSS score of at least 3 points was associated to a trend towards lower sICAM-1 levels (p=0.08). We conclude that sICAM-1 levels are related with other known CRFs, and low levels may be predictive of a better outcome after acute cerebrovascular injury. Our data also support the hypothesis that systemic inflammation may be related to the development of acute cerebral ischemia in predisposed subjects.

P580
POSTACTINIC CALCIFYING ANGIOPATHY. Solida A., Carota A., Vingerhoets F., Bogousslavsky J.Department of Neurology. CHUV. Lausanne. Switzerland

Delayed progressive cerebrovascular changes after radiation therapy are uncommon. Most cases develop symptoms within the first 8 years and latencies up to 20 years have seldom been reported. We report a case of progressive delayed postactinic calcifying angiopathy after a prolonged delay. A 64 years old woman underwent post-surgical radiotherapy for a cerebel-

lar astrocytoma at the age of 20 years. At the age of 22, she had an ischemic stroke with favorable outcome. Since the age of 42 years she experienced several migraine like-attacks preceded by altitudinal hemianopia. At the age of 57, partial complex seizures were treated with carbamazepine. At age of 64 years she developed altitudinal bilateral hemianopia, metamorphopia and achromatopia progressing over a ten week period to cortical blindness. CT showed diffuse cerebellar and occipital bilateral calcifications. Blood and CSF work-up for vasculitis was negative. Cerebral angiography showed multiple segmental stenosis of posterior cerebral arteries. The case described is consistent with a focal postactinic calcifying angiopathy progressing over a period longer than 40 years. Recurrent headaches, epilepsy, cerebral calcifications, stroke-like episodes and middle and small size arteries stenosis in the field of irradiation are strongly suggestive of a post irradiation etiology. A mineralizing angiopathy could be the distinctive feature of a radiation-induced focal encephalopathy. The pathogenetic process is not well known. The diagnosis of postactinic angiopathy should be considered, independent of delay, in every patient with neurologic signs after radiotherapy.

P581
ESPRIT: MILD ANTICOAGULATION, ACETYLSALICYLIC ACID PLUS DIPYRIDAMOLE OR ACETYLSALICYLIC ACID ALONE AFTER CEREBRAL ISCHAEMIA OF ARTERIAL ORIGIN.Els L.L.M. De Schryver, on behalf of the European / Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) Study Group, Department of Neurology, University Hospital Utrecht, The Netherlands.

Low-dose aspirin 30 mg/day prevents only 13% of the subsequent vascular events in patients with nondisabling cerebral ischaemia. Anticoagulants have been proven highly efficacious after myocardial infarction and after cerebral ischaemia and atrial fibrillation. SPIRIT showed that high intensity anticoagulation (INR 3.0 to 4.5) is not safe after cerebral ischaemia of presumed arterial origin, but also that mild anticoagulation (INR 2.0 to 3.0) was. ESPS-2 reported a 22% relative risk reduction of the combination of aspirin and dipyridamole above that of aspirin only; its results, however, are controversial. The objective of ESPRIT is to compare the efficacy and safety of mild anticoagulant therapy, combination treatment with aspirin and dipyridamole, or treatment with aspirin alone after cerebral ischaemia of arterial origin. Study design: ESPRIT is designed to randomize 4500 patients between oral anticoagulation (INR 2.0 to 3.0), the combination of dipyridamole (400 mg daily) plus aspirin (30-325 mg/day) and aspirin only (same dose). Primary outcome is the composite event of vascular death, stroke, myocardial infarction or major bleeding; outcome assessment will be blinded. The mean follow-up will be three years. About 80 hospitals in Europe and Australia will participate. Recruitment started July 1997; as of January 1999 more than 450 patients from 48 hospitals had been included.

P582
THE CEREBROPROTECTIVE EFFECTS OF VASOACTIVE INTESTINAL PEPTIDE ANALOGUES. R. R. Leker MD[1], H. Ovadia PhD[1], O. Abramsky MD, PhD[1], M. Fridkin PhD[2], D. E. Brenneman PhD[3], I. Gozes PhD[4].Dept of Neurology[1] Hadassah University Hospital, Jerusalem, Dept of Organic Chemistry[2], Weizmann Institute of Science, Rehovot, Section on Developmental and Molecular Pharmacology[3], NICHD-NIH, USA, and the Department of Biochemistry[4] Tel Aviv University, Israel.

Goal: To determine the cerebroprotective potential of 2 synthetic peptides (SNV and NAP) related to vasoactive intestinal peptide (VIP). Background: VIP is a peptidergic neurotransmitter that was shown to have anti-ischemic effects in a model of myocardial ischemia. At least part of its effects are mediated by an astrocyte derived protein – activity dependent neuroprotective protein (ADNP). The cerebroprotective effects of VIP or ADNP after focal ischemia have not been tested before. SNV and NAP are synthetic compounds related to VIP and ADNP respectively. Materials and Methods: Spontaneously hypertensive rats (SHR) underwent permanent middle cerebral artery occlusion (PMCAO) by craniotomy and electrocoagulation. The animals were injected with either SNV or NAP intravenously (3g/kg) 1hr after stroke onset. Infarct volumes were measured 24hrs later by staining with TTC and using an image analysis system. Results were compared to those obtained in vehicle injected rats. Results: Both proteins significantly reduced infarct volumes as compared to vehicle injected rats. Infarct volume reduction was of similar magnitude for both compounds (10.36 ± 3.8% hemispheric volume for SNV and 8.65 ± 3.9% hemispheric volume for NAP versus 16.23 ± 3.07% hemispheric volume for vehicle injected rats). Conclusions: VIP related proteins appear to be cerebroprotective in this animal model of focal cerebral ischemia. Further experiments are in progress to elucidate its exact mechanisms of action in cerebroprotection and to establish the optimal dosage and timing schedule in stroke.

P583
PROGNOSTIC IMPLICATIONS OF SLEEP DISORDERED BREATHING (SDB) IN ACUTE STROKE. Iranzo A, Santamaria J, Berenguer J, Chamorro A, Aguilar F, Morelló A, Sanchez M, Tolosa E, Hospital Clínic. Barcelona, Spain.

Objective: To determine the prognostic significance of SDB in acute supratentorial ischemic stroke (ASIS). Methods: We studied 44 patients (23 men, mean age 67,3 years) with ASIS. We measured severity at admission and at 1 and 3 months with Scandinavian Stroke Scale (SSS) and Barthel Index (BI); apnea/hypopnea index (AHI) by polysomnography the first night after the stroke (mean 9,6 hours after stroke) and continous pulsioximetry the first 36 hours. Infarct size was evaluated by Magnetic Resonance the first week. Results: Twenty-two patients (50%) had an AHI >20; AHI was higher in patients with stroke presenting at night/morning than afternoon/evening (p:0,022). Seventeen patients had oxyhemoglobin saturation below 90% (CT90) >5% of the time. Infarct size was related with CT90 ($p < 0.0001$), outcome at 1 month (p 0.0005) and Cheyne-Stokes pattern (p:0.01). AHI and CT90 were not related with severity at admission, 1 and 3 months neither with the difference between SSS and BI at 1 month/admission or 3 months/admission. Patients with good and bad outcome had a similar AHI and CT90. Conclusion: SDB is frequent in ASIS, particularly in patients presenting at night/morning. Although CT90 is highly correlated with size of the infarct we could not find a significant relationship between AHI or CT90 for the first 36 hours and outcome at 1 or 3 months. *Supported by CARBUROS METÁLICOS and FIS97-1088.*

P584
ACUTE HEROIN MYELOPATHY. Gomis M, Roquer J, Rodríguez-Campello A, Munteis E, Pou A. Servei de Neurologia. Hospital Universitari del Mar. Barcelona. Spain.

Neurological manifestations are quite frequent in heroin addicts involving both central and peripheral nervous system. However the development of spinal cord syndromes have been rarely described in such patients. We report the case of a 32-year-old male with active heroin overuse who experienced after intravenous heroin administration a sudden loss of consciousness remaining during 12 hours lying on the street. When he waked up he was unable to move his legs. Neurological examination showed a complete flaccid paraplegia (0/5), total anaesthesia in both legs with sensitive level at T5, and loss of sphincter control. Spinal cord MRI showed an extensive ischemic spinal cord lesion from T2 to T7, with hyperintense signal on T2 and hypointense on T1. The outcome was unfavourable and no recovery was seen after six month. The etiology of acute myelopathy in heroin addicts is usually unknown. In few cases a compressive cause such as toxoplasma abscess, staphylococcus abscess or chronic arachnoiditis could be demonstrated. In other cases a vascular mechanism has been implicated. In our patient the location of the ischemic lesion (in a spinal cord border zone) and the existence of a long period of unconsciousness suggests that a hemodinamic mechanism should be involved. The outcome of our case, such other previously described, was unfavourable.

P585
LONG-TERM DISABILITY AFTER FIRST-EVER-STROKE: RESULTS FROM A REPRESENTATIVE, POPULATION-BASED STROKE REGISTER IN GERMANY. Peter U Heuschmann, Bernhard Neundoerfer, Peter L Kolominsky-Rabas, Unit for Stroke Research and Public Health Medicine, Dep. of Neurology, Friedrich-Alexander University Erlangen-Nuremberg, Germany.

Only few studies provided data about long term outcome after stroke. Especially represenatative data on long term disability after stroke from population-based registries are lacking in Europe. Methods: The ERLANGEN STROKE PROJECT (ESPRO) is a population-based stroke register in Germany, which identifies all first-ever-in-a-lifetime-strokes (FELS) in a defined study population of 101.450 inhabitans. All patients were followed up at the time-intervalls 3 and 12 months after stroke. Disability was investigated by the BarthelIndex according to Wade. Results: In a two-years period 354 consecutive patients with FELS were identified. 12 months after FELS 132 (37%) patients were dead, 189 (85%) followed up

and 33 (15%) lost to follow-up. The number of very severe and severe disabled patients decreased from 28% at day 7 to 18% one-year after stroke, the number of independent patients increased from 26% at day 7 up to 3 1 % one-year after stroke. In the univariate analyses disability one year after stroke was influenced by 'age' ($p < 0.001$), 'diagnosis' ($p=0.02$), 'disability at day 7' ($p < 0.001$), 'numbers of risk factors' ($p=0.01$) and 'dependency pre stroke' ($p < 0.001$). In a multivariate logistic regression model only'disability at day 7' ($p \leq 0.0001$) and'dependency pre stroke' ($p=0.02$) were identified as independent predictors for the disability one year after stroke with a predictive value of 87%. The factors 'age', 'sex', 'diagnosis' and 'numbers of risk factors' showed no significant influence. Conclusion: One year after stroke only 'disability at day 7' and 'dependency pre stroke' had an independent influence on long term disability. In opposite to further studies 'age', 'diagnosis' and 'risk factors' showed no independent influence on disability after stroke. In future representative data on epidemiology, survival and outcome of stroke from population-based registries are necessary for planning new public health strategies on stròke management.

P586
REGIONAL AND NATIONAL-ETHNIC SPECIFICS OF STROKE IN UKRAINE. Bezrukov V.V., Kuznetsov V.V., Korsunskaya L.L. Institute of Gerontology, Kiev, Ukraine

The data of a 15-year complex socio-hygienic and clinical investigation of the populations of a southern (Autonomous Republic of Crimea), western (Vinnitsa region) and central parts of Ukraine are presented. Total 8,900 people at the age range 25 to 89 years participated in the study. In the south the stroke morbidity index is 3.5 per 1,000 population that appears to be significantly lower than in western (0.98) and in the central (1.45) regions. The incidence of stroke is much higher in the Russian ethnic group compared to Ukrainian, Tatar and Byelorussian groups. In the Russian ethnic group, an integral biological age exceeds by 5-7 years a calendar one, and the age-related slowing of alpha EEG rhythm begins at the age of 40-49 years while in other national-ethnic groups it occurs after 60. Among the Russians there is a high share of subjects who have displayed risk factors for developing of stroke. At 45-60 years, the incidence of persons with an increased arterial pressure is 48.2% and with hyperlipidemia is 65.7%, while in the Ukrainian group these values are 38.6 and 30.3%, respectively. Within the structure of Ukraine, the southern region has the highest stroke level and the Russian ethnic group shows a high predisposition to cerebral pathology.

P587
SUPERIOR SAGGITAL SINUS THROMBOSIS AND HOMOCYSTINURIA: EARLY ANTICOAGULATION IS ESSENTIAL. S. Yap[1], D. Annesley[2], S. Pittock[3], A. Ryan[3], P. Brennan[2], O. Hardiman[3], E. Naughten[1].. [1]National Center for Inherited Metabolic Disorders, The Children's Hospital, Depts of [2]Radiology and [3]Neurology, Beaumont Hospital, Dublin, Ireland.

Venous thrombosis is the major cause of morbidity and mortality in patients with untreated homocystinuria (HCU) due to cystathionine -synthase deficiency. Superior saggital sinus thrombosis (SSST) is a rare but well-recognised complication with nonspecific clinical manifestations including headache, focal neurological deficits, seizures and a progressive course. A 24 year old man with known pyridoxine non-responsive HCU, who had been non-compliant with treatment for 6 years, presented with headache, transient right arm paraesthesia and weakness. His level of consciousness deteriorated over 24 hours with an evolving right hemiplegia and seizures. CT and MRI/MRV revealed SSST. His total homocysteine was 290 µmol/L (normal15) and free homocystine was 86 µmol/L (normal: 0); his coagulation profile was otherwise normal. Treatment for severe hyperhomocysteinaemia consisted of methionine restricted, cystine supplemented diet, pyridoxine, B12, folic acid and Betaine. Anticoagulation therapy was started after MRI confirmation of SSST. The patient dramatically improved within 24-36 hours of anticoagulation therapy. Hyperhomocysteinaemia should be considered in the presence of idiopathic SSST. Patients with HCU and neurological signs of cerebral venous thrombosis can have a favourable outcome with aggressive management of homocysteine levels and early anticoagulation therapy.

P588
VENOUS ANGIOMA OF THE CAUDA EQUINA PRESENTING AS A SLOWLY PROGRESSIVE MOTOR NEURON SYNDROME 27 YEARS AFTER RADIATION. T.Ben-Hur MD,PhD[1], A.Ashkenazi MD[1], D.Soffer MD[2], JM.Gomori MD[3], F.Umansky MD[4] and O.Abramsky MD,PhD[1]. Departments of Neurology[1], Pathology[2], Radiology[3] and Neurosurgery[4], Hadassah University Hospital, Jerusalem, Israel.

Objective: To describe an elderly patient with venous angioma (VA) of the cauda equina presenting as a slowly progressive motor neuron syndrome (MNS). Background: Spinal VA's are uncommon vascular malformations. They may present as a rapidly progressive and fatal myelopathy (Foix-Alajouanine syndrome) or as an acute myelopathy due to bleeding. Presentation as a slowly progressive MNS has not been previously described. Case presentation: A 82 year old man presented with progressive weakness of the lower limbs and gait disturbance of 4 year duration. 27 years earlier he underwent orchiectomy and radiotherapy to the pelvis due to seminoma. On examination there was asymmetric, distal more than proximal, weakness of the legs with a left foot drop. Bilateral quadriceps atrophy was noted. DTR's were reduced or absent in the legs, with Babinski sign on the right. Sensation was intact except for a mild decreased vibration sense in the legs. There were no sphincteric abnormalities. CSF contained extremely high protein level and mild pleocytosis without evidence for malignant cells. MRI demonstrated marked nodular thickening of the cauda equina suggesting a neoplastic or inflammatory process. After a negative systemic investigation, a biopsy of the cauda was performed. Multiple abnormal blood vessels were found around cauda roots, identified histologically as venous angioma. The lesions were unresectable. Conclusions: VA of the cauda equina should be considered in patients with a progressive MNS even when CSF and imaging findings suggest a malignancy or inflammation. Spinal VA's may appear as a late complication of radiation.

P589
UNUSUAL CLINICAL AND RADIOLOGICAL PRESENTATION OF A LEFT ATRIAL MYXOMA. S. Drapier, M. Coustans, D. Tixier, A. Depatureaux, G. Edan, M. Verin. Rennes, France.

Left atrial myxoma (LAM) is a rare cause of stroke (< 1%). We report the case of a woman with LAM revealed by two ischemic strokes one four years after the other. A fifty four year-old woman with previous history of ophtalmic migraine presented in 1994 an acute coma with seizures and left hemiparesis. A magnetic resonance imaging (MRI) of the brain showed multiple focal hypersignal on T2 weighted sequences in white matter and basal ganglia. The eye ground showed several ischemic lesions in ciliary and retinal vessel. Etiologic investigations, including transthoracic echocardiographiy (TTE) remained negative and an antiplatelet treatment was initiated. Neurologic symptoms were partially regressive with persistance of pseudobulbar and pyramidal disorders until 1998. At this time she presented a cerebellar ischemic stroke. A transesophageal echocardiography (TEE, not realised in 1994) showed a 3,5 cm wide LAM which was surgically treated and histopathological confirmed. This case report emphasizes the importance of TEE in the positive diagnosis of LAM (two TTE remained normal at a four year interval) and the possibility of isolated recurent ischemic strokes as clinical revelation of LAM.

P590
DEVELOPMENT OF AUTOIMMUNE HYPERTHYROIDISM IN MULTIPLE SCLEROSIS (MS) PATIENTS TREATED WITH INTERFERON BETA (IFNβ). Holzknecht Ch+, Potrz F Th+, Rieks M+*, Halve S+, Przuntek H*, R Hörmann#, Pöhlau D+*. +Sauerlandklinik Hachen, Siepenstr. 44, 59846 Sundern, *Multiple Sclerosis Research Group Ruhr-University Bochum. #Department of Endocrinology, University Essen; Germany,

Interferon beta (IFNβ) is effective in the treatment of relapsing-remitting multiple sclerosis (MS). In rare cases autoantibodies against thyroid tissue may occur; we present two cases. Two females, 47(A) and 44 years (B); with MS since more than ten years had azathioprine prior to IFNβ. A got 44µg/week IFNβ-1a(Rebif) s.c.; B was treated for 4 weeks with IFN-β1b (Betaferon) s.c. then with 22µgr/week IFNβ-1a (Rebif)s.c. [B]. First symptoms (A: severe joint swelling, stiffness and pain; B: increased skin reactions, increased fatigue, painless dysphagia, "lump in the throat") occured about 5 (A) and 36months (B) after the initiation of IFN treatment. The higher dosage of IFNβ-1a corresponded with the shorter latency until the onset of symptoms. Both showed high titers of thyroid peroxidase autoantibodies (TPO-AB) (A: 31 924 U/ml; B: 623 U/ml), B also had thyreoglobulin antibodies (TAB). fT3, f T4 values stayed normal, TSH was pathological low in (A). None developed TSH receptor autoantibodies. In (A) after the cessation of the treatment autoantibodies declined conti-

nously, but were still pathologically high after 3 months. In B the IFNβ-therapy is continued, TAB were normalized 5 weeks later without specific therapy, fatigue was reduced. MAB were stabilized on a pathologically high level. Discussion: IFNβ may induce or enhance production of thyroid autoantibodies either by "immune deviation" or by a change of the polarisation of thyroid follicle cells by IFNβ, followed by the formation of immune complexes. In mild cases, the IFNβ therapy can be continued with monitoring of clinical signs and autoantibodies. Further analysis should reveal the amino acid sequence these autoantibodies bind to.

P591
REVERSIBLE ENCEPHALOPATHY AND DEMYELINATING NEUROPATHY INDUCED BY DISULFIRAM. A CASE REPORT. S.Greffard, D. Grabli, A. Améri, Y. Weiss, F.Chédru. Department of Neurology, C. H. de Meaux, Meaux, France.

Disulfiram is still widely used in the rehabilitation of chronic alcoholic patients. As cases of encephalopathy due to this drug are exceptionnal, we thought the present case was worth reporting. A 33 year old woman, with a past history of neurotic depression and chronic alcoholism, had been given dilsufiram at the dosage of 1 g per day (the recommended dosage is 500 to 250 mg per day) for 3 months in association with vitamins and clorazepam. Over a 4 weeks period, the following symptoms developped: swaying gait, dysarthria and intellectual impairement, then limb weakness and distal paresthesiae. Neurological examination disclosed a static cerebellar syndrome, a peripheral lower limbs neuropathy and major neuropsychological difficulties suggesting a dementia at its initial state (apragmatism, altered judgement, memory disorder, attention lability). Electroencephalography showed large bilateral diffuse theta waves. Electromyography disclosed a severe diffuse axonal and demyelinating polyneuropathy with impairement of conduction velocities in the lower limbs. Usual biological parameters, CSF analysis, vitamin assays, were normal as were cerebral CT scan and MRI. After disulfiram was discontinued, cerebral signs cleared up within 4 days. As far as the neuropathy was concerned, the patient improved slowly and a motor deficit was still present after six months.

Dementia and Higher functions disorders

P592
INFLUENCE ON COGNITIVE FUNCTION OF CHRONIC STIMULATION OF THE SUBTHALAMIC NUCLEUS. Dujardin K, Krystkowiak P, Defebvre L, Blond S, Destée A. CHRU de Lille, France

Much research is focusing on neurosurgery targeting the subthamalic nucleus (STN) in the treatment of Parkinson's disease (PD). Consequences on cognitive function of such an intervention remain sparsely documented. The aim of the present study was to control the effects of chronic bilateral stimulation of the STN on cognitive function. Six patients with severe PD (median age: 51, median Hoehn & Yahr stage: 4.5) were assessed 1 month before and 3 months after surgery. The neuropsychological examination included a cognitive screening and an evaluation of attention, memory and executive function. The group performances at both evaluations were compared by a non parametric statistical procedure. Before surgery, all patients presented normal cognitive function. Three months after surgery, their performance was stable for most tasks parameters. There was a significant enhancement of their attention abilities. A significant decline of performance was observed in the task of delayed recall from episodic memory and in the part B of the Trail Making test where they were significantly slower. Examination of individual performances showed that three patients presented stable performance in all tests. Two patients presented enhanced performance on tests evaluating executive function. One patient performed at a lower level on all tests, except those evaluating attention. Despite the small number of patients, this preliminary study reinforces the idea that chronic bilateral STN stimulation in the treatment of severe PD is cognitively safe.

P593
EXECUTIVE FUNCTION DIFFERS IN MULTIPLE SYSTEM ATROPHY (MSA) AND PARKINSON'S DISEASE (PD). Dujardin K, Degreef JF, Krystkowiak P, Defebvre L, Destée A. CHRU Lille, France

Previous studies with MSA patients revealed cognitive dysfunction close to that observed in frontal lobe pathology. According to them, the dysexecutive syndrome in MSA could be limited to a loss of spontaneous flexibility with preservation of reactive flexibility although in PD, both kinds of flexibility could be impaired. Because such a dissociation could represent a clinical interest in the differential diagnosis between MSA and PD, the aim of the present study was to verify its existence. Performance of MSA patients at tasks evaluating cognitive flexibility was compared to those of two groups of PD patients, one matched with respect to the severity of motor symptoms and the other with respect to disease duration. Compared to healthy control subjects, the three groups of patients were impaired whatever the task. Both groups of PD patients did not differ. The MSA patients did not differ from the PD patients at the tasks evaluating reactive flexibility, however, they performed significantly lower at the tasks evaluating spontaneous flexibility. These results are in opposition with our hypothesis. Indeed, the MSA patients were impaired as well in the spontaneous than the reactive flexibility tasks. Moreover, their impairment was more important than those of PD patients in tasks evaluating spontaneous flexibility. This underlines the need to better characterize the dysexecutive syndrome in MSA in order to better understand the mechanisms leading to the development of this parkinsonian syndrome.

P594
OCULAR MOTOR DYSFUNCTION AND RISK OF DEMENTIA IN EARLY HUNTINGTON'S DISEASE. Morrison P J, McGivern C, Gibson J M. Departments of Medical Genetics, Neurology and Medical Physics. Belfast, Northern Ireland

In 1992 we conducted an epidemiological study of Huntington's Disease (HD) in Northern Ireland.This identified 99 definite HD cases. 75 of these had advanced disease with severe chorea and or dementia. 23 of the remainder were defined as having early but clinically definite disease. We performed quantitative infrared oculography, video assessment, clinical examination and Mini Mental State Assessments (MMSE) on these. All had minimal motor abnormalities and all scored 27/30 or better on MMSE The horizontal saccadic system was studied using the following established paradigms which are sensitive to abnormality in brainstem,cerebellar, basal ganglia and frontal connections; reflexive, predictive, remembered and antisaccades. Initial analysis showed the following abnormalities; reflexive latencies 15%, reflexive peak velocity slowing 70%, failure of prediction 10%, abnormal remembered saccades 100 %, abnormal antisaccades 95%. Clinical follow up of these cases over 6 years has shown significant dementia in 5/23 as arbitrarily defined by MMSE of 20 or less. Review of these patients'clinical and ocularmotor data for 1992 showed that the presence of ocular motor apraxia and prolonged reflex saccadic latency were the best predictors for dementia.We postulate that abnormalities of saccadic initiation are an important clinical indicator of the onset of dementia in patients with early HD.This could have important implications for therapeutic trials.

P595
CONTRIBUTION OF FREE AND CUED RECALL TO THE EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE A. Ivanoiu, M. Vanderlinden, X. Seron, CJM. Sindic. Brussels, Belgium

The Enhanced Cued Recall Test-ECRT (E. Grober & H Buschke, 1987) is an episodic memory test that maximizes learning by inducing deep semantic processing and by controlling encoding and retrieval. We aimed to evaluate its usefulness as a diagnostic tool in early Alzheimer's disease (AD). We used a variant of ECRT adapted to the French language, also including a delayed free and cued recall and using words as items. 21 very early AD patients (MMSE ≥ 24), 21 mild and moderate AD patients and 28 controls (non-demented, anxious or mildly depressed consulting our "Memory Clinic"), matched for sex, age and cultural level, were enrolled. All were evaluated by the same neurologist (including CT-scan or MRI) and re-examined one year later when the initial diagnosis of probable AD (NINCDS-ADRDA criteria) or the absence of dementia was confirmed. The difference between the very early AD patients and controls was highly significant ($p=0.0001$, ANOVA, post-hoc comparisons) for ECRT performance. However, total recall (free+cued), considered as the most sensible measure, only classified correctly 62% of the very early AD patients (the z-scores method). A ceiling effect was observed and the test might become more sensible with a larger number of items. The best discriminator was the total delayed recall: 80% of very early and 93% of other AD patients were correctly classified.

P596
CHRONIC TRAUMATIC BRAIN INJURY IN AMATEUR SOCCER PLAYERS. J.T. Matser MSc (1), A.G. Kessels, MD (2), M.D. Lezak PhD (3), J. Troost MD (4) B.D. Jordan MD (5).

Objective: Chronic traumatic brain injury (CTBI) incurred in athletic activities, has been reported primarily among retired boxers. Mild forms of CTBI may also be encountered in professional soccer players. Whether CTBI occurs in amateur soccer was investigated in this study. Methods: Thirty-three amateur soccer players were compared to a group of 27 amateur athletes involved in noncontact sports (i.e., swimming and track). Both soccer players and controls underwent neuropsychological testing. Results: Amateur soccer players performed more poorly on tasks involving planning and memory. These deficits persisted after adjusting for history of non-soccer related concussions, alcohol ingestion, history of previous general anaesthesias and level of education. Conclusion: Participation in amateur soccer may adversely affect some aspects of cognitive functioning i.e., memory and planning. Due to the world-wide popularity of soccer (200 millions participants), this may have important public health implications. Additional investigations are warranted to further delineate the possible risk factors for CTBI in soccer, especially in youth soccer.

P597

STIMULUS INTENSITY AND FREQUENCE DEPENDENCY OF PICTURE NAMING FACILITATION BY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS). F. M. Mottaghy[1,2], R. Sparing[1], M. Hungs[1], H. Foltys[1], B. Boroojerdi[1], B.J. Krause[2] - R. Töpper[1]. [1]Department of Neurology, RWTH Aachen, [2]Department of Nuclear Medicine, HHU Düsseldorf, Germany

In previous experiments we showed facilitation of naming latencies with focal as well as repetitive TMS over Wernicke`s area preceding object presentation in normal subjects. In the study presented here the effect of rTMS over Wernicke´s, Broca´s area and the primary visual cortex at different frequencies (1Hz or 20 Hz) with forty magnetic stimuli each was investigated. In addition different stimulus intensities were applied over Wernicke's area (ranging from 35-55% of maximum stimulator output).. Fifteen healthy male right-handed subjects were presented with ten pictures of different black and white line-drawings which were randomly presented twice during each condition. The subjects were presented with the pictures immediately and two minutes after the end of the rTMS train. Naming latency was facilitated only immediately after Wernicke's area stimulation at 20Hz with a stimulus intensity of 55% ($p < 0.001$). Two minutes after Wernicke's area stimulation as well as low frequency stimulation and all other stimulation sites and intensities did not have any effect on the naming latency. Based on these results we provide further evidence for the feasibility of rTMS to produce longer lasting facilitations of higher cortical functions. However, these effects are dependent on the stimulus intensity, the frequency of the stimulus and on the stimulation site.

P598

ANTIEMETIC THERAPY FOR ALZHEIMER'S PATIENTS RECEIVING THE CHOLINESTERASE INHIBITOR RIVASTIGMINE (Exelon ®, SDZ ENA 713). Angelico Carta, M.D.[1] Ravi Anand, MD,[2] Richard D. Hartman, PhD,[2] John C. Messina Jr., PharmD,[2] Stanford S. Jhee, PharmD,[3] John J Sramek, PharmD,[3] Neal R. Cutler, MD[3] [1]Worldwide Clinical Trials, London, UK [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ [3]California Clinical Trials, Beverly Hills, CA, USA

Cholinesterase inhibitors frequently cause dose-related nausea and vomiting. This prospective, randomized, open-label pilot study was designed to evaluate the efficacy of four antiemetic treatments during a four-week forced dose escalation of rivastigmine from 3mg/d to 12mg/d in patients with Alzheimer's disease. Twenty-six of 82 enrolled patients experienced dose-related nausea and/or vomiting requiring antiemetic treatment. Patients were rated on the Emetic Process Rating Scale (EPRS) every 4h and the Clinical Global Impression (CGI) scale at 72h. Treatment success was defined as a CGI score of < 2. Glycopyrrolate 1 mg (n=3) had a 33% success rate, ondansetron 4 mg (n=4) had a 50% success rate, trimethobenzamide 250 mg (n=9) had an 89% success rate, and trihexyphenidyl 2 mg (n=10) had a 90% success rate. Thus, centrally acting antidopaminergic and anticholinergic compounds were effective in preventing nausea and vomiting with rivastigmine, indicating that these effects are centrally mediated.

P599

A DOUBLE-BLIND, COMPARATIVE STUDY OF THE ACUTE EFFECTS BILATERAL GLOBUS PALLIDUS STIMULATION AND LEVODOPA ON FRONTAL NEUROPSYCHOLOGICAL PERFORMANCE IN PARKINSON'S DISEASE. J.Kulisevsky, B.Pascual-Sedano, C.García-Sánchez, A.Gironell, M.Barbanoj, *J.Molet. Dept. Neurology, and *Neurosurgery. Hospital de Sant Pau. Barcelona, Catalonia. Spain.

Information on the neuropsychological consequences of bilateral globus pallidus internus (GPi) stimulation is lacking. We assessed and compared the acute effects of LD and GPi stimulation on frontal neuropsychological performance in PD patients. Methods: In a double-blind, randomized study, three months after bilateral GPi deep brain stimulation (DBS) implant, six patients received alternative forms of frontal neuropsychological tests (trail-making, phonetic fluency, tower of Hanoi and Wisconsin card sorting test (WCST) in four different conditions: off-LD/off-DBS; on-LD/off-DBS; off-LD/on-DBS and on-LD/on-DBS. Results: Post-hoc t-test analysis showed that, compared with basal conditions, DBS alone produced no significant changes in the studied tasks, although diminished (17 %) the time of the trail-making test. LD alone significantly diminished the time an the errors in the trail-making test ($p=0.04$) but with a significant poorer performance in the WCST ($p=0.01$). The addition of the effects of LD and GPi stimulation was also associated with a poorer performance in the WCST without reaching statistical significance. Conclusion: Bilateral DBS of the GPi at the parameters used to obtain motor improvement produced no adverse effects on cognitive performance. Our results extend previous observations on the adverse effects of acute administration of LD in frontal-related tasks. *Supported by: Telemarató TV3 (ANEP) 025/97 and CIRIT 9.501/96.*

P600

THE EVALUATION OF APOLIPOPROTEIN E GENOTYP IN PARKINSON'S DISEASE PATIENTS WITH AND WITHOUT DEMENTIA. B.Jasinska-Myga, St.Ochudlo, G.Opala, J.Tustanowski, W.Wierzba, J. Tyrpa. Department of Late Age Neurology, Department of Microbiology, Silesian Medical Academy, Katowice, Poland.

The aim of our study was the evaluation of the relationship between apolipoprotein E (APO E) genotyp and the clinical parameters in Parkinson's Disease (PD) with and without dementia. Fourty patients with PD were evaluated and within this group two subgroups were formed: PD patients with and without dementia. These patients were clinically studied. The estimation of the apo E genotyp was executed by means the Polymerase Chain Reaction (PCR). The Unified Parkinson's Disease Rating Scale (UPDRS) was used to quantify the severity of PD. Cognitive functions were assessed according to the following tests: Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS-COG), Global Deterioration Scale (DS). The frequency and the severity of depressia were screened with the Hamilton Depression Scale, the Beck Rating Scale and the Montgomery-Asberg Depression Rating Scale (MADRS). APO E allele ε4 and homozygous ε4/ε4 condition frequencies were significantly higher in the subgroup of PD patients with dementia. APO E allele ε4 played a significant role in the risk of dementia in PD in our sample.

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APOLIPOPROTEIN E GENOTYPE IN A SAMPLE OF SICILIAN PATIENTS SUFFERING FROM ALZHEIMER'S DISEASE. R.M. Ruggieri*, R. Palermo*, P. Calanni*, G. Forloni**, U. Lucca**, E. Greco*,F. Piccoli*. * Institute of Neuropsychiatry, I Division of Neurology, University of Palermo, Palermo. ** Institute "Mario Negri", Milano.

Forty-one Sicilian patients (22 men and 19 women) suffering from probable Alzheimer's Disease (according to NINCS-ADRDA criteria) underwent APO-E genotype examination. The mesn age of onset was 69,3 (SD=6,69), and the mean period of aducation was 7,41 (SD=4,18) years. Twenty-one patients reported family history of cognitive decline. Results showed that at least one allele E4 was present in 50% of patients (14: E3//4; 6: E4//4). We did not find any correlation either with age of onset ($p=0,141$) or with family history ($p=0,882$). These preliminary data suggest a higher percentage of E4 allele in our group of patients compared to other authors' reports (Poirier J. et al 1993; Frisoni G.B. et al 1995).

P602

REHABILITATION OF READING ABILITY IN ALEXIA WITHOUT AGRAPHIA: REPORT OF A SINGLE CASE E.Imbornone, M.Alberoni, N.Del Grosso Destreri, E.Farina, P.Nichelli, and C.Mariani. IRCCS Don Gnocchi Foundation, Neurorehabilitation Unit, Universities of Milan and Modena, Italy

A.Z., a 65 years-old woman, suffered an ischaemic stroke in the left posterior cerebral artery territory. First examined 5 months after the accident, she showed a right homonimous hemianopia associated with alexia with-

out agraphia, colour anomia, object agnosia and mild verbal amnesia. At the time of first examination she was able to read only 16/36 letters, and totally unable to read words. Her oral spelling ability was intact, as her visual imagery for letters. Her profile of performance in a set of subtests of the B.O.R.B. indicated an apperceptive integrative agnosia. She was able to correctly discriminate shapes of different dimensions and segment orientation while being severely impaired in recognizing drawings of objects and animals, overlapping drawings, and chimeric pictures. The cognitive rehabilitation treatment was centered on the possibility to access an intact knowledge of letters via a kinesthetic route, i.e. by tracing the contour of single letters with her index finger A.Z. progressively improved in this task, becoming after 35 sessions able to read words and sentences. The improvement acquired in reading was selective and did not involve her agnosia. At the time of dismission, she was able to read 33/36 single letters 30/36 overlapping letters, and 32/40 words. Re-tested 6 months after her visual agnosia was substantially unmodified, while she was still able to read thorough the acquired kinesthetic route.

P603

CATCHING WITHOUT MOTION PERCEPTION: A CASE STUDY OF A MOTION-BLIND PATIENT. T. Schenk, N. Mai, J. Zihl. Munich, Germany

Damage to the visual motion area V5 is known to produce profound deficits of visual motion perception in primates and humans. It is not known whether V5 is also involved in the visual control of predictive behavior. Study of a patient (LM), who suffered a bilateral loss of V5 allowed us to determine the role of V5 for the visual control of movement. Catching behavior was studied in LM and five healthy subjects. Two linear motors moved the target object within the horizontal plane, liquid-crystal shutter glasses were used to manipulate visibility; and a 3D movement registration system measured arm and hand movements. Catching performance was characterized by kinematic variables and the number of successful catches.When full vision was available, LM's performance was impaired for objects moving faster than 0.75 m/s.When vision was restricted to the first 150 ms of the object motion, her performance was also impaired for slower objects (speed=0.5 m/s). In contrast, the withdrawal of visual feedback (i.e., only the target object was illuminated; the moving hand was invisible) had a similar effect on control subjects and LM. These results suggest that V5 is involved in the visual control of predictive behavior. While V5 seems essential for the prediction of fast target motion, it appears to be dispensable for the visual monitoring of limb movement, for which positional information possibly dominates.

Extrapyramidal disorders

P604

OBSESSIVE-COMPULSIVE DISORDERS ARE NOT INDUCED BY POSTERO-VENTRAL INTERNAL GLOBUS PALLIDUS HIGH FREQUENCY CHRONIC STIMULATION. S Caloone, M Vérin, F Lallement, I Rivier, G Edan, Y Lajat, Rennes & Nantes, France.

Obsessive-compulsive disorders (OCD) have been described in man after bilateral lesions of the internal segment of the globus pallidus (GPI), element of the ventral striatopallidal system, the so-called anterior cingulate circuit. Postero-ventral internal pallidal segment is a target of choice to alleviate levodopa-induced dyskinesias in parkinsonian patients by deep brain stimulation. In order to investigate the hypothetic role of the GPI inhibition in the emergence of OCD, 4 parkinsonian patients with bilateral postero-ventral GPI chronic continuous high frequency stimulation were studied before and after surgery. The Brief Psychiatric Rating Scale, the Compulsion Activity Check-List and the Yale-Brown Obsession-Compulsion Scale were applied 1 month before and 3, 6 and 12 months after bilateral continuous GPI stimulation was turned on. No modification of the OCD scores was observed between the pre- and post-surgical stages. This observation is a strong argument against the responsibility of the ventral striatopallidal dysfunction in the emergence of OCD.

P605

NEUROPSYCHOLOGICAL TESTS IN THE ASSESMENT OF EARLY COGNITIVE IMPAIRMENTS IN HUNTINGTON'S DISEASE.Camus J.F.[1], Lisovoski F. [2], Legrand C. [2], Turpin J.C. [2]Departement de Neuropsychologie, Faculté des Lettres and 2. Service de Neurologie - C.H.U Maison Blanche. Reims. France.

Huntington Disease (HD) is primaly defined by a motor dysfunctioning and a progressive dementia. Recent data suggest that cognitive impairments in HD are observed very early. This observation is a point of major interest for a better understanding of the time course of HD, a precise evaluation of cognitive benefits to be expected from therapeutic trials, an early multifaceted medical and psychological intervention via specific cognitive practice and training. Several testable subjects with trinucleotid repeat exceeding 37 were recruited and submitted to neuropsychological tests including attention, memory and general intellectual abilities. Some of them where symptomatic (stage 2) and others were classified in a presymptomatic stage. All were compared with control subjects. Standard neuropsychological tests (Stroop, Trail Making, Mattis, Grober & Buschke) and other protocols (orientation of attention, implicit memory) were used. Significant differences were found between HD and control subjects in memory and attention tasks. HD subjects had reduced scores in episodic memory tasks. In attentional tasks, HD and presymptomatic subjects had lower scores than controls suggesting that attention deficits occur early in the clinical course of HD. This pattern of cognitive impairments is consistent with an inhibitory deficit due to an alteration in the striatofrontal circuits. The choice of new designs provide (1) more sensitive measures of cognitive (dys)functioning and (2) detailed models of cognitive processing which could be individually tested in patients.

P606

EARLIER AGE OF ONSET FOR PROGRESIVE SUPRANUCLEAR PALSY IN PATIENTS PRESENTING THE A0/A0 GENOTYPE. Molinuevo JL, Valldeoriola F, Revilla M, Muñoz E, Oliva R and Tolosa E. Hospital Clinic, Barcelona, Spain

Genetic studies have disclosed a significant overrepresentation of the gene A0 allele in patients with progressive supranuclear palsy (PSP) suggesting an involvement of the protein in its pathogenesis. Objective: To determine if patients displaying the A0/A0 genotype exhibit distinct demographic, and clinical characteristics compared to those with other genotypes (non-A0/A0). Methods: We studied twenty-six patients (twenty with the A0/A0 genotype and six with non-A0/A0 genotype) fullfilling clinical criteria for PSP and presenting similar number of years from disease onset. Demographic data, past medical history, family history and first symptoms were colllected in a standardized questionnaire. PSP symptoms were quantified following Golbe´s PSP disability scale. Statistical comparisons were done using a -square and Mann-Whitney tests. Results: All comparisons resulted non significant except the mean age at onset of symptoms, which was 65.9 years in the A0/A0 and 71.2 in the non-A0/A0 group (p=0.01). Patients from both groups presented similar degree of disability. Conclusions: Patients with PSP displaying the A0/A0 alleles of τ protein gene present the symptoms of the disease significantly earlier than patients displaying other different genotypes. This finding suggests, in agreement with previous studies, that the A0/A0 genotype is a risk factor for PSP.

P607

SUBTHALAMIC NUCLEUS STIMULATION FOR ADVANCED PARKINSON´S DISEASE. Valldeoriola F, Molinuevo JL, Rumià J, Fàbregas N, Valls-Solé J, Ferrer E and Tolosa E. Hospital Clinic, Barcelona, Spain.

Subthalamic nucleus (STN) stimulation is an alternative treatment for patients with medication resistant advanced Parkinson's disease (PD). Objective: To present the 6-months follow up results of 12 consecutive PD patients with motor fluctuations and dyskinesias who underwent STN stimulation. Methods: Twelve parkinsonian patients (mean age 58.7 ± 8 years, disease duration 13.8 ± 6 years) underwent sterotactic microelectrode guided bilateral STN stimulation. Before surgery, patient's morning first off and on were assessed following CAPIT instructions. Six months after surgery patients were assessed while on and off stimulation but only off medication. Clinical evaluation included UPDRS, Schwab&England, Hoehn&Yahr staging system and a dyskinesia scale. Results: Total motor UPDRS score decreased 64%. Limb akinesia, rigidity and tremor subscores improved by 56%, 54%, and 88% respectively. Midline symptoms decreased 66%. Activities of daily living (ADL) were ameliorated by 74%. Schwab&England ADLs changed from 32 to 85%, and Hoehn&Yahr score decreased from IV to II. All these results were statistically significant. Dyskinesias also significantly improved due to the reduction in dopaminergic medication (from 1416 ± 661 to 517 ± 444 mg/day levodopa total equivalent dose). Only two patients presented non-transient side effects (mild dysarthria and increased muscular neck tone). Conclusions: STN stimulation is an effective treatment for all motor parkinsonian symptoms. This fact is reflected in the dramatic reduction of total dopaminergic medication daily intake.

P608
LEVODOPA-RESPONSIVE PARKINSONISM AND CORTICAL MYOCLONUS. R. Assouad, P. Krystkowiak, F. Cassim, L. Defebvre, J.D. Guieu, A. Destée. CHRU de Lille, France

Myoclonus and parkinsonism is usually observed in corticobasal degeneration (CBD), multiple system atrophy (MSA), diffuse Lewy body disease, drug-induced syndromes. In Parkinson's disease (PD), myoclonus has rarely been reported and there was no evidence for cortical origin. However, Caviness et al have recently evidenced a cortical origin for two cases of myoclonus associated with levodopa-responsive parkinsonism consistent with PD whereas this usually evokes MSA or CBD. We report the case of a 68 year-old-man presenting with a 18-year history of levodopa-responsive parkinsonism with motor fluctuations. He fulfilled the UKPDSBB diagnostic criteria for PD. Examination revealed absence of rest tremor but postural, pseudo-rythmic, irregular, small-amplitude, brief jerks in his arms, consistent with myoclonus. It could not be elicited by somatosensory, photic or startle stimuli. The myoclonus was postural and was unaffected by the levodopa treatment, suggesting it was different from the levodopa-induced myoclonus. Electromyographic (EMG) study showed negative myoclonus in the four limbs. After median nerve stimulation, the amplitude of the somatosensory-evoked potentials was normal and long-latency reflexes (C reflex) were not exaggerated. However, electroencephalographic back-averaging revealed spikes preceeding the myoclonus by 20-25 ms, suggesting a cortical origin. There is evidence for cortical pathology in PD and this could explain cortical origin myoclonus. Our case demonstrate that myoclonus may manifest as a sign of cortical disease in PD.

P609
"VASCULAR PSEUDOCORTICOBASAL DEGENERATION": CLINICAL AND MRI FEATURES. B Mastain*, F Tison**, G Fénelon***, A Destée*. Dept. Neurolgy; *Lille, **Bordeaux, ***Paris, France.

Corticobasal degeneration (CBD) can be diagnosed clinically even if symptoms and presentations vary. False-positive diagnosis is rare and occur mainly with other neurodegenerative diseases such as Parkinson's disease, progressive supranuclear palsy, striatonigral degeneration or Alzheimer's disease. We report four patients in whom the diagnosis of CBD was clinically obvious who turned out to have an extensive cerebrovascular disease on brain MRI. All patients were women aged between 64 and 76. Initial presentation was a 'useless arm' in 1 case, a gait disorder in 1 case, a combination of both in 1 case and a combination of 'useless arm' with sensory symptoms in the last case. At examination there were an asymmetric dopa-resistant akinetic rigid syndrom (n = 3), upper limb apraxia (n = 4) with myoclonus (n = 3), cortical sensory loss (n = 2), gait difficulties (n = 3), pyramidal signs (n = 3), dementia (n = 2), and an alien limb phenomenon (n = 1). Brain MRI revealed extensive subcortical white matter lesions in 2 cases, right parietal vascular lesion in 1 case and extensive lesions of vasculitis in the last case. Although neuropathological studies were not undertaken, we considered such vascular lesions as the cause of the clinical picture. Brain MRI is helpful for the differential diagnosis in cases of pseudoCBD, particularly when insidious vascular lesions are responsible.

P610
COGNITIVE CHANGES IN HUNTINGTON DISEASE PATIENTS AND THEIR AT RISK RELATIVES. P. Soliveri, D. Paridi, D. Monza, S Genitrini, C. Gellera, S. Di Donato, T. Caraceni and F. Girotti. National Neurological Institute "C. Besta", Via Celoria 11, Milan, Italy

Onset of Huntington's disease (HD) is usually considered coincident with appearance of chorea, however cognitive impairment may anticipate chorea. Periodic neuropsychological evaluation in pre-symptomatic subjects can detect early cognitive alterations. We examined 30 subjects from 7 HD families; 10 had symptomatic HD confirmed by DNA testing, 10 were were symptoms-free but carrying the HD gene, and 10 were healthy and negative for the HD gene. Motor disturbances, assessed by QNE, showed moderate impairment in the HD patients. Cognitive evaluation employed a comprehensive neuropsychological battery exploring general intelligence, attention, memory, executive and visuo-spatial functions. Scores were corrected for age and education. ANOVA showed that HD patients did significantly worse than pre-symptomatic and healthy subjects in all tests, while the latter two groups did not differ. Individual analysis identified five pre-symptomatic subjects with scores in some tests 2 standard deviations below normal. Reasoning, attention and executive function tests were the most sensitive to early cognitive deterioration. Therefore, as reported by others, deficits in some cognitive functions are evident in HD before the appearance of motor symptoms. However, isolated cognitive impairment in some patients only points to rapid development of cognitive decline: if had cognitive deterioration had lasted longer, greater numbers of pre-symptomatic patients should have been compromised.

P611
COGNITIVE FUNCTIONS IN STRIATO-NIGRAL AND OLIVO-PONTO-CEREBELLAR TYPE MULTISYSTEM ATROPHY. P. Soliveri, D. Paridi, D. Monza, D. Testa, S. Genitrini,. Caraceni and F. Girotti. National Neurological Institute "C. Besta", Via Celoria 11, Milan, Italy

Deficit in frontal functions is well documented in striato-nigral-degeneration (SND) type multisystem atrophy (MSA). Other studies have shown deficits in planning, visuo-spatial, and linguistic functions in patients with cerebellar diseases. However no studies have compared cognitive functions in SND type and olivo-ponto-cerebellar (OPCA) type multisystem atrophy. We compared 7 SND patients, 7 OPCA patients, and 7 controls on a comprehensive neuropsychological battery. The groups did not differ in age or education; the OPCA and SND patients did not differ in disease duration or motor disability as assessed by NUDS. Non parametric ANOVA showed significant differences between the groups in intelligence and reasoning (MMSE and Raven test), attention, constructive apraxia, ideomotor apraxia and executive functions. Post-hoc analysis showed that SND patients were worse than controls in reasoning, attention and ideomotor apraxia tests (although mean scores were not apraxic). OPCA patients were worse than controls in these measures, and also in the executive function and constructive apraxia tests. The SND and OPCA patients did not differ significantly in any cognitive functions. Lack of different cognitive profile in these two diseases could be due to the presence of subclinical signs of one disease in patients diagnosed with the other, or perhaps to small sample size. We are currently testing more patients to improve the power of our study.

P612
ISOLATED UNILATERAL LESIONS OF THE GLOBUS PALLIDUS: A REPORT OF 4 PATIENTS PRESENTING WITH FOCAL OR SEGMENTAL DYSTONIA. A Münchau, MD, G Shahidi, MD, D Mathen, MD, NP Quinn, MD, KP Bhatia, MD, London, UK

Isolated descrete lesions of the BG, particularly unilateral lesions of the globus pallidus (GP), are rare. We report 4 patients with focal unilateral lesions of the GP. The first patient developed dystonic spasms of his left arm at the age of 19 three years after a road traffic accident. MRI revealed a lesion in the dorsal part of the right Gpe. The second patient developed dystonia of his left leg at the age of 6 months. MRI demonstrated a small lesion in the right GP involving both Gpe and GPi. Perinatal anoxia was the presumed cause. The third patient, a 27-year old man, presented with a 5-year history of dystonia of the left arm and slowly progressive mild left hemiparkinsonism with prominent micrographia and slowness of writing. Repeat MRI showed a static lesion in right Gpe and Gpi of unknown cause. The fourth patient, a 25-year old man, had an episode of anoxia during an operation at the age of 5. Several months later he developed dystonia of the right foot. The occurrence of dystonia after damage of GP in previously normal subjects is unusual, since dystonia due to focal BG damage is usually caused by lesions involving the putamen. The patients reported here emphasize the role of the GP in suppressing unwanted movements during motor performance.

P613
ANALYSIS OF SPONTANEOUS BLINK RATE PATTERNS AT REST IN NORMAL SUBJECTS AND IN PATIENTS WITH PARKINSON'S DISEASE: REPORT OF 63 CASES. Bezerra, MLS; Martínez, JVL; Freitas, GR; Moreira, PF. Department of Neurology, Fluminense Federal University, Niterói-RJ, Brazil.

Objective: To describe the spontaneous blink rate (SBR) in normal subjects and in patients with Parkinson's Disease (PD) and to determine the SBR in the different stages of PD according to Hoehn-Yahr Scale (HYS). Methods: Thirty-one normal subjects were compared to 32 patients with PD without dementia or Levodopa induced dyskinesias. Subjects were not informed that their eyes would be under observation. The subjects were divided in two groups: one with normal subjects and the other with the patients with PD, and the latter in two more groups: one with PD patients

with HYS below 2.5 and the other above or equal 2,5. The within-group medians were compared with the Wilcoxon test, two-tailed. The inter-groups medians were compared with the Mann-Whitney test, two-tailed. P-values below 0.05 were accepted as significant. Results: The SBR medians were 11 in normals and 3 in patients with PD. The analysis of SBR showed a significant lower rate in the patient group ($p = 0.001$). Comparing the two groups with patients with PD, the medians were 6,9 in the group with 2.5 at the HYS and 6.1 in the group with > 2.5 at HYS. Conclusion: This study identified the SBR as significantly lower in the PD group than in the normal individuals. In contrast with most cases in the literature there was no relationship between SBR and HYS of PD.

P614

DYSARTHRIA IN CORTICOBASAL DEGENERATION (CBD). Auzou P, Özsancak C, Hannequin D. (Fédération des Sciences Neurologiques, 76031 Rouen, France).

Aim: Evaluation of dysarthria and orofacial apraxia (OFA) in CBD. Subjects and Method: 10 patients (4 women, 6 men) with a clinical diagnosis of CBD were evaluated (mean age: 72.3 years, range: 67-78). Mean disease duration was 3 years (range: 0.5-5). The global severity of the disease was evaluated by the Schwab and England scale. Dysarthria was analyzed by using the French version of the Frenchay Dysarthria Assessment. It is a validated and quantified clinical scale which evaluates motricity of the systems implied in speech production (respiration, larynx, articulators) and intelligibility. A patient was considered dysarthric if his intelligibility score (IS) was 24/24. OFA was assessed with 12 gestures: 6 single, 4 with a noise production (such as to whistle) and 2 series of sequential gestures. By using the Pearson's method, we searched for correlations between the IS and each of the following measures: the duration of the disease, the Schwab and England score and the OFA score. Results: 1. Dysarthria and OFA were present in 9/10 patients. 2. The reduction of intelligibility was mild (mean IS = 20/24). 3.. Lip and tongue motricity were always impaired. 3. The IS was correlated to the Schwab and England score ($r = 0.91$, $p < 10^{-3}$) but neither to the duration of the disease ($r = - 0.34$) nor to the score of OFA ($r = 0.21$). 4. Sequential gestures were most sensitive to OFA. Conclusion: Dysarthria and OFA are frequent in CBD. The absence of correlation between the IS and the OFA score as well as clinical dissociations argue for independent mechanisms. The underlying pathophysiology is due to a deficit of programming and execution of repetitive movements.

P615

CHRONIC HIGH FREQUENCY SUBTHALAMIC NUCLEUS (STN) STIMULATION IN THE ADVANCED PARKINSONIAN SYNDROME (PS). Funk Th, Vesper J, Wagner F, Kern BC, Brock M. Neurochirurgische Klinik und Poliklinik, Universitätsklinikum Benjamin Franklin, Berlin, Germany.

Chronic high frequency stimulation (HFS) of the thalamus is by now an established procedure in the treatment of tremor. HFS of the globus pallidus internus (GPI) seems not to be as effective as pallidotomy. Recently, the STN has been identified as the optimal target for advanced PS. Methods: Between March 1996 and October 1998 HFS of the STN has been performed in 21 patients. Mean age was 67 years, Hoehn and Yahr scale 4,1, duration of disease 13 years (mean values). Results: All patients were examined according to Unified Parkinson's Disease Rating Scale (UPDRS) pre- and postoperatively and at six month follow-up. Significant improvement of motor symptoms was found in all patients at six month follow-up (UPDRS III preoperatively 32 - on/ 48 off vs. 15/30 at follow-up, $p < 0,001$). Mean reduction of off times was 35%. Postoperatively medication was adjusted to the patient's needs (mean L-DOPA reduction 53%, range 10-68%). Conclusion: Due to the size of the GPI and its internal organization HFS of the GPI does not achieve all the effects of pallidotomy. The smaller STN requires only a small electrical field to achieve the same results. Furthermore, through the possibility of readjusting the stimulation parameters postoperatively, the therapeutic effect can be improved and side effects can be avoided. Chronic HFS is a very effective treatment method for the various symptoms in late stage PS.

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TARGET SETTING AND OUTCOME OF CHRONIC HIGH FREQUENCY STIMULATION (HFS) IN DIFFERENT TYPES OF TREMOR. J Vesper, Th Funk, U Jahnke, M Straschill, M Brock. Neurosurgical Clinic, Medical Center Benjamin Franklin, Free University of Berlin, Germany

HFS thalamic stimulation is a nondestructive alternative approach in the treatment of drug resistant tremor. The results and final target settings obtained when applying this technique are discussed with respect to the type of tremor. Between March 1996 and October 1998, 36 patients underwent HFS of the ventral intermediate nucleus (VIM). Out of these patients, 10 suffered from essential tremor (ET), 10 from parkinsonian tremor (PD) and 16 from cerebellar tremor. Intraoperatively, target points were selected according to midline structures and determined by functional testing and single unit microelectrode recording. Postoperatively, stimulation parameters and, if needed, setting of the active electrode were adjusted. The coordinates of the active electrode were calculated in regard to the posterior commisure (PC) intraoperatively and at six month follow-up. Significant tremor reduction was achieved in all patients. The best results were obtained in the cases of ET and PD (tremor reduction according to Fahn scale 60 vs. 15 points at follow-up). In patients with cerebellar tremor the tremor was reduced from 83 to 45 points at follow-up (mean values). Calculation of final target points showed for ET and PD that the active electrodes were all located in the VIM according to Schaltenbrand-Wahren atlas. In contrast, target points for cerebellar tremor were located in the ventral oral anterior nucleus. Stimulation of the ventral thalamic region is an effective type of treatment for various types of tremor. However, in cerebellar tremor a different target point shows the best functional results.

P617

RARE SIDE EFFECTS OF AMANTADINE SULFATE THERAPY IN PARKINSON'S DISEASE PATIENTS. Kogan / A.E. Henneberg, Hospital for Parkinson's Disease, D-61231 Bad Nauheim, Germany

Introduction: Amantadine sulfate is regulary used as first medication or in combination with dopaminergic drugs in patients suffering from Parkinson's disease as general practice in the Hospital for Parkinson's Disease in Bad Nauheim, which is with 160 beds the biggest European hospital for extrapyramidal disorders. The average amantadine sulfate dose used in mild to moderate Parkinson's disease is 300 mg/day. L-Dopa induced dyskinesias with marked motor fluctuations represent a therapeutic problem which we effectively control with amantadine sulfate in doses up to 450 mg/day. When tolcapone was withdrawn from the European markets we started to use higher doses of amantadine sulfate up to 600 mg/day for patients suffering from rigidity or pulsion with fall tendency as the leading symptoms. Using high doses of amantadine sulfate combined with physiotherapy on neurophysiological basis we observed further improvement in hundreds of patients, even if they had to give up the tolcapone treatment. Amantadine sulfate in higher doses is generally well tolerated, however, in two patients we found an aggravation of the symptoms. Patient 1: The 82 year old female patient is suffering from Parkinson's disease since 1984, L-Dopa treatment was started in 1990. When the patient consulted us she had fluctuations and hyperkinetic movements on 350 mg L-dopa, 5 mg lisuride and 2,5 mg selegiline. Because of retropulsion we reduced lisuride and added 300 mg amantadine sulfate. As freezing persisted we increased the dose of amantadine sulfate to 500 mg/day. Instead of an improvement the patient showed a worsening of her retropulsion tendency and was unable to walk anymore. After reduction of the amantadine sulfate dose to 200 mg/day she improved and was able to walk shorter distances without help. Patient 2: This 66 year old male patient suffers from Parkinson's disease since 1995 and is under L-Dopa treatment since then. He presented himself because of retropulsion, fall tendencies, difficulties in walking and turning in bed. His medication was 400 mg of L-Dopa, 100 mg tolcapone, 3 mg ropinirol and 200 mg amantadine hydrochloride. We replaced amantadine hydrochloride with 400 mg amantadine sulfate, reduced tolcapone and ropinirol after which the patient's symptoms improved. After increasing the dose of amantadine sulfate to 500 mg retropulsion suddenly worsened and walking was impossible. When we reduced the amantadine sulfate dose to 200 mg and gave the patient 300 mg L-Dopa but no tolcapone and ropinirol the patient improved again and was able to walk without help. Discussion: Amantadine sulfate is a valuable drug and established in therapy of early and chronic Parkinson's disease including patients with motor fluctuations who benefit from doses up to 600 mg/day. The two case reports presented show that single cases high doses of amantadine sulfate may have the opposite effect and increase balance difficulties or retropulsion. In such cases a reduction of amantadine sulfate to 200 to 300 mg/day is recommended.

P618

OLANZAPINE IN THE TREATMENT OF IDIOPATHIC DYSTONIA. A. Memin, A. Somogyi, G. Gallouedec, M. Vidailhet, France.

Olanzapine is a new atypical neuroleptic (a serotonin-dopamine receptor antagonist). This drug shares many pharmacologic similitaries with clozapine and has the advantage to cause relatively few adverse effects (e.g. neutropenia). As there are some reports improvement of tardive dyskinesia with olanzapine treatment, we treated 2 patients with severe idiopathic dystonia, that did not respond to any other treatment. Our observations represent an early experience with olanzapine in idiopathic dystonia: Case 1.A 24-year-old man started with torticollis. Within 2 years he presented generalized dystonia predominating in the trunk and arms, with a flexed posture of the trunk up to 90° when walking. He was unsuccessfully treated with L dopa, diazepam, trihexiphenidil and botulinum toxin.Adverse effects with severe drowsiness were observed with clozapine. Olanzapine treatment was started at 5 mg/d and increased to 20 mg/d during a two weeks period. After 3 days of therapy, the patient displayed a marked reduction of dystonia (50%) which was still present at 3 months follow up. Case 2.A 42-year-old man suffered from generalized dystonia since the age of 9. He was wheelchairbound and had twisting movements and dystonic posture of 4 limbs and neck. He was very mildly improved with the association of Olanzapine. After a week, a 20% improvement of dystonia was observed. We report a preliminary experience of marked sustained improvement of generalized idiopathic dystonia with Olanzapine, with a good tolerance. To our knowledge, only few reports of improvement of axial tardive dystonia have been reported yet.

P619
TOLCAPONE INCREASES MAXIMUM CONCENTRATION (C_{MAX}) OF LEVODOPA IN PLASMA. Thomas Müller, Dirk Woitalla, Horst Przuntek, Dagmar Schulz, Brigitte Werne, Wilfried Kuhn. Department of Neurology, St. Josef-Hospital, Ruhr-University of Bochum, 44791 Bochum, Germany

Combination of levodopa/benserazide tolcapone significantly increases bioavailability but not maximum concentration of levodopa in plasma of healthy subjects. 13 hospitalized parkinsonian patients received Madopar 125 on two days within a standardized study protocol. Levodopa plasma levels were measured with HPLC at fixed time points. Concomittant pharmacotherapy remained stable except the addition of tolcapone with a daily dosis of 3 x 100 mg starting after the first day. AUC of levodopa in plasma before administration of tolcapone (mean: 83559.13 ± 36682.25 [SD] range 37029 to 147197.25 ng/ml) was significant (p = 0.0004, difference: mean 61894.83 ± 46903.39 [SD] range - 3451.5 to 151415.25 ng/ml) lower compared to the AUC with tolcapone (mean 145453.96 ± 58758.34 [SD] range 38893.5 to 219756 ng/ml). C_{max} of levodopa in plasma without tolcapone (mean: 837.73 ± 351.13 [SD] range 389.70 to 1428.19 ng/ml) was significantly (p = 0.0008, difference: mean 434.3 ± 355.24 [SD] range - 91.5 to 1185.79 ng/ml) decreased compared to the C_{max} with tolcapone (mean: 1272.03 ± 394.53 [SD] range 639.79 to 1878.69 ng/ml). We confirm the influence of tolcapone on the AUC-value of levodopa plasma levels, but the range of the C_{max} increase may explain the transient occurence of dopaminergic side effects after additional tolcapone administration despite a 30% reduction of oral daily levodopa dosage.

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WRITER'S CRAMP AND ESSENTIAL TREMOR ASSOCIATED WITH TEMPORO-PARIETAL LESION. Flavia Pauri[1,2], Emanuele Cassetta[1], Paolo Maria Rossini[1,2] - 1: AFaR-CRCCS Centro di Ricovero e Cura a Carattere Scientifico: Divisione di Neurologia, Ospedale Fatebenefratelli, Isola Tiberina 39, 00186 Roma 2: IRCCS Centro S Giovanni di Dio - FBF, Brescia

A sixty years old man complaining right hand tremor begun about two years before, went to our observation. Neurological examination revealed essential tremor affecting the right arm, the head, the voice and writer's cramp in the right arm. The tremor was responsive to acute alcohol ingestion, but not to levo-dopa and dopamine-agonist agents. Propanolol reduced the tremor intensity. The dystonia was successfully treated with the injection of botulinum toxin type-A. Before our observation the patient underwent cerebral MRI during a screening following the excision of a right forearm melanoma. MRI showed a left cortical parietal lesion, of uncertain origin – probably a low-grade astrocitoma– which remained unchanged during 18 months. The association of tremor and focal dystonia with a brain tumor lesion in the parietal cortex is an infrequent event. The possibility that the cortical lesion could be at the origin of both tremor and writer's cramp probably via the damage of the neuronal loop between basal ganglia and cortical structures should be considered.

Epilepsy

P621
PARADOXICAL LATERALISATION OF MIDLINE EEG SEIZURE PATTERN. Stephan Arnold[1], Soheyl Noachtar[1], Tarek Yousry[2], Peter A. Winkler[3], Hans O. Lüders[4] - [1]Dep. of Neurology, [2]Neuroradiology and [3]Neurosurgery, University of Munich, Germany and [4]Dep. of Neurology, Cleveland Clinic Foundation, Cleveland, OH, U.S.A.

Paradoxical lateralisation of midline EEG seizure pattern have been rarely described. We report on three patients, in whom ipsilateral seizure patterns were recorded. Case 1: A 10-year-old girl had a left peri-rolandic epilepsy since the age of 6 years. Her seizures consisted of somatosensory auras of the right leg, evolving into tonic seizures, clonic seizures of the right arm and generalized tonic-clonic seizures. Her MRI showed a cystic lesion at the border between the left precentral and superior frontal gyrus. Noninvasive EEG-video-monitoring revealed right parasagittal interictal spikes and ictal EEG seizure patterns. Case 2: A 25-year-old man had a focal epilepsy of unknown etiology. His MRI was normal. He had tonic-clonic seizures of one arm. EEG seizure patterns were ipsilateral during the tonic phase and contralateral during the clonic phase of the seizure. Case 3: A 69-year-old man had epilepsia partialis continua. MRI was normal. EEG recordings showed that the jerks of the left leg were consistently associated by ipsilateral central polyspikes, whereas interictal spikes were contralateral to the jerks. Paradoxical EEG seizure lateralisation occurs in midline epileptogenic zones and suggests an interhemispheric seizure onset. Invasive recordings to corroborate this assumption are needed.

P622
MORPHOLOGICAL DIFFERENCES IN SCALP-ICTAL EEG OF TEMPORAL VERSUS EXTRATEMPORAL LOBE SEIZURES. K. Garganis, V. Logotheti, T. Bourboulas, E. Markoudi, I. Milonas. B' Univ. Department of Neurology, AHEPA Hospital, Thessaloniki, Greece

Objective: To identify differences in scalp-ictal EEG features between Temporal and Extra-temporal lobe seizures. Material- Methods: 35 pharmacoresistant localization- related epilepsy patients undergoing presurgical evaluation. Several scalp-ictal EEG features were identified during activity at seizure onset (ASO-First 3 sec of ictal EEG) and evolution of a late significant pattern (LSP) of at least 5sec duration. Patients were assigned to a Temporal lobe (TLE) and an extratemporal lobe (ETLE) group, according to interictal and ictal activity localization, seizure semiology and location of MRI lesion. Results: 16 patients comprised TLE group (57 seizures analyzed) and 19 patients comprised ETLE group (79 seizures analysed). 1) Fast ictal rythms at ASO were significantly more often present in extratemporal seizures (50% of analyzed events versus 0% of temporal lobe seizures). 2) A well sustained LSP was significantly more often present in temporal lobe seizures (100% of analyzed events versus 60% of extratemporal seizures). 3) Most (80%) LSPs of temporal lobe seizures appeared as "rythmic sustained temporal theta". This feature has a high specificity for temporal lobe onset, as it was observed in only 2% of extratemporal onset seizures. Conclusion: Temporal and Extratemporal lobe epilepsy scalp-ictal morphological features differ. These findings may provide complementary information for ictal onset localization.

P623
CONTINUOUS BILATERAL FOCAL MOTOR SEIZURES WITH RETAINED CONSCIOUSNESS AFTER STROKE. A. Ashkenazi, Y. Kaufman, O. Abramsky. and T. Ben-Hur. Neurology Department, Hadassah University Hospital, Jerusalem, Israel.

Objective: To describe a patient with continuous bilateral focal motor seizures of the legs without loss of consciousness, after stroke. Background: Genuine seizures involving both sides of the body without loss of consciousness are rare and often mistaken for pseudoseizures. They have been described with frontal lobe foci, particularly in the supplementary motor area (SMA), usually presenting as tonic limb movements. Case presentation: A 67 year old woman presented with continuous rhythmic clonic movements of the right leg which spread to involve both legs synchronously and continued for several hours. During the attack she was completely alert and oriented. The patient had suffered a left hemispheric stroke 9 months earlier and was left with severe right hemiparesis and motor dysphasia. EEG showed continuous rhythmic sharp-wave activity over the left frontal parasagittal area, which spread to the corresponding area on the right, in accordance with seizure spread to the left leg. Brain CT showed an old left MCA infarction. The clinical and electroencephalo-

graphic phenomena disappeared promptly following intravenous Diazepam administration. Phenytoin was subsequently given, with no recurrent seizures. Discussion: The clinical presentation is compatible with a focus in the left primary motor area, rather than the SMA, with spread of activity to the corresponding area contralaterally. This type of seizure has been described with neoplastic and developmental lesions, but not after stroke. Conclusion: Continuous bilateral clonic movements with retained consciousness can represent a genuine seizure and may occur as a sequel of stroke.

P624
MOVEMENT DISORDERS RELATED TO EPILEPTIC CORTICAL POSITIVE AND NEGATIVE MYOCLONUS.W. Szurhaj, V. Leduc, F. Cassim,, P. Derambure. Department of Clinical Neurophysiology. Lille, FRANCE

Rationale: In epileptic patients, interictal movements disorders remain often misunderstood. However, they affect their quality of life and cause even sometimes an important disability with falls and drops of things. Methods: We studied 16 epileptic patients having interictal movement disorders presenting as a tremor, a flapping or an abnormal walk. The patients have been tested by neurophysiological examinations including ictal videoEEG, somatosensory evoked potentials(SEPs), and EEG-EMG polygraphy with back-averaging. Results: We found type 2 negative myoclonus in 13 patients, positive myoclonus in 9 patients, and both in 6 cases. Myoclonus were focal or multifocal. They were found in patients with partial as well as generalized epilepsy but with a predominance of frontal lobe epilepsy. Patients were unaware of their disorders in half cases. Jerk-locked back-averaging of EEG always showed a biphasic potential on contralateral central or parietal regions. SEPs were found normal in 10 cases on 16 tested. The abnormalities were represented by an absence of cortical response, or the presence of giant SEPs with a long latency EMG reflex. Conclusion: These cortical myoclonus could be induced by a non specific cortical sensorimotor hyperexcitability. The occurence of multifocal myoclonus in unifocal partial epilepsy seems to indicate that, even in partial epilepsy, there's a diffuse hyperexcitability within the motor cortex.

P625
PROTON MAGNETIC RESONANCE SPECTROSCOPY IN TEMPORAL LOBE EPILEPSY: THE CHOICE OF PARAMETERS. V. Diklic and I. Savkovic, Novi Sad, Yugoslavia.

We performed single voxel proton magnetic resonance spectroscopy in vivo (^{1}H-MRS) in 134 patients with temporal lobe epilepsy (TLE), aged 8 - 32 years. We used SE 135 sequence, with voxel size 12.5x12.5x12.5 mm^3 (SP63 Magnetom, Siemens, 1.5 T). In all patients voxels were placed in both hippocampal regions, except in 4 children where only ipsilateral side was examined. After manual shimming and Eddy currents adjustments, total patient time inside the magnet was 100 minutes for acquisitions of both temporal lobe spectra. The raw data were transferred to a workstation for fast Fourier transformation, curve fitting, plotting, and display processing. Metabolite ratios towards total creatine (tCr) or choline (Cho) were calculated after peak area integration. We calculated and compared several parameters: N-acetylaspartate (NAA)/Cho epileptogenic index; tCr/Cho index; index of asymmetry $[(NAA/tCr)_i\ (NAA/tCr)_c][(NAA/tCr_i)/2 + (NAA/tCr_c)/2]$, where $_i$ and $_c$ mean ipsi- and contralateral, respectively; NAA/(tCr + Cho) epileptogenic index and the presence of lactate (Lac). We found that in 86% of patients there was a good agreement between EEG and MRS concerning the laterality of epileptogenic region. Whenever Lac was present (in 13% of patients in our study) it was always found in the ipsilateral side and can be used as a reliable dynamic index of epileptogenic region. We found bilateral epileptogenic foci in 57% of patients. Of all indices tested, we found the NAA/Cho index as the most accurate predictor of epleptogenic region (in 97% of cases, followed by Cho/tCr, while the NAA/(tCr + Cho) index was in a good correlation with EEG data in only 82% of cases.

P626
IPSILATERAL BLINKING AS A LATERALIZING SIGN IN FOCAL EPILEPSIES. Anja Henkel[1], Stephan Arnold[1], Konrad J. Werhahn[1], Peter A. Winkler[2], Soheyl Noachtar[1] [1] Dep. of Neurology and [2] Neurosurgery, Ludwig Maximilians University of Munich/Germany

Purpose: Several lateralizing seizure phenomena have been described. Most lateralizing motor phenomena are contralateral to the seizure onset zone. However unilateral blinking has been reported as a rare ipsilateral ictal phenomenon. We reviewed our data base for ictal unilateral blinking. Methods: 239 consecutive patients with focal epilepsies considered for epilepsy surgery were included. All patients underwent ictal EEG-video monitoring and MRI, 85% had interictal FDG-PET and 60% ictal ECD-SPECT. Unilateral blinking was defined as blinking of the eyelid and the lack of simultaneous facial clonic activity or mouth deviation. Results: Ictal unilateral blinking was observed in 2 of 239 patients in our series (0,8%). In both patients unilateral blinking was ipsilateral to the seizure onset zone. Both patients had right temporal epilepsy. One patient had a cavernoma in the right medial temporal gyrus, the other patient had right sided hippocampal sclerosis and is seizure-free after anterior temporal lobe resection. Conclusion: Our data confirm that unilateral blinking is a rare, but reliable lateralizing seizure phenomenon indicating an ipsilateral epileptogenic zone. Although our patients had temporal lobe epilepsy, the symptomatogenic zone giving rise to ipsilateral blinking when activated by epileptic discharges is yet not known.

P627
SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE): CLINICAL EVALUATION OF 36 PATIENTS. Aylin Öztürk, Candan Gürses, Betül Baykan, Aysen Gökyigit, Meral Barlas, Rezzan Tunçay, Mefkure Eraksoy. Department of Neurology, Istanbul Faculty of Medical, Universty of Istanbul, Turkey

We studied that 36 patients (24 male 12 female) who all had definite SSPE with typical periodic complexes in the EEG and increased titres of measles antibody in serum and CSF. Their clinical and laboratory findings were reviewed retrospectively. The age of onset of symptoms varied from 1 to 23 years. The mean duration from the infection to the onset of SSPE was 15 months. The presenting signs were behavioral changes in 18, myoclonus or atonia in 8, visual problems such as blurred vision, hallucinations in 7 and seizures in 3 patients. Unusual symptoms, especially early in the disease were hemiparesis (7), headache (3), generalized tonic clonic seizure (6), absence seizure (1), nause, and vomiting(3). Twentyfive cranial MR and 12 CT examinations were performed. Nine patient had normal MRI. Six of these patients had mild clinical course (stage 1-2). Other 3 patients had severe clinical findings (stage 4). In the early stages lesions usually involved parietooccipital corticosubcortical regions. Later symmetrical periventricular white matter changes became more prominent. Despite the common clinical findings in cases of SSPE, reported in literature, there are some variable clinical features of the disease. There may be no correlation between clinical stages and either duration or MR findings.

P628
EARLY AND LATE STAGE EEG FINDINDS IN WERNICKE-KORSAKOFF SYNDROME DUE TO LONG STANDING STARVATION: CORRELATION WITH THE CLINICAL AND MRI FINDINGS. Demet Kinay, Aysen Gökyigit, Betül Baykan, Emel Gökmen, Hakan Gürvit. Department Of Neurology, Medical Faculty of Istanbul, University of Istanbul, Turkey

In this study, early and late EEG findings in Wernicke-Korsakoff Syndrome (WKS) due to long standing starvation were investigated. In 1996, after the termination of death fast which was performed by political prisoners, 18 patients were managed in our clinic. Their mean age was 30 years. All patients were diagnosed as Wernicke encephalopathy and 10 of them developed Korsakoff syndrome. Early stage EEG's were performed between 20 and 40 days after the termination of death fast and following the thiamine treatment. EEG examinations were repeated in 17 patients one year later. During the first clinical examination 3 patients were confused. Others were conscious and alert. In the early stage, abnormal EEG findings were determined in 5 patients (27.8%). Main abnormality was mild regular activity in the theta range which involved in frontal and fronto-temporal regions bilaterally. Paroxysmal anomalies were not observed. There was no significant relation between abnormal EEG and neither the severity of the clinical findings at the acute stage nor the clinical course of one-year follow-up. At the end of the first year, abnormal EEGs returned to normal in one case, to normal limits in 3 cases as clinical symptoms did. In the fifth patient, abnormal EEG findings continued although slight improvement was observed. Moderate-severe increased intensity in thalamus and grey matter around aqueducts were determined in MRI at the acute stage in 3 of 13 patients whose EEG findings were normal and 4 of 5 patients whose EEGs were pathological. There was positive correlation between EEG and acute stage MRI findings.

P629
VAGUS NERVE STIMULATION IN PATIENTS WITH DRUG RESISTANT EPILEPSY.Vesper J[1], Funk Th[1], Merschhemke M[2], Meencke HJ[2], Brock M[1] [1]Neurochirurgische Klinik und Poliklinik, Universitätsklinikum Benjamin Franklin, Freie Universität Berlin, Evangelisches Krankenhaus Herzberge, Berlin, Germany

Objectives: Vagus Nerve Stimulation (VNS) is now setting up as an alternative therapeutical approach in pharmaco-resistant epilepsies. Cyclic high-frequency stimulation may reduce seizure frequency and severity. This paper presents considerations on the mechanism of action, the indication for surgery, the surgical technique as well as preliminary results. Material and Methods: Nine patients (7males, 2 female) suffering from drug resistant partial seizures and not amenable to conventional epilepsy surgery have been studied. Three patients had a focus in eloquent areas (central region), one had bitemporal foci, and in one patient the focus could not be clearly localized. Electrode placement on the left vagus nerve in the midcervical region was performed under general anaesthesia. The stimulator (NCP-Generator, Cyberonics) was implanted in the infraclavicular region. Results: 50% of patients benefited from the procedure. In two patients surgery resulted in a 50% reduction of seizure frequency, another two patients reached at least a reduction of the severity of seizures with regard to the duration and the effect. Five patients reported on an improved quality of life concerning the independency and the ability to work. Stimulation dependent side effects like hoarseness were endurable and not permanent. Conclusion: The preliminary results in this study are encouraging. This confirms the need of an uniform protocol and a complete invasive diagnostic preoperatively in order to reduce the number of "non-responders" and to predict more precisely the outcome.

General neurology

P630
ADULT-ONSET KRABBE'S DISEASE. Nemec M, Bednarík J, Jankovych J, Vondrácek P, Elleder M, Dvorák K, Kadanka Z.

Krabbe's disease is a rare autosomal recessive inherited disorder caused by the deficiency of galactocerebrosidase. Although the most common form of the disease is the classical infantile form, later-onset forms also have been described. The authors described 34-year-old male patient with late onset Krabbe's disease initially presented with awkward walking. During the next 15 years he developed slight lower spastic paraparesis with brisk proprioceptive reflexes, positive pyramidal signs and he suffered from moderate bladder and sexual dysfunction; his ability to walk for a long distance was preserved. He had no clinical signs of peripheral neuropathy. Magnetic resonance imaging of the brain showed diffuse white matter disease. Somatosensory and motor-evoked potentials disclosed markedly prolonged central somatosensory and motor conduction times. Laboratory evaluation revealed an abnormally low level in leukocytes to 0,63 nnmol/mg/h (lower normal limit was 9 nnmol/mg/h). Both parents were clinically asymptomatic; they both displayed reduced galactocerebrosidase activity. Nerve biopsy of the sural nerve demonstrated inclusions consisting of globoid clusters in the cytoplasm of Schwann cells and evidence of demyelination. The same inclusions were found in skin sudomotor glands. CSF findings were completely normal, oligoclonal bands were absent. Adult-onset Krabbe's should be taken into consideration in the differential diagnosis of chronic progressive form of multiple sclerosis.

P631
MRI COMPARISON OF NERVE SHEATH TUMORS IN LUMBAR REGION – IS THERE A DIFFERENT COMPRESSION EFFECT? N. Curcin, K. Koprivsek, M. Lucic, R. Semnic, D. Kozic, S. Stajnic.Diagnostic Imaging Center, Sremska Kamenica, Yugoslavia

Purpose: To determine which type of two histologically distinct nerve sheath tumors (NST) causes larger compression effect on structures in lumbar spine. Materials and methods: Retrospective study included 19 patients with lower back pain, radicular pain and cauda equina syndrome. MRI (1.5T system) confirmed existence of intradural extramedullary mass in lateral recessus of these patients. Based on MRI findings, compression degree was graded as a) light, b) medium and c) severe compression with root displacement. Postoperative pathohistological analyses' showed presence of NST. Results: Schwanoma – Antoni A type was revealed in 10 cases (medium compression 6, severe compression 4), Schwanoma – Antoni B type in 6 (medium compression 4, severe 2), neurofibromas – NF1 in 3 (light compression 2, medium 1). Regardless of histological type, light compression was present in 11% of cases, medium in 58% and severe compression with root displacement in 31%. Medium compression was caused by Antoni A type in 55% of cases, Antoni B type in 36% and NF1 in 9%. Conclusion: There is significant difference in compression degree caused by schwannomas and by neurofibromas. Antoni A type, being composed of compact cellular tissue, causes medium and severe compressions. Antoni B type, being mucinous and microcystic, causes mostly medium and rarely severe compressions with root displacement. Neurofibromas type 1, being soft and nonencapsulated, cause compressions of lesser degree.

P632
COGNITIVE EVENT RELATED POTENTIALS DURING A LEARNING TASK. M.F.EL-Bab & E.M.Sedgwick. Clinical Neurological Sciences, University Of Southampton, UK, 1999

Event related potentials were recorded from 27 scalp electrodes on 44 normal subjects. Our aim was to determine whether there was a difference in potentials in those who learned compared to those who did not and a control group. Patterns A and B had been generated by computer program and classed according to the subjects' decision by pressing the mouse button. Clues from border effect or contrast change were eliminated. In two hundred different trials presented randomly and generated, but obeyed the rule for its type (A or B), 18 subjects learned, 16 did not. A control group consisted of 10 subjects. The learning performance was assessed. The total, the first & the last 50, and the correct & the incorrect wave responses were averaged and the mean amplitudes and reaction times were measured and compared. The control group ERPs was very similar to the base line activity. Learners showed an increase in positivity during the first window (250: 550 msecs), and the second window (550: 850 msecs). Non-learners did not show any significant increase in positivity. The increased positivity was greater for correct answers than for wrong answers and greater positivity over the right hemisphere than the left. It can be concluded that the successful learning is associated with an increase in positivity. Also the learning is predominantly a right hemisphere activity. Reaction time was quicker for the learners.

P633
CHRONIC ANAL FISSURES TREATED WITH BOTULINUMTOXIN-INJECTIONS: A DOSE-FINDING STUDY WITH DYSPORT® AND COMPARISON TO BOTOX® W.H. Jost, Dept. of Neurology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany

Botox® injection of the anal sphincter muscle cures chronic uncomplicated anal fissures in up to 80 % of patients. This study examines therapeutic efficacy and side effect profile of the British botulinum product Dysport®. 50 patients (29 women) were recruited to participate in this randomized dose-finding study, their mean age being 32.9 years. The low dose group A was treated with a total dose of 20 U injected in two sites each lateral to the fissure, the high dose group B was treated with 40 U. 82 % of patients were pain-free within a week following the injections. The fissure was healed in 78 % of treated patients after 3 months. 3 patients relapsed within half a year. The most common adverse side effect was transient incontinence (4 patients). Clinical outcome was not significantly different between the two treatment groups, the low dose can therefore be regarded sufficient for the treatment of anal fissure. Therapeutic efficacy was equivalent to published data on Botox® treatment. Botox® versus Dysport® showed healing without surgery after 3 months in 82 versus 78%, and relapse in 5 versus 6%. Both Dysport® and Botox® can therefore be used to treat chronic uncomplicated anal fissures. Both Dysport® and Botox® therapy is well tolerated, can be performed on an outpatient basis and avoid the risk of permanent fecal incontinence which complicates surgical treatment of anal fissures.

P634
NAMING INVOLVES BOTH HEMISPHERES: AN FMRI STUDY. [1]G. Fesl, [2]J. Ilmberger, [2]A. Weber, [1]T.A. Yousry. [1]Department of Neuroradiology, [2]Department of Physical Medicine, Ludwig-Maximilians University, Munich, Germany

Naming is a core linguistic abilitiy. As anomias are central symptoms of most aphasia syndromes, identification of the structures involved in naming is of considerable clinical and theoretical interest. Previous studies focused on silent naming, we report data on overt naming allowing to control responses using functional magnetic resonance imaging (fMRI).

Methods: Thirteen subjects were examined. In the "active" phase, drawings of objects were presented and had to be named aloud. In the "baseline" phase, drawings of nonsense objects were presented, and a previously defined nonsense word had to be produced. fMRI was performed using echo-planar sequences. For post-processing the Statistical Parametric Mapping program was used. Results:Individual analysis revealed significant activations in: 1) the region of the temporo-occipital junction (left: 9/13; right: 10/13), 2) inferior parietal lobule (left: 6/13; right: 10/13), 3) middle frontal gyrus (left: 6/13; right: 7/13). Group analysis confirmed activation in the right hemisphere in Brodmann areas (19, 39, 40). Conclusion:Object naming involves several steps: perception, semantic and phonological selection and articulation. Our study aimed at identification of the structures involved in recognition and semantic concept formation. The fact that most activations were bilateral indicates that these processes are in most cases represented in both hemispheres with a strong invariant right hemisphere component across subjects.

P635
MAGNETIC RESONANCE IMAGING (MRI) IN THE DIAGNOSIS OF VESTIBULAR PAROXYSMIA. Tomlinson HR, Tidswell P, Gunawardena WJ, Coutinho CMA.

Neurovascular compression syndromes of the facial and trigeminal nerves are well accepted. It is controversial whether some patients with vertigo have analogous compression of the vestibular nerve in the cerebellopontine angle (vestibular paroxysmia). The aim was to assess if MRI is a suitable test to demonstrate vascular compression in vestibular paroxysmia. We assessed patients with chronic disabling vertigo attending a general neurology clinic and referred by other clinicians. After clinical history and examination including positional testing patients with a definitive diagnosis for vertiginous symptoms were excluded. In 10 patients, vestibular paroxymsia was a possible diagnosis. These patients underwent pure-tone audiography, brain stem auditory evoked potentials and MRI including three different 3D sequences: FISP - TOF (Fast Imaging with Steady state Precession - Time of Flight), CISS (Constructive Interference in Steady State) and MP RAGE (Magnetisation Prepared Rapid Acquisition Gradient Echo) with Gadolinium enhancement. Images were assessed blind by two neuroradiologists. In 5/10 cases, both radiologists agreed on the finding of arterial vestibular nerve compression, and in two additional cases their interpretations differed. Sixty eight control patients, scanned for other reasons, underwent similar 3D protocols. Eight were positive for 8th nerve compression, of whom five had a history of transient vertigo. Vestibular paroxysmia is a significant treatable cause of intractable vertigo which can be diagnosed by appropriate 3D MRI sequences.

P636
THE MYASTHENIC SYNDROME AFTER CHLOROQUINE THERAPY. Andrzej Klimek. Dept. Neurology, Kopernik Hospital, Lodz PL

The myasthenic syndromes are usually of drug-induced. The treatment with some drugs for example; d-penicillamine, some B-blockers, antiepileptics or cytostatics may lead to myasthenic syndrome. Chloroquine is a widely used drug in malaria, and rheurnatological and dermatological diseases are also treated with it. Despite of this fact, the number of myasthenic syndrome after Arechine has been relatively small. A 52 year old woman was admitted to Dept. Neurology, Kopemik Hospital in Lodz on 24.2.98. She complained of ptosis, diplopia and weakening of voice after a longer time of speaking. The above described sings appeared first time in the end of December 1997. Since then the signs have systematically repeated in the afternoon or evenings, especially after a physical effort. On admittance in the neurological examination only apokamnosis and tensilon test were positive. The results of the basic laboratory tests were normal, except antibody anti myocardial cell with sarcolemmal luminescence type. The ratio of antinuclear antibody was 1:80. The radiological examination did not show enlargement of the thymus. The EMG examination was not performed because of a refusal of the patient. A has been supposed however that the diagnosis was established. The diagnosis of drug - induced myasthenic syndrome seemed the most probable. The patient was treated for dermatitis seborrhoea with Chloroquine with a daily dose of 250 mg in September and October 1997. In November 1997 she did not take the drug and in December the treatment was started again because of recurrence of dermatologic signs. At the beginning of hospitalization the drug was withdrawn. After four days the symptoms systematically disappeared and completely ceased after two weeks. The results of the repeated myasthenic tests were negative. They confirmed the diagnosis of post Chloroquine myasthenic syndrome. During hospitalization the patient was not taking any drugs. The control neurological examination have shown normal neurological status. The presented case is a sixth post Chloroquine myasthenic syndrome according to literature.

P637
ASSOCIATION BETWEEN CERVICAL AND LUMBAR SPINAL CANAL STENOSIS. Adamová B, Bednarík J, Chvátalová N, Prokes B, Kadanka Z.

Patients with clinically symptomatic cervical spinal stenosis seem to display frequent clinical compressive lumbosacral radicular and/or cauda equina signs and symptoms due to supposed concomitant lumbar stenosis. In order to verify this association the authors prospectively evaluated a group of 27 consecutive patients with clinically symptomatic spondylotic cervical myelopathy [SCM] due to significant stenosis of cervical spinal canal (measured by CT scans with narrowest anteroposterior [AP] diameter 11 mm). All patients were examined clinically with respect to clinical signs and symptoms of lumbosacral radicular or cauda equina compressive symptoms. CT scans were performed at L4 and L5 levels. Standard parameters of the spinal canal (i.e. anteroposterior, transversal, interpeduncular and lateral recess diameters) were measured and compared with a control group of 30 age-matched individuals in whom CT scans were performed due to abdominal symptoms. Chronic low back pain was recorded in 8 patients, radicular symptoms in 10 patients (4 were previously operated for disc herniation) and symptoms of "neurogenic claudication" [NC] in 6 patients. Clinical signs of mono- or pluriradicular lesion were observed in 7 patients (in two with NC). In five out of 6 patients with NC the CT scans disclosed multisegmental lateral or combined (central and lateral) stenosis. AP diameter measured at the middle of L4 vertebral body (reflecting mostly congenital dimension of lumbar canal in SCM patients) was normal in all patients with NC and the mean value of this parameter in the SCM group showed no difference in comparison with the control group. Moreover, there was no difference in the mean lumbar canal parameters between patients with Pavlov's index < 0.8 (as a sign of congenital narrowing of cervical canal; 12 patients) and normal Pavlov's index (15 patients). Conclusion: clinically symptomatic cervical spinal stenosis is significantly associated with clinical signs and symptoms of lumbar radicular and/or cauda equina compression. The association is based on coincidence of acquired spondylotic spinal canal stenosis in both cervical and lumbar spinal canal while congenital narrowing of the spinal canal plays no significant role in this association.

P638
CLINICAL AND MRI CHARACTERISTIC OF TETHERED CORD SYNDROME. D.Djilas, D.Kozic, K.Koprivsek, D.Bogdanovic, B.Petrovic, R.Semnic, V.Ivanovic, M. Prvulovic (Institute of Oncology in Sremska Kamenica, Diagnostic Imaging Centre, Serbia).

Purpose: to evaluate the role of magnetic resonance imaging (MRI) in revealing the diagnosis of the tethered cord syndrome as the possible cause of urinary bladder and anal problems or distal neurovegetative disorders. Material and Methods: this is retrospective study of 16 adult patients (8 male, 8 female) with tethered cord syndrome examined on 1,5T imager (Magnetom SP 63 4000, Siemens) using standard sequences for lumbar spine imaging. 10 patients have had the history of some kind of congenital malformation of spinal cord and according to that fact tethered cord was assumed; 6 patients had no confirmed explanation for the problems they suffered from. Results: after the MRI of the lumbar spine it came out that in most cases (75%) there was mechanical tethering of the cord (e.g. myelomeningocele (5 patients), filum terminale lipoma (5 patients), spur of diastematomyelia (3 patients), etc.). In 4 cases only isolated tethered cord was diagnosed. After the examination all 16 patients had undergone surgery. In 2 patients with urinary problems no clinical improvement had happend after surgical untethering. Conclusion: Tethered cord syndrome may be the cause of urinary bladder and anal problem as well as distal neurovegetative disorders. In most cases it is due to a mechanical tethering. MRI is superior method in demonstrating morphologic and tissue abnormalities of spinal cord, thus allowing optimal surgical planing.

P639
BOTULINUM TOXIN IS A USEFUL TREATMENT IN EXCESSIVE DROOLING OF SALIVA. A Münchau MD, P Brown PhD, KP Bhatia MD, London, United Kingdom

Excessive drooling of saliva or hypersialorrhea is a common problem in neurodegenerative disorders like motor neuron disease (MND) or Parkin-

son's disease (PD). There are not many treatment options. In view of its mode of action we evaluated the usefulness of BT injections into the parotid gland in 4 patients with excessive drooling of saliva with their consent. One patient had young onset secondary generalised dystonia with severe mouth-opening spasms, one had advanced PD, the third patient suffered from progressive supranuclear palsy and the fourth patient had MND. With one exception twenty units of Dysport® (Ibsen) were injected superficially subcutaneously above the angle of the mandibule at the posterior margin of the masseter muscle, avoiding the bulk of the muscle. Because worsening of dysphagia was feared only 10 Units of Dysport® were injected into each parotid gland in the patient with MND. Drooling did not significantly improve in this patient, possibly due to the low dose of BT used. All the other patients had a beneficial response beginning by the end of the first week and lasting 6 weeks in one patient and 3 to 4 months in the others. One patient had mild worsening of existing dysphagia.. Two patients had mild chewing difficulties, possibly due to diffusion of the toxin into the masseter and one patient complained of a dry mouth. None developed facial weakness. All 3 patients considered the response good enough and side effects sufficiently minimal for them to continue BT treatment at regular intervals. BT injections into the parotid gland (and other salivary glands) may be an effective and simple treatment for excessive disabling drooling of saliva in selected patients. *Acknowledgement: A Münchau is a fellow of the Jung-Stiftung für Wissenschaft und Forschung in Hamburg, Germany*

P640
BOTULINUM TOXIN FOR TREATMENT OF CRANIOFACIAL HYPERHIDROSIS. Böger, I. Müller, R. Rompel and A. Ferbert, Departments of Neurology, Pathology and Dermatology, Klinikum Kassel, Kassel, Germany

We studied the effect of botulinum toxin A (BTX) on patients with craniofacial hyperhidrosis. In order to confirm the correct placement of the intracutanous injection we performed a series of histopathological skin analyses. Design: 1. Clinical studies on five patients with hyperhidrosis. 2. Histopathological measurements on skin specimens. Subjects: 1. Five patients with localized craniofacial hyperhidrosis. 2. Skin specimens of different regions from seventeen autopsias and ten fresh surgical specimens from the forehead. Results: 1. Within one week craniofacial sweating in the area injected had completely ceased in four patients and mildly reduced in the remaining one. The efficacy was confirmed by repeated Minor's iodine starch tests. Up until now sweating has not recurred in follow-up periods of up to 27 months. 2. In the histopathological analyses localisation and diameter of eccrine sweat glands showed only slight differences (e.g. vertical gland diameter ranged from 0,27 mm in the axilla and 0,36 in the forehead). However, on the forehead they were lying most superficial (1,13 mm) and had the largest diameter (0,36 mm). Injections with permanent marker showed an enhancement in the subcutaneous fat. Conclusion: This is the first report on the use of botulinum toxin A in the treatment of idiopathic craniofacial hyperhidrosis. Botulinum toxin seems to be a promising new treatment for localized hyperhidrosis. There is no significant regional variation in the distance of eccrine sweat glands to skin surface, but care should be taken to inject as superficially as possible.

P641
PARRY-ROMBERG SYNDROME A MRI STUDY. Mann M. W.(1), Meary E.(2), Temam G.(3). St Anne Hospital, Paris, Neurosurgery (1), Neuroradiology (2) And Mondor Hospital, Créteil, Neurology (3), France

A 55 year old caucasian white woman came to our observation for focal epilepsy. There is no family history of neurological disease (9 brothers and sisters, 5 children). At age 10 she started a left hemi-facial, slowly progressive atrophy without fever or pain. Corticosteroids were given. Some years later she started a left blurred or double vision and at age 26, after having given birth, a focal refractory epilepsy. Seizure semiology is suggestive of temporo-perisylvian involvement of the dominant hemisphere, without significant progression of seizure semiology over the years. At age 42 a glass eye was inserted on the left. No further aggravation was observed. Neurological examination reveals no motor or sensitive deficit. An exclusively facial atrophy exists on the left side (photograph). Sensory, visual (of the remaining right eye) and brainstem evoked potentials are normal. EEG: slow waves and intermittent spikes over the left centro-temporal region.MRI: enlarged left sylvian fissure with normal vasculature, the insular cortical strip is replaced by a hyper signal on the first echo on the T2 weighted image, slight volume reduction of the left frontal lobe with thickening of the adjacent skull, cortical cerebellar atrophy without abnormality of the brain stem. No contrast enhancement. - There is no evolution in regard to a MRI performed 10 years before, in 1988.

P642
CALCIUM-BINDING-PROTEINS IN THE HUMAN ENTORHINAL CORTEX (HIPPOCAMPAL FORTATION) IN AGING. Carrillo-Padilla, F., Suárez-Solá M.L., González-Delgado, F.J. Servicio de Neurología. Hospital Universitario de Canarias. Spain

Aging leads to alterations in the function and plasticity of hippocampal formation and related cortical areas. The entorhinal cortex, due to its close association with the hippocampus, appears to have a role in learning and memory. We investigated age-related alterations on the distribution of the calcium-binding proteins parvalbumin (PV), calbindin (CB) and calretinin (CR), in order to shed some light on their possible neuroprotective capacity by buffering intracellular calcium. Material and methods: CR, CB and PV-immunohistochemistry were carried out in 6 young adult, 5 middle-aged and 14 old human brains, aged 16-96 years. Results: Although a large number of CB and CR neurons were found in numerous nonpyramidal neurons, both were also located in pyramidal-shaped neurons; however, no significant age-related changes were observed in CB+ (specially in the lateral entorhinal cortex), or CR+ (layer II, VI) immunoreactivity. By contrast, all PV-ir cell had a morphological appearance of nonpyramidal neurons. Normal aging was accompaied by a selective and significant loss of neurons and fibers PV+ in all entorhinal subfiels. Conclusion: The largery nonoverlapping distributions of the calcium-binging-proteins neuronal populations in the entorhinal cortex indicate that each of them may modulate a different subset to topographically organized entorhinal autputs. Loss of the calcium buffering capacity conferred by PV may leave the entorhinal cortex vulnerable to damage in aging

P643
UNUSUAL CEREBRAL MRI FINDINGS IN ARTERIAL HYPERTENSION WITHOUT ENCEPHALOPATHY. J. de Seze, B. Mastain, T. Stojkovic, D. Ferriby, JP. Pruvo, A. Destée, P. Vermersch. Lille, France

Background: Magnetic resonance imaging (MRI) findings have been reported in only a few cases of severe arterial hypertension. The most frequent lesions were supratentorial white matter T2-weighted hyperintensities prevailing in the occipital lobes. Mechanisms of these lesions remains unclear. Objective: The aim of this study was to report two cases with unusual MRI findings secondary to severe arterial hypertension without encephalopathy and discuss the possible physiopathological mechanisms. Case reports: Two patients complained of with blurred vision and headache without mental status alteration. Cerebral MRI showed a large central and extra-pontine hyperintensity on T2 weighted images, initially suspected as brainstem glioma. In the first case the complete work up revealed a thoracic phaechromocytoma with probable dramatic rise in blood pressure. The second case showed a severe renal hypertension. In the 2 cases, fundus showed a severe hypertensive retinopathy. Clinical manifestations were improved by control of blood pressure. A second MRI, performed 3 months later, showed a significant regression of the lesions. Conclusion: We suggest that severe hypertension even without encephalopathy could be responsable for the central and extra-pontine lesions, thus implying a perfect control of blood pressure. Mild regression after antihypertensive treatment argues for a partial oedematous mechanism.

P644
COURSE OF THE CORTICO-FACIAL FIBRES IN THE HUMAN BRAINSTEM. Urban PP[1], Wicht S[1], Marx J[1], Speckter H[2], Fitzek C[2], Fitzek S[1], Stoeter P[2], Hopf HC[1]. [1]Department of Neurology, [2]Institute of Neuroradiology, University of Mainz, Germany

There is a paucity of information on the course of cortico-facial fibres in the human brainstem. We included 50 consecutive patients with acute brainstem infarction confirmed by MRI. The cortico-facial pathways were investigated using transcranial magnetic stimulation (TMS). The MRI slices showing the infarction areas were normalised and projected into axial brainstem templates of the Schaltenbrand-Wahren atlas. Out of the 50 patients investigated, 23 showed a cortico-facial fibre tract involvement due to a single lesion which were considered for further analysis. Mesencephalic lesions affected the medial two thirds of the cerebral peduncle (n=2). The majority of patients (n=16) showed infarctions in the base of the pons. In the upper pons the common lesion area was widely distributed

in the centre of the pontine base. From a mid-pontine level down to the lower third of the pons we observed a shift to a more ventromedial position close to the midline. Lesions at the tegmental border of the pons and in the dorsolateral medulla affected the cortico-facial fibres in three and two subjects, respectively. In conclusion, we could demonstrate that the cortico-facial fibres may take different courses: 1. within the ventromedial base of the pons crossing the midline at the level of the facial nucleus, 2. following an aberrant bundle (Dejerine) near the medial lemniscus, 3. branching off the main pyramidal tract at the lower pons and forming a loop into the upper dorsolateral medulla oblongata. *Supported by the DFG Ur 37/2-1, Ho 293/10-1.*

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HERNIATION OF THE THORACIC SPINAL CORD: TWO CASES. M. Zuber*, E. Meary**, A. Babelon*, J. Klein**.*Service de Neurologie et **Département de Neuroradiologie, Hôpital Sainte-Anne, Paris, France *** Angers, France

Symptomatic dural herniation of the spinal cord has been exceptionnally reported. Patients are typically young females with a several-year history of myelopathic symptoms. Herniation of the spinal cord occurs in the upper or midthoracic region. Its origin remains obscur and both congenital malformation and unrecognized trauma have been hypothesized. We report on two young women (29 and 37 year-old) with no history of trauma who presented with a similar Brown-Sequard syndrome and more than one year of evolution. In both cases, sagittal MRI clearly demonstrated a ventral angulation of the spinal cord at the T3-T4 level. On axial scan, the typical presentation of a focal ventraly displacement and tethering of the spinal cord with expansion of the dorsal subarachnoid space was observed. Symptoms spontaneously stabilized in one patient. The second patient was surgically treated because of progressive disability: the spinal cord appeared as prolapsed into a space between layers of dura mater and the neck of the hernia was constricted by the inner dural lining. Symptoms stabilized after delivery of the cord without closure of the dural defect. Neurologists and radiologists should be aware of herniation of the thoracic spinal cord, a probably underdiagnosed cause of progressive myelopathy. Diagnosis is supported by typical clinical and MRI data. Surgery is required in individual cases.

P646
MR-FINDINGS IN A CASE OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.S. Eisenmann, J. Reeß, M. Palmbach, E. Mauch. Neurological Hospital Dietenbronn, D-88477 Schwendi, Germany

Subacute combined degeneration (SCD) of the spinal cord is a neurologic complication of vitamin B12 and folic acid deficiency. Neuropathologic findings are degeneration of myelin and axonal loss especially in the posterior columns. MR examination demonstrates increased signal intensity within the dorsal columns on T2-weighted images. Patients: We describe initial and follow-up MR-findings in a patient with SCD. A 57 year-old woman presented with a several-week history of imbalance, limb weakness, numbness and tingling in the hands. The neurological examination demonstrated a spinal ataxia and distal motor palsy in the extremities. Laboratory studies showed a megaloblastic anemia accompanied by a low serum B12 level due to a strict vegetarism. Initial MR-findings showed high intensity in the dorsal columns of the cervical spinal cord on T2-weighted image, which decreased 5 months after treatment as well as the clinical symptoms. Conclusion: The purpose of this report is to present that the substitution of vitamin B 12 can normalize the MR signal abnormalities in the posterior columns and the clinical symptoms in patients with low vitamin B12 serum level.

P647
PARANEOPLASTIC LIMBIC ENCEPHALITIS ASSOCIATED WITH BREAST CANCER - A CASE REPORT. R. Scheid, E. Schindler, R. Biniek. Neurologische Abteilung, Rheinische Kliniken Bonn, Germany

Paraneoplastic neurological syndromes (PNS) are disorders of the nervous system that are associated with cancer but are not caused by growth of the tumor itself or by metastasis, nor are they results from non metastatic complications. Based on the findings of specific antibodies a immune-mediated pathogenesis is considered. Among the variety of different syndromes Paraneoplastic Limbic Encephalitis is a rare disorder mostly associated with small cell lung carcinoma (80%). It is believed to be part of the "Hu-syndrome" but the exact prevalence of anti-Hu-antibodies among these patients is not known. We report of a 46 year old so far healthy woman who, after a prodromal episode with symptoms of depression, developed an amnestic syndrome of acute onset. There was no hint of a general medical disorder. Especially no signs of ischemic, infectious or metabolic CNS-disease were detactable. CSF initially showed mild pleocytosis and constantly autochthone immunoglobuline-G-synthesis. There were no classical antibodies found in serum/CSF that so far are known to be associated with PNS (anti-Hu, anti-Yo, anti-Ri, anti-CV2, anti-amphiphysin). The result of a follow-up MRI-examination was compatible with limbic encephalitis. Diagnosis of breast cancer was brought up by mammography, histopathologically it was classified as low differentiated ductal carcinoma. The case illustrates the difficulties in diagnosing Paraneoplastic Limbic Encephalitis clinically and that the established antibody screening is of limited use only. Furthermore, despite the absence of classical antibodies, it supports the autoimmune theory of PNS.

P648
BLINK REFLEX R2 CHANGES AND LOCALISATION OF LESIONS IN MEDULLARY INFARCTION. S Fitzek[1,3], C Fitzek[2], J Marx[1], H Speckter[2], PP Urban[1], F Thömke[1], P Stoeter[2], HC Hopf[1]. [1]Department of Neurology, [2]Institute of Neuroradiology, University of Mainz, Germany; [3]Department of Neurology, University of Jena, Germany

Patients and methods: To detect pathways of the late blink reflexes in 15 patients with medullary infarction MRI lesions and electrically elicited blink reflexes were investigated. The structures involved in patients with R2 and R2c blink reflex changes were identified by biplanar high resolution MRI with individual slices matched to an anatomical atlas at 10 different levels using digital postprocessing methods. Results: The blink reflexes were normal in 5 of 15 patients (33%) and showed loss or delay of R2 and R2c to stimulation ipsilaterally to the lesion (R2-i and R2c-i) in 8 (53%). Loss or delay of R2-i/R2c-i was observed in lesions covering the entire trigeminal spinal tract and nucleus (TSTN) at at least one level and were located more dorsally within the medulla. Patients with normal blink reflexes had lesions sparing or only partially involving the TSTN. They more often had incomplete Wallenberg's syndrome and MRI lesions were located more ventrally. Conclusions: Electronical matching of high resolution MRI in combination with electrophysiological and clinical data is a qualified approach to validate current understanding of functional structures and pathways in brainstem.

P649
FAVOURABLE RESPONSE OF TRUNKAL CHOREA IN ATAXIA TELANGIECTASIA WITH CLONAZEPAM. B. Legros, J. Hildebrand, M. Manto. Service de Neurologie, Hôpital Erasme, Bruxelles-Belgium

Ataxia-telangiectasia (AT) is an autosomal recessive disease affecting chromosomal repair. Its incidence is 1/40.000 to 1/100.000. Patients exhibit typically a cerebellar syndrome associated with telangiectasia in conjunctivae. AT patients also present a hypersensitivity to ionizing radiations, predisposition to cancer, and immune deficit. The responsible gene (ATM) is located on chromosome 11q-22-23. Chorea and dystonia are found respectively in 97 % and 79 % of the cases. High levels of alpha-fetoprotein in blood are suggestive of AT. We report a 18-year old woman with TA presenting apraxia of eye movements, scanning speech, ataxia of limbs movements and unsteady gait. Tendon reflexes were depressed. Signs began in childhood. Choreic movements and dystonia of trunk and proximal limb segments were present in sitting position. Blood -fetoprotein was 213.7 µg/l (normal 10). Clonazepam 1 mg was given orally twice day. Chorea disappeared completely but ataxic signs remained unchanged. Experimental studies have shown that disruption of the efferent GABA pathway from substantia nigra pars reticulata to thalamus, superior colliculus, and reticular formation can produce hyperkinetic involuntary mouvements. Since clonazepam acts at the level of the GABA-benzodiazepine-chloride ion channel, we suggest that trunkal chorea in AT might be due to dysfunction of the GABA-A receptors at the level of pathway emerging from substantia nigra. This hypothesis needs to be confirmed in larger trial.

P650
THE HORIZONTAL POINTING MANOEUVRE: A RELIABLE AND ORIGINAL CLINICAL TEST FOR UPPER LIMBS. B.Legros[1], J. Jacquy[2], M. Manto[1] - [1]Service de Neurologie, Hôpital Erasme, Bruxelles; [2]Service de Neurologie, CHU-Charleroi, Charleroi-Belgium

We investigated a new clinical test for upper limbs consisting in rapid horizontal pointing manoeuvre of one upper limb towards a target area delimited by thumb and index of contralateral hand, maintained motionless. We compared this manoeuvre with the most frequently used clinical tests of voluntary movements of upper limbs: handwriting, fine finger movements, alternate movements of hands, finger-to-nose test, Stewart-Holmes test, Barany test, to maintain arms outstretched and evaluation of muscle tone in 34 consecutive right-handed patients (24 women, 5618 years) with various definite neurologic diagnosis. Both arms were investigated. Patients were examined independently by two observers. Tests were graded as normal or abnormal. Interobserver reliability was assessed by kappa statistics (k). Concordance between our pointing manoeuvre and other clinical tests for each observer and for each upper limb was assessed by coefficient of partial association. For right upper limb, reliability was almost perfect for handwriting (κ:0.81), substantial for Stewart-Holmes test (κ:0.63) and for our pointing test (κ:0.63). For left upper limb, Kappa statistics revealed substantial agreement for Barany test (κ:0.73), Stewart-Holmes test (κ:0.67), pointing test (κ:0.63), finger-to-nose test (κ:0.60). Concordance between our new test and others was statistically significant only for handwriting (p=0.013 and p=0.01 for observer 1 and 2, respectively). In conclusion, our new horizontal pointing manoeuvre has substantial interobserver reliability and is original.

P651
CONTRAST ENHANCEMENT IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. AN INDICATOR FOR LONG-TERM SURVIVAL? V. Arbusow, M. Strupp, H. W. Pfister, K. Seelos, H. Brückmann and T. Brandt. Ludwig-Maximilians University Munich, Germany

Progressive multifocal leukoencephalopathy (PML) is a fatal opportunistic virus induced (JC virus) demyelinating disease of the central nervous system occurring in patients with impaired cellular immunity commonly due to HIV-infection or underlying lymphoid malignancy. Concerning radiological findings there is still a controversy whether contrast enhancement indicates a better immune response of the patient and long term survival of the disease. We report on a 66 year old woman suffering from systemic lupus erythematosus who developed a rapidly progressive right sided hemiplegia, dysarthria and psychomotor retardation due to chlorambucil induced PML. MRI imaging revealed bilateral subcortical demyelinisation without contrast enhancement or mass effect and JC virus-DNA could be detected in the cerebrospinal fluid (CSF). Three months after discontinuation of immunosuppressive medication contrast enhancement on cranial MRI could be observed. From that time there was no further deterioration of clinical symptoms and JC virus was no longer detectable in CSF. Subsequently symptoms improved and within 9 months the patient was able to walk with slight support. On follow-up MRI examinations subcortical demyelinisation was no longer progressive. This case supports the hypothesis that contrast enhancement in PML indicates long term survival due to restoration of the immune system and inflammatory activity to the JC-virus.

P652
SENSORY AND AUDITORY ACTIVATION STUDIES IN POST-ANOXIC COMA USING PET. S. Laureys[1,2], M.E. Faymonville[3], C. Degueldre[1], M. Lamy[3], A. Luxen[1], G. Franck[1,2], P. Maquet[1,2]. [1]Cyclotron Research Centre, [2]Department of Neurology and [3]Department of Anaesthesiology, Liège, Belgium.

We used positron emission computed tomography (PET) to study regional cerebral blood flow (rCBF) at rest and after left and right auditory and somatosensory stimulation in two patients with severe anoxic encephalopathy. H_2O^{15} PET data were analysed using SPM96 (results significant at voxel level $p < 0.05$). The control population consisted of 18 subjects (mean age 33 ± 6 y). Patient 1 was a 62 year-old woman who was found in cardiorespiratory arrest. PET scanning was performed 10 days after admission, GCS was E2M2V1. The patient eventually recovered a conscious state.Patient 2 was a 31 year-old man who attempted suicide by hanging. PET scanning was performed 6 days after admission, GCS was E2M2V1. The patient died 7 days after the PET study. The interaction group (patient vs controls) by task (rest vs AEP or SEP) showed a decreased activation in both patients in the right inferior parietal lobule (area 40), as compared to controls. Furthermore, patient 2, who finally died, showed additional impaired activation in the anterior cingulate cortex (area 24), a region known to be implicated in various cognitive function, especially attention. These preliminary results need further investigations to more closely correlate functional imaging with clinical and electrophysiological findings. *Research supported by the FNRS, the Reine Elisabeth Medical Foundation and the University of Liège*

P653
PERIPHERAL MARKERS OF EXCITOTOXICITY IN NEURODEGENERATIVE DISORDERS. C.Ferrarese[1], C. Zoia[2], B.Begni, G.Sala, C.Canevari and L.Frattola. Department of Neurology and Anatomy[2], University of Milan - Ospedale San Gerardo, Monza - Italy.

Excitotoxicity, linked to impaired glutamate uptake, is a common pathway in various neurodegenerative disorders. We investigated the expression of glutamate transporters and glutamate uptake in platelets, as peripheral markers of excitotoxicity in-vivo. 34 Parkinson's Disease (PD), 32 Alzheimer's Disease (AD), 41 Amyotrophic Lateral Sclerosis (ALS) patients and age-matched healthy controls were selected. Polyclonal antipeptide antibodies for glutamate transporters (Prof. Rothstein, Baltimore, MD) were used to assess, by Western-blot and electron microscopy, the type of transporter present in platelets. Uptake experiments were performed using [^{3}H]glutamate. Both Western blot and the immunogold studies revealed that the three transporters are present in human platelets. 50 % reduction of glutamate uptake was observed in PD ($p < 0.001$) and in AD ($p < 0.0001$) patients, compared to age matched controls. The decrease correlated with the severity of disease ($r = -0.54$; $p < 0.05$) in PD, while no correlations with severity of dementia and brain atrophy were found in AD, indicating that the uptake impairment may be an early event in this disease. Platelet glutamate uptake was also decreased by 38 % ($p < 0.005$) in ALS patients. Studies on glutamate transporter expression are in progress in this disorder. These data indicate systemic impairment of glutamate uptake in neurodegenerative disorders and suggest platelets as peripheral markers of excitotoxic phoenomena occurring in the central nervous system.

P654
NEUROSARCOIDOSIS: CLINICAL MANIFESTATIONS, COURSE, CORTICOSTEROID AND ALTERNATIVE TREATMENTS IN 40 PATIENTS. D. Ferriby[1], J. de Seze[1], T. Stojkovic[1], E. Hachulla[2], B. Wallaert[3], S. Blond[4], A. Destee[1], PY. Hatron[2], M. Decoulx[5], P. Vermersch[1]. Departments of Neurology[1], Internal medecine[2], Pneumology[3], Neurosurgery[4] and Endocrinology[5]. France

Neurological impairment is a frequent cause of morbidity and mortality in patients with sarcoidosis. The aim of this study was to evaluate the clinical manifestations of the disease, the response to corticosteroids and alternative treatments. Patients and methods: During a 10 year period, diagnosis of neurosarcoidosis was performed in 40 patients. We retrospectively analysed clinical, laboratory data and response to treatments. Results: Mean age was 43 years (range 17-72). Mean time of follow-up was 33 months. Neurosarcoidosis was the initial symptom in 34.7% of cases and an isolated manifestation in 22%. Central nervous system impairment was seen in 74%, meningitis in 26%. Other clinical manifestations were cranial nerve palsies (56.6%), peripheral neuropathy (17.4%), myopathy (13%). 78% of the patients were treated by corticosteroids. 26% required alternative treatment (including methotrexate, cyclophosphamide, azathioprin, cyclosporin) resulting to a lack of efficacy or worsening. Complete recovery was observed in only 29% of the patients confirming the severity of neurosarcoidosis. 26% were clinically stable and 13% worsened. No patient died. Conclusion: This study confirms that neurological impairment in sarcoidosis is of poor prognosis even after treatment by corticosteroid. Intensive initial treatment is often necessary to prevent irreversible lesions. Alternative treatment should be rapidly initiated in resistant forms.

P655
POMPHOLYX (VESICULAR ECZEMA) AFTER IVIG THERAPY. Sferrazza B, Quattrini A, Golzi V, Canovaro P, Smirne S, Ferini-Strambi L, Iannaccone S. Department of Neurology IRCCS H.S. Raffaele, Milan, Italy.

High-dose intravenous immunoglobulin (IVIG) therapy has been used to treat various neurological diseases. The occurrence of side effects as headache, chest discomfort, myalgia, fever is frequent. The cause of adverse reactions is unclear, but four points have to be evaluated: a) the rapid infusion rate, b) the activation of complement by aggregated immunoglobulins, c) the commercial source of the IVIG, d) the underlying disease. We describe cutaneous reaction as vesicular eczema at the hands after the first cycle in 3 patients of the 23 patients treated by IVIG therapy (dosage 0.4 gr/Kg for 5 days). In these 3 patients the rate of infusion was

very slow, the underlying disease was different (1 lower motor neuron disease, 1 Guillain Barré, 1 chronic inflammatory demyelinating neuropathy), the commercial source of immunoglobulins was the same of the other unaffected patients. The efficacy of the IVIG therapy in several diseases compared with other immunotherapy is debated, but the complete spectrum of side effects is not completely known, but its knowledge is therefore essential.

P656
SEVERE NEUROLOGICAL COMPLICATIONS FOLLOWING LOCOREGIONAL ANESTHESIA (LRA). Adams D, Lalu T, Navarro V, Pierron D, Planté V, Chapelier A, David P, Said G. Paris, France

Neurological complications following locoregional anesthesia are rare, usually transient with a favourable outcome. We report on 4 cases who developed severe and uncommon complications after LRA. Patient 1, a 30 year old man, with a history of ophthalmic migraine, developed cortical blindness and paraplegia immediately after a lumbar discectomy under spinal anaesthesia with bupivacaïne. Ischemic stroke in posterior cerebral territory was seen on brain CT scan with signs for ischemia of the thoracic spinal cord on MRI. Visual disturbances resolved within one week but patient still has walking difficulties 16 months later. Patient 2, a 56 year old man with a recent story of viral meningitis developed a flaccid paraplegia immediately after a thromboendarteriectomy under spinal anaesthesia with bupivacaïne. MRI of the spine was normal, electrophysiological study showed severe axon loss in lower limbs. He partially improved but needs a zimmer for walking 2 years later. Patient 3, a 47 year old woman, with a history of migraine with aura, developed aphasia with headache after interscalenic block with bupivacaïne for surgery of the shoulder. Brain CT scan revealed a temporal ischemic stroke 2 days later. Etiological investigations were negative. Aphasia resolved in the following days. Patient 4, a 28 year old woman developed in the postpartum period and epidural anaesthesia severe headache, gait unsteadiness and status epilepticus. Brain CT scan showed a voluminous subdural haematoma which was surgically removed with a favourable outcome. LRA with bupivacaïne could be risky in patients with history of migraine with aura, or recent meningitis.

P657
NEUROLOGIC ASPECTS OF FAMILIAL MEDITERRANEAN FEVER. Edward Linetskv (1). Eldad Ben-Chetrit (2). Alexander Lossos (1). From the departments of Neurology (1) and Internal Medicine (2), Hadassah University Hospital, Jerusalem, Israel.

Objective: To determine the frequency, spectrum and clinical features of neurologic disorders associated with FMF. Background: FMF is an autosomal recessive disorder related to the pyrin gene mutation. Systemic manifestations of FMF, in part secondary to amyloidosis, are well documented, but the association with neurologic involvement is rare and often controversial. Design/methods: Tertiary care center in-patient services data bank retrospective computerized search with subsequent file review. From among 43 FMF patients admitted to our institution from 1980 to 1998, we identified 17 patients with neurologic involvement unrelated to a defined systemic or iatrogenic course. Results: 38.3% of FMF patients had neurologic involvement with 2 of the 17 patients demonstrating multiple manifestation. 16 patients were treated with colchicin and 4 out of 5 patients who underwent molecular testing carried the 694/694 mutations in the pyrin gene. Peripheral neuropathy was observed in 7 patients, cerebrovascular disorders in 4, epilepsy in 2, demyelinative disease in 5 and increased intracranial presssure in 1. FMF attacks were not obviously concurrent to neurologic disorders. Conclusion: Neurologic disorders associated with FMF may be more common, than currently accepted, but a prospective study is required to define the nature of this association.

P658
CEREBROSPINAL FLUID OLIGOCLONAL IGG IN PATIENTS WITH SPINAL ARTERIOVENOUS MALFORMATION (AVM). Oren Cohen, Bettina Steiner-Birmanns, Iftah Biran, Oded Abramsky, Israel Steiner. Department of Neurology, Hadassah University Hospital, Jerusalem, Israel.

Objective: To report the presence of cerebrospinal fluid (CSF) oligoclonal bands in patients with spinal AVM. Background: Oligoclonal immunoglobulin bands are detected in the CSF of patients with a variety of disimmune and infectious neurological disorders, but are also present in other non inflammatory conditions. Methods: Within the last decade, 270 patients hospitalized at the Hadassah University Hospital, Jerusalem, were positive for CSF oligoclonal IgG bands as examined by agarose gel electrophoresis. Their medical records were analyzed for the putative neurological cause and for the presence of structural CNS lesions. Excluded were patients with serum oligoclonal bands and with lymphoma Results: Nineteen patients (7.1%), (10 women), aged 33-77, (mean 49) had structural CNS lesions with CSF oligoclonal bands. Spinal lesions were present in 14 patients and brainstem or hemispheric in 5. Cervical compressive myelopathy was present in 9 patients, tumors in 5 patients, spinal AVM in 3 and traumatic leukomalacia and Arnold-Chiary malformation type 1 in 1 patient each. The 3 patients with spinal AVM were all males, aged 34, 48 and 67, who presented with chronic progressive (2 patients) and relapsing (1) paraparesis. Presence of CSF oligoclonal IgG bands delayed diagnosis for up to 3 years. AVM were all located at the low thoracal area. Two were of the dural AVM type. Treatment with selective embolization (2 patients) and surgical removal (1) was associated with marked clinical improvement in 2. Conclusions: CSF oligoclonal bands due to structural CNS lesions are more common than previously noted. This is the first report of AVM associated with CSF IgG bands and should draw attention to this association that might delay diagnosis in a potentially treatable condition.

P659
BEHCET'S DISEASE IN CARIBBEAN POPULATION: PREVALENCE AND IMPORTANCE OF NEUROLOGICAL MANIFESTATIONS. A. Lannuzel, M. Strobel, V. Biousse, D A. Lannuzel, M. Strobel, V. Biousse, D. Caparros-Lefebvre. CHU Pointe-à-Pitre, Hôpital La Riboisière, Paris, France.

Objective: To assess the prevalence and clinical features of Behçet's disease (BD) in a population of African-American people living in the French West Indies. Background: BD is a chronic relapsing multisystem vasculitis. More frequent around the Mediterranean sea and in eastern Asia, isolated cases of BD have been reported in African and Caribbean people of African descent, but the prevalence in Blacks is unknown. Patients and Methods: We carried out a retrospective study including 12 patients native from Guadeloupe referred to our hospital over from 1989 to 1998. Results: The prevalence was 3.24 per 100.000. BD affected young adults mainly men, the sex ratio male/female was 8/12. Neurological manifestations occurred in 6/12 cases and included 3 meningoencephalitis or meningo-encepho-myelitis, 2 cerebral thrombophlebitis and 1 peripheral neuropathy. The most frequent systemic signs were recurrent oral (11/12) and genital ulcerations (8/12), skin lesions (10/12), neurologic involvement (6/12) and eye lesions (7/12). Treatment with corticosteroids (n=10), colchicine (n=10), immunosuppressive therapy (azathioprine and/or cyclophosphamide, (n=5), acetyl salicylic acid (n=4) and oral anticoagulation for vascular thrombosis (n=3) improved all patients. Long-term sequelae occurred only in patients with recurrent neurological disease. Conclusion: Our study suggested a higher prevalence of BD in Afro-Caribbean people than in Europe with a high rate of neurological complications. The long-term follow-up confirmed that immunosuppressive drugs are effective to control BD and suggested that they should be used early in the course of meningoencephalitis to prevent severe neurological sequelae.

Multiple Sclerosis

P660
INTERFERON BETA 1-B. DOES A RESPONDER'S PROFILE EXIST? A. Miralles, B. Fuentes, P. Barreiro, E. Díez Tejedor. Department of Neurology. Hospital "La Paz". Madrid. Spain.

Introduction and objective: Due to the variability of response to the treatment with interferon beta 1-B in patients with relapsing-remitting multiple sclerosis (RRMS) we investigate if exists a previous profile of responder. Patients and method: We selected patients with RRMS treated with interferon beta 1-B after 12 (group A, 41 patients) and 24 months (group B, 17 patients) of treatment and split them into two groups: patient with a punctuation variation in the Expanded Disability Status Scale (EDSS) <0 (Group 1), and >0 (Group 2). We analyzed sex, age at he first exacerbation, age at beginning of the treatment, evolution time until beginning of treatment, type of first exacerbation, total number of exacerbations, number of exacerbations in the two previous years to the beginning of the treatment, EDSS score before of the treatment, number of cells, oligoclonal bands and Tibling, Reiber and Tourtelotte's indexes. Results: In group A, we obtained significant results in the mean age at the first exacerbation (A1: 27'17, A2:38, p:0'01), age to the beginning of the treatment (A1:34'82, A2:43'16, p:0'031), Tibling's index (A1:1'02, A2:1'83, p:0'034), and Tourtelotte's index (A1: 9'95, A2: 33'03, p: 0'034). In group B, we found

significant differences in the evolution time until beginning of treatment (B1:5'28, B2:1'33, p:0'047). Conclusions: Our data suggest the existence of a patient's profile with trend to respond favorably to the treatment with interferon beta 1-B.

P661
EPIDEMIOLOGICAL STUDY OF THE PREVALENCE OF SPECIFIC AUTOIMMUNE DISEASES IN FIRST DEGREE RELATIVES OF PATIENTS WITH MULTIPLE SCLEROSIS IN THE UNITED KINGDOM. SA Broadley, J Deans, SJ Sawcer, DAS Compston. Cambridge, UK.

Case reports and small series suggest a higher incidence of autoimmune disease within families of multiple sclerosis (MS) patients. We carried out a case:control study by postal questionnaire in MS patients selected for genetic studies through having two living parents. 775 probands were sent two questionnaires, one relating to the occurrence of autoimmune diseases in their own family (parents and siblings) and a second identical questionnaire to be completed by a suitable control. Response rates for usable questionnaires were 75% for cases and 49% for controls. Of 373 controls, 73% were spouses or partners of the MS probands and the remainder were carers or friends. MS families were characterised as single (498) or multiplex families (68). The proportion of families with one or more relatives diagnosed with an autoimmune disease was 25% for single MS families, 40% for multiplex families and 19% for controls ($^2_{trend}$ = 14.5, P = 0.00008 with 2 degrees of freedom). This result remains significant when adjusted for age, sibship size and sex distribution (P = 0.0043). There was no significant difference in the frequency of non-autoimmune diseases. The overall relative risk for autoimmune diseases within single MS families was 1.4. The risk for all autoimmune diseases was elevated amongst MS families but the strongest associations were with pernicious anaemia and autoimmune thyroid disease.

P662
CAN DIFFUSING NITRIC OXIDE ACCOUNT FOR A TRANSIENT APHASIA OBSERVED AT THE ONSET OF MULTIPLE SCLEROSIS? Kranda K,* Horowski R,+ Schilling A,++ Haas J** and Mach R§ *Psychophysiological Laboratory, UKBF, Eschenallee 3, D-14050-Berlin, + Schering AG, D-13342 Berlin, ++Dept. of Radiology, UKBF, Hindenburgdamm 30, D-12200 Berlin, Dept. of Neurology, Jewish Hospital, D-13347Berlin, §Nuclear Physics Institute, CAS, Rez, Czech Republic.

Reports of nitric oxide (NO) being massively produced at an acute stage of multiple sclerosis (MS) before subsiding to a baseline level, raise the question whether NO, known to block nerve conduction, can account for transient deficits during MS. As neural structures subserving those functions apparently affected by MS are often distal to the site of the observed lesion, some chemical agent, possibly NO, has to diffuse from the lesion to account for such affects. We examined such a hypothesis by constructing a NO-diffusion model which iteratively fitted the time courses of several transient symptoms such as aphasia, a rare event during an MS-onset, to the distances between the affected neural centres and the surface of the lesion. In our case, the primary lesion caused by clinically-confirmed MS and detected with magnetic resonance imaging appeared as a massive sphere (about 10 ml) about 2 cm from the edge of the Broca's area. The transient symptoms completely disappeared within about two weeks, but apart from some shrinkage, the lesion is still apparent one year after the onset. The constructed model shows the plausibility of an NO-diffusion being responsible for the time course of observed symptoms.

P663
A QUANTITATIVE MR STUDY OF MS LESIONS: CORRELATION BETWEEN T1 RELAXATION TIME AND METABOLITE CONCENTRATION. PA Brex, SM Leary, PD Molyneux, GJM Parker, CA Davie, AJ Thompson, DH Miller.NMR Research Unit, Institute of Neurology, London, UK.

Brain T1 lesion load has been shown in one longitudinal study to correlate better with disability in multiple sclerosis (MS) than T2 lesion load. In order to determine the differences between lesions that appeared hypointense on T1-weighted images and those that did not, we studied both types of lesions from 10 patients with secondary progressive MS with single voxel MRS (1.5T GE scanner, TR 3000ms, TE 30ms, PROBE, PRESS). T1 relaxation time was calculated using a pair of multi-slice gradient echo acquisitions with different repetition times. Corrections were made for slice profile and head coil non-uniformity. The T1 relaxation time correlated significantly with the concentration of N-acetly aspartate (NAA) (R= -0.65, p=0.002) and myo-inositol (R= 0.51, p= 0.022). There was no significant correlation of T1 relaxation time with creatine / phosphocreatine or with choline-containing compounds. The correlation of NAA with T1 is consistent with evidence that T1 hypointense lesions contain more axonal damage. An increase in myo-inositol has been shown before in chronic MS lesions but a relationship with T1 relaxation times has not. Myo-inositol is mostly concentrated in glial cells and high concentrations may represent gliosis. T1 relaxation time measurement appears particularly promising as a quantitative, high resolution tool which reflects axonal damage and possibly gliosis in chronic MS lesions

P664
MEASUREMENT OF SPINAL CORD ATROPHY IN CLINICALLY ISOLATED SYNDROMES SUGGESTIVE OF MULTIPLE SCLEROSIS. PA Brex, SM Leary, VL Stevenson, AJ Thompson,DH Miller. NMR Research Unit, Institute of Neurology, London, UK.

Introduction: Spinal cord atrophy in multiple sclerosis (MS) is likely to indicate loss of myelin and / or axons. A previous study found cord areas from patients with benign, primary and secondary progressive MS to be significantly smaller than controls but not patients with relapsing-remitting disease. However, a longitudinal study did show significant cord atrophy over one year in this group. We aimed to determine if any change could be detected in patients with isolated syndromes, many of whom will develop MS, using this technique. Method: Volume-acquired inversion-prepared fast spoiled gradient echo (FSPGR) images of the spinal cord were acquired from a cohort of patients presenting with isolated syndromes - 37 within 3 months of presentation, 47 within 15 months of presentation and 31 at both time points. Cross-sectional spinal cord area at C2 was measured using a highly reproducible semi-automated technique. Cord area was also measured in 20 age and sex matched healthy controls and in 10 controls this was repeated after a year. Results: No significant differences were found between mean cord area in controls and patients at either time point, or in the change in cord area between controls and patients scanned at both time points, even in 13 patients who developed clinical MS during follow-up. Conclusion: The normal spinal cord area suggests that significant loss of axons / myelin in the spinal cord is not occurring. Follow-up studies are needed to determine when such changes develop.

P665
NEUROPSYCHIATRIC PHENOMENA IN MULTIPLE SCLEROSIS. Güler M, Gürvit H, Akman-Demir G, Çoban O, Eraksoy M. Istanbul Faculty of Medicine-Department of Neurology, University of Istanbul, Turkey

Studies on neuropsychiatric phenomenology of multiple sclerosis (MS) are limited. In this study, we aimed to show the spectrum of neuropsychiatric manifestations of MS, and their relationship to different disease parameters. We evaluated 100 patients having the diagnosis of clinically definite MS with Neuropsychiatric Inventory (NPI), a scale that quantifies ten different behavioral manifestations, and 31 myasthenia gravis (MG) patients without CNS involvoment matched for age, sex and functional disability were taken as controls. Barthel index and EDSS were used for measuring functional disability in MS group and the former in MG group. NPI total scores of two groups were significantly different (15.93±13 versus 10.7±10; p=0.02). NPI total score significantly correlated with both EDSS, and disease duration ($p < 0.001$ and p=0.02, respectively). NPI total scores were significantly higher in secondary progressive form (n=28) than relapsing-remitting form (n=72), (23.2±16 versus 13.1±1; $p < 0.001$), as well as 5 subscores, i.e. agitation (p=.001), irritability (p=0.001), anxiety (p=0.03), disinhibition (p=0.006), and depression (p=0.009). There was no significant difference in hallucination, delusion, apathy, euphoria, or aberrant motor behavior parameters. NPI is a useful tool in detecting a wide array of neuropsychiatric manifestations in MS. NPI total score seems to be related to disability and disease duration, and secondary progressive form. The relationship of different subscores with lesion load of different neuroanatomic loci needs to be addressed. We are planning to evaluate such a correlation in the second part of the present study.

P666
MS DATABASE -MS CLINIC OF ISTANBUL MEDICAL FACULTY (ISDMUS). Akman-Demir G, Atamer A, Ertas M, Eraksoy M. Istanbul Faculty of Medicine/Department of Neurology University of Istanbul, Turkey

There are many efforts to establish sufficient and effective databasing in many diseases among which multiple sclerosis (MS) can also be listed. We are presenting a database program which we are starting to use in our MS department. This Windows-based database program is based on Superbase version 3.5. This is a user-friendly program, easy to fill, and rather flexible, and can use Microsoft Excel and SPSS for Windows facilities in order to perform statistical analyses. Using this database program we evaluated 634 patients (F/M: 1.96) registered in the MS Clinic of Istanbul Medical Faculty. According to Poser's criteria, 437 had clinically definite MS, 128 had laboratory supported definite MS, 35 had clinically probable MS, one had laboratory supported probable MS, 32 had optic neuritis and one had acute disseminated encephalomyelitis. Mean EDSS was 3.15 + 2.17. Mean age at onset was 27.2 + 9.0 years, mean age at admittance was 33.4 + 10.3 years, and mean disease duration was 113 + 89 months. Median attack rate in the first year was 1, and in the first five years was 2. Onset was mono-symptomatic in 376 cases, and polysymptomatic in 258 cases. Symptoms at onset were sensory (n=286), motor (n=233), brainstem-cerebellar (n=185), and optic neuritis (n=148). Clinical course was relapsing remitting in 421 cases, secondary progressive in 169 cases, and primary progressive in 37 cases.

P667
MONITORING OF INTERFERON-BETA-1B TREATMENT IN MULTIPLE SCLEROSIS BY MX-PROTEIN. Heidenreich F., Kracke A., Al Masry A.N., Windhagen A., von Wussow P., Hannover, Germany

The clinical response and efficacy of interferon-beta (IFN-beta) treatment in multiple sclerosis (MS) in an individual patient is difficult to assess. MRI and blood levels of IFN-beta-induced molecules like neopterine and the Mx proteins (Mx) have been suggested as surrogate markers of treatment effects. Here we report an open longitudinal study of Mx measured by ELISA in lysed blood samples of 33 MS patients treated with IFN-beta 1b, 8 M U s.c. every second day over varying time periods. Mean values of Mx in stable IFN-beta1b treated patients were significantly higher (27.1+/–20.9 mU/ 1000 leukocytes) than in untreated (1.2+/–1.6 mU/1000L) or immunosuppressed patients (1.0+/–1.4 mU/1000mU). In serial measurements from individual patients Mx correlated with the clinical response to IFN-beta 1b. Mean Mx values in IFN-beta1b treated patients during the time of relapse were significantly lower than in stable disease. A mean Mx calculated for each patient over time correlated inversely with relapse rates. The median of this mean Mx was increased in treatment responders as compared to nonresponders. High titers of neutralising antibodies to IFN-beta1b were detected in 4 of 19 patients and were associated with low Mx levels in one case. In conclusion, the analysis of blood Mx levels in this open study of IFN-beta1b treated MS patients promises a role for Mx in monitoring IFN-beta treatment in MS but needs confirmation by data from a controlled study.

Peripheral neuropathy

P668
PERIPHERAL NEUROPATHY AS A PREDOMINANT MANIFESTATION OF A MITOCHONDRIAL DNA DELETION. C. Lacroix[1], A. Rotig[5], J. Boulloche[4], B. Parfait[5], P. Rustin[5], M. Brivet[2], A. Münnich[5], P Landrieu[3]. [1]Neuropathologie, [2]Biochimie, [3]Neuropédiatrie, Le Kremlin-Bicêtre; [4]Pédiatrie, Le Havre; [5]Département de Génétique et INSERM U393, CHU Necker, Paris. France.

Usual neurological manifestations of mitochondrial cytopathies involve CNS and muscle. Subclinical neuropathies are often associated with encephalopathies, but a neuropathy is exceptionally the predominant symptom. We report a sensory-motor neuropathy in a 17-year-old boy who complained of difficulty in walking for a few years. His parents were not related. He had moderate mental retardation and was thin. Neurological examination showed distal motor deficit and moderate hypoesthesiae in lower limbs without ataxia, abolished tendon reflexes and mild complex ophtalmoplegia. Vision and hearing were normal. Brain MRI, blood studies including lactates, ophthalmologic and cardiac evaluations were normal. CSF proteins and lactates were slightly increased. Electrophysiological studies demonstrated undetectable sensory amplitudes; motor amplitudes were not found in lower limbs and reduced in upper. Muscle biopsy found fibre II type grouping and normal histochemistry. Numerous dystrophic mitochondrias with a few large dense inclusions were observed on EM. Most myelinated fibres had disappeared on the peroneal nerve biopsy. Dense mitochondrial inclusions, similar to those observed in the muscle, were present in amyelinic fibres. A partial deficiency of complex I & IV of the respiratory chain was found. Using large PCR, an 8.3 kb deletion of mtDNA was detected. Our investigations demonstrated that a mtDNA deletion might be responsible for a severe sensory-motor neuropathy.

P669
THE RANGE OF PERIPHERAL NERVE LESIONS IN SARCOIDOSIS: A CLINICOPATHOLOGICAL STUDY OF EIGHT PATIENTS. L Lepage, V Planté-Bordeneuve, C Lacroix, L Nahum, P Rondepierre, J Mallecourt, A Fernandez, G Said. Service de Neurologie, CHU Bicêtre, France.

Peripheral neuropathies are infrequent in sarcoidosis with the exception of cranial nerves involvement. To study the spectrum of peripheral nerve lesions in this setting, we reviewed the clinical and pathological data of 8 patients with sarcoid neuropathy and characteristic peripheral nerve lesions. Five men and 3 women, aged 26 to 85 (mean 58 y-o) were included. A sensory nerve sample was obtained by biopsy in all cases, a muscle specimen in 7. The peripheral neuropathy was a residual deficit after a Guillain-Barré syndrome with facial diplegia and dysautonomia in one case, a mononeuritis in 1 patient, a multifocal subacute/chronic sensorimotor neuropathy in 3, and a chronic axonal sensory neuropathy in 3 patients. The CSF recorded in 5 cases was normal in 2 and showed an increased protein level and lymphocytosis in 3. General manifestations including fatigue, weight loss and fever were noted in 5 patients. Extraneurological manifestations of sarcoidosis were pulmonary in 5 patients, cutaneous in 4, uveitis in 1, arthritis in 1. There was no CNS manifestations. Nerve biopsies showed marked asymmetrical lesions with granuloma predominating in the epi- and perineurial areas, with multinucleated giant cells in 4 cases. Granuloma predominated around nerve blood vessels and were associated in 4 cases with necrotizing vasculitis Axonal lesions and fibre loss varied between fascicles. This study illustrates the wide spectrum of the peripheral nerves manifestations encountered in sarcoidosis and the occurrence of necrotizing vasculitis secondary to delayed hypersensitivity reaction.

P670
CLINICOPATHOLOGICAL AND GENETIC STUDY OF 13 CASES WITH HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES. Y. Parman*, N. Bissar-Tadmouri°, E. Battaloglu°, F. Deymeer*, P. Serdaroglu*, C. Ozdemir*. * University of Istanbul, Medical Faculty, Department of Neurology, Istanbul-Turkey. ° Bogazici University, Department of Molecular Biology and Genetics, Istanbul-Turkey.

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder that produces an episodic, recurrent demyelinating neuropathy. Nerve conduction studies demonstrate focal slowing and some patients may have a more generalized demyelinating neuropathy. Nerve biopsy shows the presence of "tomacula" which is focal swelling or thickening of the myelin sheaths. HNPP is associated with a 1.5 Mb deletion of the PMP 22 gene. Rarely, point mutations of the same gene have also been found. In order to explore further the spectrum of HNPP, we studied clinicopathological, electrophysiological and genetic aspects of 13 patients with this neuropathy. Clinically, eight cases showed mononeuropathy multiplex. Three had mononeuropathy and interestingly one case had a distal symmetric polyneuropathy. In all patients, nerve conduction studies demonstrated prolonged distal latencies and conduction blocks suggesting a multi-focal demyelinating neuropathy. Nerve biopsy was performed on 6 cases. All biopsies showed characteristic features of "tomaculous neuropathy". A 1.5-megabase deletion in chromosome 17p11.2-12 was found in seven cases only. Sequencing of the PMP 22 gene for point mutations is still continuing in cases without deletion. The results will be communicated in the ninth meeting of the European Neurological Society. No phenotypic difference was observed between the deleted and non-deleted ones.

P671
MOEBIUS SYNDROME: CORRELATION OF CLINICAL FEATURES WITH NEURORADIOLOGICAL (MRI) FINDINGS. J. Gamez [1], S. Pedraza [2], A. Rovira [2], T. Minoves[1], A. Codina [1], C. Cervera [1]. [1]Servicio de Neurologia. [2]Unidad de RM. Hospital Gral. Vall d'Hebron, Barcelona. SPAIN.

Objective: To describe the clinical findings and MRI abnormalities of Moebius Syndrome. Background: Moebius Syndrome is a rare genetic disorder characterised by congenital complete or partial facial diplegia (Mc

Kusick 157900). The cause is still unclear. It is usually accompanied by other cranial nerve palsies and associated with malformations of orofacial structures and limbs. We present a patient with bilateral facial nerve palsy, extremity abnormalities and other cranial nerve involvements (VI,VIII, XII). The brain MRI showed hypoplasia of the brainstem nuclei. Material/Methods: A 28 year-old woman had congenital bilateral facial palsy. She was unable to blink her eyes, smile or frown. There was a convergent strabismus with a bilateral deficit in horizontal gaze eye movements. Vertical gaze was intact. Other features were: small mandible, hearing loss, microstomia, dysarthria, swallowing difficulties, tongue hemiatrophy and metacarpophalangeal deformities. Results: MRI on the T1-weighted sequences revealed alterations in the morphology of the brainstem: rectification in the floor of the fourth ventricle, an absence of the medialis eminentia at pons level (VIth and VIIth nuclei) and an absence of the hypoglossal eminence at bulb level (trigono nervi hypoglossi) in medulla oblongata. The BAEP showed an increase in the central time conduction I-IV indicative of a brainstem dysplasia. Conclusions: MRI of patients with Moebius syndrome helps to correlate the clinical features with the neuroanatomic alterations paying particular attention to the brainstem. MRI will become the preferred technique of imaging the Moebius Syndrome in the demonstration of morphological changes present at brainstem level.

P672
TREATMENT OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) WITH INTRAVENOUS IMMUNE GLOBULINS (SANDOGLOBULIN") - EXPERIENCE OF A 7 YEAR COMPASSIONATE USE PROGRAM. P. Cras, M. Dewitte, S. Vancayzeele, A. Deblander, University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Novartis Ltd., Haachtsesteenweg 226, 1030 Brussels

Several recent studies have indicated the excellent response of chronic inflammatory demyelinating polyneuropathy (CIDP) to intravenous immune globulins. Between 1991-1998, 85 patients (1.4 male:female) with a mean age of 51 (median 51, SD 16.6, range 6-89) were treated with Sandoglobulin" in a compassionate use program. Eight patients suffered from paraproteinemia, of which one was directed to myelin associated glycoprotein. Prior treatment consisted of corticosteroids in 49/83 (59%) and plasmapheresis in 36/83 (43%). On average, the patients were treated 33 months (median 19) after the appearance of the first symptoms with a dose of 0.4 g/kg/d for 5 days. The treatment was repeated in 22 patients. Follow-up information was available for 46/85 (56%) of patients. Of these 48 patients, 37 (77%) showed a moderate or good therapeutic response. Side effects were only reported in 10 patients and were limited to headache (4), rash (4) and fever (2). We conclude that Sandoglubulin" is a safe and effective treatment of CIDP.

P673
THE SIGNIFICANCE OF PROCALCITONIN AND MYELIN AS SPECIFIC INDEXES OF INFLAMMATION IN THE DIAGNOSIS AND PROGNOSIS OF CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS. Alexiou Heleni, Latousakis B, Xifaras M, Tzimas A, Matikas N. Neurological Department of General Hospital of Nikea-Pireas, Greece.

Thirty five patients with CNS infection (mean age: 36,5 years) were enrolled in our study all of which were admitted in our department during the last two years. We measured procalcitonin and myelin in the serum and cerebrospinal fluid by the method of immunophotometry and radioimmunofixation respectively. Procalcitonin was found increased in 87,5% of patients with established bacterial meningitis on the 3rd day of their hospitalization. The levels of procalcitonin have decreased by the 9th day of the hospitalization of the above patients, reflecting closely their clinical improvement. On the contrary, myelin was found increased in only a small percentage of our patients. This discrepancy was attributed to the low sensitivity of the method of immunofixation by which myelin was measured and calls for the improvement of the technique. Procalcitonin is considered a reliable index of bacteremia, especially important in the early diagnosis of meningococcal septicemia, in the differential diagnosis from viral infections and the prognosis of patients with extensive burns, myocardial infraction or immunodeficiency. Persistently elevated levels of procalcitonin usually signify a lethal complication.

P674
POEMS SYNDROME REVEALED BY OPHTHALMOLOGICAL MANIFESTATIONS. M. Charif, M. Pages, JM Blard; service de neurologie, centre Gui de Chauliac, Montpellier, France.

POEMS syndrome is a multisystemic disorder associated with plasma cell dyscrasia. The main features are polyneuropathy, anasarca, organomegaly, endocrinopathy and skin changes. We report a case of POEMS syndrome revealed by ophthalmological manifestations. Case report: a 41-year-old man complained from oscillopsia and blurred vision. Ophthalmoscopy revealed bilateral papilledema. Neurological examination disclosed mild motor weakness of the distal part of lower limbs and generalised areflexia. CT scan, MRI and MRA of brain were normal. EMG showed signs of demyelinating neuropathy. Protein level of CSF was 159 mg/dl. Serum immunoelectrophoresis identified an IgA lambda monoclonal component. Total body CT scan showed hepatosplenomegaly and a sclerotic lesion of the fifth left rib. Surgical removal of the rib confirmed osteosclerotic myeloma but was not followed by ophthalmological or neurological improvement. The patient died from pulmonary embolism 2 months later. Comments: papilledema is a common finding in POEMS syndrome but ophthalmological complaints are rare. In our case, peripheral neuropathy was mild and the revelating symptoms were disturbances of vision. Although POEMS syndrome is uncommon, it must be searched in case of unexplained papilledema.

P675
RECURRENT GUILLAIN-BARRE SYNDROME. M.Charif, S.Goka-Degols, M.Pages, Jm Blard. Service De Neurologie, Centre De Gui De Chauliac, Montpellier, France.

Guillain-Barré syndrome (GBS) is an acute reversible demyelinating polyradiculoneuropathy. Recurrent GBS is rare and its relationships with chronic idiopathic demyelinating neuropathy (CIDP) are discussed. Methods and results: clinical and laboratory data of 3 patients who had recurrent episodes of GBS followed by complete recovery were reviewed. 2 patients were male and one female. The ages at the onset of the first episode were 27, 35 and 43 years. The intervals between attacks of GBS were 1.5 and 23 years for 2 patients with a biphasic course, 7 and 17 years for a patient with 2 recurrences. All the episodes were preceded by an infective illness: upper respiratory track infection (2 patients), recurrent herpes infection (one patient). Respiratory muscle weakness required mechanical ventilation in 2 patients and severe bradycardia occured in one. In the third case, the first episode was characterised by tetraparesia, bilateral ptosis and dysphonia, the second one by ataxia and mild tetraparesia and the third one by tetraplegia, ophthalmoplegia and acute respiratory insufficiency. CSF protein level was increased in all patients on at least one occasion..Conclusion: recurrent GBS is rare. It may be distinguished from chronic relapsing CIDP by the hight incidence of previous infective illness, the acute course and the complete recovery. The severity and distribution of motor weakness may vary considerably from an attack to another one.

P676
MRI FINDINGS IN MULTIFOCAL MOTOR NEUROPATHY (MMN). A CASE REPORT. C. Khamis, MD: Department of Neurology, Lebanese Hospital Geitawi, Beirut-Lebanon.

Case presentation: A 48 years old female presented with 9 years history of progressive asymmetrical weakness of the arms predominant on the left side distally with muscular atrophy and no sensory signs. She had electrophysiological evidence of multifocal motor conduction blocks. MRI of both brachial plexuses showed abnormalities more evident on the left side; this was diffusely swollen with increased signal intensities mainly of the lower brachial plexus on the T2-weighted images. As the patient was diagnosed of having MMN, she received intravenous immunoglobulin maintenance therapy 1g/kg/day for 2 days every 6 weeks which resulted in a nearly complete recovery of muscular strength. One year after treatment, MRI was repeated; it showed improved lesions with slight swelling of the affected nerves and non enhancement. This demonstrated that the distribution and improvement of MRI abnormalities corresponded to the distribution and improvement of symptoms. Thus, MRI of the brachial plexus may be useful for diagnosing and evaluating disease activity in MMN.

P677
VISUAL EVOKED POTENTIAL STUDY IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. T. Stojkovic,[1] J. de Seze,[1] J.F. Hurtevent,[2] A. Beaume,[4] C. Arndt,[3] J.C. Hache,[3] P. Vermersch.[1]Departments of Neurology[1], Neurophysiology[2], Neuroophtalmology[3], University of Lille, France. Department of Immunology[4], University of Poitiers, France.

The frequency of the association between chronic demyelinating inflammatory polyneuropathy (CIDP) and central nervous system (CNS) demyelinating lesions is probably underestimated (Uncini et al., 1996). Objective: To investigate the occurence of combined central and peripheral demyelination in CIDP patients and to correlate visual evoked potentials (VEP) abnormalties with brain magnetic resonance imaging (MRI) and antibodies to gangliosides. Patients and methods: Nerve conduction studies (NCV), VEP and dosage of antibody to gangliosides were evaluated in 17 patients with CIDP. Brain MRI was performed in patients with abnormal VEP. Results: The seventeen patients fulfilled the diagnostic criteria outlined for CIDP (Cornblath et al., 1991). Latency of VEP was increased in 8 CIDP patients. Among these patients, brain MRI showed demyelinating lesions in 4 patients, aged from 17 to 65 years. One of these patients had antibodies to SGLPG. Antibodies to GM1 was found in one patient who had normal VEP. Conclusion: This study confirms the high frequency of abnormal VEP in CIDP, which are poorly correlated with CNS demyelinating lesions and antibodies to gangliosides. Abnormalities in VEP may be explained by the suspectibility to immune-mediated damage of both peripheral and optic nerve.

P678
MULTIFOCAL CONDUCTION BLOCKS IN A WEGENER'S GRANULOMATOSIS. T. Stojkovic[1], ML Ferrier[2], JF. Hurtevent[3], M. Parent[4], C. Dequiedt[2], P. Vermersch[1] · Department of Neurology[1], Nephrology[2], Neurophysiology[3] and Neuropathology[4], University of Lille, France.

Peripheral neuropathy is a common feature of necrotizing vasculitis. However, evidence of conduction blocks remains rare and uncommon. Case report: A 44-year-old-patient presented numbness of lower limbs associated with a loss of weight and fever. He had a past history of chronic nasal congestion and sinusitis. Physical examination disclosed distal weakness and diminished vibratory sensation prevailing on the lower limbs. Tendon reflexes were normal except for the left ankle and right knee reflexes which were absent. Motor nerve conduction (MNC) study disclosed conduction blocks in the peroneal, median and ulnar nerves. MNC velocities were severely decreased in the peroneal and the median nerves. Electrophysiological patterns fulfilled the criteria of a demyelinating neuropathy. Erythrocyte sedimentation rate was elevated at 40 mm/h. Cerebrospinal fluid analysis revealed a protein level of 0..70 mg/dl without hypercellularity. Anti-neutrophil cytoplasmic and anti-PR3 antibodies were both detected at significant levels. Urine protein level was increased (1g/24 hours). Superficial peroneal nerve biopsy showed foci of necrotic vessels, surrounded by inflammatory cells infiltrates. Treatment with cyclophosphamide and corticosteroids improved dramatically the neurological status. Conclusion: Conduction blocks in necrotizing vasculitis neuropathy have been rarely reported. To our knowledge, this the first report of multifocal conduction blocks in Wegerner's disease, probably secondary to a segmental demyelination due to nerve ischemia.

P679
POSTMORTEM FINDINGS IN TWO BROTHER CASES OF LATE-ONSET FAMILIAL AMYLOIDOTIC POLYNEUROPATHY IN KYOTO, JAPAN. Junko Fujitake[1)], Hayato Fujii[1)], Yasuhiro Ishikawa[1)], Young-Chi Katsuyama[2)], Kosho Takasu[2)], Yoshihisa Tatsuoka[1)] Department of Neurology[1)] and Pathology[2)], Kyoto City Hospital, Kyoto, Japan

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant disease, and the age of onset of FAP type I is usually 20 to 40 years. We report two brother autopsy cases of late-onset FAP type I (met ^{30}) in Japan. Clinical courses: The elder brother first noticed numbness of the feet at age 64 and developed motor, sensory and autonomic neuropathy. Thereafter, he showed heart failure, and died at age 71. The younger brother noticed cold sensation of the feet at age 59. He developed motor, sensory and autonomic neuropathy. Thereafter, he showed vitreous opacity, glaucoma, and heart failure, and he died at age 74. Results (postmortem findings) Two brothers showed almost same findings. Amyloid deposition was remarkable in the hearts. There weights were 600g in elder patient and 515g in younger one. In the digestive system, amyloid deposition was observed mainly in perivascular walls. In the kidney, amyloid deposit was not seen in the glomeruli. In the peripheral nervous system, amyloid deposition was remarkable in the dorsal root ganglia, nerves immediately after dorsal root ganglia and sympathetic nerve ganglia. Conclusion:Amyloid deposition in our late-onset cases was different from that of the usual cases in several points. In the peripheral nerves, amyloid deposion in the proximal portion may induce severe distal nerve damage.

P680
FAMILIAL ASSOCIATION OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND MULTIPLE SCLEROSIS. S. Vlaski-Jekic, Pashu M., Kiteva G. Clinic of Neurology, Skopje, Macedonia

Coexistence of CNS and PNS demyelination has been registered in some cases suffering from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In single cases, a familial association of CIDP and multiple sclerosis (MS) has been published. We report a rare family where CIDP associated with evidence for CNS demyelination was found in a brother, while his sister had a clinical picture and laboratory findings of a definite MS. The brother was 49 years old. He suffered from CIDP of a relapsing-remitting type, diagnosed 14 years ago according to the standard diagnostic criteria for CIDP (Barohn et al 1989). Over this time he also had a number of episodes with CNS signs and symptoms of a relapsing multifocal type, suggestive for MS, accompanying the clinical picture of the PNS disorder (cerebellar ataxia, VII n. central paresis, spinal symptoms, bilateral Babinski signs). High signal white matter lesions with paraventricular, brainstem and cervical spinal localization, indistinguishable from those seen in MS, were found on T2 weighted MRI.. The patient has responded symptomatically very well to the treatment with parenterally administrated prednisone. Because of an increasing relapsing rate of the disease during the last two years, Betaferon 8 MIU was introduced a few months ago. His 45 years old sister had clinical and laboratory evidence for definite MS, partially responding to the parenteral administration of prednisone. MRI lesions indicating CNS demyelination were found in paraventricular and particularly in the cervical and thoracic spinal regions. Symmetrical subjective numbness in her feet and hands with normal electromyography and conductive velocity findings were part of the clinical picture. Nerve biopsy was not performed. Existence of centroperipheral demyelinating syndrome, as reported in our patient, and an association of this syndrome with multiple sclerosis in the same family, favors the hypothesis for a possible relationship between CIDP and MS as part of the same disease spectrum, and emphasizes the suspection of a common pathogenetic mechanism for both CNS and PNS demyelination. It may be of interest to perform a molecular genetic investigation in this family.

P681
ANTI-GALNAC-GD1A ANTIBODIES IN PATIENTS WITH GUILLAIN-BARRÉ SYNDROME ARE RELATED TO A RAPIDLY PROGRESSIVE PREDOMINANTLY MOTOR NEUROPATHY.CW Ang[1], N Yuki[2], BC Jacobs[1], M Koga[2], PA Van Doorn[1], PIM Schmitz[1], FGA Van Der Meché[1]Erasmus University Medical Centre Rotterdam, The Netherlands[1] and Dokkyo University School of Medicine, Japan[2]

The Guillain-Barré syndrome (GBS) is heterogeneous with regard to clinical manifestations, antecedent infections and the presence and specificity of anti-ganglioside antibodies. In recent years, antibodies to several gangliosides that are present in peripheral nerve have been identified in serum from GBS patients. We investigated whether the relationship between antibodies to the minor ganglioside GalNAc-GD1a, antecedent infections and clinical manifestations in 132 patients with GBS. Anti-GalNAc-GD1a antibodies could be detected in 19 (14%) of GBS patients. The presence of anti-GalNAc-GD1a antibodies was related to antecedent Camplyobacter jejuni infection ($p <• 0.001$). GBS patients with anti-GalNAc-GD1a antibodies had a rapidly progressive, more severe, and predominantly distal weakness. Furthermore, they had less sensory loss, paresthesias and cranial nerve involvement. In the majority of the patients, this reactivity was independent of reactivity to GM1. Dividing patients into separate groups based on their reactivity to GalNAc-GD1a and GM1 enabled us to delineate more homogeneous subgroups with regard to clinical features. This study provides further evidence for the hypothesis that antecedent infections and the specificity of subsequent anti-neural antibody responses determine the clinical manifestations in GBS patients.

P682
INCREASED EXPRESSION OF TNFα-R-MRNA IN BLOOD MONONUCLEAR CELLS OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME. L.M. Ossege, E. Sindern, J.-P. Malin. Institute of Neurology, Ruhr-University Bochum, BG Klinikum Bergmannsheil, Bochum, FRG

The Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy with mostly symmetrically weakness progressing for a period not exceeding 4 weeks. Besides the assumption of a disturbed humoral immunity it is thought, that activation of autoreactive T-lymphocytes and

macrophages are involved in this process. TNFα is an inflammatory mediator. Its association with disease activity in GBS has been described in several studies. The role of the TNFα-55kDa-receptor (TNFα-R) is unclear until now: on the one hand, there is evidence, that it mediates the effects TNFα. On the other hand, it has been demonstrated that soluble TNF receptors antagonize and inhibit effects of the cytokine. In this study the expression of TNFα-R-mRNA was investigated in peripheral blood mononuclear cells (PBMC) of patients with GBS by non-radioactive in situ hybridization. Ten patients were investigated. Blood samples were collected at the time of diagnosis (day 0), day 4-6, day 10-12 and day 20-28. Compared to healthy controls 7 patients showed a slight increase of TNF-mRNA at day 0. During the course of the disease the TNFα-R-mRNA expression increased significantly in all patients at day 4-6, day 10-12 and day 20-28 with a maximum at day 10-12 ($p < 0.01$, Wilcoxon-rank-sum test). Since TNFα-R potentially inhibits the effects of TNFα the observed increase of TNFα-R in PBMC during the course of GBS might be important in terminating the inflammatory response.

Poster Session 5

Sleep disorders

P683
PERGOLIDE INDUCED CHANGES IN THE SLEEP EEG IN PATIENTS WITH RESTLESS LEGS SYNDROME. E. Friess, MD, H. Tagaya, MD, T. C. Wetter, MD, J. Winkelmann, MD, M. Rubin, MS*, and C. Trenkwalder, MD, PhD. Max Planck Institute of Psychiatry, Munich; * Lilly Deutschland, Bad Homburg, Germany

Patients suffering from the restless legs syndrome (RLS) show a severe disruption of sleep onset and continuity. The treatment with dopaminergic substances has been proven as clinically very effective. We investigated the influence of the long-acting D1/D2-agonist pergolide on the sleep EEG including the EEG power spectrum. The sleep recordings of RLS patients undergoing a pergolide treatment were therefore submitted to a serial spectral analysis (Fast Fourier Transformation). The study group consisted of 15 patients with a moderate to severe primary RLS (57.1±10.1 yrs, 8f, 7m). The effects of a 14-days treatment with pergolide (mean dosage of 0.5mg/day, paralleled by 20mg domperidone t.i.d.) were compared with placebo according to a randomized, crossover study design. The pergolide treatment significantly decreased wakefulness (132±56 vs. 73±43min., $p < 0.001$) and increased stage 2 sleep (172±78 vs. 263±47min., $p < 0.001$). However, the power densities in the sigma, theta and to a lesser extend also in the delta frequencies were reduced (12.1-14.8Hz, $p < 0.03$; 4.3-7.8 Hz, $p < 0.05$; 0.78-3.9Hz, $p < 0.09$; ANOVA). Despite of the marked improvement of sleep continuity the pergolide treatment did not restore slow wave sleep including the spectral power in the lower frequencies. It may be speculated that the observed impairment of EEG synchronization during non-REM sleep is due to the dopaminergic influence on the sleep regulating mechanism.

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CIRCADIAN RHYTHM AND SLEEP DISTURBANCE ASSOCIATED WITH BILATERAL HYPOTHALAMIC LESIONS. I Eisensehr, J Kleine, S Noachtar, C Helmchen. Dep. of Neurology, Ludwig-Maximilians-University Munich, Germany

Animal studies indicate an important role of the hypothalamus in the sleep-wake regulation. However, little is known about the influence of hypothalamic lesions on the sleep-wake cycle in humans. We investigated a 58 year old, obese patient (113 kg, 156 cm) with a bilateral hypothalamic lesion of unknown etiology. She had a one-year-history of hypersomnia, hyperphagia, irritability, apathy, weight gain and circadian temperature peaks. A 24 hr-polysomnography including EEG, EMG, EOG, O2-saturation, abdominal and thoracical movements and airflow was recorded. Additionally, endocrinological blood analyses and serial MRI were performed.HR-MRI showed exclusively a bilateral symmetrical Gadolinium enhanced lesion in the hypothalamus. Total sleep time (TST) was markedly increased (17.6 hr) indicating hypersomnia with only three continuous wake phases lasting maximally 60 minutes. REM-periods only occurred between 5 pm and 6 am. The prolactin level was increased (83.4ng/ml). LH and FSH secretion could not be stimulated by Lutotropine Releasing factor (LRF). The clinical syndrom indicated a functional hypothalamic dysfunction which was confirmed by HR-MRI showing a structural bilateral hypothalamus lesion. Concomitantly, we found an excessively increased TST by polysomnography. The findings support the hypothesis that hypothalamic structures play a critical role in initiating and maintaining wakefulness in humans. *Supported by the Deutsche Forschungsgemeinschaft*

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POLYSOMNOGRAPHY RECORDINGS IN PATIENTS WITH STEELE-RICHARDSON-OLSZEWSKI SYNDROME. Zygmunt Jamrozik, Tadeusz Przybylowski*, Piotr Janik, Hubert Kwiecinski. Department of Neurology and Department of Pneumology *, Medical University of Warsaw, Poland

Brainstem is usually affected by neuronal loss, astrogliosis and the presence of neurofibrillary tangles in patients with progressive supranuclear palsy (PSP). Pontine reticular system is involved in the control of REM sleep and breathing. Although autonomic dysfunction is not a principal feature in PSP, both sympathetic and parasympathetic systems can be affected. In patients with autonomic dysfunction a defect in the respiratory rhythm generator was observed. Patients with PSP may also present with sleep disorders such as insomnia, frequent awakenings and shortened sleep latency. Objective: To determine incidence of sleep apnea syndrome (SAS) in PSP. Material and method: Eleven patients with the diagnosis of PSP (7 possible, 3 probable and one definite PSP) were studied with the screening device MESAM IV to detect sleep abnormalities. None of the patients was in the terminal stage of the disease. Results: Three of the 11 PSP patients showed polysomnographic patterns characteristic of the SAS. One patient with polysomnographic study repeated after two years revealed increased number of desaturation and oxygen desaturation index. Polysomnographic parameters of the other patient with SAS did not change during 24 months follow-up. The correlation of sleep abnormalities with clinical data will be presented. Conclusion: Our findings indicate that SAS may occur in a minority (27%) of patients with PSP.

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SLEEP STUDIES IN TWO PATIENTS WITH PONTINE HAEMATOMAS AND "PEDUNCULAR" HALLUCINOSIS. Cervera A.; Sánchez-Valle R.; Iranzo A.; Blesa R.; Santamaría J. Neurology Service. Hospital Clínic. Barcelona. Spain.

Peduncular hallucinosis (PH) is a syndrome characterized by vivid hallucinations, visual or auditory, that usually appear at bed-time associated with dream enacting-like behavior. Both mesencephalic or rostral protuberance lesions may produce the syndrome. Rapid eye movement (REM) sleep is mainly generated in pontine tegmentum. Objetive: To study sleep disturbances in two patients with PH caused by a pontine haematoma. Patients and methods: Two males, 56 and 35 year old, were admitted for sudden dizziness, right facial palsy and horizontal gaze palsy. Neuroimaging studies disclosed a tegmental pontine haematoma. During the first days both developed nocturnal vivid visual and auditory hallucinosis with sleep fragmentation and agitation. Video polysomnography (PSG) was performed the third day (case 1), and a month later when hallucinosis had disappeared (case 2). Results: Case 1. Video PSG showed anomalous grimacing and complex limb movements during wakefulness-sleep transitions, during the first half of the night, and increase of stages III-IV in the second half. REM sleep was absent. Case 2. PSG demonstrated reduced percentage of stage II and REM sleep, with periods of intermitent lack of muscle atonia. In both cases spindles were present and symmetrical. Conclusion: PH in pontine tegmentum lesions seems to appear in transitions between wakefulness and sleep in the first half of the night and are not related to REM sleep.

P687
"PEER DECOMPENSATION SYNDROME". Jean J. M. Askenasy M.D., PH.D. Israël

The important value of peer support has been well established (1-3). Peer Decompensation Syndrome (PDS) expresses the state when the peer or caregiver looses his ability of ensuring the homecare to the PD patient. The peer syndrome has a major impact on the destiny of the PD patient. Motor disability, cognitive degradation and sleep disturbances of the advancing Parkinson's Disease patient are the 3 major conditions causing the PDS. Of these three conditions the sleep deprivation of the peer caused by an impaired sleep of the PD patient is the most frequent cause of PDS. Smith et al. evaluated sleep in 153 PD patinets and their spouses using a

nationwide survey and found that the presence of an associated depression especially in female caregivers explain the early peer sleep disturbance (4). In order to prevent the PDS, two main attitude are essential: I) The therapeutic management of the PD patient. Changes in medication directed to improve the sleep disturbance in PD patients, such as nightmares (NM), hypnagogic hallucinations (HH), restless leg syndrome (RLLS) and periodic movements of legs during sleep (PMS) which induce the agravation of freezing, long trapping and frequent on-off phenomenon as side-effect, is useless. Changes in medication directed to improve the motor disability during the daytime, which induces NM, HH, RLLS and PMS at night are also useless. These two aspects impose two rules: a) replacing the algorhythm management with an around the clock management of the PD patient; b) replacing the selective therapeutic correction of symptoms with an harmonic overall treatment of the complex pathology of the PD patient. To achieve these two conditions, basic clinical, biochemical and pharmacological knowledge is necessary. II) Peer support consists in establishing relations of trust, confidence and permanent dialogue. 1. Gonyea JG. Soc. Work Health Care 1989;14:61-72; 2. Lin N et al. J Health Soc Behav 1985; 26:247-263; 3. Askenasy JJM. Acta Neurol Scand 1993;87:167-170; 4. Pilemer K, Suitor JJ. J Gerontol Soc Sci1996; 51B:S250-S257. 5. Smith MC et al.J Am Geriartr Soc 1997; 45:194-199.

Neurobiology

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MYOGENIC CONVERSION OF NIH-3T3 CELLS BY A TETRACYCLINE CONTROLLED SYSTEM: IN VITRO AND IN VIVO STUDIES. R. Del Bo*°, Y. Torrente°, S. Corti°, S. Salani°, M.G. D'Angelo°, G.P. Comi°, N. Bresolin*°, G. Scarlato°. *Scientific Institute E. Medea, Bosisio Parini, Italy. °Clinical Neurology, University of Milan, Milan, Italy.

The early senescence of myoblasts expressing a functional dystrophin gene product represents a limitation to *ex vivo* gene teraphy of Duchenne Muscular Dystrophy (DMD). In this study we describe the forced conversion of NIH-3T3 mouse fibroblasts into myoblasts by MyoD transfection. To avoid the non-proliferative state associated with MyoD expression, we controlled the exogenous gene expression through the tetracycline inducible promoter system. In stably transfected cells the promoter is virtually silent in the presence of tetracycline. After the withdrawal it becomes active obtaining the transcription of MyoD-E47, inducing myogenesis and transactivating the E.Coli β-galactosidase gene expression. Cells expressing MyoD withdrew from the cell cycle but were shown to be unable to fuse in vitro into multinucleated myotubes. Engineered cells were then injected in Tibialis anterior muscles of normal and mdx mice. 5 days after transplantation a 7-fold increase of X-gal positive cells was found in animals not treated with doxycycline (a tetracycline derivative) compared to treated animals; after 10 days the number of positive cells decreased. Three weeks after transplantation sarcolemmal expression of normal dystrophin was observed in clusters of myofibers only in mdx mice not treated with doxycycline. Our results suggest the MyoD-mediated myogenic conversion by a tetracycline-controlled transactivation system in vitro and in vivo leading to new perspectives in the cell mediated approach of DMD gene theraphy.

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JUVENILE BUT NOT ADULT INDUCED STREPTOZOTOCIN DIABETES MELLITIUS MAY DETERIORATE ACUTE EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS MANIFESTATION. I. Milonas*, C. Simeonidou**I, N. Grigoriadis*, 0. Guiba-Tziampiri** - B' Univ. Department of Neurology, AHEPA Hospital, Thessaloniki, Greece **Univ. Department of Physiology, Faculty of Medicine, Thessaloniki, Greece

Both experimental allergic encephalomyelitis (EAE) and streptozotocin (STZ) induced diabetes mellitus (DM) are the models that corrspond to two human autoimmune diseases that may coexist in some cases. The possibilty that STZ may influence the clinical manifestation of EAE is studied here. Juvenile DM was induced in ten, 17-days old Lews rats and adult DM in ten 2-month old rats (Group B). All animals were treated with 110mg/kg BW STZ, i.p. Another ten 17 day old rats (Group C) and equal number of adult rats (Group D) were treated with vehicle and served as controls to the correspondent STZ treated groups. Two months later, EAE was induced in all animals with immunization of 50mg rat spinal cord homogenate in complete Freund's adjuvant (FA). All animals were then examined daily for clinical signs of EAE, according to a 12 grade scale. Relapse duration was almost the same in all groups. The maximal clinical weakness for group A was 6,4±2,72 and for group A 3,65±3,55. Group B and D did not present any significant difference in the maximal clinical weakness score they reached (Group B: 4,50±3,80, Group D: 3,99±2,89). Although not morphometrically proven, cell infiltration was found to be more pronounced in most group A animals. Our results indicate that STZ, when injected in juveniles, may worsen the clinical manifestation of EAE, whereas there is no similar effect when STZ treatment takes place during adulthood. STZ is thought to have immunomodulatory action through T-cells. EAE was not finally induced in the same age for all animals (2 months for groups A and Q 4 months for groups B and D). However, the hypothesis that STZ differential activation of those cells throughout life may differentially influence EAE E clinical manifestation, needs further investigation with cell proliferation techniques and am cytometry.

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DORSAL ROOT GANGLIA CULTURES FROM A TRANSGENIC RAT OVEREXPRESSING PMP-22: AN *"IN VITRO"* MODEL OF CHARCOT-MARIE-TOOTH TYPE 1A (CMT1A). Schenone A, Nobbio L, Grandis M, Nave K, Sereda M, Levi G, Barbieri O, Abbruzzese M, Windebank AJ, and Mancardi GL.Genova, Italy; Heidelberg, Germany; Rochester, USA.

Organotypic cultures of rat dorsal root ganglia (DRG) have been extensively used to study *in vitro* myelination. CMT1A is associated with a duplication of the peripheral myelin protein 22 gene. Transgenic animal models of CMT1A have been generated. We established DRG cultures from 15 days old embryos of a CMT1A female rat mated with a normal male. After genotyping each embryo for the transgene, 10-12 DRGs were explanted onto separate dishes in groups of 2-4 DRGs/dish and coded. After 30 days, cultures were assessed by light and electron microscopy (EM) and morphometry was performed. Out of 9 cultures, 3 were correctly graded as normal and 5 as abnormally myelinated by two blind examiners; only one of the CMT1A cultures was misjudged as normal. Nodal region length was evaluated in 206 fibers from the normal cultures and 422 fibers from the CMT1A cultures. Mean nodal length was significantly longer in affected than in normal cultures (20.27 $\mu \pm 28.9$ vs 3.94 $\mu \pm 6.16$, $p < 0.00001$) suggesting ongoing demyelination in CMT1A cultures. EM revealed, in affected cultures, occasional neurite-Schwann cells (SC) units surrounded by concentric layers of SC cytoplasm. In conclusion reproduction of a morphological phenotype similar to human CMT1A has been obtained in organotypic DRG cultures from CMT 1A transgenic rats. This model may be used to study early changes in the myelination process due to PMP-22 duplication and to evaluate therapeutic strategies for CMT1A.

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Abstract withdrawn by author

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APPLICATION OF REPETITION SPACING IN NEUROLOGICAL STUDIES. Edward J. Gorzelanczyk, Piotr A. Wozniak.Laboratory of the Applied Research at the Department Health Sciences, Karol Marcinkowski Medical Academy, Poznan, Poland

Repetition spacing is a procedure that is used to determine optimum inter-repetition intervals in the process of learning. For a given level of knowledge retention, for example 95%, repetition spacing is supposed to produce optimum learning schedule that minimizes the overall number of repetitions. The authors have developed accurate algorithms for determining the optimum repetition spacing as well as a software implementation that can easily be reused by other applications. The repetition spacing procedure implies the existence of a little studied property of memory that the authors call the stability of memory. The stability of memory is likely to be strongly correlated with molecular variables responsible for, but not equivalent to, long-term memory. It can be demonstrated mathematically that application of optimum repetition spacing is the fastest way towards increasing the stability of memory. We would like to call the attention of the entire neurological society to the following applications of repetition spacing in neurological studies: research on molecular aspects of memory. Including the research on determining the molecular correlates of the stability of memory. Note that most of researchers focus on memory changes that last for hours and days. These provide little true insight into long-term memory! therapeutical treatment in neurological disorders (e.g. enhancing the nerve cell metabolism in memory disorders, Alzheimer disease, etc.) behavioral studies of learning (the discussed algorithms may be used both in human learning and animal training)

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TRACE ELEMENTS AND ANTIOXIDANTS IN CEREBROSPINAL FLUID (CSF) OF PATIENTS WITH SEVERAL NEUROLOGICAL DISEASES. B.W. Walther*, L.E. Walther**, S. Streck***, K. Winnefeld***, E. Beleites**, H.W. Kölmel**Department of Neurology, Hospital Erfurt, Germany.**Department of Otorhinolaryngology and ***Department of Clinical Chemistry, Friedrich-Schiller-University Jena, Germany

The nervous system is suspectible to lipid peroxidation because of its high content of polyunsaturated fatty acids and high aerobic metabolism. Malondialdehyde (MDA) and the selenium containing encyme glutathione peroxidase (GSHPx) reflect partially radical formation and removal. Trace elements and electrolytes as a part of various antioxidative encymes play a key role in generation and prevention of free radicals to lipids and proteins. Method The concentration of electrolytes (Na, K, Ca, Mg), trace elements (Fe, Cu, Zn, Se), MDH and the activity of GSHPx were determined in CSF of patients with several neurological diseases such as Multiple sclerosiš, encephalitis, epilepsia, polyneuropathy and neuroborreliosis. For determination of electrolytes flame atomic absorption spectrometry (Ca, Mg) and atomic emission spectrometry (K, Na), for detection of trace elements graphite furnace atomic absorption was applied. Lipid peroxidation products (MDH) were measured as thiobarbituric acid-reactive substances (Yagi 1982) and GSHPx activity in CSF by using the method of Paglia et al. (1967). Results/Conclusion Our results show changes of electrolyte, trace elements and MDH con-centrations as well as GSHPx activity in several diseases without and with changes of blood/ brain barrier. Findings suggest the conceivable possibility of a pathogenic role of free radicals and changes in trace element and electrolyte concentrations in several neurological diseases.

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IGFBP-5 OVEREXPRESSING MICE AS A MODEL OF AXONAL NEUROPATHY. M. Braga*°, J. Gunnersen*, J. Zielasek*, B. Holtmann*, E. Wolf+, K.V. Toyka*, M. Sendtner* - *University of Würzburg, Germany, °IRCCS, Milan, Italy, +University of Munich, Germany.

Insulin-like growth factor binding proteins (IGFBPs) modulate the biological effects of IGFs on Schwann cells, myoblast and motoneurons. IGFBP-5 is the major inhibitory binding protein for IGF-1 in peripheral nerves. In order to investigate the role of this binding protein in the peripheral nervous system, we have generated transgenic mice in which IGFBP-5 is overexpressed in motoneurons under control of the NFL-promoter. Results: Western blot analysis in different transgenic mouse lines showed significant elevations of IGFBP-5 in particular in peripheral nerves, resulting from production in motoneurons and anterograde transport to axons. In 3-week old IGFBP-5 transgenic mice, significant axonal loss was observed in the phrenic nerve, and changes suggestive for axonal loss were detectable in the sciatic nerve. Quantitative histological analysis of the brainstem showed mild motoneuron cell loss in the facial nucleus. Motoneuron survival after facial nerve lesion was not significantly influenced by IGFBP-5 overexpression. Conclusion: Phenotypical analysis of IGFBP-5 overexpressing mouse shows progressive postnatal axonal loss, confirming the role of IGFBP-5 as a blocking protein for IGF-1 and suggesting a potential role of IGF-1 pathway in some axonal neuropathies. Further experiments have to show if this axonal loss is due to interference with Schwann cell metabolism or reduced availability of IGF-1 for motoneurons. *Support: Deutsche Forschungsgemeinschaft, Grant To 61/8-4 (Klinische Forschergruppe Neuroregeneration); Dino Ferrari Center, Milano, Italy*

Child neurology

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PAROXYSMAL DYSKINESIAS: CLINICAL FEATURES AND CLASSIFICATION. Erba, C. Conti, A. Pazzi, L. Canafoglia, L. Angelini, N. Nardocci. Istituto Nazionale Neurologico "C. Besta", Milano, Italy

We report on 18 patients (10 males-8 females) affected by paroxysmal dyskinesias(PD), classified according to the circumstances of occurrence of attacks as kinesigenic (PKD, 11pts.), non kinesigenic (PNKD, 4pts.) and exertion induced (PED, 3pts.). All patients underwent laboratory, EEG, CT or MRI investigations. Mean follow-up was of 5.5 yrs. PD were directly observed in 14 patients. Age at onset ranged from 15 months to 15 years. All patients with PKD had short attacks(5'); both short and long attacks (>5') were present in patients with PNKD and PED. Fourteen patients had idiopathic PD (10 PKD, 1 PKND, 3 PED), among these 10 had an autosomal dominant pattern of inheritance. Etiology of the symptomatic cases included cerebral palsy, multiple sclerosis and Arnold-Chiari malformation. Anticonvulsants were effective in 7 patients (4 PKD, 1 PKND, 2 PED). A severe impairment in daily life activities was present in 1 pt. with PKD; 5 out of 7 relatives of pts. with PKD, not included in our series, referred a spontaneous remission of attacks by the age of 30, suggesting a benign course of the disease. The circumstances of occurrence of attacks are the more useful criteria for classifing patients with PD, however in our series 2 pts. with PKD presented sporadic attacks at rest and 1 with PKND had attacks induced by movement; demonstrating a clinical overlapping between the two forms.

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FARBER'S DISEASE: DESCRIPTION OF A CASE WITH LONG SURVIVAL AND ATYPICAL CLINICAL FEATURES. A Cucatto[1], A Calvo[1], AA Terreni[1], G Mora[2], AH Fensom[3], A Chiò[1] - [1]Turin, [2]Veruno, [3]London

Farber's disease (FD) is an extremely rare autosomal recessive disease due to a disorder of the lipid storage caused by deficiency of the lysosomal enzyme acid ceramidase, with a consequent accumulation of ceramide in various tissues. Usually the onset of the disease ranges between two weeks and four months of age. Clinical manifestations include deforming and painful arthropathy; subcutaneous, periarticular and visceral nodules (lipogranulomatosis); hepatosplenomegaly; laryngeal stridor; poor growth and neurologic impairment (muscular and peripheral nervous system manifestations, mental retardation and, sometimes, seizures). Also heart, lungs and lymphatic ganglions can be involved. The diagnosis is confirmed by enzyme assay on cultured skin fibroblasts or leukocytes. The prognosis of the disease is poor: usually patients die in a few years. Only three cases with longer survival have been described, but they developed a severe mental retardation. In this paper we describe a 20 years old man, whose diagnosis of FD has been confirmed by enzyme assay on leukocytes. The onset of FD was at one year of age. The course of the disease was exceptionally slow, with a progressive impairment of articulations and osteolysis involving feet and hands. Now he is wheelchair-bound, and has a laryngeal involvement. Recently he has developed myoclonic nocturnal seizures, which are well controlled with valproate (300 mg bid). The patient has no sign of mental retardation.

P697
THE ROLE OF MRI IN EVALUATION OF SPINAL DISRAPHISM. V.Ivanovic, D.Djilas, O.Adic, M.Lucic, A.Zvezdin, M.Prvulovic (Institute of Oncology in Sremska Kamenica, Diagnostic Imaging Centre, Serbia).

Purpose: to evaluate the distribution of spinal disraphisms due to morphologic abnormality as well as to confirm the importance of magnetic resonance imaging (MRI) in their characterisation. Material and Methods: we examined 43 patients retrospectively (23 male, 20 female), mean age 21,5. Most of them were sent for MRI of lumbar spine with diagnostically proven or just suspected congenital malformation, others (about 20%) had disturbances of lumbosacral region. Patients were examined on 1,5T imager (Magnetom SP 63 4000, Siemens) using standard sequences for imaging of lumbosacral spine. Later on we classified detected abnormalities due to patomorphological classification based on the type of developmental disorder during embriogenesis. Results: in 37 cases (86,05%) anomalies of premature dysjunction were diagnosed; they included spinal lipoma in 22 patients (in 70% localised in cervicothoracal region and in about 30% in filum terminale region), and lipomyelomeningocele in 15 patients. 20 patients (46,51%) have had tethered cord syndrome (which is anomaly of retrogressive differentiation): only in 4 cases (9,3%) as isolated abnormality, and much more often together with other dysraphic anomalies such as: spinal lypomas and lipomyelomeningocele (32,56%), diastematomyelia (4,65%). Conclusion: MRI is highly recommended non-invasive method for evaluation of spinal dysraphism as well as for surgical planing due to its high tissue differentiation, multiplanar imaging, and spatial resolution. In this study spinal lypomas end tethered cord syndrome were predominant.

P698
LONGITUDINALLY USED VALPROATES AND CHANGES OF THE PERIPHERAL BLOOD. A. Jucaite, J. Sinkeviciene. Vilnius University Children's Hospital, Vilnius 2600, Lithuania

Various antiepileptic drugs, especially valproates (VPA), have numerously been reported to express hepatotoxic, pancreatotoxic and changes of the peripheral blood. We reegzamined the relationship of the doses, serum levels of hepatic enzymes (alanin and asparaginaminotranferases, AlTA and AspTA), urea, hemoglobin levels (Hb), granulocyte, trombocyte, monocyte counts. 160 children were examined during the years 1996-1997. VPA monotherapy was administered in 138(86%) cases. The mean duration of treatment was 27,2± 9,5 months. The VPA dose administered was 24,3± 8,4mg/kg and blood serum levels reached 55.9 ± 21.4μg/ml (mean SD). Serum levels of AlTA and AspTA were within normal limits: 18,6±6,3 and 31,4±14,2, rp. Childs age, duration of treatment and dose of VPA had significant correlation with the count of erythrocytes and thrombocytes. Multiple regression analysis revealed significant effect of VPA only on the trombocyte count (r^2=0.43, F=4,08, $p < 0.09$). Thus there was no evident toxic effect on liver enzymes neither disturbances of urea, that brings into question their monitoring. But evaluation of trombocyte count should not be forgotten in a long-term use of valproates in childrens' age.

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SEIZURES AFTER ISCHEMIC STROKE IN CHILDHOOD. A. Michalak -Wilczek, B. Paradowski*.Department of Children Neurology, Wroclaw. *Department of Neurology Medical University, Wroclaw, Poland

From the available data the overall incidence of seizures is higher in the children than in adults stroke. Reports on epileptic seizures in ischemic stroke in childhood are rare. Methods: We retrospectively reviewed 50 patients (age from 6 months to 16 years, 23 boys and 27 girls) conscutively admitted to our Department from 1987 to 1997 with ischemic stroke (IS) to evaluate the incidence of seizures and to determine risc factors of reccurent seizures. Cause of IS was searched with: angiography, laboratory tests, blood coagulation, antibodies, TCD, angio-MRI in selected cases. An EEG was performed in all seizures patients. Results: Seizures were documented in 18 patients – 36%, of which 13 had early seizures (75% from the onset of IS to 15 days) s\and 5 (28%) had late seizures (occuring one month after IS). Epilepsy was noticed in 17 patients (34%). Seizures occured in 14 children with IS due to distinct underlying disease (in 6 patients – 43% vascular anomalies, 4 patients – 29%, cardiogenic origin. Cortical involvement in 14 patients of 18 with seizures. Conclusions: 1.Our study revealed a greater incidence of epilepic seizures after IS in childhood than it was indicated by the majority of similar studies in the adult population. 2.Risk factors of current seizures after ischemic stroke were the presence of cortical involvement and a known etiology for infarct.

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USE OF INTRAMUSCULAR BOTULINUM TOXIN IN TREATING SPASTICITY OF UPPER LIMB IN CHILDREN WITH CEREBRAL PALSY. [1]Virginia Wong, [2]Annie Ng, [3]Patsy Sit. [1]Division of Neurodevelopmental Pediatrics, Department of Pediatrics, The University of Hong Kong, Queen Mary Hospital, Hong Kong, Peoples Republic of China (PRC) - [2,3]Children's Habilitation Institute (CHI), Duchess of Kent Children's Hospital, Hong Kong, Peoples Republic of China (PRC)

A pilot study in the use of Intramuscular Botulinum Toxin (Botox) in treating upper limb spasticity of children with cerebral palsy (CP) was conducted in 1998 July–1999 January. This consisted of 11 children (7 boys, 4 girls). The mean age was 6 years 2 months (range = 2 years–15 years 6 months). The type of CP was hemiplegia (n=8; 4 left and 4 right); spastic diplegia (n=1); spastic triplegia (n=1) and spastic tetraplegia (n=1). Baseline evaluation prior to Botox injection consisted of objective measurement of upper limb function with various standardized tests for function by the physiotherapist (PT) and occupational therapist (OT). The same management programme prior to injection was continued, which included continuous training of the corresponding antagonistic muscles. The spastic muscles injected consisted of biceps (B), pronater teres (PT), flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS) and adductor pollucis brevis (APB) depending on the severity of spasticity. The dose of Botox used also depends on the muscle mass and the body weight; with a range of 4-6 IU/kg given (maximum = 100 IU; i.e. 1 vial given to each upper limb). Post-Botox assessment of efficacy and tolerability was conducted in weeks 1, 2, 4, 8, 12 and 16 by PT and OT. The peak onset of action and the duration of efficacy were assessed. The preliminary results of short term follow up of up to 7 months will be analysed. All children had good initial response. The most dramatic response occurred within 1 second of Botox injection into the small intrinsic muscle of the hand (APB) with marked decrease of spasticity and abduction of the cortical thumb in a few young children after 20 IU injection. The duration lasted as long as 6 months in some children in this preliminary analysis. None of the children had any side effects. And the tolerability of Botox was good. Our preliminary results showed that Botox is particularly useful in children younger than 5 years with a relatively larger dose was given to the small intrinsic muscles of the hand to improve abduction of the thumb. However, as the price of Botox was relatively high, one should concentrate on giving a relatively higher dose of Botox to specified spastic muscle of the upper limb to which one would like to improve the fine hand function and coordination after training of the antagonistic muscles. The cosmetic effects of improving flexor spasticity of the biceps muscle should be left to one's discretion depending on the availability of an extra vial of Botox. At present, as the toxic dose of Botox in children is unknown, one should concentrate on giving Botox to a targeted spastic muscle of the upper limb with a specific objective to complement other re/habilitation management regime.

P701
MORPHOGENESIS OF THE BASILAR ARTERY IN THE HUMAN FETUS. N. Kubis and M. Catala. Hôpital Lariboisière and Groupe Hospitalier Pitié-Salpêtrière. Paris. France.

The development of the basilar artey during human fetal life is poorly understood. Since these developmental features could be interested to unravel the causes of congenital aneurysms formation, we decided to study this artery in human fetus. Fifteen fetuses entered the study and were separated into two groups according to their gestational age. The first group (8 cases) consists in the fetuses aged from 19 to 24 weeks of gestation. The second one to 7 fetuses around birth (33 to 37 weeks of gestation). We performed hematein-eosin, Masson's trichrome, orcein stainings and immunhistochemistry using specific antibodies raised against smooth muscle actin (SMA), desmine and vimentin. Smooth muscle fibers in the media were all decorated with SMA, but they showed a heterogeneity some of them being positive for desmin, and some being positive for vimentin. Furthermore, the luminal size, the thickness of interna elastica limitans and the medial thickness increased markedly suggesting that two elementary mechanisms can account for the arterial growth like in other animals. First, an accretion phenomenon responsible for the radial growth and an interstitial proliferation responsible for the circumferantial one.

P702
BRAIN STEM REFLEXES IN PATIENTS WITH MYELOMENINGOCELE AND CHIARI II MALFORMATION.J. Koehler[1)], M. Schwarz[2)], D. Voth[2)], H.C. Hopf[1)][1)]Department of Neurology, [2)]Department of Neurosurgery, University hospital Mainz, Langenbeckstr.1, 55131 Mainz, Germany

Chiari II malformation associated brain stem dysfunction is the main cause of death in children with myelomeningocele. We investigated the use of

brain stem reflexes in the assessment of brain stem dysfunction in Chiari II malformation. Patients and methods: Masseter reflexes (MR) and blink reflexes (BR) were investigated in 76 patients (m=39, f=37, age 3-32). The patients were subdivided in three groups. Group I comprised 47 patients with asymptomatic Chiari II malformation, group II 18 patients with brain stem signs and symptoms. Group III consisted of 11 patients investigated after craniocervival decompression. Results: BR showed higher sensitivity (BR=0.83, MR=0.50) than MR. The MR findings were more specific than BR and were significantly different in symptomatic and asymptomatic patients (χ^2=5.27, df=1, p=0.01). In BR recordings the R2 and R2c components were mainly affected. In the post surgery group improvement of brain stem reflexes was closely related to clinical outcome. Conclusion: According to our results brain stem reflexes and particulary MR are of great predictive value in the decision of further treatment in patients with Chiari II malformation. We feel that this is due to anatomic and physiologic peculiarities of the brain stem structures mediating BR and MR.

P703
NEUROLOGICAL COMPLICATIONS OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IN CHILDREN. Rudic Sandra, Gebauer Ksenija, Kelemen Ana, Bozic Ksenija.Institute for Neurology, Psychiatry and Mental Health; Medical Centre Novi Sad. University Childrens Hospital, Novi Sad, Yugoslavia

We retrospectively analyzed (from 1984 to 1997) 76 children hospitalized at the University Childrens Hospital in Novi Sad with ALL for type, frequency and timing of neurologic complications and intellectual deterioration. Ten patients had CNS leukemia according to the presence of blast cells on CSF sediment. All of these patients had neurological symptoms and signs: one patient had meningeal syndrome; seven patients had cranial nerve involvement (most frequently the facial nerve and bulbomotors were affected); three had painful polyneuropathy; two patients were with dominant spinal root symptomatology caused by pathological infiltration of either spinal roots or meninges surrounding them; one patient had cerebellar symptoms. Two patients developed seizures. Six of these 11 patient died, due to relapse or progression of the disease. From the rest of the patients two had mild spasticity (paraparesis), one had seizures and 21 mild predominantly sensor polyneuropathy. We found lower than normal (< 80) IQ in 27 of the patients. There were no significant differences between the group of neuroleukemia and the rest of the patients. CNS complications of leukemia relate either to failure or adverse effects of the therapy.

P704
SPINA BIFIDA: A SERVICE FOR ADULTS. GV McDonnell, JP McCann. Belfast, Northern Ireland.

Objective: To establish the profile and management issues of patients attending a clinic for adults with spina bifida and hydrocephalus (CASBAH). Background: Ireland has one of the highest rates for spina bifida (SB) in the western world. Due to improvements in medical care in the past 3-4 decades, an increasing number of SB patients go on to prosper in adult life. Since 1990 there has been a regional CASBAH service for Northern Ireland in Belfast. Methods: 237 patients with SB remain on the live register at CASBAH. All records were reviewed with regard to site of lesion, ambulatory ability, shunt placement, sphincter function, musculoskeletal problems and incidence of epilepsy. Results: There are 122 males and 115 females, average age 28 years. 36% of patients are wheelchair dependent, 8% have some ambulatory capacity but largely wheelchair dependent, 22% are ambulatory with aid and 34% are independently ambulatory. There are 211 with myelomeningocele, 20 with SB occulta and 6 with a variety of other lesions. Of those with myelomeningocele, clinical examination would suggest that 1.9% are cervical, 16.6% thoracic, 12.8% thoracolumbar, 37.4% lumbar, 21.3% lumbosacral and 10.0% sacral. Intraventricular shunts are in situ in 37% of patients. Just 8.4% of patients have normal bladder function, 29.5% having surgically constructed means of voiding and 28.4% performing intermittent self-catherisation. Scoliosis is present in 49.5% and 69.7% have joint deformities or contractures. 8.8% have epilepsy. Conclusion: This data reflects the considerable range of disability in adult SB patients and the challenges presented in long-term management.

P705
MAGNETIC RESONANCE IMAGING FINDINGS IN CHILDREN WITH MOTOR DISABILITY. Candan Gürses, Engin Deniz, Mehmet Calay, Sevim Bezci*, Muammer Sagir*, Mefkure Eraksoy, Meral Barlas, Hifzi Ozcan. Dept. Of Neurology, Istanbul Faculty Of Medical, University Of Istanbul. *Dept. Of Pediatrics, Turkish Spastic Children's Society, Turkey

We investigated thirty-nine children with motor disability. Thirteen were born at preterm and twenty-six at term. Thirty (76.9%) of 39 patients had abnormal Magnetic Resonance Imaging (MRI) findings. The most common findings was Periventricular Leukomalacia (PVLM) in preterm (61.5%) and in term (42.3%) group. Spastic diplegic patients born preterm** and who had pre- or perinatal causes had abnormal lateral ventricles ($p < 0.045$, $p < 0.044$**, $p < 0.027$). Cortical and Peripheral white matter abnormalities were seen more often in the term group (42.3%). Focal or diffuse cortical thinning in one hemisphere was seen in 4 term patients with spastic hemiplegia ($p < 0.05$). Fifteen epileptic patients out of 16 had several type of MRI abnormalities ($p < 0.05$). Ten (62.5%) of the epileptic patients started to have seizures before the age of 2 years.The cortex was thinned either focally or diffusely in five epileptic patients with cerebral palsy ($p < 0.037$). MRI findings are related to the degree of insult and the gestational age of the infant. In our study MRI findings showed both preterm or term may have either deeply or superficially lesions due to the time of insult.

P706
PHENOTYPE-GENOTYPE CORRELATIONS STUDIES IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY. A. Pou*, JA Muñoz*, A. Cano ** E. Bakker***, M. Jeanpierre****, P. Gallano*****. Services of Neurology: * Hospital del Mar – Barcelona ** Hospital de Mataró – Barcelona and Genetic Departments:*** KGCL-Leiden, **** Cochin – Paris, ***** St Pau – Barcelona, Spain

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant neuromuscular disorder localized to 4q35. It is characterized by marked inter- and intra-familial heterogeneity in its clinical expression. At present DNA fragment size (DFS) is considered pathological if it is 38 kb instead of 28 kb. The objective is to study phenotype-genotype correlations in FSHD. Method/Patients: 18 patients including 12 familial cases from 4 families, 5 sporadic and 1 indetermined case (with several other members of this familily presenting Poland´s syndrome) with an unequivocal diagnosis of FSHD were included. We studied the reported first symptom age, the first symptom, gender, parent of origin, manual muscle testing (MMT), auditory test, histopathological data and DFS obtained by EcoRI-BinI double digestion (DFS 38 kb was considered as pathologic). Results: 1 - Presence of a significant correlation between DFS and MMT; MMT and onset age. 2 - Absence of correlation was observed between DFS and clinical form; DFS and auditory tests. 3 – Sporadic cases were associated with smallest DFS, youngest onset, marked facial diplegia and more clinical severity. 4 – Patients with clinical predominanly scapuloperoneal forms had DFS ranging between 22 to 28 kb. Conclusions: Our study revealed a correlation between DFS and the clinical severity, DFS and onset of age. Scapuloperoneal forms of FSHD are associated with DFS ranging between 22 to to 28 kb. Inflammatory form of FSHD is more frequent in sporadic cases. We have not observed tendency to increase severity in subsequent generation.

P707
LAMBERT-EATON MYASTHENIC SYNDROME IN CHILDHOOD., A CASE REPORT. Mefkure Eraksoy, Emre Oge, Zuhal Yapict, Engin Deniz, Ffisun Erdogan. Meral Barlas Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey

The Lambert-Eaton Myasthenic Syndrome (LEMS), a defect in neuromuscular transmission in association with malignant tumours, is well recognized in adults. To our knowledge, there is only one documented report in a child who had a myasthenic syndrome and was later developed leukaemia. Myasthenic syndromes in childhood have also been reported in associated with systemic lupus erythematosus and juvenile rheumatoid arthritis. We describe a 10-year-old girl who developed LEMS when she was 8-year-old. This girl was admitted to the our child neurolgy unit because of generalized weakness, difficulty in walking and slowness of her movement. Her birth, developmental and familial histories were unremarkable. Past medical history revealed that she had a nephrotic syndrome at five years of age and completely improved with steroids. At the age of 8, two weeks after ail tipper respiratory tract infection, she developed leg pain with difficulty in walking. In the following months, mild ptosis, difficulty in speaking and writing added to the clinical feature. One and a half year difficulty in swallowing, skin flushing and palpitation appeared. The clinical picture progressed. Neurologic examination revealed progressive

generalized weakness, most prominent in the lower proximal leg muscles. Craniobulbar involvement occurred, producing ptosis, diplopia and dysphagia. Deep tendon reflexes were absent. Autonomic dysfunction such as skin flushing and tachicardia were present.The electrographic results confirmed the diagnosis of LEMS. Voltage-gated calcium channel antibody titre was 1765 pM (>100pm=positive). There was no any clues supported autoimmune or malignant etiologies during follow up period in spite of extensive investigations. The clinical picture failed to response to intravenous gailiniaglobtilin but remarkable improvement was seen with steroids and pyridostiginine. To our knowledge, this patient showed the earliest onset of LEMS in childhood without malignencies and other diseases. This report also revealed the remarkable improvement with steroids and pyridostigmine ill childhood LEMS.

P708

Abstract withdrawn by author

P709

METACHROMATIC LEUKODYSTROPHY. NEUROPHYSIOLOGICAL ASSESSMENT. G.Galardi, L Wrabetz, L.Maderna, T.Locatelli, S.Medaglini, G Comi, GM Severini. Istituto Scientifico San Raffaele, Milano, Italy

Metachromatic Leukodystrophy (MLD) is an autosomal recessive disorder caused by a deficiency of arylsulfatase A (ASA). This deficiency is responsible for cerebroside sulfate accumulation in the white matter of both the central and peripheral nervous system, with resulting dysmyelination in both. Different forms of MLD have been described according to the age of onset and severity. Several neurophysiological measures have been used to evaluate both the central and peripheral nervous system in MLD, but their usefulness has probably been understimated due to the restricted anatomic target of each neurophysiological measure, in combination with the clinical heterogeneity and small sample size of the patients studied in literature. In this study, 4 patients with late infantile MLD were studied by means of Visual Evoked Potentials, Brainstem Auditory Evoked Potentials, Somatosensory Evoked Potentials, Motor Evoked Potentials and Motor and Sensory Conduction Velocity, in order to identify a quantitative measure(s) of the clinical changes of the disease and to monitor the efficacy of eventual treatment. All neurophysiological tests demonstrated their ability to detect abnormalities of the corresponding neurological system. Multimodal Evoked Potentials and Sensory Nerve Conduction abnormalities consisted mainly of the disappearance of their responses. On the contrary, Motor Nerve Conduction abnormalities consisted of severe slowing of motor conduction velocity, and provided the only reliable, quantitative measure of clinical changes. These data provide a useful guide to endpoints that may be used to evaluate future treatment strategies.

P710

CHILDHOOD MULTIPLE SCLEROSIS WITH ONSET AT PRESCHOOL AGE. (1,2) Martino Ruggieri, (1) Agata Polizzi, (1) Lorenzo Pavone, & (3) Luigi ME Grimaldi. Division of Pediatric Neurology, Department of Pediatrics, University of Catania; (2) IBFSNC, CNR, Catania; and (3) Neuroimmunology Unit, Department of Neuroscience, DIBIT, H. San Raffaele, Milan, Italy

Objectives: To characterize multiple sclerosis (MS) patients with the earliest onset of disease. Background: MS - primarily a disease of young adulthood - begins in childhood in 3-5% of cases. Onset before age 10 years, however, is considered exceptional. Accordingly, inclusion age of onset is generally between 10 and 59 years. Methods: Information on MS patients seen at our Institution (n=6) or reported in Medline or bibliographies whose onset of disease was before six years of age, for a total of 52 patients (29 F, 23 M). Results: All patients had clinically defined MS according to Poser's criteria; 22 were also laboratory supported. The recorded female/male ratio [1.4] was lower than that usually recorded for adult onset MS [2.0] and that of MS with onset between six and 15 years [2.2–3.0]. The group of patients (n=5) with onset before age 24 months showed the lowest ratio [0.6] and carried the most unfavorable prognosis. Among initial symptoms ataxia was preponderant (61%). Optic nerve involvement became more frequent with age. Seizures occurred in 22% of cases. First inter-attack interval was < 1 year in 63% of the cases. At follow-up (mean length = 6.8 years) the disease was relapsing-remitting in 84% patients and the grade of recovery was complete in 74%. Conclusions: MS patients with the earliest onset of disease can be consistently diagnosed as definite MS by current criteria for adult onset MS. These findings may suggest a reconsideration of current lower limits for MS diagnostic criteria.

Cerebrovascular disorders

P711

MULTIPLE INTRACRANIAL ANEURYSMS ASSOCIATED WITH VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS. Szurhaj W[1], Hénon H[1], Soto Ares G[2], Lucas C[1], Pruvo JP[2], Leys D[1]. [1]Department of Neurology B, Hôpital R. Salengro, LILLE[2]Department of Neuroradiology, Hôpital R. Salengro, LILLE

Cerebrovascular abnormalities are rare in Von Recklinghausen's disease. The most common findings are arterial occlusions with collateral circulation (Moya-Moya phenomenon), arteriovenous malformations and aneurysms. We report the case of a 24-year-old woman who presented with an unusual rapidly increasing headache with vomiting. She was known as having von Recklinghausen's neurofibromatosis and a refractory arterial hypertension without evidence of renal artery stenosis, polycystic kidneys nor pheochromocytoma. Computed Tomography scan showed a spontaneous hyperdensity of the right cavernous sinus with sphenoidal osteolysis, without sign of subarachnoid hemorrhage. CSF was normal. Magnetic Resonance Imaging demonstrated a giant fusiform aneurysm of the petrous and intracavernous right internal carotid artery (ICA), without sign of dissection, occupied by a recent thrombus. Cerebral angiography showed an obstruction of the right ICA and revealed a saccular aneurysm at the posterior face of the left ICA. The clinical outcome was spontaneously favourable. The saccular aneurysm was clipped 3 months later. The development of saccular aneurysm in patients with von Recklinghausen's disease is usually explained by a proliferation of Schwann cells within the arterial wall, causing fragmentation of the muscularis and elastica. The physiopathology of fusiform aneurysm remains unknown: our case is to our knowledge the sixth case of the litterature and histology is unavailable in all of the recognized cases.

P712

SECONDARY PREVENTION IN STROKE PATIENTS: FROM THEORY TO PRACTICE. Henon H, Kowalski C, Dudeu I, Guerouaou D, Daems C, Pasquier F, Leys D, France.

Control of vascular risk factors and antithrombotic drugs reduce the risk of recurrent stroke. Aim of the study: to determine the proportion of patients who still received appropriate antithrombotic therapy (AAT) 2 years after stroke. Patients and methods: We collected in 202 consecutive stroke patients the vascular risk factors and presumed cause of stroke. Were considered as AAT: anticoagulant for cardioembolic stroke; antiplatelet drugs for stroke related to atheroma, lipohyalinosis, unknown etiology and for cardioembolic stroke in patients with contraindication to anticoagulant; absence of treatment in patients with contraindications to antithrombotic drugs and with spontaneous cerebral hematoma; Qv) either anticoagulant either antiplatelet drugs for stroke of undetermined etiology. Treatments were recorded at discharge from the acute stroke unit, before and after each visit by the neurologist at 6,12 and 24 month (M6, Ml 2, M24). Re-

sults: At discharge, 95% receceived the AAT. At M6, M12 and M24, patients received the AAT in respectively 85, 84 and 97% of cases before the consultation with the neurologist. The rate increased to 90% (M6), 97% (M 12) and 99% (M24) after the consultation. The rate of patients with treated arterial hypertension and dyslipemia increased respectively from 82 to 92% and from 38 to 65% between discharge and M24, the rate of patients with treated diabetes mellitus decreased from 95% to 67%. Conclusion: Recommandations derived from the recent clinical trials about antithrombotic treatments were respected in most cases. Treatment of vascular risk factors should however be improved.

P713
CEREBRAL VENOUS THROMBOSIS: CORRELATION BETWEEN RECANALIZATION, PARENCHYMAL LESIONS, AND CLINICAL OUTCOME – A LONG-TERM FOLLOW-UP IN 40 PATIENTS. M Covi[1], M Strupp[1], K Seelos[2], H Brückmann[2], and Th Brandt[1], Dept. of Neurology[1] and Neuroradiology[2], University of Munich, Germany

The aim of this study was to determine the correlation between long-term recanalization and long-term clinical outcome of patients with cerebral venous thrombosis (CVT). We re-evaluated 40 patients with CVT established by digital subtraction angiography in 33 patients or magnetic resonance angiography (MRA) in the remaining patients, who had been admitted to our hospital between 1977 and 1996 (mean age at time of diagnosis 38.5 y, range 19 – 66 y). The mean follow-up time was *9.1 y* (range 8 months – 20.4 y). All patients were treated with heparin initially. For follow-up investigations both conventional MR imaging and MRA were performed. Recanalization was differentiated in complete, partial, or none. Recurrence of the CVT was observed in none of the 40 patients. Eleven of 40 were still suffering from mild focal neurological deficits (mainly paresthesia, incomplete cranial nerve palsy or mild aphasia), 6 of 40 had chronic headache. Complete recanalization was achieved in 21 of 40 patients, partial recanalization in 12 of 40, and no recanalization in 7 of 40. Focal neurological deficits or headache were observed in 28% (6/21) of the patients with complete recanalization, in 42% (5/12) with partial recanalization, and 86% (6/7) with no recanalization (chi-square test, $p < 0.005$ complete vs. no recanalization). Further, conventional MRI revealed parenchymal lesions in 14 of 40 patients; 9 of these 14 patients had focal neurological deficits, whereas only 7 of 26 of the patients without parenchymal lesions ($p < 0.05$). We conclude, that patients with CVT treated with heparin (a) have a good long-term prognosis with low risk of relapse and (b) their final neurological outcome correlates with the recanalization rate and the incidence of focal parenchymal lesions.

P714
CEREBRORETINAL VASCULOPATHY MIMICKING BRAIN TUMOR. A CASE OF A RARE HEREDITARY SYNDROME. S.Weil[1], MD.; G.Reifenberger[3], MD; C. Dudel[1], MD; TA Yousry[2], MD; S. Noachtar[1]. Departments of Neurology[1], Neuroradilogy[2], University of Munich, Germany, Department of Neuropathology[3]; University of Bonn, Germany.

Cerebroretinal vasculopathy (CRV) is a rare hereditary syndrome characterized by frontoparietal lobe pseudotumors and retinal capillary abnormalities. We report a 35-year old patient with CRV, in whom cerebral MRI findings were misinterpreted as a brain tumor. Case report: The 35 year-old man had a one year history of progressive visual loss on his left eye. The patient´s mother and two further relatives had reportedly died of "brain tumors". Cerebral MRI of this patient revealed a 3 cm right frontal mass lesion surrounded by a large edema and with irregular contrast enhancement. This mass lesion was resected completely. Histopathological examination of the resected tissue showed no neoplasia, but cerebral microvasculopathy and coagulative white matter necrosis. Fluorescein angiography of the retinal vessels revealed an opticus atrophy in the left eye, shunt vessels around the papille in the left eye, and perivascular exudations in both eyes. The histological specimens were reexaminend and compared to those of the patient´s mother who reportedly died of a brain tumor 25 years ago. Identical findings of a microvasculopathy were seen in both patients. Conclusion: Taking together all clinical, serological, opthalmological, neuroradiological and histopathological findings, we diagnosed a hereditary cerebroretinal vasculopathy closely resembling the syndrome first reported by Grand et al., 1988.

P715
INTENSIVE CARE AND MECHANICAL VENTILATION IN ISCHEMIC AND HEMORRAGIC STROKE. INDICATIONS, TIMING AND OUTCOME. Dunac[(1)], Mh. Mahagne[(2)], M. Chatel[(1)]. Dpt Of Neurology. CHRU Nice. (2) Emergency Dpt. CHRU Nice - France

Objective: Evaluation of mechanical ventilation in strokes in neurological intensive care unit. Background: Mechanical ventilation (MV) in ischemic (ISC) and hemorragic (HEM) strokes remains controversial, despite of poor outcomes previously reported. Because of the lack of evidence based guidelines, we attempt to compare incidence, indications and outcomes to litterature data. Methods: A review of ISC and HEM stroke patients admitted between January 1st and October 31-1998 was performed. Age, sex, type, location of stroke, rate of patients, timing and indications of MV and status at discharge were analysed. Results: 110 stroke patients were admitted; 78 (70.91%) ISC and 32 (29.09%) HEM. 20 patients were under MV, 10 control patients (non vascular acute neurological diseases) and 10 strokes: 5/78 (6.41%) ISC and 5/32 (15.62%) HEM. MV was started at an average 2.3 days after admission. The mean age of intubated patients was 60.1 years, while the whole stroke patients population had a mean age of 67.7 (ISC=66.8 and HEM=68.6); sex ratio M/F = 1.5 (men=1 ISC and 5 HEM, female= 4 ISC). 8 were in the internal carotid territory. MV was performed for brainstem dysfunction in the 2 posterior fossa cases and for brain herniation syndrom in all 8 other cases. All patients required controlled ventilation; all but one hemorragic stroke (90%), had fatal evolution, versus 3/10 (33%) of controls. Conclusion: These results are in accordance with litterature data: MV is not likely to improve outcomes in acute stroke patients (ISC or HEM) with brain herniation. However, the benefit of early preventive intubation, common procedures and clinical criteria predictive of good outcome in moderate strokes, still have to be defined.

P716
A CASE OF INTERNAL CAROTID ARTERY DISSECTION. M. Zikic, I. Divjak, S. Gvozdenovic. Novi Sad, Yugoslavia.

This Case Report describe recently treated patient, a previously healthy person, with internal carotid artery dissection occurred during the frequent head rotations while loading corn. A previously healthy middle aged man was hospitalized because of consciousness disturbance, cervical pain, and left side headache at the first attack, and ipsilateral painful Horner's syndrome he developed later. The brain magnetic resonance imaging (MRI) didn't reveal morphological lesions. The magnetic resonance angiography (MRA) revealed internal carotid artery dissection on the left side beginning four centimeter distal to the carotid bifurcation. A conventional angiography was performed four days later, and it's confirming the same finding. Above mentioned head rotations seemed like a possible causing factor. The patient received anticoagulant treatment. The course of illness was mild and outcome was encouraging.

P717
CLINICAL AND NEURORADICOLOGICAL ASPECTS OF SNEDDON'S SYNDROME AND PRIMARY ANTIPHOSPHOLIPID ANTIBODY SYNDROME: A FOLLOW-UP STUDY. Fetoni V., Grisoli M., Salmaggi A., Carriero R., Girotti F. Isituto Nazionale Neurologico "C. Besta" - Milano - Italy

Abortion, gestosis, cardiac valvulopathy, cerebral ischemia and thrombocytopenia are characteristics shared by Sneddon's syndrome and primary antiphospholipid antibody syndrome (PAS). Recently, anticardiolipin antibodies have been found in some patients with Sneddon's syndrome. In order to clarify relations between these two conditions, we carried out a long-term follow-up study (mean four years) on nine patients with Sneddon's syndrome and 11 with PAS. The clinical and MRI findings indicated that Sneddon's syndrome and PAS are distinct entities. In the patients diagnosed with Sneddon's Syndrome, the course was progressive and invalidating, being characterised by loss of autonomy and cognitive deterioration. By contrast patients initially diagnosed with PAS had a more benign course. The antiphospholipid antibodies were absent in our patients with Sneddon's syndrome. However, careful monitoring of PAS patients is essential, both clinically and with laboratory tests, since the condition may turn out to be systemic lupus erythematosus. The aetiologies of these two illnesses are incompletely understood, and the significance of antiphospholipid bodies in some cases of Sneddon's syndrome remains to be clarified.

P718
CEREBROVASCULAR DISEASE AND HYPERHOMOCYST(E)INEMIA. P. Cerrato, C. Baima, D. Imperiale, P.Maffeis, E. Verdun, R. Gam-

bino*, M. Cassader*, N. Alemanno*, G. Pagano* and B.Bergamasco. Department of Neuroscience, Department of Internal Medicine*. University of Turin. Italy

Rationale. Hyperhomocyst(e)inemia is an independent risk factor for coronary artery disease and cerebrovascular disease (CVD). Aim. To evaluate the role of hyperhomocyst(e)inemia as risk factor in different CVD subtypes. Methods. According to clinical, instrumental and laboratory findings we classified 64 CVD patients in four groups: large vessel disease (LVD), small vessel disease (SVD), (3) cardioembolism (CE), (4) other (including cryptogenetic stroke) (OTH). In each patient we measured fast homocyst(e)ine plasma level. Results. Homocyst(e)inemia (mean SD, nmol/ml) was significantly higher (p=0.001) in CVD patients (20.5 ± 15.4) versus controls (12.75 ± 5.33). It was 22.6 ± 16.2 in LVD group, 21.35 ± 16.12 in SVD, 11.63 ± 6.75 in CE, 19.5 ± 16.23 in OTH. There was a trend toward an higher prevalence of hyperhomocyst(e)inemia (>13 nmol/dl) in LVD and SVD subtypes versus CE one (69% and 60% versus 25%). Conclusions. Hyperhomocyst(e)inemia is an important risk factor in CVD particularly in LVD and SVD substypes. Its importance is still greater as regards that it is a modifiable vascular risk factor.

Extrapyramidal disorders

P719
DISTURBANCES OF DYNAMIC BALANCE IN PHASIC CERVICAL DYSTONIA J. Müller, M. Sojer, G. Ebersbach, J. Wissel, C. Brenneis, W. Poewe. University Hospital Innsbruck, Austria

Objective - To quantitatively assess postural sway under static and dynamic conditions in patients with tonic and phasic cervical dystonia (CD). Methods - Ten patients with purely tonic CD with fixed postural deviation and twenty CD patients with phasic head movements were investigated >3 months following previous botulinum toxin injections. Seventeen age-matched volunteers served as controls. Static posturography was performed on a force platform with measurements of displacement of centre of foot pressure. Dynamic equilibrium was studied on a stabilometer, which requires the subject to continuously adapt posture to an unstable tilting surface. Measurements of maximum amplitude and linear displacement of the pivot were taken with and without visual control. Results - Sway path values in static posturography differed not significantly between CD patients and controls. On dynamic posturography, phasic CD patients demonstrated significantly higher measures (maximum amplitude and linear displacement of the pivot) with eyes open and closed compared to controls and tonic CD patients. In contrast, none of the dynamic platform measures differed significantly between tonic CD patients and controls. Conclusions - Normal measures of dynamic equilibrium in tonic CD argue against a primary abnormality of balance control in CD. Impaired dynamic equilibrium in phasic CD is likely to reflect erroneous vestibular input due to repetitive involuntary head oscillations. The clinical implication of these findings is still unclear and the effect of botulinum toxin treatment on balance control in phasic CD deserves further study.

P720
ACUTE DOPAMINERGIC RESPONSIVENESS IN YOUNG-ONSET PARKINSON'S DISEASE. Del Dotto P.*, Gambaccini G, Dell'Agnello G., Bellini G., Bonuccelli U.*Neurology Unit, Hospital of Viareggio and Department of Neuroscience-University of Pisa, Italy

Young-onset Parkinson's disease (PD) patients (40 y.o.) frequently show a marked response to low doses of levodopa, an early appearance of motor fluctuations and dyskinesias. The objective of this study was to evaluate whether peculiar pharmacological features to acute dopaminergic drugs are present in these patients. Fifteen young-onset PD patients underwent an acute drug challenge with both apomorphine (50 g/Kg s.c.) and levodopa (250 mg p.o.). The motor response was assessed by means of specific subitems of UPDRS-motor examination and the tapping test at baseline and every 10 minutes for 3 hours following apomorphine and every 20 minutes for 5 hours following levodopa administration. Fifteen PD patients matched for sex, disease duration and disease severity served as control. Most patients were untreated at the time of drug challange. All patients were then followed-up for at least 3 years to improve the accuracy of the diagnosis. Young-onset PD patients showed a greater magnitude of the motor response to both drug challenge than late-onset PD patients (42.3% vs 26.3%, $p < 0.01$, for levodopa and 35.5% vs 21.4%, $p < 0.05$, for apomorphine). The duration of the motor response was significantly shorter in young-onset PD patients after both levodopa and apomorphine administration. No involuntary movement was observed during drug testing. Our data suggest that early-onset PD patients have a different pharmacological response to dopaminergic drugs; this may have some pathophysiological role in the early development of motor fluctuations in these patients.

P721
EFFECT OF ACUTE INTRAVENOUS AMANTADINE ON MOTOR SYMPTOMS OF MULTIPLE SYSTEM ATROPHY. Del Dotto P.*, Gambaccini G., Brotini S., Dell'Agnello G., Bonuccelli U. *Neurology Unit, Hospital of Viareggio and Department of Neuroscience-University of Pisa, Italy

Pharmacological treatment of multiple system atrophy is disappointing; dopaminergic drugs provide moderate benefit in a minority of patients. Therapeutic efficacy of the N-methyl-D-aspartate antagonist amantadine has been reported in some patient suffering from multiple system atrophy; however, no controlled trial have been performed. This study was designed to evaluate the acute effect of N-methyl-D-aspartate antagonist amantadine, parenterally administered, on motor symptoms of multiple system atrophy. Six patients with multiple system atrophy (striatonigral type) received a 2-hour intravenous infusions of amantadine (200 mg) or placebo in a double-blind fashion on two different days. Dopaminergic therapy was withdrawn 12 hours before testing, while amantadine (if taken) was discontinued at least 1 week before the trials. Extrapyramidal motor symptoms were assessed at baseline and every 30 minutes by means of tapping test and UPDRS (motor examination) during the infusion and for 3 hours thereafter. Amantadine administration, but not placebo, induced a significant improvement of both tapping test (34%, $p < 0.01$) and motor examination of UPDRS (24%, $p < 0.05$). This improvement was clearly observed in 5 out of 6 multiple system atrophy patients. No significant side effects were observed. The findings of this study may have relevance to the treatment of multiple system atrophy and suggest that basal ganglia glutamatergic neurotransmission may be impaired in this disease.

P722
HEMICHOREA REVEALING NON KETOTIC HYPERGLYCEMIA. M. Coustans, A. Michel, J.Y. Poirier, G. Edan, M. Verin. Rennes, France.

Chorea has many causes, metabolic disorders are one of these causes. Neurologic abnormalities accompanying severe non ketotic hyperglycemia include many troubles. We report the case of a 72 year – old woman admitted to our hospital for right arm and leg movement disorders which had started a couple of weeks before. These disorders were associated with polyuria, polydipsia and fatigue. The neurologic examination disclosed a continuous right hemichorea, but no other abnormalities. In her medical history we note hypertension treated for thirty years, and she was taking three therapies (atenolol, prasozine, clonidine) for it. She had no diabetes mellitus known in her history medical. As for biology the glucose serum level was 19.8 mmol, ketones were absent. The movement disorders regressed with the treatment of hyperglycemia by insulin and hydratation. The magnetic resonance imaging (MRI) revealed bilateral lesions of basal ganglia with multilacunar aspect of the striatum on both sides. The results of the MRI are showed and the possible etiologies of this hemichorea are discussed. First a preexisting lesion of caudate nuclei vascular origin, then a acute metabolism disorder like hyperglycemia which reveal movement disorders. Both are supposed to reveal chorea. This association of abnormalities explains the poor number of cases reported in the world. Other published cases of hemichorea with non ketotic hyperglycemia are reported and physiopathologic mecanism are discussed.

P723
LARYNGEAL FUNCTION AND SLEEP DISTURBANCES IN MULTIPLE SYSTEM ATROPHY (MSA). Iranzo A, Santamaria J, Aguilar F*, Valls-Sole J, Morello A*, Valldeoriola F, Muñoz E, Molinuevo JL, Marti J, Pou A** and Tolosa E. Neurology, ENT* Services. Hospital Clinic. Hospital del Mar**. Barcelona, Spain.

Objective: To evaluate laryngeal function and sleep disturbances in MSA. Methods: We prospectively studied laryngeal function and sleep characteristics in 11 MSA patients(six men, mean age 62 years). Vocal cord function was evaluated with indirect fibreoptic laryngoscopy during wakefulness. In nine patients we performed percutaneous intrinsic laryngeal electromyography (EMG) evaluating thyroarytenoid and posterior crycoarytenoid (PCA) muscles during wakefulness. Nocturnal polysomnography (PSG) with audiovisual recording was also performed. Results: Three pa-

tients reported nocturnal stridor which was confirmed by PSG. In these patients laryngoscopy showed vocal cord abduction restriction in two and abduction paralysis in one, while EMG demonstrated PCA denervation and poliphasic motor units in two and was normal in one. Eight patients did not reported nocturnal stridor and PSG excluded it, while laryngoscopy showed abduction restriction in five, abduction paralysis in one and was normal in two, and EMG showed no PCA activation in one and was normal in five. Thyroarytenoid EMG was normal in all eleven cases. PSG disclosed REM behaviour disorder (RBD) in all patients and periodic limb movements (PLM) in six. **Conclusion:** In MSA, laringeal studies are useful to detect vocal cord abductor dysfunction, but this abnormality do not predict the presence of nocturnal stridor. PSG discloses a high prevalence of RBD and PLM.

P724
ELECTRICAL STIMULATION OF THE SUBTHALAMIC NUCLEUS IN PARKINSON'S DISEASE: EFFECTS OF THE VARIATION OF STIMULATION PARAMETERS. M. Rizzone*, P. Pollak§, N. Van Blercom§, J. Xie§, A. L. Benabid§. I Divisione Neurologica, University of Turin - Italy; § Service de Neurologie, C.H.U. Grenoble – France

High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a valid treatment for advanced Parkinson's disease, but its precise mechanism of action is still unknown. We studied the effects of varying electrical parameters on akinesia and rigidity. To assess the respective effects of voltage and pulse width, we used a narrow (60μs), intermediate (210μs) and wide (450μs) pulse width combined with a high, intermediate and low voltage respectively, in order to maintain the total electrical amount constant. Pulse rate was the same for each of the three conditions of stimulation. Nine patients operated on, with bilateral STN DBS were evaluated in off-medication condition. Rigidity and akinesia were assessed using both a subjective scale (UPDRS motor examination part, items 22-25) and objective methods, namely a device capable of quantifying muscular rigidity of the wrist and the hand tapping test for akinesia. In all patients, the benefit on akinesia and rigidity was negatively correlated with pulse width. The greatest improvement occurred with a pulse width of 60μs, whatever the assessment method used. This finding suggests that a) DBS action may be preferentially mediated by stimulating fibers than somas, since myelinated fibers have chronaxies of 50-100μs whereas soma chronaxies are longer; b) as a shorter pulse width is coupled with a higher voltage responsible for a greater spreading of current, improvement in effects may result from a larger area of tissue involved by stimulation.

P725
UBIQUITIN (LEWY BODY) FORMATION IN THE BRAIN IN PARKINSON'S DISEASE (PD) AND INCIDENTAL LEWY BODY DISEASE. A. Krygowska-Wajs, G.Zwolinska, T.Bujny, D.Adamek, J.Kaluza, A.Szczudlik. Dpt. of Neurology and Dpt.of. Neuropathology Coll.Med. Jagiell.Univ. Cracow, Poland

Background: Incidental Lewy body disease (ILBD) appears to be a presymptomatic form of PD where individuals are neurologicaly normal, but at post-mortem examination a pathology similar to PD is present. Thus ILBD may precede this degenerative pathological process in PD and can be used to examine early stages in PD. Material and methods: The immunochemistry of ubiquitin (as a marker of Lewy bodies) was examined in the brains of patients with PD and in normal brains to detect the presence and any modification of Lewy bodies. Samples of the brain from four patients with Parkinson's disease and sixteen age-matched controls (mean age 66.5 years) were obtained at autopsy. We also measured the levels of dopamine (DA) and its metabolites and the density of DA receptors. Results: Lewy bodies were observed in neurons in patients with PD and in five subjects of the normal group. In two parkinsonian patients typical Lewy bodies were found in the substantia nigra and the locus coeruleus. In patients from the normal group Lewy bodies were only seldom found in the region of the locus coeruleus. Furthermore, in normal brains we did not find a decline levels of receptor density and dopamine concentration, while in parkinsonian brain the level of dopamine, and density of dopamine receptors were greatly decreased. Conclusion: (1) brain regions from individuals with ILBD (putative presymptomatic PD) may represent those who do not have the DA deficit necessary to initiate clinical symptoms. (2) a decreased density of dopamine receptors occurs late in PD brain.

P726
HETEROGENEITY OF DOPA-RESPONSIVE DYSTONIA (DRD) PHENOTYPE IN TWO SWISS FAMILIES. Ghika J., Solida A., Hauf M., Vingehroets F., Schorderet D*, Albanese A.Université de Lausanne, Service de Neurologie et *Division de Génétique médicale, Lausanne, Switzerland

Classical DRD can be included in a broader group of "levodopa responsive disorders". Most cases are caused by mutations of GCH I gene, the first and regulatory enzyme of the cycle of BH4, however, other abnormalities of pteridine metabolism (such as 6-pyruvoyl-tetrahydropterine synthetase and dihydropterine-reductase deficiencies) may be found in patients with a DRD-like phenotype. We report two Swiss families with an heterogeneous DRD phenotype. The following phenotypes were observed in family 1. Childhood onset and progression to generalized dystonia (with diurnal fluctuations and dramatic response to levodopa) in 4 cases, two of whom progressed to overt parkinsonism; writer's cramp (5 cases); mild dystonia (e.g., scoliosis, foot eversion during exercise; 3 subjects); mild parkinsonian signs (3 subjects); dystonia, mental retardation and epilepsy were present in 1 subject. Family 2 presented a gender-related phenotype with late onset dystonia: two sisters developed (at 48 and 68 years, respectively): bilateral limb dystonia with diurnal fluctuations and dramatic response to low doses of levodopa, and rest tremor. Their two brothers had parkinsonism. This report provides further evidence for intra- and inter-familial variations of DRD. The underlying biochemical and genetic heterogeneity has to be clarified further. Linkage analysis of these families is in progress. *Supported by grant n° 4038- 052782/1 of Swiss National Research Foundation*

P727
CONTINUOUS INTRATHECAL BACLOFEN INFUSION IN A PATIENT WITH DELAYED ONSET GENERALIZED DYSTONIA. S. Amadio, P. Marchettini, MA. Volonté, S. Lalli, M. Lacerenza, G. Comi, G. Galardi. Scientific Institute Ospedale San Raffaele - Milan

There are conflicting reports in the medical literature on the efficacy of continuous intrathecal infusion of baclofen (CITB) in dystonia. We report the case of a 41-years-old woman with a delayed-onset, severe generalized dystonia. Several pharmacological treatments like trazodone, clonazepam, trexiphenidile, gabapentin, L-DOPA, did not provided any improvement. Botulinum toxin injection into the neck muscles gave her only a transient and local relief, while oral baclofen, up to 60 mg/day, gave no improvement at all. Therefore, after two intrathecal test administration of baclofen (25 and 50 μg respectively) which provided a considerable improvement, an intrathecal catheter was inserted at D9 level and connected to a subcutaneous pump. The infusion began at a rate of 50 μg per day and was gradually increased up to 370 μg per day. She reported an improvement of muscle tone, posture and functional abilities like walking, attending personal care, etc., and a decrease of pain as well. The score of the Fahn-Marsden dystonia's scale, which was 55/120 before CITB, decreased to 34/120 after the treatment. In this case, the continuous intrathecal infusion of baclofen has proved to be an useful treatment. However further studies are needed to stabilished if CITB could be the treatment of choice of selected patients with dystonia not responsive to other treatments.

P728
BOTULINUM TOXIN IN SPASMODIC DYSPHONIA: OCCASIONAL FAILURE IN RESPONSIVE PATIENTS. G. Galardi, S. Amadio, G. Cantarella, R. Guerriero, G. Melloni, R. Teggi, G. Comi

Spasmodic dysphonia is an action dystonia of the laryngeal muscles. Two subtypes of laryngeal dystonia are recognized: adductor and abductor dysphonia. In adductor dysphonia, the more frequent subtype, patients have strained, strangled voice with intermittent breaks as a consequence of hyperadductions of the vocal folds during phonation. Botulinum toxin injections into vocalis muscle is considered the first choice treatment, giving a voice recovery for an average period of three months. We observed occasional failures of botulinum toxin efficacy in patients who usually respond to this therapy. To understand the causes of this phenomenon we evaluated the failure occurence according to the toxin injected (Botox or Dysport) and the methods of injection (EMG or laryngoscopic guidance). Fifteen patients with adductor dysphonia had repetetive treatments for a total of 140 injections into vocalis muscle. Injections were performed with EMG monitoring in 107 and under laryngoscopic guidance in 33. Botox was injected in 106 and Dysport in 34 treatments. In 29.2% of total amount of injections, neither subjective and objective results nor side effects were observed. Treatment under EMG guidance failed in 28.1% and under laryngoscopic guidance in 33%. Treatment with Botox failed in 30.2% and treatment with Dysport failed in 26.5%. Neither the injection modality nor the type of toxin can explain the treatment failure.

P729
DEMENTIA IN PARKINSON'S DISEASE: ARE MRI LINEAR MEASURES USEFUL? I. Appollonio[1], V. Isella[1], M. Grimaldi[2], S. Iurlaro[1], P. Melzi[1], R. Piolti[1], L. Frattola[1]. 1) 5th Neurological Dept., Univ. Milan and 2) Neuroradiological Dept., S. Gerardo Hospital, Monza, Italy.

The dementia associated to Parkinson's disease is common, yet often difficult to diagnose early and precisely due to its heterogeneity and overlapping with non-cognitive symptoms. Studies based on linear and volumetric MRI measures have given promising results in Alzheimer's and other cortical dementias. Aim of the study. We tested the discriminative ability of MRI linear frontal and temporal measures in a PD population. Subjects and Methods. Demographic, clinical, neuropsychological and neuroradiological data were collected from 38 subjects and data analysed in the present study refer to three subgroups: moderately to severely demented PD patients (n=8), high functioning PD (n=6) and high-functioning normal controls (n=6). Results. Brain width at frontal level was significantly lower for demented PD compared to controls and hippocampal height was significantly lower in demented PD compared to both non demented PD and controls; these two indexes correlated significantly with executive and memory tests, respectively. No additional frontal and temporal MRI measures differed between demented and not demented subjects. Hippocampal height had the highest discriminative power at multivariate analysis which correctly classified the cognitive status of 17/20 subjects (85%). Conclusions. We suggest that sensitivity and specificity of quantitative neuroimaging for dementia in PD should be further verified, possibly extending the assessment to subcortical structures.

P730
CAN PALLIDAL STIMULATION IMPROVE DYSARTHRIA IN PARKINSON DISEASE?.M. Rousseaux, V. Hoquet, P. Krystkowiak, B. Bayle, L. Defebvre, A. Destée. Service de Rééducation Neurologique, Institut d'Orthophonie, Service de Neurologie et Pathologie du Mouvement. CHU Lille, France.

The chronic stimulation of the ventroposterolateral part of the internal pallidum has been reported to dramatically improve dysarthria in 2/3 patients with Parkinson disease (PD; Siegfried, 1994); however, this effect has never been clearly confirmed by further studies, and the respective effects of the micropallidotomy and stimulation have not been differentiated. This study aimed to investigate these effects. Patients and methods. Four patients presenting with idiopathic PD were included in a prospective study of the effectiveness of pallidal stimulation. The severity of dysarthria was assessed at 3 different phases of the procedure (pre operative, post operative without stimulation, and post operative with stimulation; post operative delay: at least 3 months), and in 2 conditions for each phase (with and without levodopa treatment). We used clinical semiquantitative assessment (modified Frenchay dysarthria assessment) of 8 parameters: sustained /a/, phoneme production, voice, articulation, speaking rate, variation in amplitude, prosody (from 0= most severe impairment, to 8=normal). The effect of within subject factors (parameter, phase and condition) was assessed using ANOVA (p=.05). Results. We found a significant effect of parameter (p=.0001), as the performance level progressively declined from sustained /a/ to speaking rate, phoneme production, variation in amplitude, voice, and prosody. A weak effect of condition was also observed (p=.06), as the mean performance was higher at the preoperative phase (m=4.42), then at the post operative phase with stimulation (m= 4.03), and finally at the post operative phase without stimulation (m= 3.83). Individual assessment of each patient revealed that 2 of them were more severely impaired in the post operative phase, without (2 cases) and with (1 case) stimulation, 1 was not affected, and 1 other improved (after stimulation only). Discussion. This study suggests (1) that the operative procedure required by the intracerebral introduction of the stimulating electrode may increase dysarthria in PD; (2) that the pallidal stimulation can discreetly improve the speech output in comparison with the basal post operative state; and (3) that the patient dysarthria do not benefit from the complex procedure of pallidal stimulation (micropallidotomy+stimulation).

P731
FOCAL MYOSITIS CAUSING NON-DYSTONIC TORTICOLLIS. A.Cardozo, M.J.Martí, T.Ribalta, E.Tolosa. Servei de Neurologia, Hospital Clínic. Barcelona, Spain

Focal myositis is an unusual inflammatory lesion of skeletal muscle. It usually affects the extremities, but is rare in the head and neck. We present a case of a boy with focal myositis of the sternocleidomastoid (SCM) muscle causing torticollis. A 17-year-old boy was refered to us with the diagnosis of spasmodic torticollis, without response to anticholinergic drugs, to be evaluated for botulinum toxin treatment. Symptoms started four years before and two months after his left clavicle was broken. He noticed head tilt to the left and a feeling of discomfort on the neck. He was the product of a normal pregnancy without perinatal complications. On examination his head was constantly tilted to the left, with elevation of the ipsilateral shoulder, without superimposed spasms. The left SCM was notably swelled and firm on palpation. The rest of the neurological examination was normal. MRI showed an increased volume of the left SCM with areas of high and low intensity on T2-weighted images. Computed tomography scans did not evidence calcification. The patient underwent partial resection and byopsy of the SCM. The histologycal examination of formalin-fixed, paraffin-embedded tissue showed the diagnosis of focal myositis. Although focal myositis is really infrequent it should be considered between the differential diagnosis of non-dystonic torticollis.

P732
EVOLUTIVE MRI ABNORMALITIES IN A RECURRENT SYDENHAM'S CHOREA: IS CHRONIC DOPAMINERGIC SENSITIVITY A MYTH ? David Devos*; Pascal Martinat**; Isabelle Delalande**; Alain Destée*. From the *Departement of Neurology, **Departement of Pharmacology CHRU Lille, France

A nine- year- old girl presented a progressive onset of choreic movements predominant on the right arm and leg. The CT scann was normal. She was treated with penicillin and corticoïds until she was asymptomatic, after two months. She remained asymptomatic during eleven years and presented the same episod of isolated choreic movements with hypotonia predominant on the right side. MRI showed abnormalities on T2 hypersignal antd T1 hyposignal of the left internal globus pallidus (Gpi) close to the external globus pallidus, of the left caudate, of the right pre rolandique white matter and cortex. The rheumatoïde tests remained negative, there were negative tests for antinuclear antibodies, antiphospholipids antibodies, anti DNA antibodies, neurosyphilis and pregnancy test. She had a oestroprogestative treatment for a long time, the antiethyniloestradiol antibodies were negative, but it could be a sensitizing factor. The same treatment was leading until she became asymptomatic. She had a compatible course of Sydenham chorea, without argument for other causes of chorea. After several months a control MRI revealed the disparition of the left Gpi abnormality, the persistance of the other abnormalities, and new asymptomatic abnormalities of the right putamen and caudate, with aftereffect appearance of both caudate. It is interresting to note the persistance and even the asymptomatic evolutivity of MRI abnormalities in Sydenham chorea, and the correlation of the right choreic movements and the left Gpi abnormality.

P733
CHANGES IN CIRCADIAN SECRETION PATTERN OF MELATONIN IN PARKINSONIAN PATIENTS WITH LEVODOPA-INDUCED MOTOR COMPLICATIONS. D. Devos[1], R. Bordet[2], S. Brique[3], Y. Touitou[4], J.D. Guieu[5], C. Libersa[2,3], A. Destée[1] - [1]Service de Neurologie A, CHU Lille; [2]Service de Pharmacologie Hospitalière, Faculté de Médecine, Lille; [3]Centre d'Investigation Clinique, CHU & INSERM, Lille; [4]Service de Biochimie, CHU Pitié-Salpêtrière, Paris; [5]Service de Neurophysiologie, CHU Lille, France

Levodopa would induced a phase advance in circadian secretion of melatonin in Parkinson's disease. The aim of the study was to analyse changes in melatonin secretion pattern and biological rythms in patients with or without levodopa-induced motor complications. We investigated circadian rhythms of temperature, motor activity, plasma cortisol and melatonin in three groups: patients "de novo" without treatment (group I); levodopa-treated patients without motor complications (group II); levodopa-treated patients with motor complications (group III). There was no difference between the 3 groups for the rhythm of temperature. Area under time-concentration-curve (AUC) of plasma cortisol and motor activity were significantly increased in groups II and III without changes of other parameters and this was significantly correlated with levodopa daily dose. There was a significant phase advance of melatonin secretion rhythm between group I (acrophase: 3:43 ± 45 min) and group II and III (acrophase: 1:59 ± 30 min) and a significant earlier Dim Light Melatonine. Onset between group I and II (21:18 ± 21 min) and group III (18:21 ± 2 h), and this was correlated with levodopa duration. The AUC were not different between the 3 groups but the diurnal AUC of melatonin was significantly increased in

group III with a nocturnal AUC/diurnal AUC ratio significantly decreased. Circadian secretion pattern of melatonin is impaired in parkinsonian patients with levodopa-induced motor complications, without desynchronization of other biological rhythms. Melatonin could be a future pharmacological target in Parkinson's disease.

P734
INFLUENCE OF PALLIDAL STIMULATION ON PREPARATORY POSTURAL ADJUSTEMENTS IN PARKINSON'S DISEASE. L. Defebvre, P. Krystkowiak, J.L. Blatt, M. Périna, S. Blond, A. Destée. Lille, France.

Postural instability is a common problem in patients with severe Parkinson's disease (PD) who presented Levodopa induced dyskinesias (LID). If the beneficial effect of bilateral internal globus pallidus (GPI) stimulation on LID is well known, influence on postural instability has not been specified yet. Preparatory postural adjustments associated with a lateral leg raising task were studied in 7 patients with PD before and 3 months after bilateral GPI stimulation using quadripolar electrodes in two conditions: off drug (6 cases) and on drug (5 cases). Recording included ground reaction forces and kinematic parameters. Before surgery the amplitude of initial displacement of center of pressure (CP) toward the moving leg were markedly reduced compared to controls, with an increase of the interval between the earliest force changes and the onset of leg elevation. After the bilateral GPI stimulation an increase of this initial peak was observed in 6 patients (2 in on-drug condition, 3 in off-drug condition and 1 in both) with a clear decrease of the interval between the forces changes and the onset of leg movement which appeared to be similar to controls. Moreover, the peak of velocity of ankle increased for all patients and the amplitude of shoulder displacement was also significantly reduced after surgery in 5 cases. This study seems to confirm that bilateral GPI stimulation can induce beneficial effects on preparatory postural adjustments in PD.

P735
EFFECT OF CHRONIC GLOBUS PALLIDUS STIMULATION IN PARKINSON'S DISEASE. P. Krystkowiak, M. Périna, L. Defebvre, S. Blond, A. Destée. Lille. France.

Chronic high frequency internal globus pallidus (GPI) stimulation can be proposed for the treatment of severe Parkinson's disease (PD) with Levodopa induced dyskinesias (LID). Variable beneficial effects on the different features of parkinsonism (akinesia, tremor, rigidity and other symptoms as gait disorders) have been reported). The aim of the present study was to evaluate the effect of bilateral GPI stimulation in patients with PD. Eight patients underwent bilateral GPI stimulation. The Unified Parkinson's Disease Rating Scale (UPDRS) and LID scale were compared in on and off drug conditions, before surgery and 3, 6 and 12 months after surgery. In off drug condition (12 months after surgery), the motor UPDRS score was improved by 51 % on average. The improvement of other symptoms was: tremor 61 %, akinesia 52 %, rigidity 55 %, gait 52 %. In on drug condition, an improvement of LID by 60 % was observed. The mean levodopa dose was increased by 38 %. The following adverse effects were observed: hypophonia (n=8), transient (n=1) or persistant (n=3) cognitive impairment, transient visual field deficit (n=2) and dysarthria (n=2). This study seems to confirm that chronic GPI stimulation is effective not only on LID but also on parkinsonism.

P736
EFFECTS OF BILATERAL SUBTHALAMIC NUCLEUS STIMULATION IN PARKINSON'S DISEASE. P. Krystkowiak, M. Périna, L. Defebvre, D. Devos, G. Touzet, S. Blond, A. Destée. Lille. France.

Chronic high frequency stimulation of the subthalamic nucleus (STN) can be proposed for the treatment of severe Parkinson's disease (PD). This technique has been reported to improve the different features of parkinsonism (akinesia, tremor, rigidity and other symptoms such as gait disorders) but also the levodopa-induced dyskinesias (LID). The aim of the present study was to evaluate the effect of bilateral STN stimulation using quadripolar electrodes in 8 patients with PD. The Unified Parkinson's Disease Rating Scale (UPDRS), time motor tests from the Core Assessment Program for Intracerebral Transplantations (CAPIT) and LID scale were compared in off and on drug conditions, before surgery and 3, 6 and 12 months after surgery. In off drug condition (3 months after surgery), the motor UPDRS score was improved by 38 % on average. The improvement of other symptoms was: tremor 97 %, akinesia 19 %, rigidity 64 %, gait 34 %, CAPIT 59 % (hand-arm movement between 2 points). In on drug condition, a marked improvement of LID (mean 80 %) was observed. Similar results were noted in 6 patients followed so far, 6 months after surgery. The levodopa dose was decreased (n=4), increased (n=2), or there was no change (n=2). The following adverse effects were observed: dysarthria (n=3) and mild cognitive impairment (n=1). This study confirms that chronic STN stimulation is effective on both parkinsonism and LID.

P737
HSV VECTOR-MEDIATED EXPRESSION OF BCL-2 PREVENTS 6-HYDROXYDOPAMINE INDUCED DEGENERATION OF NEURONS IN THE SUBSTANTIA NIGRA IN VIVO. Marina Mata, Masanobu Yamada, Thomas Oligino, James R. Goss, Joseph C. Glorioso, and David J. Fink. Pittsburgh, PA, USA.

6-hydroxydopamine (6-OHDA) is widely used to selectively lesion dopaminergic neurons of the substantia nigra (SN) in the creation of animal models of Parkinson's disease. In vitro, the death of PC-12 cells caused by exposure to 6-OHDA occurs with characteristics consistent with an apoptotic mechanism of cell death. We created a replication-defective genomic herpes simplex virus (HSV)-based vector containing the coding sequence for the antiapoptotic peptide Bcl-2 under the transcriptional control of the simian cytomegalovirus immediate early promoter (SCMV IEp). Transfection of primary cortical neurons in culture with the Bcl-2 producing vector protected those cells from naturally occurring cell death over 3 weeks. Injection of the Bcl-2 expressing vector into SN of rats one week prior to injection of 6-OHDA into the ipsilateral striatum increased the survival of neurons in the SN, detected either by retrograde labeling of those cells with fluorogold (FG) or by tyrosine hydroxylase (TH) immunocytochemistry, by 50%. These results, demonstrating that death of nigral neurons induced by 6-OHDA lesioning may be blocked by the expression of Bcl-2, are consistent with the notion that cell death in this model system is at least in part apoptotic in nature, and suggest that a Bcl-2 expressing vector may have therapeutic potential in the treatment of Parkinson's disease

P738
TREATMENT OF DROOLING WITH BOTULINUM TOXIN IN PARKINSON'S DISEASE. W.H. Jost, Dept. of Neurology, Deutsche Klinik für Diagnostik, Wiesbaden, Germany

Drooling is very common in patients with Parkinson's disease (PD). The symptom is not caused by increased salivation, but rather by disturbed swallowing. In some cases sialorrhea is refractory to prokinetic drugs, anticholinergics etc. and may be so extensive, that the patient is disabled socially. For the past 18 months we have been using botulinum toxin (BoTx) for the treatment of therapy refractory drooling. BoTx inhibits presynaptic acetylcholine release in muscular synapses – its autonomic effects include reduced sweating, lacrimation, ear wax production etc. Currently we have treated 6 patients (3 male, 3 female, 60.3 years on average). We inject 10 units (0.4 ml) of Botox® (Allergan, S.F., USA) with a 1-ml-syringe and a thin (27 g) needle in the superficial portion of the parotid gland, as it is the largest salivary gland. We obtained good results in one patient (normal salivation), moderate results in 3 patients (decreased salivation), and no change in two patients. Adverse effects were slight weakness of the masseter muscle in two patients, and weakness of mouth opening in two patients. The duration of action in the patients with good results extended over 5 months, in the three patients with moderate results 4 to 7 months. In our opinion BoTx is a useful new mode to treat drooling in patients with PD. Further results have to be awaited, especially for the use of higher dosages.

P739
PLASMA LEVELS OF LEVODOPA CORRELATE WITH BODY WEIGHT IN PARKINSONIAN SUBJECTS.Thomas Müller, Dirk Woitalla, Carsten Saft, Gisela Schweibold, Wilfried Kuhn, Horst Przuntek. Department of Neurology, St. Josef-Hospital, Ruhr-University of Bochum, 44791 Bochum, Germany

Antiparkinsonian comedication and altered gastrointestinal motility and resorption in Parkinson's disease (PD) may influence plasma levels of levodopa. Other putative factors may be body weight. Aim of the present study was the relation between body weight and levodopa in plasma of parkinsonian subjects. 20 patients were enrolled into the study with a standardized protocol. Blood samples for estimation of levodopa plasma lev-

els with HPLC were taken at fixed timepoints. AUC of levodopa bioavailability in plasma (mean: 84495.1 ± 40581.2 [SD] range 24798.7 to 160548.2 ng/ml) significantly correlated with body weight ($p = 0.003$, correlation coefficient [R] = -0.633). C_{max} of levodopa in plasma (mean: 1052.7 ± 508.5 [SD] range 273.8 to 2000.9 ng/ml) was significantly associated with body weight ($p = 0.004$, $R = -0.615$). No influence of sex, age and severity of disease appeared on levodopa plasma levels. These results suggest, that prior long-term levodopa studies should be reevaluated, using body weight as covariates, because body weight reduces during the course of PD in approximately 50 % of the patients (Toth et al. Neurology 1997;48:88-91). Appearance of dyskinesias as consequence of long-term levodopa treatment may also partially be due to weight loss resulting in an increase of maximum concentration of levodopa in plasma.

P740
[^{123}I]-β-CIT-SPECT REFLECTS PROGRESSION IN PARKINSON`S DISEASE. Thomas Müller *, Ernst G. Eising+, Dirk Woitalla*, Christina Zander+, Andreas Bockisch+, Horst Przuntek* & Wilfried Kuhn* - *Department of Neurology, St. Josef-Hospital, Ruhr-University of Bochum, 44791 Bochum, Germany; +Department of Nuclear Medicine, University GHS Essen, 45122 Essen, Germany

Parkinson`s disease is characterized by presynaptic degeneration of dopaminergic neurons in the basalganglia, which may be visualized by single photon emission tomography with a single-head -camera in combination with the cocaine analogue [^{123}I](1R)-2-β-Carbomethoxy-3-β-(4-Iodophenyl)-tropane ([^{123}I]-β-CIT-SPECT). Aim of our study was to evaluate progression of disease with [^{123}I]-β-CIT-SPECT and the Unified Parkinson's Disease Rating Scale (UPDRS) in 17 idiopathic Parkinsonian patients over a period of two years. Significant differences appeared when comparing the ratios of striatum/cerebellum of [^{123}I]-β-CIT uptake ($p = 0.021$; difference (D): -1.72 ± 2.78 standard deviation (SD), range -7.43 to 3.04 [n =3 with positive values]) and the UPDRS scores ($p = 0.005$; D: 17.23 ± 22.21 SD) range –12 to 75 [n = 3; with negative values]) with the data of these patients two years ago. An improvement of the UPDRS score and an increased striatal uptake of [^{123}I]-β-CIT occurred with both methods in three but not identical subjects. We assume, that both - determination of striatal [^{123}I]-β-CIT uptake and scoring with the UPDRS - suffer from investigator variability. [^{123}I]-β-CIT-SPECT even with a single-head -camera may monitor progression in Parkinson's disease.

P741
NEUROTOXIC EFFECTS OF AN INDUSTRIAL CHEMICAL ON MIDBRAIN DOPAMINE NEURONS. [1]Rafik Masalha, [1]Yuval Herishanu and William F. Silverman, Departments of [1]Neurology and Morphology, Soroka Medical Center, Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer Sheva, Israel, 84 105

In searching for potential environmental causes of Parkinson's disease [PD], we have tested a number of chemicals used in heavy industry in a part of Israel previously shown to have a higher than average number of PD cases. One of these chemicals, a widely employed UV light stabilizer, Tinuvin 123, demonstrated robust, apparently specific toxicity for dopaminergic (DA) neurons in cultures of rat mesencephalon and following unilateral, intraparenchymal injection. Following weekly unilateral injections of 0.04 mg Tinuvin 123 into the internal carotidof mature rats, we have observed a striking and widespread activation of the proto-oncoprotein c-fos in neurons throughout the brain. The appearance of activated central neurons may indicate that Tinuvin 123 may have more generalized effects than previously believed. Systemic introduction of Tinuvin 123 also induced severe loss of DA neurons in the SN as well as their projections to the caudate-putamen. The effect at low doses was largely ipsilateral, and produced transient apomorphine-induced rotations towards the side of the injection, followed by bradykinesia. At higher doses the lesion produced was asymmetric, albeit clearly bilateral, and induced akinesis in the subjects. A caudal-rostral gradient of DA fiber loss was noted in the chronically-injected animals. The significance of a nearly ubiquitous industrial chemical exhibiting characteristics of a dopamine-specific neurotoxin is readily apparent. Current efforts are focused on establishing the ability of Tinuvin 123 and related compounds to cross the blood-brain barrier. Supported by a grant from the Israel Ministry of Health.

P742
HEMIMASTICATORY SPASMS AND PAROXYSMAL SPASMS OF THE JAW. Report of 2 clinical cases. MH MARION*, P KLAP** *National Hospital for Neurology and Neurosurgery - London **Clinique Turin – Paris, France.

Hemimasticatory spasms and paroxysmal spasms of the jaw are rare conditions. We wish to report 1 case of hemimasticatory spasm associated with facial hemiatrophy, and the first case of paroxysmal closing spasms of the jaw following radiotherapy of an amygdal (tonsil) neoplasm. Both conditions had in common paroxysmal spasms of the masseters, lasting seconds or minutes, very painful and resulting in tongue biting and broken teeth. Speaking, chewing or even voluntary opening of the mouth was totally impossible during the spasms. The hemimasticatory spasms were unilateral, precipitated by mastication at the beginning but then occurring day and night with progression of the disease. The paroxysmal spasms of the jaw were bilateral, predominant on the side of the irradiation with hypertrophy of the right masseter and without any precipitating factors. Cranial nerve examination was otherwise normal, in particular without any sign of a trigeminal lesion in either case. The 2 patients were dramatically improved by injections of botulinum toxin in the masseters.

P743
MODAFINIL IN HYPERSOMNOLENCE COMPLICATING PARKINSON'S DISEASE. L McKee, H Sheppard, Z Cowen, K Anderson, P McKee, PK Newman. Middlesbrough U.K.

Sleep disorder and daytime somnolence are common -in late Parkinson's disease (-PD). Modafinil -improves daytime sleepiness in narcolepsy although The action -is unclear. A double blind crossover pilot trial evaluated modafinil 200mg and 400mg -in six PD patients with excessive daytime sleepiness, UPDRS and Hoehn and Yahr scales evaluated symptoms the Epworth sleepiness scale (ESS) and diaries gauged daytime wakefulness. The subjects had mean age 71.5 and duration of PD- 8,6 years. Two patients were withdrawn due to failure to maintain adequate diaries. No subject bad significant changes in PD disability, Two patients bad no changes in the assessments of daytime sleepiness. In one patient a reduction of cumulative ESS from 16 to 8 was seen with modafilul 200mg and to 9 with 400mg. A second patient had ESS reduced from 8 to 5 and periods of daytime wakefulness doubled Modafinil 200mg but could not tolerate, 400mg. All subjects had adverse effects. Evaluation of ESS and daytime wakefulness patterns in this pilot study has suggested that Modafinil may have some influence but any potential clinical benefit is outweighed by side effects. Adverse effects are likely to be more troublesome in PD patients than th ose with narcolepsy because of relatively advanced age and possible interaction with other medication. If further studies were undertaken with modafinil in PID, then lower doses may achieve clinical responses without deleterious effects.

P744
USE OF BETA-CIT SPECT SCANS IN THE DIFFERENTIAL DIAGNOSIS OF ATYPICAL TREMOR. K Bhattacharya, A Cluckie, M Buxton-Thomas, MTM Hu, K Ray Chaudhuri. London, UK

Considerable confusion may occur in predicting whether patients with atypical tremor (postural and resting tremor associated with mild bradykinesia ± alcohol sensitivity) have Parkinson's disease (PD) or essential tremor (ET). Methods: Eleven patients with atypical tremor (initial diagnosis of probable ED (7) and PD (4)) were scanned using beta-CIT SPECT and clinically evaluated by two neurologists at 6 month intervals for 24 months. SPECT scans were performed with regions of interest (ROI) over the striatum and cerebellum. Results were evaluated by a blinded observer and correlated with final clinical outcome at two years. Results: Beta-CIT ratios were intermediate in the atypical tremor group (4.85 ± 1.05; our parkinsonian range 2.2 ± 1.1, normal range 8.5 ± 1.6). Four patients (mean beta-CIT ratio 3.9 ± 0.62) initially mis-diagnosed as ET had a final diagnosis of tremulous PD. The rest (beta CIT ratio 5.45 ± 0.85) were finally diagnosed as ET on the basis of CIT results and clinical profile. Conclusion: Beta-CIT SPECT scan is widely available and can be a useful supportive tool in the prognosis of atypical tremor disorders and prediction of development of parkinsonism.

P745
BOTULISMUS TOXIN-A APPLICATION IN HEMIFACIAL SPASM. Ozkan Mustafa, Kesken Serdar, Zorlu Yasar, Izmir-Turkey

There is a lack of in neurology practice especially related with the movement disorders treatment for many years. Classical treatment methods

couldn't provide any improvement in this kind of patients' daily life. Since Botulismus Toxin-A, has been used there is an important clinical improvement exists. We used BotulismusToxin-A treatment on 35 Hemifacial Spasm (HFS) cases in Social Security Hospital, Tepecik-Izmir Neurology Department.There was 23 female and 12 male cases. Mean of the ages of all cases was 50.4 (ranged-34-70). Beginning period of the disease was differentiated between 8 months to 22 years. All of the cases couldn't get any profit by wellknown classical treatments. We did computerized tomographie and magnetic resonance imagining investigations for all cases. Findings was neuroradiologically normal. After that, we did pre-injection electromyographic eveluations.We inticated that treatmnet period as six months. We applied Botulismus Toxin-A (Botox- A Flakon, 100 U) according to clinical condition, usefulness of treatment and complications. We called back all cases for regular control every months. We evaluated amounth of clinical improvement with Jankovic Disability Rating Scale. We injectedBotox-A 10-40 U for every injection (Dilution ratio, 12.5 U / ml). Results eveluated by semi logaritmic regression modal analysis: Improvement in clinical condition and disability was related with the using of the HFS and usefulness of HFS.

P746
REPETITIVE HAND MOVEMENTS FOR VISUALIZATION AND QUANTIFICATION OF MOVEMENT DISORDERS IN PARKINSON'S DISEASE. Polzer UF, Hundt H*Department of Neurology, Center of Parkinson's disease, Landesfachkrankenhaus Stadtroda, Stadtroda, Germany. *University School of Medicine Benjamin Franklin, Department of Neurology, Berlin, Germany

The most characteristic manifestation of Parkinson's disease (PD) is the impairment of voluntary movement. The reduction (hypokinesia) and slowness of movement (bradykinesia) can be observed particularly in repetitive hand movements (RHM). Methods: RHM of diadochokinesia, extension/flexion of the wrist and fingertapping for large (l) and small (s) targets were measured of both hands before (t1) and one hour after (t2) a single dose of 100 mg L-Dopa/ 25 mg Benserazid was given to 37 Parkinson patients (mean duration = 5,2 years; average age = 66,5 years; 16 hours without specific Parkinson medication). Using an ultrasound-based 3-D-measuring device (Zebris) it was possible to register and analyse the RHM qualitatively and quantitatively. In qualitative analyses track/time plots and angle-velocity/time diagrams were applied. For quantitative analyses the measurements of maximum velocity at t1 and t2 were compared with the Wilcoxon Test. Results: All above mentioned RHM showed an explicit harmonization of movement at t2 compared to t1. The maximum velocity measured in all RHM revealed a significant improvement at t2 in both hands: fingertapping (l):more affected side (mas) p=.0000, less affected side (las) p=.0001 fingertapping (s):mas p=.0000, las p=.0000; diadochokinesia:mas p=.0004, las p=.013; extension/flexion:mas p=.0001, las p=.00035; Discussion: A definite effect of medication on all RHM in PD could be demonstrated. The fingertapping, diadochokinesia as well as the extension-flexion of the wrist are suitable for visualization (qualitative analysis) and quantification of movement disorders in Parkinson's disease. Further experiments will evaluate the effect of L-Dopa in subclinical stages of PD.

P747
VOLTAGE-GATED NA^+ CHANNEL INHIBITION AS A STRATEGY FOR NEUROPROTECTION AND FOR THE PREVENTION OF DYSKINESIAS IN PARKINSONISM. M. C. Obinu, M. Reibaud, V. Blanchard, S. Moussaoui, A.Imperato* Rhone-Poulenc Rorer, 94403 Vitry sur Seine, France

Impairment of energy metabolism appears to be a common feature both in neurodegenerative diseases as well as in aging processes. There is evidence that the aetiology of Parkinson's disease could be associated to an oxidative stress-mediated disturbance in complex I of the electron transport chain leading to a bioenergetic defect which may predispose neurons to premature death. The aim of the present study was to investigate whether down modulation of Na^+ channels, involved in regulating neuronal activity and energy utilization could be of relevance for neuroprotection. In order to study this hypothesis we used Riluzole, which is a Na^+ channel blocker with preferential activity on its inactivated conformation. Riluzole was administered to marmosets in which Parkinson's disease was induced by the mitochondrial toxin MPTP. The protocol was as follows: MPTP (2 mg/kg s.c.) was injected in two doses 6 days apart, and Riluzole was given orally for 4 weeks (10 mg/kg, b.i.d.) starting from the first day of MPTP. Riluzole improves both the neurological and locomotor activity in these marmosets. The histological examination showed that Riluzole protects the dopaminergic neuronal cell bodies of the substantia nigra. In a second study we observed that Riluzole given to parkinsonian marmosets, together with the initiation of a high dose L-DOPA therapy (25 mg/kg, t.i.d.), markedly reduces the appearance of dyskinesias. These results support the concept that inhibition of neuronal Na^+ channels by reducing neuronal excitability and energy demand could help neurons to survive in conditions of defective energy supply, as in the case of neurodegeneration in Parkinson's disease.

P748
VOLTAGE-GATED Na^+ CHANNEL BLOCKADE IMPROVES PARKINSON'S DISEASE SYMPTOMS THROUGH A "NEUROPROTECTIVE" AND NOT THROUGH A "DIRECT SYMPTOMATIC" EFFECT. M. Reibaud, M. C. Obinu, M. Mazadier, A. Imperato* Rhone-Poulenc Rorer, 94403 Vitry sur Seine, France.

The aim of the present study was to exploit the interest of Na^+ channel modulation as therapy for Parkinson's disease. We used Riluzole, a Na^+ channel blocker with preferential activity on its inactivated conformation. Riluzole reduces neuronal excitability, energy demand and also attenuates the release of several neurotransmitters including glutamate which has shown to be involved in the symptoms of Parkinson's disease. We designed two different protocols, one aimed at the investigation of its eventual neuroprotective action and the second at the evaluation of its eventual "pure symptomatic" effect in parkinsonian marmosets. The assessment of neuroprotection has been extensively described in the abstract of Obinu et al. Briefly, Riluzole, given orally for 4 weeks (10 mg/kg, b.i.d.) starting from the first day of MPTP, has been found to protect dopamine neurons with beneficial consequences on Parkinson's disease symptoms. In the second protocol, Riluzole was studied in marmosets with stable parkinsonian symptoms by receiving MPTP at the dose of 2 mg/kg s.c. over 5 months (11 injections). Riluzole was administered for the first time 5 weeks after the last MPTP injection when regular neurological and motor assessment had ensured stable Parkinson's disease symptoms. Riluzole (10 mg/kg p.o., given b.i.d.) did not improve significantly the behavioral deficits of the parkinsonian marmosets during the four weeks of treatment, as evaluated by neurological and locomotor assessments. These results show that Riluzole has no symptomatic effect when administered to parkinsonian marmosets with stable long standing disease and also they reinforce the hypothesis that the behavioral improvement observed in the previous study is a consequence of the neuroprotective effect of this drug.

P749
SELEGILINE MODULATES NITRIC OXIDE AND PEROXYNITRITE PRODUCTION BY POLYMORPHONUCLEAR LEUKOCYTES IN PARKINSON'S DISEASE. EM Gatto, NA Riobó, MC Carreras and JJ Poderoso. Laboratory of Oxygen Metabolism, University of Buenos Aires, Buenos Aires, Argentina.

Selegiline is a selective monoamine oxidase type B inhibitor that delays the progression of Parkinson's disease (PD) and spares levodopa dose. The finding of tyrosine nitration in Lewy bodies supports a role of nitric oxide ($^{\cdot}NO$),and its byproduct peroxynitrite ($ONOO^-$),in the pathogenesis of PD. In accord,selegiline protects dopaminergic cells from apoptosis induced by $^{\cdot}NO$ and $ONOO^-$. We previously reported an increased $^{\cdot}NO$ and hydrogen peroxide (H_2O_2) production rates by phorbol-12-myristate-13-acetate (PMA) activated polymorphonuclear cells (PMN) from PD patients. The objective was to study the $^{\cdot}NO$ and H_2O_2 production rate and protein tyrosine nitration in PMN from 5 PD patients before and after 1 month of 10 mg/day selegiline intake and 10 age matched controls (mean±SEM 49.8±1 vs. 50±1 years). $^{\cdot}NO$ was measured by oxymyoglobin oxidation and H_2O_2 by fluorometric assay. Selegiline decreased the previously enhanced $^{\cdot}NO$ and H_2O_2 production of PMA activated PMN from PD patients ($^{\cdot}NO$: PD 0.89 ± 0.09*;PD + selegiline 0.63 ± 0.09,controls 0.56 ± 0.09;H_2O_2: PD 4.25 ± 0.17*,PD + selegiline 2.5 ± 0.17,controls 3.15 ± 0.47; * $p < 0.05$) as well as the augmented tyrosine nitration,as determined by Western blot. These results suggest that neuroprotection by selegiline could be related to a diminished $^{\cdot}NO$ and $ONOO^-$ production.

P750
SPORADIC ACETAZOLAMIDE RESPONSIVE EPISODIC ATAXIA. Thomas A, Paci C, D'Andreamatteo G, Melchionda D, Toma L, Onofrj M. Department of Oncology and Neuroscience, University "G.D'Annunzio" Chieti, Italy

Acetazolamide Responsive Periodic Ataxias mostly occur as dominantly inherited "familial" conditions, in which affected individuals experience attacks mainly consisting of gait ataxia and dysartria often brought on by physical or emotional stress, without neurological abnormalities between attacks. This rare disorder is depicted as "often unrecognised". Most reports describe families from the United States, Canada and France, only three cases were recently described in the British Literature. Sporadic forms of Acetazolamide Responsive Periodic Ataxia are even rare, and in our review of the literature we could find only 4 sporadic patients descriptions, 4 of whom had also electroencephalographic abnormalities. We describe in this report one further patient affected by repeated attacks of ataxia and dysartria, that we could document on videotape, who responded to Acetazolamide therapy, who had normal MRIs, EEG and normal laboratory examinations.

P751
PALLIDO-PYRAMIDAL DISEASE: CLINICAL, NEURORADIOLOGICAL AND POSITRON EMISSION TOMOGRAPHY STUDY. C Dupel-Pottier, P.-F Pradat, L Lacomblez, F Salakas, I Bonneau, M.-J Ribeiro, P Remy, Y Samson and V Meininger. Paris, France

The association of pyramidal signs and of a dopa-responsive parkinsonian syndrome in a young patient with consanguinity in the parents is characteristic of the pallido-pyramidal disease (PPD). Only 14 cases have been previously reported. We report here a new case of a 28-year-old man, with consanguinity in his parents, who progressively developed a spastic paraparesis and dysarthia. Few years later appeared a global bradykinesia and a rigidity involving both upper and lower limbs. The patient also complained of a resting, static and intention tremor affecting mainly upper limbs. Seven years later, clinical examination showed a pyramidal spasticity of lower limbs without weakness, pseudo-bulbar palsy and parkinsonian symptoms. Neuropsychological tests disclosed signs of frontal dysfunction. Cerebral IRM revealed a frontal atrophy. Parkinsonian syndrome was dopa-responsive. A Fluoro-dopa positron emission tomography (PET) study to this patient revealed a marked dopaminergic devervation of the striatum, which confirms that PPD corresponds more to a nigropallidopyramidal dysfunction. We also performed the first flumazenil PET study in PPD. Interestingly, it demonstrated a marked neuronal loss in the frontal lobe (bilateral premotor areas, right frontal operculum and medial frontal gyrus). These findings suggest that a cortical degeneration, involving the frontal lobe, can also be present in PPD.

P752
MCLEOD SYNDROME PRESENTING AS CHOREA-ACANTHOCYTOSIS: CLINICAL, HISTOLOGICAL AND MOLECULAR STUDY OF A NEW CASE. Dotti MT, Rubio JP*, Battisti C, Malandrini A, Monaco AP*, Federico A. Unit of Neurometabolic Disaeses, University of Siena, Italy. *Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, England, UK.

We report a 56-year-old man with adult onset progressive neurological picture caractherised by generalized choreic movements, orofacial dyskinesia, and mild psychic disturbances presenting at the age of 42. Acanthocytosis and persistent muscle creatine kinase elevation were detected. Electrophysiological study showed peripheral neuropathy. Neuromuscular biopsy evidenced mild axonal neuropathy and significant myopatic abnormalities. The Kell blood group examination on erythrocytes disclosed a weak expression of Kell antigens. Bilateral signal abnormalities of the caudate nuclei were evident at MRI. Molecular genetic study showed that the patient had a point mutation C→T at position 479 of the DNA sequence which results in the formation of a truncated XK protein which would be non-functional. Clinical and molecular studies indicate that our patient suffers from McLeod syndrome, a rare X-linked disorder involving neurological defects and acanthocytosis. We suggest that McLeod syndrome may be considered in the differential diagnosis of late onset psychiatric disturbances and involuntary movements.

P753
DEVELOPMENT OF A STRIATAL CELLULAR SYSTEM TO INVESTIGATE THE ROLES OF MUTANT AND WILD-TYPE HUNTINGTIN, THE GENE CAUSING HUNTINGTON'S DISEASE. D. Rigamonti, E. Barbaria, C. De-Fraja, L. Conti, S. Govoni[1], E. Cattaneo. Inst. Of Pharmacological Science Univ. Milano,Via Balzaretti 9 MI; [1]Inst.Pharmacol., PV and IRCCS S.Giovanni Dio, BS., Italy.

Huntington's Disease (HD) is an hereditary neurodegenerative disease resulting in a selective neuronal loss prominent in the striatum. The defective gene is characterized by an unstable CAG repeat encoding for a polyglutamine sequence. The number of CAG repeats is polymorphic in the normal population (between 9 and 35 units) and is observed to be of larger size (between 36 and 250) in patients affected by HD. The mechanism of cell death and the functions of either the normal or the mutant huntingtin, which have an ubiquitary pattern of expression, are still unknown. Cellular models of HD would greatly assist this analyses. Striatal derived conditionally immortalized ST14A cells (Cattaneo and Conti, Journal Neurosci. Res., 1998) have beeen transfected with various constructs containing different portions of the HD protein in the wild-type (20-28 CAG) and in the mutated form (80-128 CAG). Immunocytochemistry and Western blot analyses on the different stable clones isolated revealed the presence of the exogenous protein. Expression was mantained over time. To analyse the effect of the normal and mutant *huntingtin* we performed growth curves and survival assays after apoptotic stimuli. We found that clones expressing mutant *huntingtin* are more susceptible to cell death compared to parental and wild-type expressing cells. DNA laddering analyses in the same conditions confirmed the above findings. This cellular system is therefore suitable for the syudy of the mechanisms underlying HD and represents an interesting model for the assessment of different therapeutics preventing the neurodegeneration (supported by the Huntington's Disease Society of America and the Hereditary Disease Foundation, USA to E.C., Telethon)

P754
BLOOD PRESSURE MONITORING AND NOREPINEPHRINE (NE) LEVELS IN PARKINSONIAN PATIENTS LONG TERM TREATED WITH SELEGILINE. R.Stryjer,C. Klein,T. Prokhorov,J.M. Rabey-Assaf Harofeh Medical Center - Zerifin

Selegiline (SEL) an irreversible MAO B inhibitor has been largely utilized in Parkinson disease (PD) due to its beneficial therapeutic effect and possible protective ones. However, recently it was reported that SEL may be a risk factor for sudden death in PD patients. (PDpts) (BMJ, Jun, 95).In the present study we tested the effect of SEL (10mg/day) chronic treatment on blood pressure and NE plasma levels in PD pts. The study group included: a) 10 PD pts randomly selected treated chronically with Levodopa (group D) (mean age 63.9, 7 males). b) 10 pts randomly selected treated chronically with sel + Levodopa (group S) (mean age 57.1, 7 males) c) 8 healthy controls (CTRL) (mean age 49.1, 6 males). They were examined in the morning (12 hours off medication). The examination included blood pressure and pulse measurements, obtained while they laid down for 5 minutes and at 1, 3 and 5 min. after standing. The procedure was repeated 90 minutes later after taking 5mg sel +125 Levodopa (group S) or 125 Levodopa alone(group D). Blood was obtained for plasma NE determinations at each time.(HPLC procedure). RESULTS: 5 out of 10 pts from group S showed postural hypotension, (one was symptomatic); 3 out of 10 patients from group D had asymptomatic postural hypotension; 3 out of 8 patients from CTRL group had asymptomatic postural hypotension. NE levels after standing (no medication) increased by 211% (group S), 212% (group D) and 253% (CTRL). NE levels after standing (90 minutes after treatment) increased by 266% (group S) and 182% (group D). In summary, the results obtained, suggest that PD pts treated chronically with sel may suffer from increased episodes of orthostatism which might be symptomatic. In addition those pts after standing, showed increased NE release which may be a compensatory mechanism trying to overcome postsynaptic sub-responsive adrenergic receptors. Those receptors may be sub-responsive due to increase levels of peripheral NE (secondary to chronic sel treatment).

P755
AN AMBULATORY DYSKINESIA MONITOR.AJ Manson, P Brown, J O'Sullivan, P Asselman, D Buckwell, AJ Lees.National Hospital for Neurology and Neurosurgery, and MRC Human Movement and Balance Unit, Queen Square, London, UK.

We have developed a portable device based on a triaxial accelerometer and data recorder that can record levodopa-induced dyskinesias at home. A computer programme plots the time varying acceleration profiles over 0.5 Hz bands for a given time period throughout the day. The frequency varying acceleration profiles can be compared with the raw data trace for verification. This method enables the identification and exclusion of confounding activities such as tremor and walking. We assessed the validity of this device on 13 patients and 8 age-matched controls by comparing it with established clinical rating scales. Whilst wearing the monitor, sub-

jects were videorecorded sitting and during dyskinesia provocation tasks, including mental activation tasks, eating, drinking, writing, putting on a coat, and walking. The dyskinesias were graded with both modified AIMS and Goetz scales. The clinical ratings were then compared to the mean acceleration scores in the 1-3 Hz frequency bands. All tasks correlated well for acceleration against both scales. Walking correlated least well and produced large accelerations, even in controls. With walking excluded, the mean acceleration over the rest of the recording time correlated strongly against both the modified AIMS (Spearman-rank rho=0.972, $p < 0.001$) and Goetz (rho = 0.951, $p < 0.001$) scales. Acceleration produced by normal voluntary activity was small compared to dyskinetic activity. This method provides an accurate, objective means for dyskinesia assessment.

P756
CLINICAL AND [^{18}F]DOPA PET STUDY OF 3 CASES WITH JUVENILE PARKINSONISM. Broussolle E., Ginovart N., Pollak P., Remy P., Durr A. CERMEP and Hôpital Neurologique, Lyon; Hôpital Nord, Grenoble; SHFJ, Orsay; France.

Juvenile parkinsonism (JP) is a rare entity of levodopa-responsive parkinsonian syndrome starting at age 20 or below. Family cases of autosomal recessive-juvenile parkinsonism (AR-JP) have been reported. The heterogeneous presentation and etiology of JP is debated, particularly as referred to adult-onset Parkinson's disease (PD) and Dopa-responsive dystonia (DRD). We present 3 cases of JP with positron emission tomography (PET) measure of striatal [^{18}F]Dopa uptake. Age at onset was 13-17 years, and age at inclusion was 20-47. Patients had 2/3 of akinesia, rigidity and tremor, no exclusion criteria at step 2 of the UKPDSBB and positive and sustained response to levodopa. One case had a sister with Dopa-resonsive PD and another case a dystonic posture of the trunk. None had diurnal fluctuation of signs before treatment. At the time of study, patients had moderate to severe levodopa-induced motor fluctuations. Striatal PET [^{18}F]Dopa uptake Ki was dramatically reduced down to 28% and 44% of control subjects values (n=7) for putamen and caudate respectively. In summary, most of clinical and PET diagnostic criteria of adult-onset PD are found in our 3 JP patients. PET makes easy the differential diagnosis with DRD were [^{18}F]Dopa uptake is reported to be normal. Molecular biology is currently under way to determine whether these 3 JP cases have mutations in the Parkin gene, as recently described in familial AR-JP.

P757
HUNTINGTON'S DISEASE COGNITIVE BATTERY (HDCB): A 20 MINUTE NEUROPSYCHOLOGICAL BATTERY FOR THE ASSESSMENT OF HUNTINGTON'S DISEASE. Roberto Monastero, Marco D'Amelio, Carmela Pipia, Roberto Cammalleri, °Alessandro Padovani, Domenico Raimondo, Cecilia Camarda and Rosolino Camarda. Neurologic Clinic II, Palermo, Italy; °Neurologic Clinic, Brescia, Italy.

The Unified Huntington's Disease Rating Scale (UHDRS) was recently developed as a clinical rating scale to assess six domains of clinical performance and capacity in HD: motor function, behavioural abnormalities, functional assessment and capacities, independence scale and cognitive functions. We perform a wide battery of neuropsychological tests in 13 HD patients and 13 age, sex, and education matched controls in order to detect which test better correlates with other five domains of the UHDRS and to define a simple, rapidly, cognitive battery in Italian for HD. The HD diagnosis was assessed basing on the UHDRS and definitely confirmed by CAG length repeat sequence at the 5' end of the IT15 gene. The battery includes tests for the evaluation of cognitive general deterioration, language, verbal and visuo-spatial memory, selective and divided attention, executive functions, calculic functions, apraxia and visuospatial abilities. By a regression analysis the tests highly correlate with the motor, behavioural, functional assessment and capacity and independence sections of UHDRS are the Raven Coloured Progressive Matrices (p from.01 to.00002) the Visual Retention Test Copy (p from.01 to.006), the Trial Making B (p from.01 to.00006), and the Category Fluency (p from.01 to.002). None of these tests are included and recommended to use in the UHDRS. Therefore, we suggest to use the HDCB which in a time of around 20 minute is able to detect cognitive impairment in HD patients.

P758
THE EFFECT OF NEUROSTIMULATION ON REACHING AND CATCHING IN PATIENTS WITH PARKINSON'S DISEASE. B.Baur, T.Schenk, N.Mai, K.Bötzel. Munich, Germany

Majsak et. al. (Brain, 1998, 12, 755-766) recently confirmed that bradykinesia in patients with Parkinson's disease (PD) disappears when they reach for a moving object rather than a stationary object. This phenomenon is assumed to be caused by moving targets activating a cerebellar motor circuit that bypasses the impaired basal ganglia pathway. If this is true, we would predict that stimulating the basal ganglia in PD patients should ameliorate reaching for static but not for moving objects. The reaching kinematics of healthy controls and a group of PD patients with electrodes implanted in the internal segment of the globus pallidus were analyzed. Reaching performance was quantified by peak velocity. Subjects were required to grasp an object that was moved within the horizontal plane at different velocities (between 0.25 and 1.00 m/s) by two linear motors. In addition, subjects had to grasp a stationary object. PD patients performed all tasks without medication but with neurostimulator on and off. All patients showed clear signs of bradykinesia with the stationary target. These were clearly reduced by neurostimulation. Under the condition with moving target reaching velocity was twice that of stationary reaching, but the neurostimulator had no effect. The finding that neurostimulating the basal ganglia in PD patients affects movement speed when reaching for stationary but not for moving objects provides evidence that these two kinds of movements are subserved by different neuroanatomical pathways.

P759
INTERRATER RELIABILITY OF THE UPDRS MOTOR SCORE IN AN INTERNATIONAL MULTICENTRE TRIAL. Althaus, Michael, Jörg, Johannes for The European DHEC Study Group. Desitin Arzneimittel GmbH, D-22335 Hamburg, Germany

The efficacy and tolerability of -dihydroergocryptine (DHEC, Almirid®), a novel dopamine agonist, was investigated in 166 patients suffering from Parkinson's Disease with motor fluctuations in a 6-month, double-blind, placebo-controlled, international multicentre study. Changes in on/off time and the Unified Parkinson's Disease (UPDRS) motor score were the primary outcome variables in this trial. The participating centres showed a substantial heterogeneity. A rater training was performed at the investigator's meeting prior to the start of the study to ensure the quality of the study data. In order to assess the interrater reliability, every investigator was asked to rate a video examination of 4 patients representing mild, moderate, moderate to severe and severe stage of the disease (published by Goetz et al, Mov Disord 1995; 10:263-266). 23 centres from 10 countries (Scandinavia, Central and Eastern Europe) participated in this trial. 94 % (n = 46) of the investigators completed the test. Agreement among the raters for the 22 items of the UPDRS motor score (excluding rigidity) was assessed for each of the 4 patients using Kendall's coefficient of concordance (W). Further, interrater reliability of the total scores was calculated. Descriptive statistics were used to compare the results with those published by Goetz et al. The rate of agreement for the total scores was very high ($W = 0.99$, $^2 = 136.83$). The rate of agreement for the 22 items of the Motor Score ranged from fair to good (patient No 1: $W = 0.45$; patient No 2: $W = 0.71$; patient No 3: $W = 0.81$; patient No 4: $W = 0.58$). The results were all significant (Asymp. Sig < 0.001) and within the published range. 50 % of the raters made their assessment in at least 3 of the 4 patients within interquartile ranges. Comparison of the means, 95 % C.I. and interquartile ranges with the results as published by Goetz et al. showed a good correspondence. Despite considerable differences in culture, economics, health systems and medical standards in the 10 countries, the investigators participating in this trial showed a high rate of agreement in their assessment of the UPDRS motor score. Our investigation corroborates the utility of the UPDRS teaching tape for the assessment of the interrater reliability in international studies and demonstrates the quality of the study data.

P760
PORTO-SYSTEMIC SHUNT WITH BASAL GANGLIA MR LESIONS: DESCRIPTION OF TWO CASES. (M Coletti Moja, L Ambrogio, L Gozzoli*, PC Gerbino Promis, U Dimanico, F Perla, P Meineri, MG Rosso, C La Piana and E Grasso; Department of Neurology and Neuroradiology*, S. Croce Hospital, Cuneo, ITALY)

Hyperintense basal ganglia on T1-weighted MR (Magnetic Resonance) sequences is a described finding in patients affected by liver cirrhosis. This signal alteration was correlated with the severity of liver failure and Portal-Systemic Shunt (PSS), but its origin and clinical significance is unsettled. MR changes may reflect subclinical encefalophaty prior to the onset of neurological symptoms. We describe two patients who underwent PSS. A 68 years old man underwent Trans-jugular Intra-hepatic Porto-systemic Shunt (TIPS) to treat severe liver cirrhosis and portal hypertension; 4 years

later he developed a parkinsonian syndrome with MR brain lesions; he started L-DOPA 250 mg daily improving rigidity and akinesia but after 1-2 years choreo-athetosis, hypotonia and oral-facial dyskinesias appeared so that L-DOPA was tapered and Haloperidole 1,5 mg daily was therapeutic to movement disorders control. The second patient is a 20 years old female who underwent a PSS; MR was performed to detect the cause of a hypothalamic-hypophyseal axis impairment and while neurological examination and liver function tests were normal, MR images showed subcortical hyperintense lesions. It is supposed that MR lesions could be due to a PSS and TIPS role in neurotoxic substances release, like Manganese, which tend to accumulate in basal ganglia areas; its onset time from surgical setting is still to be cleared so that a careful patient clinical and MR follow-up is suggested.

P761
PALLIDAL ELECTROSTIMULATION IN PARKINSON'S DISEASE: A SPET ACTIVATION STUDY. K. Van Laere, P.Santens, C. Van Der Linden, V. Vandewalle, P. Lahorte, J. De Reuck, R. Dierckx. Departments of Neurology, Neurosurgery and Nuclear Medicine, University and University Hospital of Gent, Belgium

High-frequency stimulation of the internal pallidum has recently been advocated as a potential treatment in advanced Parkinson's disease. It has demonstrated beneficial effects on motor symptoms, especially L-DOPA induced dyskinesia. Objective: To describe the changes in cerebral perfusion following acute pallidal stimulation and to correlate these changes with the well-known clinical effects. Methods: Ten patients were included. The mean age was 54 years and the mean post-operative time-interval was 2.2 months. A single-day split-dose study was performed before and immediately after starting the deep brain stimulation. The images were analyzed using Brass pixel-by-pixel analysis and Statistical Parametric Mapping, both after reorientation for identical electrode implantation side and co-registration to a normal template. Results: Following pallidal stimulation a decreased perfusion was found in the thalamus bilateral, the ipsilateral sensorimotor cortex and bilateral parietal cortex. Increased perfusion was found in the contralateral cerebellar hemisphere. Conclusion: Mainly deactivation patterns were found following pallidal stimulation. The thalamic and sensorimotor cortex deactivation might correlate with the alleviation of dyskinesia and the well-described increase of akinesia during on-phases in some patients with pallidal stimulation.

P762
EKBOM'S SYNDROME AS ONSET OF HUNTINGTON'S DISEASE. T Cuomo, L Di Maio, G Napolitano, G De Michele, Naples, Italy.

Huntington's disease (HD) is an autosomal dominant degenerative disorder clinically characterized by abnormal involuntary movements, cognitive impairment and psychiatric manifestations. Psychiatric symptoms are well recognized in HD and include schizophrenia, depression, paranoia, suicide and personality changes (alcoholism and criminal behaviour). The prevalence rate of psychiatric symptoms in HD varies widely (36-81%). Ekbom's syndrome (ES) or parasitophobia, "delusion of animal life in the skin", is a syndrome characterized by the patient's belief to be infested. ES has been described in some neurological disorders such as Alzheimer's disease, brain tumors and cerebral infarction. Morris et al (1996) reported three out of 800 patients who in the course of HD presented ES. We describe a 44 year old woman who presented ES as onset of HD at age of 31 years. She had a 8 year history of delusion of infestation by worms and ants which caused scratching, especially at the upper limbs. She also presented auditory and visual hallucinations (she heard voices and talked to her deceased brother). Treatment with pimozide at the dosage of 8 mg daily markedly improved the psychiatric symptoms. IT15 mutation analysis showed a peculiar genotype with an expanded allele (45 triplets) and the other one in the intermediate range (33 triplets).

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WHICH FEATURES MAKE A NEUROLOGIST CONSIDER SURGERY FOR TREATMENT OF PARKINSON'S DISEASE? Rosa, MM., Sampaio, C., Coelho, MH., Ferreira, JJ., Levy, A., Castro-Caldas, A. Neurology Department of Santa Maria Hospital, Lisbon, Portugal

Surgical advances in the treatment of Parkinson's Disease (PD), have not been followed by guidelines to direct neurologists through the several options available from surgical and non surgical treatment. In this study we prospectively evaluated the clinical and practical features of a PD population to assess which factors influence this decision. Methods: From September to November 1998, all consecutive and non duplicate Parkinsonian patients (pts) observed in our outpatients' clinic were evaluated for 1) past history; 2) presence, type and severity of complications of PD; 3) performance when ON-phase; 4) present drug history; 5) cognitive impairment; 6) co-morbidity; 7) "easiness" of medical treatment and reasons for clinical miscontrol; 8) type of suggested surgery (target and lesion or stimulation) when applicable. The main objective was the characterisation of the PD pts considered amenable for surgery among the studied sample, and the features more frequently expressed among those. The secondary objective was the assessment of the homogeneity of criteria among the 6 experienced PD clinicians. Results: One hundred and forty four (73 males, 71 females) consecutive PD pts have been analysed at this moment. Of these, 12 (4 males, 8 females) have been considered amenable for surgery. There are several differences between the "surgery" and "nonsurgery" pts: "surgery" pts had younger onset (50.7 vs 59.9 years), earlier onset of complications (2.58 vs 7.7 years after beginning complaints), presence of motor fluctuations and dyskinesias (67 vs 55%), daily LDOPA intake (621 vs 460 mg) and were bilateral (83 vs 59%). No single investigated factor was a sure predictor for surgery: even the difficulty in managing or intolerance to drugs were not significantly different. Living far from the hospital, having important cognitive impairment and bad compliance to medical therapy were the only features absent on the surgical pts and present in some non surgical pts. Conclusion: These preliminary results show that in our sample, 8% of the observed patients were considered to benefit from a surgical treatment in the near future. Differences between groups were detected, being the precocious presence of PD complications the most striking. We found no predictor for "surgery", and at most, three factors caused exclusion for "non-surgery" pts.

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USEFULNESS OF APOMORPHINE SUBCUTANEOUS INFUSION FOR ACUTE PSYCHIC DISTURBANCES IN Parkinson's Disease. Vanderheyden J.-E. Neurology Department, Parkinson Unit. CHU - Vesale - B - 6110 Montigny-Le-Tilleul (Belgium)

The author reviews 17 consecutive hospitalisations for acute psychic disturbances in Parkinson's Disease (hallucinations, delirium or psychosis). The patients were treated by continuous subcutaneous Apomorphine infusion and progressive decrease of dopatherapy. Apomorphine (10 mg/cc) were delivered in the abdominal wall by a Deltec pump (24 h/day) at a rate of 0,5 to 4 mg/h according to tolerance and efficacy during 1 to 2 weeks. The features of the 17 patients are the following: Age when starting Apomorphine: 71.4 y. 6,6 (59- 82); Duration of the disease: 12.5 y. 6.2 (6 – 29); Duration of the motor fluctuations: 4.5 y. 2.2 (1 - 9); ADL and Hoehn and Yahr score before Apomorphine: 33.2 % 9,5 (10 - 50); 3.8 0.3 (3 - 4); Mean rate of Apomorphine: 1.8 mg/h 0.9 (0.5 - 4). We have encountered significant side effects in 50 % of the patients including 1 worsened akinetorigid state, 2 cases of non transient nausea, 1 case of evening hallucinations and 3 moderate to severe subcutaneous nodules. Transient nausea have been unfrequent, weak and easily treated by domperidone. The efficacy has been good to excellent concerning mentation and thought in 90 % of cases (except in demented) with a global increase of Hoehn and Yahr score (+ 0,5; N. S.) and ADL score (+11,3; $p < 0,02$). Dopatherapy has been decreased to 0 - 30 % (mean = 17 %) of initial dosage during minimum 2 weeks. We conclude that continuous Apomorphine infusion may be useful and well tolerated in Parkinsonians with acute psychic problems, especially in older patients that could untolerate other psychotropic treatments such as Clozapine.

P765
THERAPEUTIC EFFECT OF TRANSCRANIAL MAGNETIC STIMULATION ON PARKINSONIAN SYMPTOMS. Judit Málly, Erzsébet Hospital, 9400 Sopron, Hungary

Transcranial magnetic stimulation (TMS) has been used in the diagnosis of neurological lesions and has been introduced into the therapy of central nervous diseases. Lately it has been claimed that TMS would be useful not only in the treatment of depression, but also in relieving symptoms of Parkinson's disease. In this study we sought evidence of the effect of repetitive TMS on the symptoms of Parkinson's disease, the dose dependency between the applied elecromagnetic field and the Parkinsonian symptoms, and the maintenance of the improvement. Forty-nine patients with Parkinson's disease were divided into four groups each given one stimulus, repeated 30 times, once or twice a day ~0.34Tesla (T), ~0.57T, ~0.80T). Patients were followed for three months and assessed using two

different parkinsonian scales - the graded clinical rating scale and Unified Parkinson Disability Rating Scale - and with a short term memory test (Ziehen-Ranschburg word pair test). No effect was seen in the group treated with ~0.34T \ 30 stimuli once a day. In all of the groups receiving TMS twice a day the parkinsonian scores were significantly decreased compared with that of baselines after one month of treatment. The greatest improvement in the hypokinesia was detected in the group treated with ~0.57T \ 30 stimuli twice a day (baseline total UPDRS: 30.62 ± 15.23, one month after treatment: 17.08 ± 7.04, $p < 0.01$, three months after treatment: 16.08 ± 7.06, $p < 0.01$). A dose-dependent difference was observed between the two groups after three months. The total UPDRS in Group II (~0.34T \ 30 stimuli twice a day) significantly differed from Group III (~0.57T \ 30 stimuli twice a day) (22.43 ± 8.87, 16.08 ± 7.06, $p < 0.05$). The long-lasting improvement effect with TMS would seem to suggest it as an appropriate tool in the therapy of Parkinson's disease.

Multiple Sclerosis

P766
SCAPULA ALATA: TWO UNUSUAL CAUSES. Demarquay G, Grimaud J, Bouhour F, Confavreux Ch.Service de Neurologie, Hôpital de l'Antiquaille, Lyon, France

A 23-year old woman, with no previous medical or traumatic history, developed left shoulder palsy and a Lhermitte sign. Physical evaluation revealed an isolated *serratus anterior* muscle paralysis. Electromyography confirmed left thoracic nerve palsy. Cervical MRI showed a intraspinal C4-C5 hypersignal on T2-weighted images. Three years later, the patient presented a clinically definite multiple sclerosis. The diagnosis was confirmed by brain MRI and CSF analysis. A 42-year old man presented a progressive non systemic amyotrophia of the left upper, and right lower limbs. One year later, the first neurological examination revealed a right *scapula alata*. Electromyography showed persistent, multifocal, partial motor conduction blocks outside the usual sites of nerve compression and not in sensory nerves. A *scapula alata* could reveal both a multiple sclerosis or a multifocal motor neuropathy with blocks.

P767
MBP GENE POLYMORPHISM DISTRIBUTION AND HLA DR15 ASSOCIATION IN ITALIAN AND RUSSIAN MULTIPLE SCLEROSIS PATIENTS. F.R. Guerini, L. Losciale, D. Caputo, M. Cervellati, A. Boiko#, O. Favorova#, E. Gusev#, P. Ferrante*Don C.Gnocchi Foundation, IRCCS, *Chair of Virology LITA Sacco, University of Milan, Italy, #Dept of Neurology and Neurosurgery, Medical State University, Moscow, Russia.

The distribution of a Myelin Basic Protein (MBP) gene polymorphism, due to the presence of an highly repetitive sequence (TGGA)n has been studied in Italian and Russian Multiple Sclerosis (MS) patients and healthy controls (HC). Performing PCR and gel electrophoresis analysis from 1116 nt to 1540 nt located in a region 5' flanking the first exon of the MBP gene, three different band patterns were observed: one homozygous with a 354bp long fragment, one homozygous with a 424bp long fragment and one heterozygous with both bands present. Both in the Italian (112 MS, 266 HC) and the Russian group (138 MS, 127 HC) the short fragment was statistically more frequent in MS patients than in HC ($p < 0.05$). The long fragment was more present in HC. Nucleotide sequence analysis of the two fragments showed that the short fragment has a deletion of 70bp and two point mutations. The association of HLA DR15 and of the MBP 354bp allele was more common in MS cases than in controls both in the Italian ($p < 0.05$) and the Russian ($p < 0.05$) groups. Our data, obtained studying two distinct European populations, confirm that susceptibility to MS is under a polygenic control.

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COGNITIVE PATTERN IN PATIENTS WITH PRIMARY AND SECONDARY PROGRESSIVE COURSE OF MULTIPLE SCLEROSIS.H. Tribukeit U. Wachowius K. Schrecke,H.-J. Heinze, D. Pöhlau*, M. Sailer. Dept. of Neurology II,* Sauerlandklinik Hachen. Otto-von-Guericke-University, Germany

Patients with multiple sclerosis (MS) of primary (PPMS) and secondary (SPMS) progressive type present more frequently with cognitive deficits than MS patients with a relapsing remitting (RRMS) course of the disease. The present study evaluated the pattern of cognitive performance in the two different chronic progressive disease courses. Patients and Methods: We examined 33 patients with PPMS (18 male, 15 female) and 63 patients with SPMS (22 male, 44 female). The two groups did not differ in their degree of physical disability, age or education. The disease duration of SPMS patients was significantly longer. Neuropsychological evaluation included assessment of memory (digits forward and backward, Corsi Block-tapping Test; the Auditory Verbal Learning Test (VLMT), Benton Visual Retention Test), attention (Stroop-Test (FWIT)) and executive functions (verbal fluency and a screening category test (Kramer)). Results: The two groups did not differ significantly in the number of pathological tests. Significant difference in the neuropsychological performance between the MS subgroups was found only in the verbal learning capacity (VLMT). Specifically, there was no difference in the first trial, but in the subsequent trials the PPMS patients showed a significantly impaired learning. Conclusion: Our results indicate that populations of both types of MS patients comprise profound cognitive deficits, although we cannot confirm an overall significant difference between the two groups as shown in previous smaller studies. This variability may be due to the underlying pathological heterogeneity, i.e. the quality and amount of plaques in SPMS and the degree of axonal loss and atrophy in PPMS. The latter could account for more specific deficits such as impaired verbal learning.

P769
INCREASED BLOOD PLASMA CONCENTRATIONS OF TGF-β1 IN PATIENTS WITH MULTIPLE SCLEROSIS AFTER TREATMENT WITH IVIG.K. Schrecke, D. Reinhold*, E. Perlov*, S. Ansorge*, D. Pöhlau§, H.-J. Heinze, M. Sailer. Dept. of Neurology II and Institute of Experimental Internal Medicine*, Otto-von-Guericke-University, §Sauerlandklinik Hachen, Germany

Introduction: Immunomodulatory treatment constitutes the main therapeutic approach in multiple sclerosis (MS). There have been several controlled studies employing intravenous immunoglobulins (IVIg) reporting a reduction in relapse rate and some evidence of decreased MRI activity[1,2,3]. A recent study has shown that the powerful immunosuppressive cytokine TGF-β is present in substantial amounts in commercially available IVIg preparations[4]. In this study we wanted to assess whether TGF-β in MS patients is significantly increased after IVIg-infusion. Patients and Methods: Blood samples from 19 patients with clinically definite MS enrolled in a double blind placebo controlled IVIg study were collected and processed without breaking the blinding. The TGF-β1 concentration was measured using a specific TGF-β1-ELISA[5] before and after infusion with IVIg or placebo, respectively. Results: We found a significant increase in TGF-β1 serum levels in patients treated with IVIg (n = 11) from 6.4±1.78 ng/ml (before infusion) to 8.35±1.31 ng/ml (after infusion). We did not find significant change in TGF-β1 serum concentration in the placebo group (6.82±1.55 ng/ml and 6.61±1.83 ng/ml TGF-β1, respectively). Conclusion: Our results support the hypothesis that at least some of the effects of IVIg therapy in MS could be explained by the presence of TGF-β in IVIg and possibly could vary between different IVIg preparations. 1: Fazekas et al.; Lancet 1997 1; 349 (9052): 589-93; 2: Achiron et al.; Neurology 1998; 50: 398-402; 3: Sorensen et al.; Neurology 1998;50:1273-81; 4: Kekow et al.; Lancet 1998 17; 351 (9097): 184-5; 5: Danielpour et al.; J. Immunol. Meth. 1993;158: 17-25

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THE EFFECT OF TREATMENT WITH INTERFERON ?-1B ON GADOLINIUM ENHANCING MRI LESION VOLUMES IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS. Molyneux PD, MacManus DG, Barker GJ, Brex P, Fogg C, Gregory S, Lewis S, Middleditch C, Miller DH. NMR Research Unit, Institute of Neurology, Queen Square, London., UK

The recently published randomised, placebo controlled phase III trial of interferon β-1b (betaferon) in patients with secondary progressive multiple sclerosis (MS) confirmed a significant beneficial treatment effect on clinical outcome measures [Lancet 1998;352:1491-1497]. A number of MRI outcome measures were also assessed in the study, one of which, the gadolinium (Gd) enhanced MRI brain lesion volume, is reported here. Methods: A subgroup of 125 patients from 7 of the European Centres involved in the trial underwent monthly imaging over two scanning intervals, months 1-6 and 19-24, using a single dose (0.1 mmol/kg) of gadolinium and a T1 weighted sequence. MRI data was then transferred to the Central analysis centre. All Gd-enhancing lesions were identified on hard-copy and the volume of enhancing lesions was subsequently quantified using a semi-automated local thresholding technique. Results: A significant beneficial treatment effect was apparent even at one month post treatment

($p = 0.001$) and by six months the cumulative Gd enhanced lesion volumes in the placebo ($n = 58$) and treated ($n = 62$) group respectively were 1.8 and 0.8 cm^3 ($p < 0.005$). For the second frequent scanning period, the cumulative Gd enhanced lesion volume by month 24 in the placebo ($n = 49$) and treated ($n = 55$) groups respectively were 1.7 and 0.3 cm^3 ($p = 0.005$). Conclusions: Treatment with interferon β-1b results in a profound, significant and sustained effect on the volume of Gd enhanced brain lesions, supporting the concept of an anti-inflammatory therapeutic mechanism.

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THE IMPACT OF CONSENSUS GUIDELINES ON THE REPRODUCIBILITY OF VISUAL ANALYSIS OF SERIAL T2 WEIGHTED MRI IN MULTIPLE SCLEROSIS. [1]Molyneux PD, [1]Miller DH, [2]Filippi M, [3]Yousry T, [4]Radu EW, [5]Ader HJ, [5]Barkhof F- NMR Research Unit, Queen Square, London., UK; [2]Dept of Neurology, Hosp. S. Raffaele, Milan, Italy; [3]Dept of Diagnostic Radiology, Klinikum Grosshadern, Munich, Germany; [4]Dept of Neuroradiology, Kantonspital, Basel, Switzerland; [5]Free University Hospital, Amsterdam, The Netherlands

We have evaluated the effect of consensus formation and training on the agreement between observers in scoring the number of new lesions on serial T2 weighted MRI studies. Methods: The baseline and month 9 MRI studies of 16 multiple sclerosis (MS) patients with a range of MRI activity were used in this study (dual echo CSE sequence, TR 2000ms, TE 34 and 90ms, 5 mm contiguous slices, in-plane resolution 1mm). First, the serial studies were visually analysed for the presence of new lesions scored on two occasions by five experienced observers in isolation, without adopting any consensus strategy. Next, the observers met to identify the common sources of inconsistencies in reporting between observers and formulate consensus rules. Finally, a further independent reading session was performed on the same MRI dataset, this time applying the consensus rules. Results: Without the consensus rules, inter observer kappa scores for the first and second reading sessions for new lesions were 0.35 and 0.39 respectively. The mean intra observer kappa scores for new lesions was higher at 0.72, reflecting the fact that the observers were consistently applying their individual assessment strategies. Application of the consensus rules increased the inter observer kappas to 0.46. Conclusions: While consensus guidelines do improve the reproducibility of visual analysis of serial T2 weighted MRI, the level of agreement between observers is still only moderate. Sub-optimal repositioning is likely to be a major source of residual variability and this suggests a future role for image registration strategies.

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LONGITUDINAL EVALUATION OF METHODS FOR OPTIMISING DETECTION OF FOCAL CONTRAST ENHANCING LESIONS IN MULTIPLE SCLEROSIS. NC Silver, CD Good, GJ Barker, DG MacManus, DH Miller. NMR Research Unit, Institute of Neurology, University College London, UK.

By detecting focal blood-brain barrier breakdown, gadolinium (Gd-DTPA) contrast-enhanced T1-weighted MRI allows assessment of inflammatory activity in MS and, as such, provides a useful means of monitoring immunomodulatory therapies in phase 2 trials. We have carried out serial monthly studies in 8 relapsing-remitting and 8 secondary progressive patients to assess new optimised imaging methods. Brain and spine imaging was carried out at 1.5 Tesla on 2 occasions 24-72 hours apart using "conventional" (brain 7 minutes and spine 30 minutes following 0.1mmol/kg Gd-DTPA) and "optimised" imaging protocols (spine 30 minutes and MT-presaturated brain imaging 45 minutes following 0.3mmol/kg Gd-DTPA). For each, the total numbers of enhancing lesions (97 paired studies) and new enhancing lesions (81 paired studies) were assessed. Compared with conventional brain imaging alone, additional conventional spine imaging increased sensitivity of enhancing lesion detection by 28% (with 4% more active studies), optimised brain imaging alone increased this by 85% (with 6% more active studies) and a combination of optimised brain and spine imaging increased sensitivity by 129% (with 15% more active studies). For new enhancing lesions, such increases were 34% with additional conventional spine imaging (8% more active studies), 57% for optimised brain imaging alone (with 19% more active studies) and 102% for combined optimised brain and spine imaging (with 25% more active studies). For all comparisons, the increased number of enhancing lesions seen with optimisation was significant ($p < 0.0005$). In conclusion, a combined "optimised" brain and spine imaging protocol is most sensitive for detecting focal inflammatory activity in MS.

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DEPRESSION AND CYTOKINES IN MULTIPLE SCLEROSIS. E. Koutsouraki, V. Tsavdaridou, Th. Karapanagiotidis, Hr. Aggouridaki, D. Doubodias, St. Baloyiannis, Tessaloniki, Greece.

We examined the correlation between depression and cytokines among a group of 40 definite MS patients, all of whom had experienced recent significant disease activity and a control group matched closely and age and education. We used BDI, GHQ- questionnaire and Hamilton scale and we examined subtypes lymphocytes (especially CD+4/CD8+ ratio), IL-6, IL-6 receptors, IL-2, IL-2 receptors and anti-MAG antibodies. 48% of MS patients and 10% of healthy individuals showed depression. 95% of depressed MS patients and 43% of non-depressed patients showed abnormal values in one at least of the above mentioned immunological markers. Our results indicate that: depression is very common during clinical exacerbation of multiple sclerosis, there is an association between cytokines and depression during the exacerbation of multiple sclerosis.

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TUMOR NECROSIS FACTOR-α (TNF-α) AND INTERLEUKIN-10 (IL-10) CHANGES IN PLASMA, WHOLE BLOOD, AND SUPERNATANT OF MONONUCLEAR CELLS DURING THE FIRST MONTH OF BETA-INTERFERON-IA THERAPY. Paysant J, Chevallier F, Vasse M, Vannier JP, Soria C, Coquerel A. Neurobiology department, University Hospital, and Federal Research Institute N°61, 76031 Rouen, France.

The immunomodulator beta-interferon-Ia [β-IFN-Ia] (Avonex®, Biogen®) induces positive effects on relapsing-remitting forms of Multiple Sclerosis (RR-MS). During the initiation of the β-IFN treatment, a flu-like syndrome is usual. TNF-α and IL-10 are major cytokines implicated in immulogical stimulation and suppression, respectively. Mononuclear cells are able to induce TNF-α or IL-10 secretions. Monocytes adhesion capacities to vascular endothelium depends on ligands which bind to inter-cell adhesion molecules (ICAM); LFA-1 (other named CD11a) binds to ICAM-1 and MAC-1 (CD11b) to ICAM-1,2&3. In 10 RR-MS patients we tested TNF- and IL-10 levels, with ELISAs (Immunotech, Marseille France), in plasma, whole blood and in supernatants of mononuclear cultures during the first month of β-IFN-Ia therapy. Simultaneously, CD11a and CD11b were quantified by flow-cytometry, with FITC-conjugated monoclonal antibodies. Results: (i) compared to control values MS showed an increase in plasma TNF-α with a decrease in IL-10 until D30. (ii) in whole blood the amplitude of these changes were dramatically increased (i.e. TNF-α release with a IL-10 decrease) at D7, but IL-10 was increased at D30. (iii) same variations are observed in monocyte supernatants but neither in the whole mononuclear population nor in lymphocyte supernatants. (iv) adhesion molecules are also changed during β-IFN treatment: compared to controls, CD11a is depressed at D0 and normalized at D30. On the contrary CD11b, increased at D0, remained increased at D30. Conclusion: the cytokine changes (TNF-α and IL-10) are concomitant with flu-like symptoms. Monocytes seem to be the most influent cells in these precocious reactions.

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ORGAN-SPECIFIC AUTOANTIBODIES AS MARKERS OF AUTOIMMUNE DISORDERS IN MULTIPLE SCLEROSIS (MS) PATIENTS. S. Fausti, M. Spadaro, R. Fantozzi, M.A. Amendolea*,C. Masala* - II Clinica Neurologica -*Servizio Malattie Autoimmunitarie Universitê di Roma "La Sapienza", Italy.

The occurrence of autoimmune diseases and the finding of organ-specific autoantibodies is probably understimated in MS patients. Poor attention has been paid to associated subclinical autoimmune disorders in the course of MS. Objective. The aim of the present study is to evaluate the frequency of the organ-specific autoantibodies in MS patients and when their apprearance has to be considered as an expression of associated autoimmune diseases. Matherials and Methods. 154 MS patients were studied. No anamnestic data nor clinical signs of thyroid or gastric disfunction were found. We tested all patients for the following serum autoantibodies: anti-gastric parietal cells (PCA), anti-thyroglobulin (ATG) and anti-thyroid peroxidase (TPO). Thyroid hormonal dosage and ecography and gastric biopsy in Ab+ patients were carried out. Results. Forty-one (26.6%) of 154 MS patients were positive for at least one of the organ-specific autoantibodies studied. The occurence of anti-thyroid antibodies was related to abnormalities of the thyroid ecography, whereas the hormonal dosages were in the normal range. The gastric biopsy releaved signs of chronic gastritis in all PCA+ patients. Conclusion. Our findings suggest that the presence of organ-specific autoantibodies could be an expression of sub-

clinical associated autoimmune disorders in MS patients. A long-term follow-up is needed to evaluate how many patients will develop clinical symptoms and signs of thyropathy or gastropathy and their influence in MS course. In our opinion, a careful immunological investigastion in MS patients is crucial to point out other "misdiagnosed" autoimmune diseases.

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PATTERN OF ABNORMALITIES OF THE SYMPATHETIC SKIN RESPONSE IN MULTIPLE SCLEROSIS.Giovanni Cossu[1], Josep Valls-Solé[2], Luis E Gonzalez[2], Albert Saiz[2], Esteban Munoz[2], Maria Giovanna Marrosu[1,1]Centro Regionale Sclerosi Multipla.Cagliari.Italy - [2] Neurology Service.Hospital Clinic.Barcelona.Spain

The sympathetic skin response (SSR) is absent or abnormally reduced in a percentage of patients with multiple sclerosis (MS). In this study we have taken advantage of the fact that the SSR is a generalized reflex response to investigate whether the abnormalities found in MS patients lie more often in the afferent somatic or in the efferent sympathetic central nervous system pathways. Patients & Methods[{CA}]: We recorded the SSR to electrical, magnetic and acoustic stimuli from the upper and lower limbs of both sides in 19 patients with definite MS who had an extended disability scale score ranging between 3 and 7.5. We also recorded somatosensory evoked potentials (SEPs) of the median and tibial nerves and motor evoked potentials (MEPs) of hand and leg muscles to transcranial magnetic stimulation. The results were compared with those of 22 age and sex-matched healthy volunteers. Results: SSR was abnormal in 12 patients (63.1%). In 8 of these 12 patients (66.6%) the SSR was consistently abnormal in a given site regardless the stimulation modality. Abnormalities of the SEPs and MEPs were not correlated with those of the SSR. Conclusion[{CA}]: The abnormalities of SSR in MS predominate in the efferent pathway. The study of the SSR is a useful addition to the neurophysiological examination of patients with MS to strategically explore a larger part of the central nervous system.

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PROSPECTIVE POST-MARKETING SURVEILLANCE WITH INTERFERON β-1B AND β-1A IN FRENCH PATIENTS WITH RELAPSING-REMITTING (RR) MULTIPLE SCLEROSIS (MS).Olivier Heinzlef, Pierre Lecanuet, Dominique Pez, Sonia Alamowitch, Etienne Roullet, Neurology Department, Tenon Hospital, Paris, France

More than 3,000 RR MS patients have been treated with interferon β-1b Betaferon®, Schering) or β-1a (Avonex®, Biogen) in France, but there are no data on selection of patients, safety profile, efficacy of the treatment, or causes of drug withdrawal in day-to-day practice. Design/Method: All MS patients treated by β -interferon in our MS clinic were enrolled in the study. Patients were examined at 1, 2, 3, 6, 12, 18, 24 months. In case of relapse a timely close examination appointment was made. Results: 57 patients (pts) were included (Betaferon®: n=37; Avonex®: n=20). The mean EDSS at entry and relapse rate in the last 12 months were 3.0 ± 1.6 and 2, respectively. The mean duration of follow-up was 13 ± 10 months (2-50). The safety profile was similar to phase III studies, except for high frequency of depressive symptoms (depression, 13 pts (23%); suicide attemps, 2 pts). Six patients stopped treatment for adverse events, and 3 for inefficacy (mean duration of treatment: 9 months, range 2-14). There was a high correlation between the relapse rates in the year before treatment and in the first year of treatment ($r = 0.6$; $p < 0.0001$). Conclusions: These preliminary results reflect the use and safety in the practical use in a French MS clinic. Our data suggest an association between pre and post treatment relapse rate that may be useful to determine a "responders" profile.

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MULTIPHASIC DISSEMINATED ENCEPHALOMYELITIS (MDEM): A REPORT OF THREE CASES. Emmanuelle Duron, Olivier Heinzlef, Dominique Pez, Marie-Germaine Bousser, Etienne Roullet.Neurology Department, Tenon Hospital, Paris, France

MDEM is a rare disease characterized by two or more separate acute episodes of demyelination that differ in clinical presentation (J Neurol Neurosurg Psy, 1995;58:467-470). This entity is differentiated from Multiple Sclerosis and recurrent acute disseminated encephalomyelitis. Objectives and methods: To report on three cases of MDEM. Results: These 3 women were aged 40 to 50 years; they had no relevant familial history of demyelinating or autoimmune diseases. Two had only 2 relapses after 5 and 8 years of follow-up, and one 3 relapses in 3 years. Onset of relapse was acute in all cases, and triggered by infections in one. Unusual signs such as cephalalgia, nausea, vomiting, aphasia, acalculia, visual field defects, or memory deficits were common. CSF analysis showed no oligoclonal bands. One patient had a monoclonal gammopathy of unknown significance. MRI showed large demyelinating lesions with extensive gadolinium enhancement and mass effect. On sequential MRI no new lesions occured between clinical relapses, and the volume of the lesions decreased with time. Cerebral biopsy (in one case) was not diagnostic. All patients improved after corticosteroid therapy. At last follow-up examination was normal in 2 patients, and showed mild disability in one; Conclusions: MDEM is caracterized by distinctive time course, unusual clinical symptoms, lack of oligoclonal bands, and large lesions on MRI with gadolinium enhancement. Diagnostic is often difficult and MRI appearance might suggest lymphoma. Pronostic is variable and best preventive treatment is undetermined

P779
HETEROGENEITY IN MULTIPLE SCLEROSIS (MS) PATIENTS WITH AND WITHOUT FAMILIAL AUTOIMMUNE DISEASES (AID). Caroline Papeix*, Olivier Heinzlef*, Laurence Nahum-Moscoc*, Sonia Alamowitch*, Etienne Roullet*, and the GRAID group. Neurology, Tenon Hospital, Paris, France.

Objective: To determine if MS patients with and without a familial history of AID have different clinical characterisics. Background: In unselected MS patients, we reported a high frequency (19.4%) of multiplex families, ie first-degree relatives with MS or an other AID (Alamowitch SA, et al. J Neurol, 1997;244: S38-39). We compare now the clinical and demographic features of MS.patients belonging to multiplex or simplex (no AID families). Design/Method: Extended pedigrees of 88 clinically definite MS patients were established by standardized interviews of index cases and of 497 first degree relatives. Diagnosis of AID was confirmed by direct examination or rewiew of médical records. Results: In multiplex families (n=37), MS index patients were more likely to have optic neuritis at onset than in simplex families: 14/36 (39%) vs. 9/49 (18%) $p < 0.03$. There were no significant differences for sex-ratio, age at examination, age at onset, R1-R2 interval, clinical course, and severity of MS between the 2 groups. Four out of 9 male MS patients had a progressive onset in the multiplex group, vs. 0/14 in the simplex group ($p < 0.02$ by Fisher's exact test). Conclusions: Our results show phenotypic heterogeneity of MS patients with and without a familial history of AID; these results suggest genetic heterogeneity in MS, possibily related to non specific susceptibility genes to autoimmune diseases.

P780
PARENT-OF-ORIGIN EFFECT OF HLA GENES IN SARDINIAN MULTIPLE SCLEROSIS. Marrosu M.G.*, Murru R.*, Lai M*., Murru M.R*., Costa G.*, Cocco E*, Sotgiu S.^, Pugliatti M.^, Cucca F.ˣ. *Multiple Sclerosis Center, Department of Neuroscience, ˣDepartment of Pediatrics, University of Cagliari, ^Neurologic Clinic, University of Sassari.

Objective: in order to obtain information about inheritance of predisposing HLA alleles in Sardinian MS patients, we studied the transmission of HLA-DRB-DQA-DQB haplotypes in a large set of Sardinian families. Materials and Methods: amplification of the polymorphic second exon of the DRB1, DQA1, DQB1 genes and dot-blot analysis of amplified DNAs with sequence-specific oligonucleotide probes were carried out on 378 MS families. All patients had clinically defined MS according to the criteria of Poser et al. (1983). The analysis was also done on 438 healthy sibs. Transmission disequilibrium test (TDT) analysis was performed according to Spielman et al. (1993). Results: the DRB1*0301-DQA1*0501-DQB1*0201 and the DRB1*0405-DQA1*0501-DQB1*0301 haplotypes was preferentially transmitted by fathers to MS offsprings ($p= 0.004$ and 0.03, respectively), while no deviation was observed in healthy offsprings. Considering sex of patients, the parent-of-origin effect was confined to haplotypes transmitted by fathers to females with MS, (for the DRB1*0301-DQA1*0501-DQB1*0201 haplotype $p=0.0005$ and for the DRB1*0405-DQA1*0501-DQB1*0301 haplotype $p=0.03$). No significant distortion in the transmission of these haplotypes from mothers to affected children was observed. Discussion: these data demonstrate that he HLA-DRB1*0301-DQA1*0501-DQB1*0201 and the HLA-DRB1*0405-DQA1*0501-DQB1*0301 predisposing haplotypes are prefentially transmitted from fathers to affected females. Such sex-unbalanced transmission suggests that the HLA-DRB1*0301-DQA1*0501-DQB1*0201 and the HLA-DRB1*0405-

DQA1*0501-DQB1*0301 predisposing haplotypes are inherited by affected females in association to the chromosome X.The association of predisposing MHC/HLA haplotypes to the chromosome X supported by these data suggests the presence of other genes located in chromosome X acting sinergically with MHC genes in inheritance to MS. We cannot exclude that the unbalanced transmission we observed in Sardinian patients may be linked to the particular genetic structure of Sardinians. *Supported by Dompé Biotec, Federazione Italiana Sclerosi Multipla and Istituto Superiore Sanitê.*

Neuro-Oncology

P781
GLIOMA, MELANOMA AND PANCREATIC CANCER: IS THERE A FAMILY ASSOCIATION? J. Fueyo, C. Gomez-Manzano, A.P. Kyritsis, W.K.A. Yung, M.L. Bondy. Houston, Texas, U.S.A.

Although the majority of gliomas are sporadic, a number of syndromes have been associated with an increased risk of glioma. In addition, each form of familial glioma has the potential to provide insights to elucidate the genetics of gliomas. In turn, the results of these analyses may provide clues about the etiology of apparently sporadic gliomas. The objective of the study presented here was to study the possible family association of gliomas with pancreatic cancer and melanomas. We examined the family history of 639 patients with glioma. All patients in this study provided a blood sample and consented to a complete in-person or telephone interview. The interview consisted of a detailed series of questions on the patient's medical and family history of cancer, smoking history, previous radiation, and other demographic data. The study population is a subset of cases from an on-going genetic epidemiological study of gliomas being conducted at University of Texas M. D. Anderson Cancer Center, and we were able to confirm all cancers reported in the relatives with medical records or death certificates. In this series of 639 patients with glioma, 32 families had a total of 87 relatives with either melanoma or pancreatic cancer. In addition, 16 of the glioma patients had a first-degree relative with melanoma (O/E=16/9.06; 95% CI=1.01-2.87). This aggregation of glioma and melanoma was higher in younger patients who were diagnosed before age 45 (O/E 13/4.45=2.92; 95% CI= 1.55-4.99). Furthermore, the mothers of 7 glioma patients suffered from pancreatic cancer (O/E=7/2.35=2.98; 95% CI= 1.19-6.14). Preliminary studies sequencing the p16 gene did not uncover any germline mutation in 16 of the patients (50%)with available blood. This is the first report of the familial association of glioma, pancreatic and melanomas. Patients with glioma should be interviewed for possible melanoma or pancreatic aggregation. Further studies are in progress to ascertain whether mutations of the p16 gene are relevant in isolated cases of this subset of patients.

P782
LAMBERT- EATON MYASTHENIC SYNDROM (LEMS) AND ADENOCARCINOMA OF THE PROSTATE.Kerstin Hellwig, Volker Hoffmann, Sebastian Schimrigk, Sandra Szymanski, Ludger Schöls.Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital, Gudrunstr.56, D-44791 Bochum, Germany

LEMS is a rare autoimmune disease of the neuromuscular junction with a 60% risk of haboring or developping a small cell lung cancer. There is little evidence for another than incidential association of LEMS with non pulmonary malignancy. One case report describes LEMS and adenocarcinoma of the prostate with improvement of the neuromuscular symptoms after orchidectomy was published. Case report: A 52 year old man developed gait difficulty and bilateral muscular weakness in 1990. In 1991, he was diagnosed with LEMS having typical electrophysical findings and positive voltage calcium channel gated autoantibodies, while no malignancy was found. In 1992, the patient developed severe myasthenic decompensation with the need for fully controled artificial ventilation for 9 months. Since then nocturnal respiratory continous positive airway pressure support is necessary. Repetitive tunor screening revealed no malignancy. Due to a slightly elevated PSA (4,6 ng/ml), a prostate biopsy ensued, dissolving a high differentiated adenocarcinoma of the prostate. Surgical therapy is intended after pacemaker adjustment. Conclusion: This case provides evidence for an association of LEMS with an adenocarcinoma of the prostate with an 8 year interval between myasthenic symptoms and diagnosis of malignancy.

P783
SIGNALING THROUGH THE JAK/STAT IN HUMAN BRAIN TUMORS. L. Magrassi[1,2], C. De-Fraja[3], L. Conti[3], G. Butti[1], S. Govoni[4], E. Cattaneo[3,1]Neurosurgery Department IRCCS Policlinico S. Matteo, University of Pavia, Pavia-Italy; [2]I.G.B.E.-CNR, Pavia-Italy; [3]Institute of Pharmacological Sciences, University of Milano, Via Balzaretti 9, 20133 Milano-Italy; [4]Institute of Pharmacology, University of Pavia, Pavia-Italy.

Cytokines are produced by brain tumors and exert a multitude of effects in a autocrine or paracrine fashion. It has been also demonstrated that specific cytokine receptors, not detected in peritumoral tissue or in normal brain, are found in brain tumors. Our aim was to analyze the presence and activation of the JAKs and STATs superfamiles of proteins in human brain tumors. The JAK/STAT constitute the cytokine signalling pathway and have been found present in the normal brain (for a review see Cattaneo, Conti and De-Fraja, TINS, 1999. In press). In this study, Western blotting analyses were performed on lysates from medulloblastomas, astrocytomas, anaplastic astrocytomas, glioblastomas, ependimomas, neurinomas and meningiomas. Antibodies against JAKs (Jak1, 2, 3 and Tyk2) and STATs (Stat1-6) were used. Our analysis shows that Jak3 and Tyk2 are undetectable or present at very low levels in all tumors studied. On the contrary, Jak2, Stat1, Stat3, Stat5 and Stat6 immunoreactivities are always higher in tumoral tissues compared to control specimens. Jak1 is expressed at low levels in control and tumor samples, with the exception of medulloblastomas and meningiomas, while Stat2 levels are significantly higher with respect the controls only in meningiomas. We also tested the levels of tyrosine-phosphorylated Stat1 and Stat3 in meningioma specimens, and have compared the levels of the phosphorylated vs. unphosphorylated proteins. Finally, we studied the activation of Stat1 and Stat3 in in vitro meningioma cells exposed to IFNα-2B. In these conditions we detected phosphorylation and nuclear translocation of Stat1 and Stat3, suggesting a direct effect of IFNα-2B on meningioma cells. (Supported by AIRC #442/96 to E.C.).

P784
FOTEMUSTINE(F)/CISPLATIN(CDDP)/ETOPOSIDE(VP16) IN THE TREATMENT OF 33 NON OPERABLE GLIOBLASTOMAS (GB). A PILOT STUDY. Lebrun C*, Frenay M**, Bondiau PY**, Marcy PY**, Grellier P***,.(*) Service de Neurologie. (***) Service de Neurochirurgie. Hôpital Pasteur, 30 voie romaine, (**) Centre Antoine Lacassagne, Nice, France.

Despite combinations of surgery, radiotherapy (RT) and chemotherapy (CT) used in the treatment of glioblastomas (GB), mean and median survival rates in most patients remain 12 months or less after diagnosis. RT and nitrosourea after surgery are the standard combination for GB. They may induce acquired resistance and, consequently, non operable GB is a unique biological and clinical situation allowing evaluation of intrinsic chemosensitivity. Purpose: Comparison of F (100mg/m^2 day1)/CDDP (33/m^2.d1-3) / VP16 (75mg/m^2·d1-3) q21-28d regimen efficacy in inoperable GB at presentation. Methods: Between 1995 and 1998, 33 consecutive patients with symptomatic inoperable histologically proven GB were treated; none of them had previously received chemotherapy, irradiation, or surgical debulking. Objective response was evaluated by contrast enhancement with CT scan or MRI after each treatment. Results: Toxicity was moderate and mainly hematological (grade III-IV thrombopenia= 20/171cycles; leucopenia=25/171). No treatment-related deaths were noted. Objective response rates were 9/33 (27.3%) with stabilization=17/33. Mean survival time was 14.4 months for the whole group 1 (11.2 months in the 26 deceased patients) with a median survival of 10 months. Median survival rates at 6 and 12 months were 88% and 42 % respectively. Seven/33 patients are still alive with median survival of 34.6 months. Seven/33 (4/7alive) were long-term survivors (range:19-67). Conclusions: Neoadjuvant CT in inoperable patients is safe allowing delayed RT. Sequence effect may synergistically interact with efficiency. Phase II CT trials should include studies with a subgroup of inoperable patients representing more than 20% of all GB patients.

P785
VALPROIC ACID AND NITROSO-UREA: INCREASE OF HAEMATOLOGIC TOXICITY. Bourg V(*), Lebrun C (*), Thomas P (*), Chichmanian RM (**), Frenay M(***),Centre anti-cancéreux "Antoine Lacassagne" (*) Service de neurologie, Pr Chatel, (**) Pharmacovigilance, Hôpital Pasteur NICE, France.

The incidence of hematological toxicity of valproate (VPA) is ranging from 1 to 32 %, and mainly consists of asymptomatic, dose-dependent thrombopenia. We describe a potentiation of hematologic side-effects of nitroso-urea (NU) when prescribed in association with VPA. Patients/

methods: We followed a cohort of 43 patients (26 men, 17 women, mean age 53yrs, range 20-73). Patients were treated with chemotherapy followed by radiotherapy for a high-grade glioma (32 glioblastoma, 6 anaplasic oligodendroglioma, 5 anaplasic astrocytoma). Chemotherapy regimen was: fotemustine (d1: 100 mg/m^2), cisplatine (d1-3: 33 mg/m^2) and etoposide (d1-3: 75 mg/m^2). Thirty-eight patients required anti-epileptic drugs (AED) for either a single, well-documented epileptic seizure, or immediately after neurosurgical procedures. AED included VPA (27/38; 71%), phenobarbital (PB) (6/38; 15.8%), carbamazépine (3/38; 7.9%) and phenyto∞n (PHT) (1/38; 2.6%). A single patient had both PB and PHT. Results: Hematological toxicity (grade III/IV thrombopenia or neutropenia, or both) was observed in 18/43 patients (41,8 %). Seventeen patients on 18 (89 %) were taking VPA. Among these patients, 3 of them required emergency platelets transfusion. The last patient with severe hematologic toxicity had combination therapy with PB and PHT. Conclusion: When prescribed in association with nitrosourea, VPA produce reversible tenfold thrombopenia. Hematological side-effects decrease after AED modification.

P786
THE DIAGNOSTIC AND PROGNOSTIC VALUE OF CEREBROSPINAL FLUID (CSF) IMMUNOHISTOICHEMISTRY IN LEPTOMENINGEAL METASTASES (LMM).P. Polo, M.C. Vigliani, A. Chiÿ, R. Soffietti, D. Schiffer.Dept of Neuroscience, University of Turin, Turin, Italy

Objective: To evaluate the diagnostic value of a monoclonal antibody panel in CSF cytology and the prognostic significance of some CSF parameters in patients affected by LMM. Methods: CSF of 33 patients with suspected LMM was analyzed. A panel of monoclonal antibodies (pancytokeratine, vimentin, NSE, HMB-45, CLA, Kp1, CEA and Ki67) was immunohistochemically applied to atypical and neoplastic CSF. Prognostic significance of a proliferation index (MIB index) was statistically established but some other clinical (age, sex, primary tumor, Karnofsky index, symptoms at onset, disease extension and therapy) and CSF (number of cells, glucose and proteins concentration). parameters were also taken into consideration. Results: Twenty patients had a LMM. In five patients immunohistochemistry was determinant for the diagnosis. Only in one patient out of five with unknown tumor our monoclonal panel allowed the identification of the primary tumor. MIB index had a prognostic significance ($p < 0,05$) but some other CSF and clinical parameters, as a decrease of CSF glucose ($p < 0,01$), primary breast tumor ($p < 0.05$) and spinal involvement ($p < 0,003$) had a high prognostic significance, too.Conclusions: The application of a panel of monoclonal antibodies can enhance CSF cytology sensitivity but it rarely allows the identification of the primary tumors of unknown origin. MIB index and some other CSF parameters have a prognostic significance.

P787
MALIGNANT BRAINSTEM GLIOMA FOLLOWING RADIOTHERAPY FOR PITUITARY ADENOMA. D. Felten, P. Camparo, J.M. Delmas, J.L. Renard, J.L. Sarrazin, D. Béquet. Hôpital du Val de Grâce, Paris, France

Induction of cerebral neoplasia, particularly glioma, is an uncommon complication of radiotherapy in adulthood. We report the case of a 60-year-old man who was admitted for fast increasing features of brainstem disease: weakness of the four limbs, cerebellar ataxia, dysphagia and vegetative disorders. He died four months after the first symptoms. Initial brain MRI showed an extensive process located in the brainstem. There were heterogeneous T2-hypersignals, T1-hyposignals and nodular contrast enhancements. On further examinations lesions were extended to the both thalamic areas. A stereotactic biopsy was realized. Histologic features were consistent with an aggressive glioma which was classified as a grade B oligodendroglioma (Dr. Daumas-Duport). Seventeen years before, the patient was treated for a non-secreting pituitary adenoma. Surgical removal was complete and followed by a local irradiation (51 Gy). Radiation-induced tumors are today well known. They belong to the so called "late delayed complications" of the radiotherapy. They must arise in the field of irradiation, appear after a long latency period and differ from any preexisting tumor. Most frequently they are secondary to a cranial irradiation in childhood. Indications for radiotherapy in adulthood are rarely long survival tumors; for that reason, the emergence of late delayed complications are uncommon. Meningiomas are the most common radio-induced tumors, far more than gliomas and sarcomas. Post-radiation gliomas do not seem to have particular histologic features.

P788
MULTIPLE INTRACEREBRAL LATE METASTASES OF A GRANULOSA CELL TUMOR. A. Baier, J. Ree°, M. Heibel, M. Palmbach, E. Mauch.Neurological Hospital Dietenbronn, D-88477 Schwendi, Germany

We report the rare case of a patient with intracerebral metastasis of a granulosa cell tumor. In 1987 a granulosa cell tumor was diagnosed in a female patient. Due to metastases in multiple lymphnodes the patient underwent surgical intervention, radiation and several courses of polychemotherapy. The growth of the tumor couldn't be stopped. The patient showed up in our hospital with personal changes. She was desoriented, showed psychomotoric retardation and aphasic and apractic disturbances. Neurologic examination revealed a slight rightsided hemiparesis. After a generalized cerebral seizure she became comatose without regaining consciousness. Cranial MRI showed seven cystic and one solid mass lesion with ring-enhancement after i.v. gadolinium. In the cerebrospinal fluid a slight mononuclear pleocytosis and an intrathecal IgM- and IgA-synthesis was found. Oligoclonal bands showed up in both serum and CSF. Unfortunately a postmortem couldn't be performed. Conclusion: Only 1,4 % of patients with tumors of the female genitals show intracerebral metastases. Since less than 2 % of all ovarian neoplasms are granulosa cell tumors, the development of intracerebral metastases due to this tumor type is really rare. Nevertheless in our case there is a high possibility of a cerebral tumor manifestation due to the clinical and imaging findings as well as the patients history. But as we weren't allowed to perform a postmortem, a cerebral mycosis or multiple abscesses due to an opportunistic infection because of longterm immunosuppression must be also discussed as reasons for the MRI findings.

P789
ONCOGENE EXPRESSION AND PROGNOSIS IN GLIOBLASTOMA MULTIFORME. Schlegel, U., N. Glesmann, M. Wenghoefer, U. Berweiler*, W. Roggendorf*, S. Diete**, K. Dietzmann**, K. Heuser***, B. Müller# and A. V. Deimling## - Dpt. Neurology, University of Bonn, *Dpts. Neurosurgery, Neuropathology, Universisty of Würzburg, ** Dpts. Neurology, Neuropathology, University of Magdeburg, *** Dpt. Neurology, University of Kiel,#Dpt.Neurology, Rehabilitation Hospital Kreischa and ##Dpt. Neuropathology, University of Berlin, Germany.

Objective: To investigate the expression of oncogenes bcl-2, Waf1/p21, p53 and mutations of the TP53 gene in glioblastoma for prognostic relevance. Material and methods: De novo glioblastomas of 40 patients with "long term" survival (time to tumor progression, ttp, > 12 mo, mean age 51 ys) and of 53 patients with *short term survival* (ttp 6 mo, mean age 50 ys) were investigated. Waf1/p21, bcl-2 and p53 proteins were detected immunhistochemically. TP53 mutations were screened by PCR-SSCP (Polymerase Chain Reaction - Single Strand Conformation Polymorphism) analysis and were confirmed by direct sequencing. Results: TP53 mutations were found in *10 out of 53 (19%) short term survivors* and in 10 out of 38 (26%) "long-term" survivors. The respective numbers were for p53 protein accumulation *12/53 (23%)* and 10/38 (26%), for Waf1/p21 expression *14/52 (27%)* and 9/36 (25%), for bcl-2 expression *31/52 (60%)* and 22/38 (58%). In a subgroup of 17 patients with a survival > 24 mo TP53 mutations were found in 21%, p53 protein accumulation in 25%, Waf1/p21 expression in 27% and bcl-2 expression in 59%. Conclusion: TP53 mutations and p53 accumulation, Waf1/p21 and bcl-2 expression were equally frequent in patients with an unusual long or short survival. Therefore, alteration of these oncogenes/oncoproteins does not seem to influence the clinical course in de novo glioblastomas.

P790
CEREBRAL ANGIOENDOTHELIOMATOSIS - A RARE DIFFERENTIAL DIAGNOSIS OF MULTIPLE CEREBRAL INFARCTION. Lehrieder G[1], Molitor H[1], Klein R[2] - [1]Juliusspital Würzburg, Department of Neurology; Juliuspromenade 19, 97070 Würzburg, Germany. [2] Department of Pathology, University of Würzburg, Josef-Schneider-Strasse 2, 97080 Würzburg, Germany.

Neoplastic angioendotheliomatosis (intravascular lymphomatosis) is a rare disease characterized by multifocal, intraluminal neoplastic proliferation of mononuclear cells within small blood vessels. Prognosis is fatal and in most cases diagnosis made by autopsy. We report the case of a 41-year-old woman who was admitted because of disturbance of consciousness, fever and confusional state. Computed tomography showed a hypodense lesion in the left basal ganglia. Cerebrospinal fluid revealed a lymphoplasma-cellular pleocytosis and breakdown of the blood-brain-barrier. Anticonvul-

sive therapy (phenytoine), antibiotics (ceftriaxone) and antiviral therapy (aciclovir) brought nearly complete recovery. Search for pathogen and serological evaluation remained without signs for an inflammatory disease. Readmittance was done two weeks later because of rapid progredient psychoorganic disturbances, headache, fever and worsening of consciousness. In CT and MRI we found new (vascular?) hypodense lesions. Again CSF showed a mild pleocytosis. Neither broad-spectrum antibiotics nor corticosteroids were able to change the fatal course. Seven weeks after first admittance patient died. We present CT- and MRI-Scans, macro- and histopathological findings. Autopsy revealed brain edema, occlusion of many small cerebral arteries and intravascular thrombosis with large, neoplastic lymphoma cells of B-cell-origin. Angioendotheliomatosis formerly was supposed to be an intravascular tumour of endothelial origin. Our case, according to the newer literature, gives further evidence that angioendotheliomatosis is an angiotropic large-cell lymphoma.

P791
RESPONSE TO PCV CHEMOTHERAPY OF LOW GRADE NONENHANCING OLIGODENDROGLIAL TUMORS.R. Soffietti, R. Rudê, M. Borgognone, Dept. of Neurosciences, Division of Neurology, Univ. of Torino, Italy

PCV chemotherapy is highly effective in anaplastic oligodendrogliomas and oligoastrocytomas, whereas its role in the treatment of low grade tumors is still unclear. Objective[{CA}]: The objective of this study was to determine the benefits and toxicity of PCV chemotherapy in patients with low-grade nonenhancing oligodendroglial tumors. Design/methods. Patients with both newly diagnosed after biopsy or partial resection (13) and recurrent (7) oligodendrogliomas and oligoastrocytomas (grade II WHO) were treated with up to 6 cycles of standard PCV. Tumors were nonenhancing on MR. Volumetric estimates of T2-signal abnormalities on axial MR images were determined, and tumor response was evaluated by the criteria of Macdonald et al. (1990). Results[{CA}]: Among patients with newly diagnosed tumors we observed a partial response (PR) in 3/13 (23%) and a stable disease (SD) in 10/13 (77%), with 3/10 showing a reduction of tumor volume of 20-40%. Two out of 5 symptomatic patients improved (1 PR, 1SD). Among patients with recurrent tumors, we observed a PR in 2/7 (28%) and a SD in 5/7 (62%) with 2/5 showing a reduction of tumor volume of 20%. All 3 symptomatic patients improved (2 PR, 1 SD). Time to tumor progression is now 24 months (6-60 months). Conclusions. PCV chemotherapy is by far less effective in low grade nonenhancing oligodendrogliomas and oligoastrocytomas than in the anaplastic and "aggressive" forms.

P792
SAFETY AND EFFECTIVENESS OF LOCO-REGIONAL CHEMOTHERAPY IN GLIOBLASTOMA PATIENTS. Zappacosta MB, Silvani A, Salmaggi A, Eoli M, Boiardi A. Milano - Italia

In a preliminary study we have evaluated the safety and the effectiveness of antracyclines locally administered. We studied 21 operated on glioblastoma (GBM) patients (age 44.52, standard deviation 8.92), 13 of them primary GBM, and 8 previously anaplasic astrocytomas worsened to GBM. All patients were treated with radiotherapy and sistemic chemotherapy, with nitrosureas and platinum, and, after tumour progression, with antracyclines delivered through an Ommaya reservoir left in the residual cavity after tumour debulking. The median time to tumour progression (TTP) and the total survival of the primary GBM patients were 5.2 and 20.1 months respectively. All primary GBM patients received locally, via Ommaya reservoir, antracyclines (doxorubicine, daunorubicine and mitoxantrone, single dose of 1, 3 and 3 mg. respectively, delivered every two weeks, median total dose of 27 mg.) over 9.1 months. The second group, of reoperated on GBM patients, coming from a grade III anaplasic astrocytoma, had a disease free and survival time (ST) of 6.8 and 16 months respectively. At recurrence they were given local chemotherapy treatment with the same schedule of antracycline, (total median dose 10 mg.) over 6.5 months. No toxicity or side effects occurred. We conclude that the loco-regional chemotherapy via reservoir probably prolongs ST in primary and recurrent GBL patients. Data are encouraging and it is necessary to validate the results in a randomized study.

P793
ALTERNATE RADIOTHERAPY-CHEMOTHERAPY IN TREATMENT OF ANAPLASTIC ASTROCYTOMAS. Fariselli L*;Boiardi A*;Silvani A*; Broggi G*; Botturi M°.*C.Besta Institute- °Niguarda Hospital. Milan Italy.

Multidisciplinary approach seems to be a better method to achieving best results in menagement of malignant gliomas.There is difference in clinical behaviour between Glioblastoma (GBM) and Anaplastic astrocytoma (AA). Biological and molecolar studies confirmed the difference. In our analysis we present preliminary results of combined chemo-radiation treatment schedule for 23 patients with histologically confirmed diagnosis of Anaplastic Astrocytoma (15) or Oligoastrocytoma (8). No patient with diagnosis of GBM was inserted in the protocol. 2 cycles of chemotherapy (CDDP-PCZ-CCNU) were administred soon after surgery and before the starting of radiotherapy. Patients received 52 Gy to Planning Target Volume (ICRU50), 1.3 Gy BID (6 hours apart) in 21 days. After completed radiotherapy 3 cycles of CT (with the same scheme) completed protocol. All patients received salvage therapy at time of tumor progression (21 pt chemotherapy with PVC scheme; 2 pt surgery). Minimum follow up is 24 months. Median survival time for the group has not been reached. The percentage of patients alive at 2 and 3 years is 75 and 65% respectively. Based on Kaplan Maier estimate, the median time to tumor progression is 31 months. Age was factor found to be associated with a statistically improved survival. Toxicity evaluation was conducted according to the RTOG toxicity scale and was found well tolerated. These encouraging preliminary results suggest that local control could be achieved with strictly combined CT -RT therapy.

P794
MEDULLOBLASTOMA (MD) AND PRIMITIVE NEUROECTODERMAL TUMOR (PNET) IN ADULTS: THE ROLE OF TREATMENT. Boiardi A.,Eoli M.,Salmaggi A., Zappacosta B., Fariselli L., Silvani A.Istituto Nazionale Neurologico " C. Besta" Milano, Italy.

Between 1987 and 1997, 39 patients aged at least 18 years with newly diagnosed MD or PNET were consecutive treated according to the same protocol. All patients received (mean 30 Gy boost + 20 Gy whole brain) but only 28 had spinal axis radiation and 11 spinal chemotherapy. 24 patients received systemic chemotherapy (PCV) concomitantly with and after irradiation. The overall survival rates at 3, 5 and 10 years were 75, 44, 22 % respectively. The median time of progression free survival for the whole group was 48.1 months. Out of 26 patients with tumor recurrence, 7 underwent a second surgery and 24 were treated with a second line chemotherapy (Carboplatin + Etoposide). After the diagnosis of recurrence the median survival time of the whole group was 15.8 months, but in the 18 patients responding to chemotherapy 34.5 months. Brainstem involvement, cerebellar peduncle infiltration, persistence of malignant cells in CFS correlated with a poor outcome for overall survival.Some considerations may be formulated: recurrence in posterior fossa occurred also in patients receiving a boost greater than 50 Gy; low-dose craniospinal radiotherapy was delivered in the majority of patients receiving chemotherapy and the combination of these 2 treatments avoided a possible increased percentage of failure; more than half of recurrent patients had a partial response to chemotherapy that could extend survival for longer than 3 years.

P795
CISPLATIN AND BCNU CHEMOTHERAPY FOR ANAPLASTIC OLIGOASTROCYTOMAS. Silvani A., Eoli M., Fariselli L., Salmaggi A., Giovagnoli AR., Boiardi A. Istituto Nazionale Neurologico "C. Besta" Milano, Italy.

In this study were enrolled 32 newly diagnosed anaplastic oligoastrocytoma patients (median age of 41 years range 10-63; median KPS of 90 range 70-100). All patients were treated with Cisplatin (100 mg/sqm) and BCNU (160 mg/ sqm). The chemotherapy started in the first week after surgery and it was administered every 6 weeks (5 scheduled cycles) for a total of 127 cycles. After the second cycle of chemotherapy all pts received radiotherapy (52.7 Gy). The median follow- up was 44 months (10-91). Nine patients were reoperated-on. The median time to progression (TTP) and median survival time (ST) for the whole group of patients were 54.6 and 70.1 months respectively. A proportional hazards model was used to look at potential prognostic factors for survival, including: lower age (40 years), extent of surgery (total/subtotal vs partial) and reoperation. When we analysed the group of patients with total/ subtotal surgery or age under 40 years the median ST could not be assessed due to the high number of surviving patients after a follow up of 52 months. The median survival time for the older patients or for patients with partial resection were: 54.1 and 42.2 months. In our group of patients only radical surgery predicted for longer survival ($p < 0.001$).

P796
CSF IL10 LEVELS IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL). M. Eoli, M. Gelati, A. Silvani, S. Frigerio, A. Boiardi, A. Salmaggi. Neurological Institute C. Besta, Milan, Italy

PCNSL is a lymphoid tumor localized in the CNS, the management of which includes early chemotherapy and subsequent radiotherapy; local recurrence eventually develops in most cases. Biological markers predictive of disease evolution or response to treatment are lacking. Some evidence suggests that levels of serum IL10 (a B lymphocyte derived cytokine) may be of prognostic value in systemic lymphoma (Blay et al Blood 1993), but only few data are available on CSF levels of IL10 in PCNSL (Whitcup et al, Arch Ophtalmol 1997). We investigated CSF and serum levels of IL10 in 12 PCNSL and 12 patients with other neurological diseases, in 11 patients with other CNS tumors and (serum only) in 10 healthy controls. CSF IL10 levels were significantly higher in PCNLS patients in comparison with OND and other CNS tumor patients (14,4 pg/ml vs 0.33 pg/ml and 0.23 pg/ml respectively). Serum IL10 level were also sligtly higher in PCNLS patients as compared with healthy controls and other CNS diseases. High CSF IL-10 levels were related to poor clinical outcome and inversely low levels were associated with good clinical response; in at least two cases high CSF IL10 levels preceded clinical-radiological worsening. Overall, CSF IL10 levels might have some prognostic relevance in the outcome of PCNSL patients.

P797
MOLECULAR ANALYSIS OF THE CDR3 ENCODING REGION OF THE IMMUNOGLOBULIN HEAVY CHAIN LOCUS IN CEREBROSPINAL FLUID CELLS AS A DIAGNOSTIC TOOL IN LYMPHOMATOUS MENINGITIS. B. Storch-Hagenlocher, J. Haas, C. Grond-Ginsbach, M. Vogt-Schaden, A. Biessmann, B. Wildemann. Department of Neurology, University of Heidelberg, 69120 Heidelberg, Germany.

The diagnosis of leptomeningeal involvement by B-cell lymphoma may be difficult if a low percentage of lymphoma cells is present in the cerebrospinal fluid (CSF) and cytology does not allow unequivocal distinction between neoplastic lymphoid cells and reactively transformed mononuclear cells. Individual B-cell clones can be identified on the basis of DNA sequences that encode highly diverse third complementarity determining region (CDR3) of the immunoglobulin heavy chain locus (IgH). Methods: Using polymerase chain reaction (PCR) based high resolution capillary electrophoresis and automated fluorescence detection of PCR fragments we studied CSF samples from 5 patients with B-cell malignancies and cytologic evidence of leptomeningeal involvement. We also assessed CSF specimens from 7 individuals with inflammatory neurologic disorders and from 3 normal controls. Results: CSF samples from patients with B-cell malignancies yielded a single PCR product indicating that CDR3 specific fragments were derived from monoclonal cell populations. From CSF cells of patients with inflammatory diseases multiple CDR3-amplicons were generated suggesting the presence of a polyclonal B-cell activation. CDR3-specific PCR of CSF cells obtained from normal controls was repeatedly negative. Conclusions: Automated fluorescence detection of CDR3 amplicons is highly sensitive and can rapidly distinguish neoplastic monoclonal and reactive polyclonal B-cell populations in the CSF.

P798
SIGNIFICANT PATTERNS OF PURKINJE CELL DEGENERATION IN CEREBELLAR CELL CULTURES AFTER TREATMENT WITH ANTI-YO ANTIBODIES.Zipko-HT 1), Rausch-WD 1+2), Setinek-U 2), Bodenteich-A 2), Drlicek-M 2), Grisold-W 2) - 1) Institut fuer Medizinische Chemie, Veterinaermedizinische Universitaet. 2) LBI for Neurooncology Vienna-Linz, Austria

Objective: To induce Purkinje neuron degeneration in long-term murine neuronal cell cultures (>10 days-in-vitro, DIV) after treatment with anti-Yo antibodies (Yoab) evaluated by morphometric analysis. Background: Patients with Paraneoplastic Cerebellar Degeneration (PCD) often harbour antibodies against Purkinje cells called Yoab. The most obvious histopathological effect is an almost complete loss of Purkinje cells, yet the basic mechanisms of this neuronal degeneration remains unclear. Even more, there have only been a few attempts to study neuron degenerations associated with Yoab using in-vitro techniques and long-term exposure to induce alterations of Purkinje neuron morphology. Design-Methods: After 10 DIV Purkinje cells in primary cerebellum cell cultures were incubated with growth medium containing serial dilutions of human sera samples with and without Yoab. Dilutions ranged from 0 (control group), 1:100 and 1:1000, respectively. Cultures were fixed in 2 day intervals up to 20 DIV. Morphometric data of Purkinje neurons, visualised with anti-Calbindin and ABC-technique were obtained with digital image processing methods. Results: Neuron Morphology of cultures neurons showed significant changes and damage patterns in cell shape associated with several alterations of dendritic outgrowth and differentiation after treatment with Yoab. In addition numbers of surviving Purkinje cells decreased already after 4 days of Yoab treatment. Conclusions: Morphological changes and degenerations of cultured Purkinje neurons in cerebellar cell cultures treated with Yoab represent a useful model to study PCD in-vitro.; Study supported by the BGM Fonds Vienna N°1481/97

Poster Session 6

Neurogenetics

P799
SEQUENCE ANALYSIS OF THE NIEMANN-PICK C1 (NPC1) DISEASE GENE IN 12 NIEMANN-PICK TYPE C (NP-C) AFFECTED GERMAN PATIENTS. Bauer, Peter (1), Lindberg, Nicole (1), Harzer, Klaus (2), Rolfs, Arndt (1). (1) Klinik für Neurologie, Universität Rostock, Rostock, Germany; (2) Institut für Hirnforschung, Universität Tübingen, Tübingen, Germany *Study supported by Genzyme, Germany (Dr. Stefan Maeser)

Niemann-Pick type C disease (NP-C), a fatal neurovisceral disorder, is characterized by lysosomal accumulation of low density lipoprotein (LDL)-derived cholesterol. By positional cloning NPC1 has been characterized as the major candidate gene for NP-C phenotype. Expression of NPC1 corrects NP-C fibroblast's excessive lysosomal storage of LDL cholesterol. In order to clarify the segregation and genotype-phenotype correlations in NP-C disease, it was our first goal to establish direct sequencing of NPC1 in affected patients. Direct sequencing of NPC1 cDNA was done in human leukocyte RNA preparations obtained from seven German families and five individuals affected with NP-C disease. These samples were reverse transcribed (SuperScript, Gibco) and PCR amplified with NPC1 specific primers followed by a direct sequencing procedure (ALF DNA Sequencer, Pharmacia). Up to now, 13 novel missense mutations have been identified in the patients. Five of them were homozygous, two of them were silent. Moreover, six intron-exon-boundaries have been characterized in the 3# coding sequence. Genotyping will be the basis for simple diagnostic procedures and will allow a heterozygous screening in suspected families.Our sequencing data provide the basis to work out genotype-phenotype correlations and in-vitro expression of mutant NPC1 proteins to assure the impact of observed mutations.

P800
A MUTATION OF THE ACETYLCHOLINE RECEPTOR (ACHR) EPSILON SUBUNIT (ε1267DELG) IS A FREQUENT CAUSE FOR SPORADIC AND AUTOSOMAL RECESSIVE CONGENITAL MYASTHENIC SYNDROMES (CMS). A. Abicht, V. Karcagi, A. Herczegfalvi, W. Mortier, W. Müller-Felber, D. Pongratz, R. Rüdel, H. Lochmüller.

The homozygous mutation ε1267delG in exon 12 of the AChR e subunit was recently described in CMS patients. This mutation leads to a frameshift disrupting the cytoplasmatic loop and the transmembrane region M4 of the esubunit. In this study, 43 patients from 35 non-related families were clinically classified as sporadic cases of CMS (group III according to ENMC consensus) and were analyzed for e 1267delG. PCR amplification, restriction analysis and direct sequencing of AChR esubunit DNA was carried out for each patient. Homozygous e 1267delG was identified in 13 (30%) out of 43 CMS patients from 11 (31%) out of 35 independent families. All e 1267delG families were of Gypsy or south-east European origin. Phenotype analysis revealed an uniform pattern of clinical features including bilateral ptosis, mild to moderate fatiguable weakness of ocular, facial, bulbar and limb muscles. In general, ε1267delG-patients were characterized by the onset of symptoms in early infancy, the presence of ophthalmoparesis, positive response to anticholinesterase treatment and the benign natural course of the disease. In Europe, ε1267delG is a frequent mutation in autosomal recessive and sporadic CMS patients. Further genetic analysis of CMS patients will reveal more genotype/phenotype correlations, and hopefully facilitate genetic diagnosis, counseling and therapy.

P801
EXPRESSION OF HUMAN β-HEXOSAMINIDASE α-SUBUNIT GENE IN THE CENTRAL NERVOUS SYSTEM OF THE TAY-SACHS ANIMAL MODEL. [1,2]S. Martino, [1]C. Emiliani, [1]B.Tancini, [1]C. Cavalieri, [3]An. Orlacchio, [2]D. Dolcetta, [2]A. Consiglio, [2]A.Trojani, [2]C. Bordignon, [1]A. Orlacchio, [2]G.M. Severini. 1 Dipartimento di Biologia Cellulare e Molecolare, Universitê di Perugia, Italy; 2 Thelethon Institute for Gene Theraphy, S. Raffaele Hospital, Milan, Italy; 3 Centre for Research in Neurodegenerative Disease, University of Toronto, Canada

In humans, β hexosaminidase α-subunit deficiency prevents the formation of a functional β-hexosaminidase A heterodimer (Hex A), resulting in the severe neurodegenerative disorder Tay-Sachs disease (TSD), characterized by a massive accumulation of GM2 ganglioside and related lipids mainly in neuronal lysosomes. For this disease there is presently no cure. Our present understanding of the pathophysiology of the disease suggests that in order to correct the enzymatic defect, the direct delivery of the therapeutic enzyme to the central nervous system (CNS) is necessary. Consequently, we developed a gene therapy strategy which consists of the transduction of bone marrow stromal cells by a retroviral vector for the expression of the Hex A enzyme, the differentiation of genetically engineered stromal cells into astrocytes and finally, the local implantation of the differentiated cells.The implanted engineered cells will provide a continuous source of enzyme which will be secreted into the environment and "re-uptaken" by all neighbouring cells. This approach could provide a solution for TSD and have implications for treating neurologic diseases characterized by inherited single gene mutations.

P802
A SECOND CHROMOSOMAL LOCUS FOR LEIGH SYNDROME ASSOCIATED WITH CYTOCHROME C OXIDASE DEFICIENCY. Galimberti, V. Tiranti, G. Comi, A. Bordoni, P. Corona, M. Zeviani - Milano (Italy)

Several defects of mitochondrial enzyme complexes can result in Leigh syndrome (LS), an early-onset mitochondrial disorder characterized by rapidly progressive, symmetric degeneration of brainstem, diencephalon and basal ganglia. The most frequently reported biochemical abnormality in LS is an isolated, severe, and generalized defect of complex IV (cytochrome c oxidase, COX). However, direct screening approaches have failed to detect mutations in the COX subunit genes themselves. By using a functional complementation assay based on fusion between LS^{COX} cells with a panel of several rodent/human rhoí hybrids, we have recently mapped a disease locus for LS^{COX} on chromosome 9q34. Analysis of a candidate gene in the region, SURF-1, revealed deleterious mutations in most of the LS^{COX} patients investigated. The same functional screening has been performed to exclude most of the human chromosomes from containing a gene complementing a severe COX deficiency in a fibroblast cell line presenting no mutations of SURF-1. Finally, the rescue of the COX-defective phenotype was obtained by fusing our proband cell line with a rhoí hybrid containing a single specific chromosome as the only human contribution. The proband cell line belongs to a baby girl affected by a Leigh-like syndrome, but with additional or unusual clinical features, including onset at birth with severe congenital lactic acidosis, microcephalia, facial dismorphisms, and limb malformations. To make progress toward the identification of the responsible gene, chromosome-specific linkage analysis and analysis of chromosome-specific potential candidates have been undertaken.

P803
CLINICAL PRESENTATIONS AND MISDIAGNOSES OF NEUROFIBROMATOSIS TYPE 2 (NF2) IN CHILDHOOD. Martino Ruggieri, Susan M Huson.Department of Clinical Genetics, Oxford Radcliffe Hospital, Oxford, UK

Nf2 is a genetic disorder leading to the development of multiple nervous system tumours. Although initial signs and/or symptoms may be evident in childhood these are often unrecognised and their significance appreciated later when other signs become manifest or because of a positive family history. Objectives: To identify the early signs and symptoms which should alert a physician for Nf2. Methods: Data on 19 patients (8 M, 11F) fulfilling the National Institutes of Health criteria for Nf2 seen at the Oxford neurofibromatosis clinic in the period 1990-1998 who had their clinical presentation in childhood. Results: Causes of referral prior to a definitive diagnosis of Nf2 were: 1) Ophthalmologic problems: early onset symptomatic lens opacities (n=3); early onset optic nerve sheath meningioma misdiagnosed as isolated optic nerve glioma (n=1); intermittent visual loss (due to underlying brain tumours) treated as amblyopia (n=2). 2) Otolaryngology problems: hearing loss (n=4) or tinnitus and vertigo (n=1) in early teens disregarded or treated as ear infections; hoarseness (n=2) attributed to chest infection or infectious laryngitis. 3) Neurological problems: root lesions presenting with focal limb muscle wasting (n=2) but no associated tumour. 4) Skin problems: Schwannomas misdiagnosed as neurofibromas because of associated CAL spots (n=3); Nf2-plaques unrecognised (n=4). Conclusions: Children with Nf2 often first come to medical attention because of ocular, skin or subtle neurological problems the significance of which is often realised when they later present with more classical symptoms due to bilateral vestibular schwannomas.

P804
COGNITIVE DEFICITS IN SPINOCEREBELLAR ATAXIA TYPE 1 (SCA1) AND 2 (SCA2). Bürk, MD[1], C. Globas, MD[1], C. Zühlke, PhD[2], M. Abele, MD[3], A. Brice, MD[4], I. Daum, PhD[5], T. Klockgether, MD[3], J. Dichgans, MD[1]. [1]Tübingen, Germany, [2]Lübeck, Germany, [3]Bonn, Germany, [4]Paris, France, [5]Bochum, Germany.

The cognitive impairment in patients with genetically confirmed spinocerebellar ataxia type 2 and 3 was studied using a neuropsychological test battery comprising tests for IQ, general intellectual abilities, attention, verbal and visuospatial memory, and executive function and compared to age - and IQ - matched controls. Patients' test performance was not related to motor disability, repeat length or the age of onset. Therefore, intellectual impairment is neither likely to result from progressive motor disability nor to depend on the length of the extended polyglutamine stretch. Tests of visuospatial memory and attention were not significantly impaired in both patient groups. Interestingly, 25 % of the SCA2 subjects presented with dementia while none of the SCA3 individuals had general intellectual impairment. In SCA3 and (non-demented) SCA2 subjects, there was evidence of defective verbal memory. Additional executive dysfunction was prominent in SCA2, a finding that is likely to be contingent upon disruption of cerebrocerebellar the connections.

P805
STROKE IN YOUNG ADULT AND HYPERHOMOCYSTEINEMIA. LINK TO THE ASSOCIATION OF C677T AND A2756G MUTATIONS. Chatel M.(1), Candito M. (2),Ben Sakel S.(1), Bedoucha P.(1). Service De Neurologie (1), Laboratoire De Biochimie (2) CHRU Nice, France

A 19 years old male was admitted for a sylvian stroke. On biology tests, high levels of homocysteinemia were found. Methionine load test led to an increase of homocysteinemia levels. The hyperhomocysteinemia has been proved to be a risk factor in myocardial infarctus and in stroke. High levels of homocysteinemia come from abnormalities in the enzymatic pathways of synthesis or catabolism of homocysteine. Coenzymes (B6, B12 vitamines or folic acid) may also play an important role in absence of mutated enzymes. In the reported case, the homocysteine level was 20 micromol/l (N12) and 150 micromole/l after methionine load (N50). Analysis of the enzyme genes showed two mutations: the C677T on the Methyl-TetraHydroFolate Reductase (MTHFR) and the A2756 on the Methionine Synthase (MS). The C677 mutation is a substitution Cytosine/Thymine, at position 677 on chromosome 1p3-63; this mutation leads to a reduced activity and to a thermolability of the enzyme. It is a frequent heterozygous mutation and in this case, high levels of folates are necessary for coping with the required turn over of homocysteine. The A2756 mutation is a substitution adénosine/guanine at the 2756 position on the Methionine Synthase gene, on chromosome 1q42.3-43. In this patient, supplementation with folic acid (5mg/d) led to return homocysteine to normal levels (6 micromole/litre). Conclusion: The association of the two mutations, C677T and A2756G, may have led to hyperhomocysteinemia which increased the risk for thombosis and stroke. We are not aware of any report of such association in the litterature and this case raises the question of systematic screening for enzymatic mutations in every young adult stroke. The return to normal of homocysteine with the adjunct of small doses of vitamine or folate acid raises also the issue of primary prevention in subjects at risk in their family.

P806
CYTOGENETIC MARKERS OF A GENETIC PREDISPOSITION TO STROKE. Kuznetsov V. Institute of Gerontology, Kiev, Ukraine

Stroke is a genetically predisposed disease. To study the mechanisms responsible for the formation of a hereditary disposition to this disease, we examined a morpho-functional organization of the chromosomes. The relatives of patients with stroke had a higher frequency of chromosomal aberrations and a lower frequency of cells with the associations in comparison with the relatives of long-lived. The peripheral blood lymphocyte cultures and the differential colouring method modified by Prokofyeva-Belgovskaya (1986) was used to examine the chromosomal polymorphism variants. In the group of 58 patients with stroke aged 40-59 years we determined the cytogenetic factors of C-heterochromatin on 1,9,16 and Y chromosomes. The age-matched relatives of the long-lived (n=30) made a control group. We found that the distribution of homologous pairs on 1,9 and 16 chromosomes by heteromorphism was the same in stroke patients and control persons. In male subjects of both groups there was a positive correlation between relative sizes of C segments on homologues of 1,9 and 16 chromosomes. The females showed inter-group differences in the correlation coefficients of C segment on 16 chromosome homologues. In both male and female stroke patients there was a statistically lower variability of summary sizes of C segments on 1,9 and 16 chromosomes. The male patients had a shorter Y chromosome and a smaller C block compared to healthy subjects. The above features of chromosome polymorphism can be considered as cytogenetic markers of stroke. These findings may contribute to our knowledge about the risk factors of this disease, to perfecting the system of medico-genetic consultancy and primary prophylaxis.

P807
SUBCUTANEOUS MICRODIALYSIS IN MITOCHONDRIAL CYTOPATHY. W.Sauter, M.S.Damian, H.Reichmann, Dept. of Neurology, Univ. of Dresden, Germany

Mitchondrial cytopathies (MC) are characterized by lactic acidosis and an elevated lactate-pyruvate-ratio (LPR) due to disordered respiratory chain function. Serum lactate is generally measured discontinually as repeated rest values or during standardized exertion tests. We examined the use of subcutaneous microdialysis (MD) for continuous monitoring of patients with MC. Methods: Informed consent was obtained from six patients with confirmed (n = 3 with A3243G transition; n = 2 with common deletion; n = 1 unclassified MC) and one with suspected MC. The patients were classified into three groups according to clinical severity. All were provided with an abdominal subcutaneous MD probe (CMA 60) for continuous monitoring of glucose, lactate, pyruvate and glycerine over 3 – 5 days according to standard techniques (CMA 600). During this time nutrition and all activities were documented and glucose tolerance and bicycle exertion tests performed in addition to magnetic resonance spectroscopy and PET of the brain. Results: MD was well tolerated without complications in all cases. In all cases repeated measurements of resting lactate and pyruvate showed intermittent normal values and in only 4 intermittent pathological evaluations. The bicycle exertion test was diagnostic in 3 patients, but the others only tolerated reduced exertion levels. The average LPR per patient for the whole period varied between 0,012 and 0,079. The patient with the most serious disease consistently had the most pathological values, whereas the patient with suspected MC (later never confirmed) was the only one clinically and biochemically normal throughout. The patients with intermediate disease severity showed a close correlation of clinical status with s.c. MD data in contrast to their largely non diagnostic results of discontinuous serum measurements. Individual diurnal stress factors (e.g. fasting, glucose load, dialysis) were reflected by LPR and other MD values. Conclusions: Subcutaneous MD is a promising method for minimal invasive longtime monitoring of metabolic conditions in patients with confirmed or suspected MC. Potential uses include increased diagnostic certainty in suspected MC without molecular confirmation and monitoring of therapeutic trials.

P808
EMERY DREIFUSS MUSCULAR DYSTROPHY. Vytopil M., Vohçnka S., Bednarík J., Kadanka Z., Schildberger J., Lukç_ Z., Toniolo M. Brno, Czech Republic

Emery-Dreifuss muscular dystrophy (EDMD) is a rare muscular dystrophy presenting with serious cardiac rhythm defects and/or cardiomyopathy, early contractures and wasting and weakness. X-linked inherited EDMD is caused by the mutation of Xq28 located gene encoding nuclear membrane protein - emerin. The objective of the study is to determine whether X-linked form of EDMD plays a significant role in young patients with cardiomyopathy and/or heart conduction defects. Inclusion criteria: Patients suffering from dilated cardiomyopathy and/or heart conduction defect requiring a pacemaker. Exclusion criteria: Onset of heart disease after the age of 40 years, atherosclerotic heart disease, diabetes mellitus, alcoholism. Patients who met these criteria were performed muscle biopsy including detection of emerin. We searched through the database of the Department of cardiology University Hospital Brno. One of ten relevant patients showed deficiency of emerin in muscle biopsy: Male, 28, serious heart rhythm defects since the age of 16, pacemaker implemented in the age of 26. Neurological examination: areflexia, wasting and weakness of triceps a biceps muscles bilaterally, slight wasting of facial muscles. No contractures, no pseudohypertrophies. Intelect unimpaired. Electromyography (EMG) showed myogenic pattern. DNA analysis proved mutation in the 6th exon of the responsible gene. DNA studies showed no abnormality in either parents or sons of the patient. In the second step we now search through databases of cardiological centers in the region of Southern Moravia with population of two million.

P809
A NEW SYNDROME OF FAMILIAL ESSENTIAL TREMOR AND GENERALIZED TONIC CLONIC SEIZURES. CLINICAL AND GENETIC STUDY OF A FAMILY.: P Labauge (MD)*/**, F Attané (MD)***, C Tannier (MD)***, E Tournier-Lasserve (MD)*, A Ducros (MD,PhD)*. INSERM U25. Faculté Necker, Paris. **CHU Caremeau. Nömes. ***CH A Gayraud. Carcassonne. FRANCE.

Objectives. To analyse the clinical and genetic features within a four generation family associating FET and generalized tonic clonic seizures (GTCS). Background. Essential tremor is one of the most common neurological disorder. Familial essential tremor (FET) accounts for 17 % to 78 % of all cases. Two genes (FET1 and FET2) were recently mapped to the chromosome 3 q13 and 2p22-p25. Design / methods. A total of 14 living relatives were directly interviewed and examined. ET was diagnosed based on the criteria proposed by Bain et al. (1994). Seizures were classified according to the International Commission Criteria. Linkage analysis was performed with 4 markers spanning FET1 interval (D3S1278, D3S1267, D3S1292, D3S1279) and 5 markers spanning FET2 interval (D2S162, D2168, D2131, D2S320). Results: Eleven family members (6 females and 5 males), including 3 deceased subjects, had a similar definite essential tremor. In addition, 8 of these 11 subjects had generalized tonic clonic seizures. Linkage analysis was conducted on a total of 17 family members including 8 subjects with tremor (affected) and 5 subjects without tremor (unaffected). Negative maximum LOD scores were obtained with all markers spanning the FET1 genetic interval. Positive LOD scores were obtained with three chr. 2p22-p25 markers. Conclusions.This is the first report of a family in which ET was inherited as an autosomal dominant trait together with GTCS. This family is consistent with linkage to the FET2 locus on 2p22p25.

P810
PAROXYSMAL NON KINESIGENIC DYSKINESIA: A BELGIAN FAMILY. Dupuis MJM. - Frederick A.M. (Hospital St Pierre - Ottignies) - Wood N.W. (University College London -Institute of Neurology).

We describe a new family of Paroxysmal non Kinesigenic Dyskinesia (PNKD) originating from Brabant in Belgium. By history the family included 14 members of 6 generations, 8 males and 6 females. Five are dead or lost to follow up. In this family, PNKD appears early sometimes before one year, can be induced by stress, fatigue or alcohol but not exercise, movements, caffeine or nicotine. Therapeutic trials with antiepileptics have been disappointing and carbamazepine induced worsening; we are planning other therapeutics trials. PNKD is a rare genetic disease and it has been postulated as maybe another channelopathy. Genetics studies have been performed in 3 families with paroxysmal dystonic choreoathetosis (a form of PNKD) and all have shown linkage to 2 q 33-35. Genetic linkage analysis in this family is in progress.

P811
ANALYSIS OF NAT-2 AND CYTOCHROME P450 2D6 GENE POLYMORPHISMS IN PARKINSON'S DISEASE (PD) IN WESTERN AUSTRALIA.Garlepp, MJ,[1,2] Bolitho E,[1] Kelly N,[1] Phillips BA,[2] Stell, R[2], Mastaglia FL[2]. School of Pharmacy, Curtin University of Technology[1] and the Australian Neuromuscular Research Institute (ANRI)[2], QE II Medical Centre, Perth, WA, Australia.

Mutations in the N-acetyl transferase-2 (NAT-2) and cytochrome P450 2D6 (CYP2D6) genes have been reported to be increased in frequency in

PD, although conflicting data have been published. We conducted a genotypic analysis of 53 patients with sporadic PD seen in the Movement Disorders Clinic at the ANRI. The CYP2D6 null alleles *3, *4, *5, *6, *7, *8 and *10 were defined. The overall null allele frequency was 21% in PD and 15% in our control group, being consistent with published frequencies for populations of European origin. Only one PD subject was homozygous for a CYP2D6 null genotype. The vast majority (82%) of the mutant alleles in both groups were CYP2D6*4 as might be expected from published data. Analysis of the NAT-2 alleles M1, M2 and M3 in PD showed 56% to be genotypically slow acetylators. These frequencies are similar to those reported by other groups in PD and in Caucasian controls. Of particular interest was the observation that 8 of 11 (73%) patients with onset under 50 yrs had the slow acetylation genotype. No particular allele was responsible for the increased frequency of slow acetylators. These data are consistent with a previously published observation. Analysis of the NAT-2 genotypes in conjunction with the CYP2D6 genotypes provided no indication of an interaction between these two loci in conferring susceptibility to PD. These data do not support a role for the CYP2D6 locus in determining susceptibility to PD although the role of NAT-2 slow acetylator phenotype is worthy of further research, particularly in early onset disease.

P812
LINKAGE ANALYSIS IN EIGHT BRITISH FAMILIES WITH DOMINANTLY INHERITED PURE ESSENTIAL TREMOR. Sian Spacey, Peter Bain, Leslie Findlay, Paul Worth, Nicholas Wood.Neurogenetics Unit, Institute of Neurology, Queen Square, London, England.

Objective: To genetically map essential tremor in 8 British families with dominantly inherited "pure" essential tremor (ET). Background: Essential Tremor is the most common movement disorder in humans and estimates suggest that over 90% of essential tremor cases are dominantly inherited. A dominantly inherited ET locus has been identified at 2p22-p25 in an American Czech family and to 3q13 in 16 Icelandic families We present 8 British families with "pure" autosomal dominant essential tremor and describe the clinical features and results of genetic mapping. Methodology: Eight British families with dominantly inherited pure essential tremor were studied. Linkage was sought using ~400 polymorphic microsatellite markers 5-15 cM apart throughout the genome. Lod scores were generated using the MLINK program. Results: To date there is no evidence for linkage in these families to the 2p22-p25 and 3q13 loci previously identified in other ET families. A genome wide linkage search is currently underway. Conclusion: Eight British families with autosomal dominant pure essential tremor did not map to the previously described loci on 2p22- p25 or 3q13. Our results suggest the existence of at least one more locus that contributes to the essential tremor phenotype.

P813
ANALYSIS OF THE MYELIN OLYGODENDROCYTE GLYCOPROTEIN-HLA EXTENDED HAPLOTYPE IN SARDINIAN MULTIPLE SCLEROSIS. Marrosu M.G*., Murru R.*, Lai M.*, Murru M.R*., Costa G.*, Melis C.*, Cocco E.*, Cucca F.[x], * Multiple Sclerosis Center, Department of Neuroscience, [x] Department of Pediatrics, University of Cagliari (Italy).

Objective: to study the association between alleles of the extended myelin oligodendrocyte glycoprotein (MOG)-HLA-DRB1-DQA1-DQB1 haplotype in Sardinian MS families. Materials and methods: the study has been carried out on 216 MS Sardinian families. All patients had clinically defined MS according to the criteria of Poser et al. (1983). DNA was amplified for MOG (TAAA)10 repeats using MOG 51 fluorescent dye labelled and MOG 52 primers, according to the method of Malfroy et al (1995). Amplification products and internal standard were analyzed by A.L.F. Sequencer. Amplification of the polymorphic second exon of the DRB1, DQA1, DQB1 genes and dot-blot analysis of amplified DNAs with sequence-specific oligonucleotide probes were carried out. TDT analysis was performed according to Spielman et al. (1993). In order to exclude any spurious association with MS owing to segregation distortion, we also compared the TDT results in healthy siblings. Results: TDT of extended MOG (TAAA)10-HLA-DRB1-DQA1-DQB1 haplotype showed an excess of transmission of the 226 bp-DRB1*0301-DQA1*0501-DQB1*0201 haplotype (p=0.003) and of the 226 bp-DRB1*0405-DQA1*0501-DQB1*0301 haplotype (p=0.03) in MS, but not in healthy sibs. Discussion: present data demonstrate that extended MOG226 bp-DRB1*0301-DQA1*0501-DQB1*0201 and 226 bp-DRB1*0405-DQA1*0501-DQB1*0301 haplotypes are in linkage disequilibrium with MS in Sardinians. These data can suggest two hypotheses: (i) the predisposing region of HLA is constituted by the whole DRB1-DQA1-DQB1/ MOG-associated haplotypes and requires a combination of alleles at these loci, or (ii) the primarely responsible gene is located inside or stricly near to the predisposing haplotypes. A fine mapping of the region can help to identify the region most commonly shared by identical-by-descent MS patients. *Supported by Dompé Biotec and Federazione Italiana Sclerosi Multipla.*

P814
CORRELATION BETWEEN CLINICAL COURSE AND HLA-DRB1-DQA1-DQB1 HAPLOTYPES IN SARDINIAN MULTIPLE SCLEROSIS PATIENTS. Marrosu M.G.*, Lai M.*, Murru R*., Costa G.*, Murru M.R*., Melis C.*, Cossu G.*, Cucca F.[x], Multiple Sclerosis Center, Department of Neuroscience, [x] Department of Pediatrics, University of Cagliari (Italy).

Objective: to identify whether the HLA predisposing haplotypes modify clinical aspects of MS, using for the study both an association analysis and the transmission disequilibrium test. Materials and methods: 245 patients were classified on the basis of the EDSS reached in a defined time of the disease course: benign (EDSS < 1.5 reached within 10-15 yrs; EDSS 2-3 within 16-20 yrs; EDSS 3.5 beyond 20 yrs); intermediate (EDSS < 5 reached within 10-15 yrs from onset; EDSS from 5.5 to 6.5 reached within 16-20 yrs; EDSS > 6.5 reached after 20 yrs) and progressive (EDSS > 6, disease course < 5 yrs; EDSS between 6.5-7.5, disease course 6-10 yrs; EDSS > =8, disease course between 10-15 yrs). 102 patients were typed from the population case study: 28 patients were included in the benign course, 42 in the intermediate and 32 in the progressive. 143 patients with both parents (not included in the association analysis) were typed for the TDT test: 43 had a benign course, 67 intermediate and 33 progressive course. Amplification of the polymorphic second exon of the DRB1, DQA1, DQB1 genes and dot-blot analysis of amplified DNAs with sequence-specific oligonucleotide probes were carried out. Results: a) Association analysis. An increased of the HLA-DRB1*0301-DQA1*0501-DQB1*0201 haplotype was found in benign patients compared to C (p=0.02). Progressive patients showed an increase of the HLA-DRB1*0405-DQA1*0301-DQB1*0302 haplotype compared to C (p=0.0003), to overall (unsplitted) patients (p=0.05), to intermediate (p=0.005) and to benign (p=0.05) MS. b) TDT analysis. Benign patients showed an excess in the transmission of the HLA-DRB1*0405-DQA1*0501-DQB1*0301 haplotype (p= 0.03). An increased transmission of the HLA-DRB1*0405-DQA1*0301-DQB1*0302 haplotype in progressive patients compared to overall (p= 0.03) and to benign (p= 0.03) MS subjects. Discussion: Results of the association study suggest that MS course can be influenced by different HLA haplotypes. Particularly, the HLA-DRB1*0405-DQA1*0301-DQB1*0302 haplotype seems to be peculiar of progressive MS, suggesting that these molecules have a role "per se" or acting together other gene(s)/gene products. *Supported by Dompé Biotec and Federazione Italiana Sclerosi Multipla.*

P815
AUTOSOMAL-DOMINANT PARKINSON'S DISEASE LINKED TO 2P13 IS NOT CAUSED BY MUTATIONS IN TRANSFORMING GROWTH FACTORα (TGFα). Zink M, Grimm L, Gasser Th., Munich, Germany

Hereditary factors emerged recently as causes for Parkinson`s disease (PD). Three susceptibility genes have been mapped: Missense mutations in the gene for α-synuclein (PARK1, 4q21-q23) segregate with the illness in an autosomal-dominant fashion. A second locus (PARK2) has been mapped on 6q25.2-27 and the gene (Parkin) has been isolated in families suffering from autosomal-recessive juvenile PD. The third gene maps to 2p13 (PARK3). In the present study we examined the candidate gene transforming growth factorα (TGFα) wich is located in the PARK3-region. The polypeptide mitogen TGFα exerts trophic actions on dopaminergic neurons in vitro and TGFα-deficient mice have fewer dopaminergic neurons in the substantia nigra. In order to obtain intronic sequences flanking the exons of the TGFα-gene a library of P1-derived artificial chromosomes (PAC) has been screened with the TGFα-cDNA. After digest of positive PAC-clones with Sau3A and PstI followed by religation we performed an inverse PCR with primers binding to exon-sequence but directed to the 5'-orientation of the gene. After sequencing the product intronic primers have been used to sequence the coding regions. We did not find any mutations in the exonic or exon-flanking intronic sequences of index patients. This result is consistent with a necessary function of TGFα for dopaminergic neurons but excludes mutations in the coding region of this gene as a cause for hereditary PD linked to 2p13.

P816
ANALYSIS OF THE TNFα AND IL 10 PROMOTOR IN MS PATIENTS. Mäurer, M., N. Kruse, R. Gie°, K.V. Toyka, P. Rieckmann. Department of Neurology, University of Würzburg, 97080 Würzburg, Germany

The objective of this study was to determine wether sequence variations in the tumor necrosis factor alpha (TNFα) gene and the interleukin 10 (IL 10) gene are associated with with MS course or severity. A G to A nucleotide transition in the TNFα promotor at position -308 (TNF2 allele) was shown to be associated with increased TNFα production whereas a G to A substitution at position – 1082 in the IL 10 promotor resulted in a higher IL 10 protein production. Methods. With regards to course and clinical severity of disease we examined the TNFα -308 and the –1082 IL 10 polymorphism with an allelic discrimination PCR to detect the G to A transition in the genomic DNA of MS patients. Disease severity was defined by the progression index (PI) and by progression to the important clinical landmarks EDSS 3.5 and EDSS 6. In addition we evaluated the mRNA expression in whole blood with quantitative PCR. Results. DNA samples from 283 MS patients were analysed. The TNF2 allele was not associated with a certain disease course. No association was found for the accumulation of neurological deficits and progression to clinical landmarks. Although MS patients with the TNF2 allele tended to progress more rapidly from EDSS 3.5 to EDSS 6 this difference was statistically not significant ($p = 0.2$). Likewise we found no association between the –1082 polymorphism in the IL 10 promotor and severity and course of multiple sclerosis. Moreover we could not detect a statistically significant interaction between the polymorphisms in the TNFα and IL 10 gene, resepectively. Nevertheless, a significantly higher TNFα mRNA expression in blood cells of patients carrying the TNF2-allele in comparison to the group with the wild type ($p = 0.024$) was detected. Therefore the TNF2-allele is associated with higher TNFα mRNA baseline levels but this allele appears not to contribute to MS susceptibility or severity. Conclusion. Our data indicate that the resulting haplotypes are not likely to contribute to MS susceptibility or severity. Although the dimorphisms in the promotor regions of the TNFa and IL 10 genes are associated with altered cytokine production in vitro.

P817
DNA POLYMORPHISM OF PARTIAL EPILEPSY IN MACEDONIAN POPULATION. Ilievska Liljana[1], I.K. Gorgoski[2]. 1-Clinic of Neurology, Faculty of Medicine; 2-Institute of Biology, Faculty of Science; Skopje, Republic of Macedonia

The main aim of the work is to evaluate the possible molecular basis of partial epilepsy in these patients by determination of RFLP in the region of 2 million base pair of human chromosome 21. Genomic DNA from seven families with a total of 42 members having partial epilepsy were examined. DNA from these subjects was diagnosed with two restriction enzymes (Bam HI and Ava II), and fragments were identified by hybridization with 500-bp cystein B cDNA probe. Our analysis with both restriction enzymes (Bam HI and Ava II) showed presence of polymorphic restriction sites in part of the region of 2 million base pair of human chromosome 21. These results slightly suggest that there is a non-randomly association of these polymorphic restriction sites the partial epilepsy. In one family in which the father has partial complex seizures by in situ hybridization method, an abnormal 21 chromosome was found, which results should be checked in a number of cases.

P818
POSTPARTUM PARAPARESIS AS INITIAL PRESENTATION OF NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES. A. Mergam[1], S. Laureys[2,3], E. Schmedding[3], P. Maquet[2], G. Ebinger[3] - [1]Department of Internal Medicine, ULB Brussels; [2]Department of Neurology, CHU LiÅge; [3]Department of Neurology, VUB Brussels, Belgium

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominantly inherited neuropathy, which classically presents with recurrent palsies or sensory disturbances - often precipitated by minor trauma. We report an atypical presentation of a sporadic form of HNPP: the acute development of a paraparesis of the legs after delivery. A 30 year old primipare who developed an areflexive flasque paresis of both legs directly after delivery was transferred to our department with the clinical diagnosis of Guillain Barré syndrome. Personal and familial medical history was without major events. Delivery was uneventful and was performed without anaesthetics. Cerebrospinal fluid was normal. Motor and sensory conduction velocities of median, ulnar, tibial, peroneal, and sural, nerves were examined bilaterally. Distal latencies of motor action potential were all markedly increased. Conduction velocities were reduced in all nerves. Sensory and motor action potential amplitude was at the lower normal limit. A marked conduction slowing of motor velocity of the ulnar nerves at the elbow groove and of sensory velocity of the median nerve at the wrist was detected bilaterally. Needle examination showed chronic potentials in the distal muscles of both legs. Molecular analysis confirmed a deletion of chromosome 17p11.2. This atypical presentation of HNPP stresses the importance of its early electrophysiological recognition.

P819
NEUROFIBROMATOSIS AND MULTIPLE SCLEROSIS: IS THEIR ASSOCIATION COINCIDENTAL? A CASE REPORT. A Calvo, A Cucatto, AA Terreni, A Chiÿ. Department of Neuroscience, University of Turin, Italy.

We describe a case with a rare association of two apparently distinct neurological disorders in a young man of 32 years: a neurofibromatosis type I (NF-1) and a severe form of definite multiple sclerosis (MS). NF-1, a disorder of ectodermal tissues proliferation, inherited with dominant autosomal trait, was recognized during the childhood, due to the presence of multiple coetaneous lesions (neurofibromas and "milk-coffee" maculae) on face, trunk and limbs. Until adult age, the patient had no clinical evidence of neurological involvement by NF-1. MS had its clinical onset at the age of 23 years, when the patient firstly came to our observation for dizziness, action tremor and sensorimotor impairment of right limbs. MS was confirmed by magnetic resonance, evoked potentials and cerebrospinal fluid findings. After 2 years of remitting-relapsing course, MS evolved to a secondary progressive form. A "non coincidental" relationship between the MS and NF-1 has been postulated, on basis of the identification, in the *NF-1* gene of chromosome 17, of a nucleotidic sequence identical to the oligodendrocyte-myelin related glycoprotein (OMPG) gene. It's here also discussed the difficulty of evaluating neuroimaging findings (MRI), since both entities involve similar anomalies.

P820
SWITCHING OFF THE PMP22 GENE IN OVEREXPRESSING MICE. Javier Perea, Andrea Robertson, Tanya Tolmachova, P.K. Thomas. Clare Huxley, London, UK

Hereditary motor and sensory neuropathy Ia is associated with a segmental 1.5 Mb duplication on chromosome 17p11.2 which includes the gene for peripheral myelin protein 22 (*PMP22*). In order to determine whether the phenotype is reversible we have made a conditional mouse model where overexpression of mouse pmp22 can be switched off by feeding the mice with doxycycline. We have made transgenic mice which have either *pmp22* or β-*galactosidase* (βGal) cDNAs under the control of a conditional promotor which depends on the tTA protein, and transgenic mice with tTA driven by the PMP22 promotor. Activation by the tTA protein is repressed by doxycycline. β-Gal staining was used to assess the tissue specificity of the tTA inducer. Staining was found specifically in peripheral nerve tissue along (and sometimes within) the myelin sheath and around Schwann cell nuclei. Other tissues were negative except in associated nerves. To examine the degree to which the tTA inducer could be turned off, 2 month animals were fed with doxycycline for various times. Staining in nerves decreased progressively from 1 to 3 weeks and by 4 weeks was not detectable. Animals expressing *pmp22* cDNA had a distinct pathology including a population of thinly myelinated and amyelinated fibres. When fed doxycycline from before birth or from 9 days the pathology was almost, but not completely, abolished. We are now feeding adult mice with doxycycline to determine whether the phenotype can be corrected in adult mice.

P821
A STUDY OF MITOCHONDRIAL DEAFNESS IN A LARGE PEDIGREE. A.Siddiqui[1], T. Pulkes[1], I.P. Nelson[1], M.G. Sweeney[1], D. Stephens[2], M. Francis[2], N.W.Wood[1], W.Reardon[3] and M.G.Hanna[1]-Department of Clinical Neurology, Institute of Neurology, London, England[1] - Department of Audiological Medicine, University of Wales College of Medicine, Cardiff, Wales [2] - Department of Clinical Genetics and Fetal Medicine, Institue of Child Health, London, England [3]

The aim of this study was to define the genetic molecular basis of maternally inherited sensorineural deafness in a large pedigree. This was studied by automated sequencing of the entire mitochondrial genome in an af-

fected individual from this pedigree. The pedigree contained 16 affected members with sensorineural deafness and extended over 5 generations. Some of the affected members also exhibited thyroid disease, but Pendred's syndrome was excluded. There were no other neurological symptoms. The 1555,7445 and 3243 mutations had been excluded. Five previously unreported nucleotide changes were found which were as follows: one change in tRNA Threonine at 15905 T to C, two changes in theND5 subunit gene at 12634 A to G, and 13630 A to G, and two changes in the 16S ribosomal RNA at 1721 C to T, and 2755 A to G. This is one of the largest pedigrees reported where deafness is inherited in a matrilineal fashion which strongly suggests that a mitochondrial mutation is responsible. Any of these changes represent possible candidates for causing sensorineural deafness in this family.

P822
CLINICAL AND GENETIC FINDINGS IN AUTOSOMAL DOMINANT LIMB-GIRDLE DYSTROPHY.[1]E.M. Wicklein, [2]U. Orth, [1]G. Pfeiffer, [1]S. Schröder, [2]A. Gal, [1]K. Kunze. Departments of [1]Neurology and [2]Human Genetics, Hamburg, Germany

Limb-girdle muscular dystrophy with autosomal dominant inheritance pattern (LGMD1A) is more rare than autosomal recessive limb-girdle muscular dystrophy. Clinical reports of a few families exist, most of these reports not yet including genetic studies. The disease locus has recently been mapped to chromosome 5q31-q33. We report a family with LGMD1A with 15 affected individuals known in 3 generations. Patients were clinically examined. Linkage analysis was performed. The disease locus was mapped to chromosome 5q. Symptom onset in this family was in the second or third life decade. Clinical findings are presented. Contrasting previous reports on this disorder, cardiac abnormalities were not found. Clinical investigations in this family give evidence of clinical heterogeneity in LGMD1A. To decide whether there is also genetic heterogeneity, further studies are required to confirm or exclude linkage to the LGMD1A locus.

P823
SCREEN FOR NUCLEAR-ENCODED MITOCHONDRIAL DISEASES BY LARGE SCALE ENU MOUSE MUTAGENESIS. Florian Gekeler, Martin Hrabé de Angelis and Thomas Klopstock, Munich, Germany

Mitochondrial diseases are diseases with impaired function of mitochondrial metabolic pathways. Approximately 1000 genes may code for mitochondrial proteins, but only 13 polypeptides of the respiratory chain are coded by the mitochondrial DNA (mtDNA). The majority of genes is located in the nuclear genome. In the ENU (ethylnitrosurea) mouse mutagenesis screen mutant mice are screened for dominant and recessive nuclear-encoded mitochondrial disorders. The project includes a phenotype screen which looks for symptoms that may be associated with an impaired energy metabolism. In addition, blood samples are analyzed for blood lactate. If lactate exceeds mean + 2 standard deviations (SD), a control blood sample is taken. If the control value is also elevated or mice show phenotypic abnormalities, a strain is established. Up to now we have screened the blood lactate in 1632 C3H-F1 mice (dominant screen), the recessive screen started recently. We found a mean lactate of 2,407 mmol/l with a SD of 0,8 mmol/l. A control blood sample was taken in 39 mice of the dominant screen and in 4 mice of the recessive screen. A confirmation cross has been initiated with 3 mice of the dominant screen and 2 mice of the recessive screen. The screening of chemically mutagenized mice should be an effective way to identify new mouse mutants with nuclear-encoded mitochondrial diseases. Moreover, animal models for mitochondrial diseases will hopefully result from this project.

P824
A NEW FAMILY WITH AUTOSOMAL RECESSIVE PARKINSONISM NOT LINKED TO THE PARKIN GENE. Enza Maria Valente[1], AnnaRita Bentivoglio[2], Tamara Ialongo[2], Alessandro Ferraris[2], Marina Frontali[3], Nicholas Wood[1], Alberto Albanese[2]. [1]Neurogenetics, Institute of Neurology, London; [2]Department of Neurology, Catholic University, Rome; [3]Institute of Experimental Medicine, CNR, Rome.

A large Italian family affected by familial autosomal recessive (AR) Parkinson's disease (PD) is reported. We studied the history of this family during the course of 6 generations. Among 27 people examined, 4 were definitely affected and 2 probably affected. Eight other people, who were not available for examination, have also been reported as probably affected. The proband, a 44-year-old woman, has been affected by PD for six years; the first symptoms were resting tremor, upper limb stiffness and a shuffling, short-stepped gait. Her symptoms progressed slowly and, on examination, she had typical asymmetric parkinsonian signs of bradykinesia, rigidity and tremor at rest. She had remarkable benefit with L-dopa, but developed dopa-induced dyskinesias. All the other affected members of the family presented with a similar phenotype. Linkage of the disease with the Parkin gene on 6q, responsible for AR juvenile Parkinsonism, has been excluded in the family by analysing 4 microsatellite markers close to the gene and 1 intragenic marker. The two described mutations in the α-synuclein gene were not detected in affected members. Currently, Parkin is the only identified gene responsible for an AR form of parkinsonian syndrome. This family is a good resource to attempt to localise a novel gene responsible of AR Parkinsonism. Homozygosity mapping of the genome is in progress and other family members will be examined soon.

P825
THE PHENOTYPE OF WOLFRAM SYNDROME: CLINICAL FINDINGS IN 12 PATIENTS WITH MUTATIONS IN THE WOLFRAMIN GENE. Thomas Klopstock, Michaela Jaksch, Tim Strom, Sabine Hofmann, Konstanze Hörtnagel, Thomas Meitinger and Klaus-Dieter Gerbitz; München, Germany

Wolfram syndrome (WFS) is an autosomal recessive neurodegenerative disorder defined by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD). Mutations were recently found in a novel gene on chromosome 4p16 encoding a putative transmembrane protein. We now provide a detailed clinical description of 12 patients with mutations in the WFS1 gene. Mean age at onset was 6,9 years (range 3 - 11 years), diabetes mellitus being the first symptom in 10 of 12 cases. Optic atrophy and sensorineural deafness were found in all patients beginning at a mean age of 10,8 (5 - 17) years and 14,3 (1 - 22) years, while diabetes insipidus was an inconstant finding. Magnetic resonance imaging in one patient revealed marked atrophy of brainstem and cerebellum. While mitochondrial deletions have earlier been reported in WFS and a deleterious interaction of nuclear and mitochondrial genomes has been assumed, we could not find any mitochondrial mutations in our WFS patients. In conclusion, genetically confirmed WFS patients show a remarkably uniform phenotype, but no evidence for a substantial role of mitochondrial DNA. Mutation detection now allows a reevaluation of the phenotypic spectrum and the molecular pathogenesis of WFS.

P826
ROLE OF DYT7 IN PRIMARY LATE-ONSET FOCAL DYSTONIA IN SOUTHERN GERMANY AND AUSTRIA. [1]Kamm C, [2]Naumann M, [3]Müller J, [1]Mai N, [4]Ceballos-Baumann A, [3]Wissel J, and [1]Gasser T.Departments of Neurology, [1]Klinikum Grosshadern, LMU München, [2]Julius-Maximilians-Universität, Würzburg, [3]Universitätsklinik Innsbruck, [4]Klinikum Rechts der Isar, TU München

Primary late-onset focal dystonia is the most common form of primary dystonia in central Europe. Recently, linkage to chromosome 18p (DYT7) for this dystonia subtype has been reported in a large family from northern Germany, as well as linkage disequilibrium between several chromosome 18 markers and primary late-onset focal dystonia, both in sporadic patients from northern Germany and in members of affected families from central Europe, suggesting the existence of a founder mutation as the predominant cause of dystonia in this population. To evaluate the role of DYT7 in focal dystonia, we tested 100 patients with primary focal dystonia from southern Germany and Austria for linkage disequilibrium at chromosome 18p markers D18S1105, D18S1098, D18S481 and D18S54. We did not find evidence for linkage disequilibrium as compared to 100 age- and sex-matched controls, arguing against the existence of a founder mutation on chromosome 18p and suggesting other genetic or environmental factors underlying focal dystonia in this population.

P827
EVIDENCE FOR FURTHER PARKINSON LOCI IN TWO UK FAMILIES WITH AUTOSOMAL DOMINANT PARKINSON'S DISEASE. E.A.Graham, J.R.Vaughan, N.L.Khan,, J.D.Gayton, P.Piccini, D.Nicholl, M.B.Davis, N.W.Wood. Institute of Neurology, London, UK

We have identified two large multi-generation kindreds with autosomal dominant Parkinson's disease (ADPD) originating from Suffolk and Lincolnshire. Since such kindreds are extremely rare, identification of two large kindreds suitable for a genome–wide search represents a significant

step towards discovering a new PD locus. Currently there are four loci - Chr 4q (α-synuclein), 4p (ubiquitin hydrolase?) and 2p (gene not known), and 6q (parkin). An extensive genealogical search for affected members as well as performing PET scans of clinically unaffected members has enabled us to extend the two kindreds. The families were screened for the known PD loci by linkage analysis and DNA sequencing of the coding regions of α-synuclein and ubiquitin hydrolase. Twenty-five affected members from one kindred and twelve from the second kindred have been identified over four generations. The known loci in PD have been excluded as a cause of the clinical phenotype in these families under the accepted model. Linkage of the disease phenotype in these families to the autosomal recessive parkin locus on 6q has also been excluded. The coding regions of α-synuclein and UCHL-1 were sequenced and no mutations found. These families appear to be genetically distinct from other phenotypically identical ADPD kindreds linked to the three loci identified so far. Presently a genome-wide linkage analysis is being performed to identify a fourth locus in these kindreds, at the time of writing 33% has been excluded. The identification of another PD locus will further our understanding of the pathogenesis of PD.

P828
A NOVEL NONSENSE MUTATION IN THE MITOCHONDRIAL CYTOCHROME B GENE ASSOCIATED WITH EXERCISE INTOLERANCE AND COMPLEX III DEFICIENCY. T. Pulkes[1,2], A. Siddiqui[1,2], J.A. Morgan-Hughes[2], N.W. Wood[1], M.G. Hanna[1,2]Neurogenetics[1] and Muscle[2] Sections, Department of Clinical Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, U.K.

The objective of this study was to define the molecular genetic basis of mitochondrial myopathy in a patient with mitochondrial respiratory chain complex III deficiency. The patient had exercise intolerance, proximal limb weakness and lactic acidosis. There was no family history. Automated mitochondrial DNA sequencing of the respiratory chain complex III subunit (cytochrome b) gene was undertaken. A novel heteroplasmic G to A mutation at nucleotide position 15723 in the cytochrome b gene was identified. The mutation leads to a change from an encoded tryptophan (UGA) to a stop codon (UAA) resulting in loss of 55 amino acids at the C-terminal of cytochrome b. It was absent in 80 healthy controls and 90 patients with mitochondrial encephalomyopathy. These data strongly support the pathogenicity of this mutation. This is the second stop codon mutation in cytochrome b to be reported in association with human disease.

P829
INTRAFAMILIAL VARIABILITY IN INFANTILE MITOCHONDRIAL DNA DEPLETION. Perini M.P., Napoli L., Bordoni A., Comi G.P., Toscano A., Agennouz M., Sciacco M., Strazzer S., Prelle A., Martinuzzi A, Scarlato G. Milano, Messina, Conegliano; Italy

We describe a familial mitochondrial disorder affecting three male sons of a marriage of unknown consanguinity. The parents were healthy. Clinical picture was variable in that the first son was affected by an early-onset encephalomyopathy and died at age 7 yrs, the second showed muscle involvement with proximal lower limb muscle weakness at age 3 yrs and survive at age 11 yrs and the last (now aged 2 yrs) experienced epileptic crisis during the first year of life. Muscle biopsies of all three patients showed a severe diffuse Cytochrome c oxidase (COX) deficiency, while their mother's muscle biopsy was normal. A severe COX defect was present biochemically. Mitochondrial DNA analysis excluded microrearrangements, point mutations within tRNA genes, COX I, II, III subunits, D-loop, O_H and O_L regions. Quantitative Southern bot analysis of muscle mtDNA performed in the two younger patients demonstrated a relevant depletion (8.4% and 9.2% residual mtDNA). The muscle mtDNA depletion was confirmed by immunohistochemistry with antiDNA antibodies and by in situ hybrization. Skin fibroblast cultures from one patient showed a partial mtDNA defect (54% of normal values) by quantitative slot blot. An autosomal recessive inheritance is described in some mtDNA depletion families (including ours), although the different patterns of tissue involvement in affected members belonging to the same pedigree need still to be understood.

P830
MUTATION ANALYSIS OF AMYLO-1, 6-GLUCOSIDASE, 4-α-GLUCANOTRASFERASE GENE IN GLYCOGEN STORAGE DISEASE TYPE IIIA PATIENTS. G.P. Comi, Lucchiari S., A. Bordoni, J. Shen, Y.-T. Chen, G.M. Hadjigeorgiou, A. Toscano, G. Scarlato. Milano, Italy.

We describe four novel mutations observed in six independent patients affected with Glycogen Storage Disease (GSD) type IIIa. GSD type III is an autosomal recessive disease due to Amylo-1, 6-glucosidase, 4-α-glucanotransferase (AGL) deficiency. Patients population include five adult and one infantile case, all of them with positive history for early-onset hepatomegaly and later evidence of myopathy. Three mutations affect AGL gene donor splice sites. In five patients reverse transcription of muscle AGL cDNA showed the skipping of exon 4, 21 (in three) and 26. These exon skipping were accounted for by one homozygous T->A transversion at position +2 of the 5' intron 4 splice site, one homozygous and two patients reverse transcription of muscle AGL cDNA showed the skipping of exon 4, 21 (in three) and 26. These exon skipping were accounted for by one homozygous T->A transversion at position +2 of the 5' intron 4 splice site, one homozygous and two patients reverse transcription of muscle AGL cDNA showed the skipping of exon 4, 21 (in three) and 26. These exon skipping were accounted for by one homozygous T->A transversion at position +2 of the 5' intron 4 splice site, one homozygous and two heterozygous G->A transition at position +1 of the 5' intron 21 splice site, and one homozygous G->C transversion at position +1 of the 5' intron 26 splice site. Western blot analysis of muscle homogenate showed the lack of AGL protein. The fourth mutation is a homozygous C to T at codon 17 of AGL exon 4 and results in a premature stop codon (CGA to TGA). These new mutations involve sequence elements shared by AGL mRNA isoforms expressed in different tissues, including liver and muscle, thus correlating with the GSD type IIIa phenotype. The expanding repertoire of AGL gene mutations confirms a great genetic heterogeneity of GSD IIIa.

P831
NARROWING THE DUANE SYNDROME CRITICAL REGION AT CHROMOSOME 8Q13. Bordoni R. (1), Calabrese G. (2), Capodiferro F. (2), Morizio E. (2), Telvi L. (3), Silani V. (1), Stuppia L. (2), Palka G. (2), Pizzuti A. (1). (1) Ospedale Maggiore di Milano, Italia. (2) Dip. Scienze Biomediche/Sez. Genetica Medica, Universitê di Chieti, Italia.(3) Laboratoire de Cytogénétique, Hopital Saint-Vincent-De-Paul, Paris, France.

Duane syndrome (MIM126800) is an autosomal dominant disorder characterized by primary strabismus, bilatera globe retraction, and narrowing palpebral fissure. Although mostly reported as an isolated disorder, Duane syndrome has been related to a 8q12-13 contiguous gene deletion syndrome. We have recenntly identified a < 3cM region of overlap (SRO) in a patient with an interstitial deletion at band 8q13. Now we report on another patient with Duane syndrome carrying a reciprocal translation t(6;8)(q24;q13). FISH analysis using a YAC contig spanning the SRO identified two YAC clones, 925D9 and 820E6, which bridged the 8q breakpoint. Further analysis with a panel of ten Yac clones within the SRO placed the breakpoint between markers SHGC37325 and WI4901 in an interval of < 1cM. PAC and BAC libraries and cosmid library subclones prepared YAC 820E6 are currently screened by PCR and FISH to further characterize the narrowed SRO associated with Duane syndrome. Two PAC clones flanking the breakpoint have been isolated. We have also relocated at 8q13 centromeric to Duane locus and EYA1 a putative candidate gene, AMYB, which is expressed in brain cortex and genital crests and was previously mapped at 8q22.

P832
GLOBOID CELL LEUKODYSTROPHY MIMICKING HEREDITARY SPASTIC PARAPLEGIA. D. Pareyson, M. Savoiardo, B. Bertagnolio, S. Selleri, L. Farina, G. Lauria, A. Bizzi, G. Finocchiaro, A. Sghirlanzoni. Milan, Italy.

Globoid cell leukodystrophy (GLD or Krabbe disease) is a recessive disease caused by mutations of the gene encoding the lysosomal enzyme galactocerebrosidase (GALC). While GLD typically starts during early infancy, late-onset forms have rarely been reported and are clinically more heterogeneous. A female patient aged 33 and her 35-year-old brother had pes cavus since childhood and slowly progressive spastic paraparesis since their teens. Brain magnetic resonance imaging (MRI) showed atrophy of precentral gyri with increased signal intensity along the corticospinal tracts from the cortex down to the midbrain in the female patient. The same alteration was barely detectable in the less severely affected brother. Electrodiagnostic studies revealed a mild demyelinating sensory neuropathy. Visual evoked potentials were normal. H-MR spectroscopic imaging demonstrated increased choline and myo-inositol peaks in the white matter. GALC activity was 0-11% of controls in leukocytes and fibroblasts of the two siblings. They were compound heterozygotes for a deletion of exons 11-17 and a missense mutation in the GALC gene. In these patients,

Krabbe disease had early onset but very slow progression and mimicked hereditary spastic paraplegia. Thus GLD should be considered in the differential diagnosis of non-dominant or sporadic spastic paraplegia. MRI abnormalities, although very subtle, may raise the suspicion and prompt the appropriate biochemical and genetic evaluations. Supported by Telethon-Italy grants to A.S. and G.F.

P833
SPINOCEREBELLAR ATAXIA TYPE 7: CLINICAL AND MOLECULAR CHARACTERIZATION OF 2 FAMILIES. [1]Mariotti C., [1] Riggio M.C., [2]Pandolfo M., [1]Salmaggi A., [1]Gellera C.,[1]Di Donato S. [1]Istituto Neurologico Nazionale "C. Besta", Milan; Italy; [2]Centre de Recherche "Charles-Louis Simard", Montreal, Canada.

Autosomal dominant cerebellar ataxia type II (ADCAII) is characterized by the presence of macular degeneration, and associated with a single genotype, i.e. a highly unstable CAG repeat expansion on 3p12-13, (SCA7). We recently identified 4 patients from two unrelated families, carrying the SCA7 mutation. The earliest onset was found in a young man with no family history, who begun to complain of progressive decrease of visual acuity since age 14 and showed the first signs of cerebellar ataxia at age 16. He presented very slow saccades, ophthalmoplegia in the vertical gaze, mild gait and limb ataxia, increased reflexes, and mildly decreased vibration sense in the lower limbs. An expansion of 67 CAG repeats was found in the SCA7 gene (normal 37 repeats). The other patients were siblings who received the expanded gene from the mother, deceased at age 85 with only a mild gait ataxia. The size of the expansion varied from 47 to 63 triplets, and was correlated with the age of disease onset. Interestingly, macular degeneration was present only in one sib. Imaging studies showed in all of the patients variable cerebellar and brainstem atrophy. Our data confirm the great instability of the expanded CAG repeat region in the SCA7 gene, and the marked variability of the clinical phenotype.

P834
CAMPTOCORMIA AND MYOTONIC DYSTROPHY WITHOUT MYOTONY. Guiraud-Chaumeil C, Echaniz-Laguna A, Tranchant C, Warter J.M. Hôpitaux Universitaires, BP 426, 67091 Strasbourg, France.

Camptocormia is a rare low back disorder characterized by an acquired kyphosis which increases during walking and reduces in decubitus. This usually familial disease is more frequent in the elderly. CT scan reveals selective involution of the paravertebral spinal muscles. Histological findings are of low specificity and diverse. Pathophysiological hypotheses include neurogenic atrophy of spinal muscles, myositis or delayed primary myopathy. We report the case of a 62 year-old woman with camptocormia revealing Steinert's muscular dystrophy. This woman had no familial history. She developped since the age of 55 an abnormal posture of the neck (anteflexion) then a progressive anterior curvature of the trunk with increasing difficulties to walk. Neurological examination revealed severe paravertebral muscles deficiency with mild facial and proximal muscular limbs involvement. There was no myotony. EMG showed myogenic patterns in paravertebral muscles. CT scan revealed fatty involution and atrophy of cervical and lumbar paravertebral muscles. Histological analysis of deltoideus sample was non specific with some irregular and atrophic fibers. Biological molecular analysis showed an expansion of 400 CTG repeats in the DM-kinase gene leading to the diagnosis of Steinert's muscular dystrophy. This observation emphasizes that lack of myotony does not exclude Steinert's muscular dystrophy and that expansion in DM-kinase gene should be research in camptocormia.

P835
DOPAMINE RECEPTOR D2 (DRD2) INTRONIC PLYMORPHISM IN SPANISH PARKINSON'S DISEASE (PD).P. Pastor, E. Muñoz, V. Obach, M.J. Martí, F. Valldeoriola, M.Francés, R.Oliva*, E. Tolosa. Department of Neurology and Genetics*. Hospital Clínic. Barcelona. Spain.

A significant overrepresentation of the DRD2 allele 3 in European PD patients as compared to controls has been reported, suggesting anormal association between the intronic polymorphism of the DRD2 gene and PD (Planté-Bordeneuve et al, 1997). Objective: To determine whether the intronic polymorphism of the DRD2 gene is associated to an increased risk to develop PD in the Spanish population. Methods: We genotyped using PCR the DRD2 polymorphism in 154 PD cases and in 125 healthy controls. 47 patients had family history of PD, in 13 cases the presence of familial history of PD was uncertain, and 94 cases were sporadic. Results: The distribution of the DRD2 alleles did not differ significantly between patiens and controls. The allele 3 was present in 55.2% of the controls and in 60.3% of the patients. The genotype 33 was found in 34% of the controls and in the 36.6 % of the PD patients. No statistical differences were detected in the allelic frequency in PD patients when they were classified according to different criteria such as age of onset of symptoms, family history of PD or clinical presentation. Conclusion: Our data suggest that, at least in the Spanish population, there is no association between DRD2 polymorphism and susceptibility for developing PD, in both, familial and sporadic cases.

P836
DENTATO-RUBRO-PALLIDO-LUYSIAN ATROPHY (DRPLA) IN A SPANISH FAMILY. E. Muñoz[1], R. Sanchez[1], M. Revilla[1], M. Milê[2], A. Sanchez[2], P. Latorre[3], A. Ariza[4], E. Tolosa[1] - Departments of Neurology [1] and Genetics [2]. Hospital Clínic i Universitari, Barcelona, Spain. Departments of Neurology[3] and Pathology[4]. Hospital Universitari Germans Trias i Pujol, Badalona, Spain.

DRPLA is a rare inherited neurodegenerative disease with few cases reported outside Japan. The clinical misdiagnosis of Huntington's disease (HD) is not infrequent. Objective: To describe the clinical, radiological and pathological findings in a Spanish family with DRPLA. Material and Methods: Pedigree analysis and clinical data from a family with a disease characterised mainly by ataxia, dementia, choreathetosis and seizures were collected. Cranial magnetic resonance imaging (MRI) and genetic study were performed in two patients. Pathological information was obtained from the autopsy of one patient. Results: 12 patients were identified. Age at onset varied from 5 to 55 years. All patients but one presented ataxia, 8 patients had choreoathetosis, 7 had dementia and 4 had seizures. Cranial MRI revealed brain stem and cerebellar atrophy and white matter changes. Genetic study confirmed DRPLA. Pathological study demonstrated atrophy of globus pallidus and lipofuscin deposits in the brain. Conclusions: DRPLA shows an intrafamilial phenotypic heterogeneity. Clinical and MRI data could differentiate DRPLA from HD but definitive diagnosis requires molecular studies. Pathological studies are still necessary to correlate DRPLA brain involvement with the clinical and molecular findings.

P837
CEREBRAL HEMODYNAMICS IN SUBJECTS WITH A HEREDITARY PREDISPOSITION TO STROKE Glazovska I., Novikova S., Kuznetsova S. Institute of Gerontology, Kiev, Ukraine

Stroke is the disease which is present by heredity. The hereditory predisposition to stroke is realized at various levels, and the state of cerebral blood circulation is being one of them. In the 1st degree relatives of patients with stroke (n=120, aged 20-59 years), we examined the main head and neck vessels by means of transcranial ultrasound dopplerography (Logidop5). With age, the linear blood flow velocity (LBFV) decreased more intensively in patient relatives than in control subjects (n=80). Thus, at 30-39 years the LBFV along common sinus carotid was 100 cm/s both in relatives of patients and and in control subjects, at 40-49 years these values were 78 and 88 cm/s, and at 50-59 years - 66 and 75 cm/s, respectively. In the relatives of patients, at 40-49 years the LBFV asymmetry along sinus carotid was diagnozed in 25% of cases and at 50-59 years in 34% (8% and 7%, respectively, in control subjects), and along the brain artery - in 20% at 40-49 years and in 32% at 50-59 years (no asymmetry was observed in control subjects). In the relatives of patients, we established a correlation between the blood flow asymmetry, localization of morpho-functional changes in vascular wall of sinus carotid artery extracranial compartments and localization of an ischemic focus in the proband. The relatives of patients have displayed a significantly reduced level of HDL (high-density lipoproteins) antiatherogenic cholesterol and a low level of apoA1 (less than 1.1 mg/l), that evidences for the risk of atherosclerosis. Changes of the cerebral circulation combined with reduced values of the blood antiatherogenic status can be considered as a manifestation of realization of the disposition to stroke.

P838
INFLUENCE OF THE TRANSTHYRETIN-MET119 VARIANT ON MET30 FAMILIAL AMYLOID POLYNEUROPATHY (FAP) IN PORTUGUESE AND FRENCH CASES. A. Ferreira, V. Planté-Bordeneuve, M. Misrahi, D. Adams, G.Said. Department of Neurology, CHU BicÉtre, France.

FAP is a dominantly inherited disorder caused by extracellular deposition of mutated transthyretin (TTR). The disease identified mainly in northern Portugal and occasionally in France has a stereotyped clinical presentation except for a late age of onset in the French kindreds. The TTR-Met30 mutation is by far the most common pathogenic variant. The Met119 mutation is an apparently non-pathogenic TTR variant found with a frequency of 0.007 in Portugal. In 9 Portuguese FAP patients the association Met30/Met119 was linked up to an unusual delayed or benign course, suggesting a protective role of the Met119 variant. To elucidate its possible influence on FAP phenotype, we screened a group of Met30 individuals including French late onset and Portuguese FAP for the Met119 mutation. Genomic DNA was available from 46 Portuguese (33 affected, 13 unaffected) and 52 French (22 affected, 30 unaffected) Met30 individuals. Mean age at onset was 56.8 (range 29-78) years in the French and 37.9 (range 24-68) in the Portuguese patients. The Met119 was screened by a previously described technique of amplification/restriction of the TTR-exon4 and was detected only in one case. This compound heterozygote Met30/Met119 was a 62 y-o Portuguese man, free of symptoms. His son, who did not carry the Met 119 mutation, developed the disease at age 28. We conclude that the TTR-Met119 variant is not associated with FAP of late onset in Met30 French kindreds. However, the newly identified compound heterozygote Met30/Met119 case indicates that the Met119 might influence towards a mild phenotype in a subgroup of Met30 patients through a yet unknown mechanism.

P839

CLINICAL AND ELECTROPHYSIOLOGICAL STUDY OF A LARGE FAMILY WITH PARAMYOTONIA CONGENITA. R.Gouider, A. Gargouri, F. El Bahri, M. Fredj, A. Mrabet.,Neurological department, EPS Charles Nicolle, Tunis, Tunisia.

We report a large family with paramyotonia congenita with study of disease variabilty and evolution. Patients and methods: we examined 18 patients belonging to a large family with 94 at risk subjects from whom 53 were affected. We performed EMG studies in 8 patients. Molecular biology analysis is ongoing. Results: mean age at examination was 28,9 years. Paramyotonia congenita was transmitted in an autosomal dominant trait with complete penetrance. age at onset was precocious, at birth mostly. Myotonia was triggered by cold and effort in all cases, face muscles were frequently affected. Deep tendon tricipital reflexes were diminished in 11 cases and abolished in three. Six patients aged more than 18 years presented permanent partial eyes closure. Four patients aged more than 35 years presented a deficit of intrinsic hand muscles and extensors hand muscles. Nerve conduction velocities were normal and myotonic discharges were observed in 6 cases. Conclusion: paramyotonia congenita may present with altered reflexes in upper limbs. In adult patients partial eyes closure,or distal upper limbs deficit may be permanent.

P840

A SCREENING FOR *ALA53THR* MUTATION IN -SYNUCLEIN GENE IN ITALIAN FAMILIES WITH PARKINSON'S DISEASE. Bonifati V, Vaughan JR, Fabrizio E, Volpe G, De Michele G, Filla A, Meco G, Wood N, The Italian Parkinson Genetics Study Group, and The European Consortium on Genetic Susceptibility in Parkinson's Disease *(Roma, Napoli, I, London,UK)*

Two point mutations (Ala53Thr and Ala30Pro) in the gene for -synuclein (on chromosome 4q) have been recently identified in families with autosomal dominant forms of Parkinson's Disease (PD) and European ancestry. The Ala53Thr mutation has been found in a large family of Italian origin, called the "Contursi kindred", and in a few smaller families of Greek origin. The Ala30Pro mutation has so far been detected in only one German pedigree. Methods: We screened 27 Italian PD probands with a pattern of familial PD aggregation compatible with autosomal dominant transmission. The presence of the Ala53Thr mutation was investigated using PCR amplification of genomic DNA and digestion with Tsp45I restriction enzyme. Results: Only one patient had the Ala53Thr mutation. This man, aged 34, refers PD onset at age 32. His father and other 4 more distant deceased relatives were affected by history. Moreover, another living affected relative remains to be examined. This family originates from the area of Salerno in Southern Italy, suggesting a genealogical link with the Contursi kindred. Conclusions: This study extends our previous investigations on Italian and European patients (Vaughan et al, Ann Neurol 1998; 44: 270-273) and confirms that the Ala53Thr mutation is a rare cause of familial PD among Italian patients.

P841

SOD1 GENE: MOLECULAR SCREENING IN AMYOTROPHIC LATERAL SCLEROSIS ITALIAN FAMILIES. [1]Riggio M.C., [1]Botti S., [1]Gellera C., [1]Morandi L., [1]Testa D., [1]Bugiani O., [1]Sghirlanzoni A., [2]Casali C., [1]Taroni F., [1]Zeviani M., [1]Mariotti C.[1]Istituto Nazionale Neurologico "Carlo Besta", Milano; [2]Universitê "La Sapienza", Roma, Italy.

Mutations in the SOD1 gene, coding for the cytoplasmic Cu/Zn superoxide dismutase (SOD) has been identified in 20% of familial amyotrophic lateral sclerosis (FALS) patients. We found mutations of SOD1 in 4/29 (14%) unrelated FALS cases. Two patients harboured a heterozygous A4V mutation in exon 1, the most frequent FALS-associated mutation, usually causing a severe form of the disease. In the other patients we found two new heterozygous missense mutations: G12D, in exon 1 and K45C, in exon 2. The G12D was associated with a late onset (age 63) and realtively mild course. Slow progression was also reported in his affected relatives. SOD1 was also analyzed in 24 sporadic cases. In one patient we identified a homozygous missense mutation, D90A, in exon 4. This mutation is generally associated to a mild form of ALS, and, when heterozygous, is a frequent polymorphism in Sweden and in Finland. In our patient, the D90A mutation was associated with an atypical phenotype. The proband, a 41 year old woman, developed progressive weakness in lower extremities, followed by milder weakness in upper limbs. Cranial nerves were normal. EMG showed diffuse signs of muscle denervation and the presence of a sensory neuropathy in the lower limbs. *[Partially supported by A.R.I.N.: "Maurizio Pettirossi" donation].*

P842

HOMOZYGOUS EXON 7 DELETION OF THE SMNc GENE IN SPORADIC LOWER MOTOR NEURON DISEASE. Echaniz-Laguna A, Guiraud-Chaumeil C, Tranchant C, Blumenfeld S, Melki J, Warter JM. Hôpital Civil, CHU de Strasbourg, BP426, 67091 Strasbourg, France

Homozygous exon 7 deletion of the telomeric copy (t) of the Survival Motor Neuron (SMN) gene is found in 98% of patients with infantile spinal muscular atrophy. In contrast, homozygous exon 7 deletion of centromeric SMN (SMNc) is found in 5% of the general population and has been suspected to be a susceptibility factor for lower motor neuron disease (LMND) in adults (Moulard et al, 1998). AIM. To study SMNt and SMNc exon 7 in a group of patients with LMND. Patients And Methods. Ten patients suffering from LMND were studied. All had an asymmetrical and distal onset of amyotrophy with progression throughout the years, no familial history of MND and no signs of cortico-spinal tract disease. Lymphoma, malignant plasma cell dyscrasia, motor neuropathy and Kennedy disease had been excluded. Study of SMNt and SMNc exon 7 was performed using amplification created restriction site analysis using primers RIII and X7-Dra. Results. No homozygous exon 7 deletion of the SMNt gene was observed in this population. Interestingly, we found homozygous exon 7 deletion of the SMNc gene in three patients. Conclusion. This report shows an excess of patients affected with LMND and carrying homozygous deletion of SMNc exon 7, leading us to speculate that homozygous exon 7 deletion of SMNc gene could be a susceptibility factor for LMND. However, other abnormalities such as intragenic mutations of the SMNt gene should be searched in LMND patients.

P843

A FAMILY WITH PROMM NOT LINKED TO THE RECENTLY MAPPED PROMM LOCUS DM2. T. Wieser; K. Eger; D. Bönsch*; W. Schulte-Mattler; S. Zierz. Klinik und Poliklinik für Neurolgie, Martin-Luther-Universität Halle/Wittenberg, Germany. *Institut für klinische Chemie und Laboratoriumsmedizin, Friedrich-Schiller-Universität Jena, Germany

Proximal myotonic myopathy (PROMM) is a newly described, autosomal dominantly inherited multisystem disorder similar to myotonic dystrophy. PROMM is characterised by weakness of the legs, myotonia, cataracts, and slight elevation of liver enzymes. Since PROMM patients do not harbour the trinucleotide expansion on chromosome 19 causing Myotonic dystrophy (DM), PROMM is a genetically distinct disease. A recently mapped second locus for myotonic dystrophy (DM2) was thought to be an attractive candidate locus for PROMM, and this hypothesis was supported by reports of linkage to this locus in some PROMM families. We present a German pedigree with PROMM, large enough to formally show or exclude linkage to this locus. Nine markers were used spanning the 8 centimorgan interval comprising the DM2 locus. Lod scores below -2 excluded linkage to this locus. The genetics of the multisystemic myotonic dystro-

phies besides classical DM seem to be complex. Exclusion of the DM2 locus in our family is further evidence of genetic heterogeneity of PROMM and stresses the broad genetic variety in this small group of disorders, for which the acronym DOMMOPS (dominant myotonic myopathies) was recently introduced. The situation seems comparable to the situation in the dominant ataxias where the broad clinical spectrum underlies an even broader genetic variety.

P844
MENTAL RETARDATION IN ADULTHOOD: PRELIMINARY EPIDEMIOLOGICAL DATA AND CLINICAL-ETHIOPATOLOGICAL RESEARCH. Verri AP, Maraschio P*, Vallero E, Belloni G.**, Federico Aí. Neurological Institute C. Mondino, *Institute for Biology and Medical Genetics, Internal Medicine, University of Pavia - íNeurometabolic Disorders Unit, University of Siena, Italy

Our purpose was to investigate the biological causes of Mental Retardation (MR) and the associated specific medical conditions. In the Pavia ASL area we performed a first census of MR adult patients, using the civil invalidity register. Among 691 registered patients (395 M, 296 F-age range 18-53 yrs), 73 were randomly chosen. These patients (33 F, 40 M), mean age 31 yrs (range 18-53 yrs) were investigated from the clinical, genetic and neuroradiological perspectives. When appropriated, metabolic laboratory evaluations were performed. Results: prenatal causes were postulated in 44 patients (60%) (genetic 33- chromosomal abnormalities 28, mendelian disorders 5; CNS malformations 8; other conditions 3). Chromosomal abnormalities are listed below: +21 23 pts; 5p- 1pt; 9q22.1-31.3 duplication 1pt;18 p- 1pt; 10p- 1pt; complex chromosomal rearrangement 1pt. Mendelian disorders were: C. De Lange syndrome 1; fragile-X 2; phenylketonuria 1; Williams s. 1. Perinatal events were found in 6 (8%). In 23 patients (32 %), no causes could be identified. Associated medical conditions were found in 31patients (43%): neurological in 12 (10 cerebral palsy, 2 epilepsy), behavioral-psychiatric in 12, other physical conditions in 7. Conclusions: MR results most frequently from prenatal factors (Curry 1997). Still in 25-40% of cases, the cause is undetermined. MR frequently coexists with a number of other disabilities. For preventing MR it is necessary to identify the known biomedical causes and other medical conditions that are present among MR patients (Yeargin-Allop 1997). A correct diagnosis has to be reached also in adult MR patients.

P844a
A LOCUS FOR MOEBIUS SYNDROME ON CHROMOSOME 10Q - H. T. F. M. Verzil*, B. van den Helm*, B. Veldman*, L. P. Kuyt", B. C. J. Hamel+, H. Kremer+, G. W. Padberg*/* Department of Neurology, + Department of Human Genetics, University Hospital Nijmegen;" Department of Human Genetics, Free University Amsterdam, The Netherlands

Moebius syndrome consists of congenital paresis of the VIIth cranial nerve, frequently accompanied by dysfunction of other cranial nerves. Additionally, orofacial and limb malformations, musculoskeletal system defects, and mental retardation are seen. Most patients are sporadic but familial cases can occur. Different modes of inheritance are suggested. Genetic heterogeneity of Moebius syndrome has been suggested by cytogenetic studies and linkage analysis. Previously, we identified a locus on chromosome 3q21-q22 in a Dutch family with autosomal dominant Moebius syndrome consisting essentially of asymmetric facial paresis. Here, we performed linkage analysis in a second Dutch family with autosomal dominant facial palsy. We identified the locus in this family on chromosome 10q. The maximum lod score in a two-point analysis is 4.47 at a recombination fraction of 0.05. Herewith, we have proven genetic heterogeneity for autosomal dominant Moebius syndrome. After proving linkage in this family the penetrance is recalculated leading to a value of 60%. It suggests that at least part of the seemingly sporadic cases might be members of a family with a low penetrance of Moebius. The significance of the identification of the gene involved in the present family, for mutation analysis in sporadic patients and the developmental biology of brainstem and of cranial nerves, will be discussed.

Infection nervous system

P845
SPINAL EPIDURAL ABSCESSES IN THE CERVICAL REGION CAUSED BY BRUCELLOSIS. REPORT OF TWO CASES. PJ Modrego, MA Pina, MT Cuesta. Hospitals of Alcaûiz and Teruel, Spain.

Spinal epidural abscesses are an uncommon complication of several infectious processes. Forunculosis and wound infections are the most frequent causes but it may also develop in chronic medical diseases such as brucellosis. Treatment depends on the nature of the causative process. We present two cases of cervical spondylodiscitis with epidural abscess due to brucellosis. First case. A 74 year old patient was admitted because of malaise, fever and abdominal pain with subsequent tetraparesis. Computed Tomography and Magnetic Resonance imaging (MRI) showed cervical spondylodiscitis and epidural abscess with extension to the retropharyngeal space. The serologic tests for brucella were positive. The treatment consisted of surgical drainage plus antibiotics: Rifampin, Streptomycin and Doxicyclin. The outcome was completely favourable. Second case: A 53 year old woman presented with fever, malaise and right cervicobrachialgia after two months of intermittent fever. The strenght and bicipital tendon reflex were impaired in the right arm. The serologic tests for brucella resulted positive and MRI of the cervical region revealed spondylodidscitis C5-C6 with epidural abscess and narrowing of intervertebral foramina. The patient got better with antibiotics and did not need surgical drainage. Brucellosis has not been eradicated in Spain and, from time to time, may cause neurologic complications: lumbosacral painful radiculitis,meningitis, myelitis, polyneuropathy and, in fewer cases, epidural abscess that uses to be located in the lumbar spine and rarely in the cervical region.

P846
NEUROTRICHINOSIS. CASE REPORT WITH MRI AND SPECT STUDIES. M. Herpe, P. Girard, M. Charif, H. Jafari, P. Andre, D. Basset, I. Descours, M. PAGES Department Of Neurology, Infectious Diseases And Parasitology, Montpellier, France.

Trichinosis is a parasitic disease which occurs after ingestion of infected meat by Trichinella Spiralis (TS). Neurological complications are rare. They consist of diffuse encephalopathy and focal neurological symptoms. We report a case of neurotrichinosis (NT) with MRI and SPECT studies. Case Report: A 42 year-old patient presented with fever, loss of weigh and myalgias which were followed by subacute encephalopathy. According to his family, he used to eat undercooked horse meat. Neurological examination showed mutism, bradypsychia, loss of attention, anosognosia. Laboratory examinations revealed marked hypereosinophilia, increased creatine kinase levels, moderate high protein level in CSF and significantly high anti TS antibodies in blood and CSF. The patient gradually improved after a 2 month treatment with albendazole and corticosteroid therapy. MRI showed bilateral nodular subcortical lesions with high signal on proton density and T2-weighted images. They gave isosignal on T1- weighted images and did not enhance by gadolinium. SPECT studies revealed hypoperfusion of both frontal lobes. One month later, the size of lesions had decreased. Conclusion: Several mechanisms of brain damage (toxaemic, allergic, larval, ischaemic) have been suggested in NT: Our case support the hypothesis of frontal lobe dysfunction due to basal ganglia infarction.

P847
ACUTE MYELOPATHY: COMPARATIVE ANALYSIS OF ETIOLOGICAL DIAGNOSIS IN 42 CASES. G Breteau, J de Seze, T. Stojkovic, JY Gauvrit, E Hachulla, JP Pruvo, P Vermersch. Departments of Neurology, Internal Medecine and Neuroradiology, Lille, France

Acute myelopathies have been rarely studied over long term periods. Aim: To assess the various etiological profiles of acute myelopathies supported by clinical and MRI outcome. Patients and methods: We studied 42 cases with acute myelopathy. Cases were classified as multiple sclerosis (MS), systemic diseases (SD), viral myelitis (VM) or myelopathy of unknown origin. Initial clinical presentation, brain and spinal MRI, cerebrospinal fluid (CSF), evoked potentials, clinical and spinal MRI follow-up were compared. Results: 41% cases were diagnosed as MS, 19% as SD, 4% as VM. 36% remains undetermined. Clinical symptoms were not different comparing the four groups. MRI showed posterior or lateral hypersignal on T2 weighted sequences involving one segment in 57% of MS, centromedullary hypersignal with involvement of more than one segment in 66% of SD and cervico-dorsal centromedullary hypersignal in 100% of VM. Brain MRI was most frequently abnormal in MS (77%) than in the other etiologies. Oligoclonal bands were present in 87.5% of MS but absent in SD and VM. After 6 months of follow-up, the outcome was good in 81% of MS and poor in 75% of SD. Conclusion: Acute myelopathy occuring in MS, SD or VM may be differenciated on MRI findings, CSF oligoclonal bands and severity of outcome. These findings allow to determine a probable diagnosis in undetermined cases.

P848
NEUROLOGICAL COMPLICATIONS IN AIDS. W.Halota, A.Olczak, M.Ziùlkowska. Department of Infectious Diseases L.Rydygier Medical University in Bydgoszcz, Poland

The aim of the study is to determine the prevalence and ethiology of central nervous system disorders in AIDS patients in Bydgoszcz. AIDS was recognised in 60 out of 222 HIV infected patients observed from 1989-1998. Neurological complications occurred in 23 (38,3%) and in 12 cases were the initial symptoms of AIDS. All neurological patients were severely immunodeficient with CD4 cell count less then 200. The diagnosis was made under clinical features, routine CSF examination (culture, cytology and serological findings). The neuroimaging (CT or MRI) was performed in all patients with predominantly focal disorders. Progressive multifocal leucoencephalopathy (PML) was confirmed with postmortem brain autopsy. Diagnosis included 6 menigitis (tuberculosis - 2, cryptococcal - 3, staphylococcal - 1), AIDS- dementia - 10, PML - 2, cerebral toxoplasmosis - 5. Antigen p24 HIV-1 was detected in plasma in 21 and in CSF 6 cases. In 3 patients with dementia treated with antiretroviral therapy clinical condition had improved and antigen p24 disappeared from CSF. Conclusion: The neurological complications are common in severely immunodeficient patients. In our experience the most common was AIDS-dementia. Antigen p24 occurs occasionally in CSF and its diagnostic value is limited.

P849
SINUS SIGMOIDEUS THROMBOPHLEBITIS AS ONE OF THE OTOGENIC INTRACRANIAL IMFLAMMATORY COMPLICATIONS. V. Jekic, I. Filipce, S. Vlaski-Jekic, B. Gogusevski, E. Kaja, G. Micevski. Clinic of Otorhinolaryngology, Clinic of Neurology, Skopje, Macedonia

Sinus sigmoideus thrombophlebitis is serious otogenic intracranial inflammatory complication of the inadequately treated chronic suppurative otitis media. A total of 1490 patients with chronic suppurative inflammation of the middle ear were treated surgically over a period of last twenty years at the ENT Clinic in Skopje, Republic of Macedonia. Intracranial otogenic inflammatory complications were found in 168 cases (11,2%). Otogenic sinus sigmoideus thrombophlebitis (OSST) was present in 29 cases (17,3%) of them. With this frequency OSST is on the third place among the otogenic intracranial complications in our operative material, just after the otogenic meningitis (33%) and the extradural abscess (30%). In 6 cases OSST was an isolated intracranial complication[{CA}] (20,6%), in one case it was associated with cerebellar abscess (3,4%), in 2 cases with suppurative meningitis (6,9%), and in 14 patient (48,2%) there was an association with extradural abscess. The septic thrombosis was spread to the internal jugular vein even in 6 patients (20,6%). Sinus sigmoideus thrombophlebitis is a serious otogenic inflammatory intracranial complication needing urgent surgical treatment: radical trepanation of the temporal bone, denudation of dura mater and evacuation of pathological collection. A surgical approach to chronic inflammation of the middle ear with cholesteatoma and osteitis is the only way to prevent the occurrence of otogenic intracranial inflammatory complication in general, and for the otogenic sinus sigmoideus thrombophlebitis respectively.

P850
THE SIGNIFICANCE OF PROCALCITONIN AND MYELIN AS SPECIFIC INDEXES OF INFLAMMATION IN THE DIAGNOSIS AND PROGNOSIS OF CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS. Alexiou Heleni, Latousakis B, Xifaras M, Tzimas A, Matikas N. Neurological Department of General Hospital of Nikea-Pireas, Greece.

Thirty five patients with CNS infection (mean age: 36,5 years) were enrolled in our study all of which were admitted in our department during the last two years. We measured procalcitonin and myelin in the serum and cerebrospinal fluid by the method of immunophotometry and radioimmunofixation respectively. Procalcitonin was found increased in 87,5% of patients with established bacterial meningitis on the 3rd day of their hospitalization. The levels of procalcitonin have decreased by the 9th day of the hospitalization of the above patients, reflecting closely their clinical improvement. On the contrary, myelin was found increased in only a small percentage of our patients. This discrepancy was attributed to the low sensitivity of the method of immunofixation by which myelin was measured and calls for the improvement of the technique. Procalcitonin is considered a reliable index of bacteremia, especially important in the early diagnosis of meningococcal septicemia, in the differential diagnosis from viral infections and the prognosis of patients with extensive burns, myocardial infraction or immunodeficiency. Persistently elevated levels of procalcitonin usually signify a lethal complication.

P851
CEREBROSPINAL FLUID OLIGOCLONAL FREE LIGHT CHAIN PROFILES IN AIDS. E. Fainardi, L. Vaghi, M. Castellazzi, A. Bedettií, R. Cultrera*, C. Contini*, E. Paolino, E. Granieri.Section of Neurological Clinic, íDepartment of Infectious Diseases, *Department of Clinical and Experimental Medicine, Section of Infectious Diseases - Ferrara, Italy

AIDS-related neurological involvement is frequently associated with an intrathecal humoral immune response. In order to clarify the role of the immune activation within the cerebrospinal fluid (CSF) compartment, we studied the immunoglobulin free light chains (FLC) composition in paired CSF and serum samples from 29 HIV-1-infected patients belonging to Group IV of the Centers for Disease Control classification of Atlanta: 12 with primary and 17 with secondary central nervous system (CNS) manifestations. We observed a blood-CSF barrier dysfunction by CSF/serum albumin quotient (QAlb) in 62.1% and an intrathecal IgG production by IgG Index in 41.4% of the cases. A local synthesis of IgG, kappa FLC and lambda FLC oligoclonal bands, respectively, was detected in 55.2%, 83.3% and 33.3% of the patients. Among these subjects, all but one displayed CSF-restricted oligoclonal FLC bands, either kappa or lambda or both. AIDS-associated neurological complications appear to be characterized by a strong intrathecal synthesis of FLC, mainly kappa, probably suggestive of a profound dysregulation of immunoglobulin production by locally activated B cells. CSF oligoclonal kappa profile could represent the most sensitive marker to establish an intrathecal immune response and demonstrate an ongoing infection within the CNS.

P852
TWO CASES OF MYELITIS RELATED TO TOXOCARA CANIS INFECTION. Goffette S., Jeanjean A.P., Duprez T.P.J., Bigaignon G., Sindic C.J.M., Brussels, Belgium.

A 58-year-old man who suffered from dysaesthesiae and causalgia in his legs, presented severe sensory disturbances to all modalities in the left arm and below the T10 dermatome with hyperreflexia and left Babinski sign. Spinal Magnetic Resonance Imaging (MRI) showed a high-signal area within the swollen cord from C2 to C5 on T2-weighted images and patchy contrast-enhancing foci within the posterior segment at C2 and C3 on T1-weighted images. Blood tests revealed eosinophilia (3270/mm3) and cerebrospinal fluid (CSF) examination was normal with CSF-restricted oligoclonal Ig G bands. The second case was a 40-year-old woman presenting dysaesthesiae between T8 and T10 level on the right side and progressive weakness of the right leg with right Babinski sign. Spinal MRI demonstrated high signal from D8 to D10 on T2-weighted images with contrast-enhancing foci on T1-weighted images. Blood tests showed slight eosinophilia (920/mm3) and CSF contained 26 cells/mm3 (40 % eosinophils) with CSF specific oligoclonal Ig G bands. In both cases, blood serology was highly positive for Toxocara canis. They received an oral treatment combining methylprednisolone and mebendazole with clinical and radiological recovery after a few months. *Toxocara canis* is a roundworm in the dog which can cause visceral larva migrans syndrome in humans. Beside infestation of liver, lungs and eyes, neurological involvement is described but very uncommon.

P853
FREQUENCY OF SPECIFIC LABORATORY MARKERS FOR EHRLICHIOSIS IN PATIENTS WITH POSSIBLE NEUROBORRELIOSIS STAGE II. C.N. Homann, M. Feichtinger, K. Wenzel, K. Suppan, K. Pierer*, B. Santner*, D. Stünzner, R. Crevenna, E. Ott, E. Marth*, HP Hartung, Dept. of Neurology and *Dept. of Microbiology, K.F. University Graz, Austria

Ehrlichiosis, a tick born disease known as Human Granulocytic Ehrlichiosis, which is caused by intracellular bacteria, presents with myalgia, fever and nausea, and can affect the central nervous system. Lymphocytic meningitis (LM), peripheral facial nerve palsy (PFNP) or plexus neuropathy. Clinical neurological presentations of Ehrlichiosis are similar to Neuroborreliosis (NB) stage II, but Ehrlichiosis is associated with laboratory abnormalities such as thrombocytopenia, anemia and elevated liver parameters, distinct from NB. Specific treatment for infection of the CNS by Ehrlichiae is considered different from that of NB, making a correct diagnosis important. To assess the frequency of laboratory abnormalities that

can be found in patients with possible NE, we retrospectively analysed 49 cases with typical features but without serological proof of NB, by applying strict diagnostic criteria to 179 patients admitted for NB to our wards from 1995 to 1997. An unexpected large number of 17 patients (34%) showed specific changes: 5 patients had isolated liver enzyme elevation, 5 isolated anemia, 1 combined anemia and thrombocytopenia, and 6 patients combined changes in FBC and liver parameters. As these changes partly subsided after treatment they may have at least partly been caused by acute infection. 1 of those patients with and 2 without any specific changes had elevated IgG antibodies to *Ehrlichia equi* related agents. Our study reveals that laboratory abnormalities typically associated with Ehrlichiosis are not uncommonly found in patients with LM or PFNP, but a prospective study of IgM antibody responses is needed to exactly determine their specificity in these patients.

P854
Distribution of HSV-1 in human geniculate and vestibular ganglia: implications for vestibular neuritis.V. Arbusow, P. Schulz, M. Strupp, M. Dieterich, A. v. Reinhardsstoettner, E. Rauch and T. Brandt.Ludwig-Maximilians University Munich, Germany

Vestibular neuritis (VN) a common cause of a partial unilateral vestibular paralysis usually spares posterior semicircular canal function. Viral reactivation of latent herpes simplex virus type 1 (HSV-1) in human vestibular ganglia (VG) is the assumed aetiology. The anastomosis between the intermediate nerve and the superior vestibular nerve raised the question whether selective affliction of the superior vestibular nerve is due to migration of HSV-1 from the geniculate ganglion (GG) along this facio-vestibular anastomosis. Reactivation of the latent virus in the superior vestibular nerve would then cause failure of the anterior and horizontal semicircular canals (SCC) typical for VN. Distribution of HSV-1 among GG, VG and within Scarpa's ganglion was examined in 35 human temporal bones by polymerase chain reaction. HSV-1 was found in 66% of GG and 60% of VG with all examined parts of VG nearly equally HSV-1 infected (stem 24%, superior portion 29%, inferior portion 14%, combined infections 33%). Our data provided no support for viral migration along this anastomosis and preferential latency of HSV-1 in the superior vestibular nerve. Thus the regular preservation of posterior canal function in VN still awaits plausible explanation. The common double innervation of the posterior ampulla by two nerves running in a separate bony canal offers an alternative for sparing function.

P855
BENIGN OUTCOME IN THE SEVERE FORM OF ACUTE DISSEMINATED ENCEPHALOMYELITIS S. Bohlega, W. Al-Sous, N. Ghaus, M. Z. Al-Kawi, E.J. Cupler; Riyadh, Saudi Arabia

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated encephalitis affecting the brain and spinal cord and accounts for approximately 20% of all acute encephalitis. We describe 1 female and 3 male patients aged 18-35 years who presented with acute encephalitis as seizures and coma (1), sleepiness and behaviour change (1), lethargy and right hemiplegia (1) and stupor and transverse myelitis (1), preceded by febrile illness in 2. Examination of CSF disclosed mild leukocytic pleocytosis in 2 (9-26) with increased IgG/albumin ratio in 3, positive oligoclonal bands in 2. MRI showed multiple, large, white matter enhancing lesions in all; haemorrhagic changes were noted in 1 patient and spinal cord lesion in 1. Other probable causative aetiologies, such as direct infection, intoxication or systemic disorder, were excluded. All patients received corticosteroid therapy and were followed for 2 months-5 years. All showed remarkable recovery and became fully independent; no relapse occurred. Regression of brain lesions was noted on repeat MRI scanning. The complete recovery in these patients suggests that a sub-entity of ADEM may carry a good prognosis regardless of initial, striking severity and MRI burden load. Early institution of steroid therapy may improve outcome in this sub-group

P856
REVERSIBILITY OF EXTENSIVE SYMPTOMATIC SPINAL CORD LESIONS IN PATIENTS WITH MYCOPLASMA PNEUMONIAE INFECTION: A SERIAL MRI STUDY. - N. Goebels, C. Helmchen, T. Gasser, H.-W. Pfister. Dept. of Neurology, University of Munich, Germany

Myelitis is one of the neurologic complications associated with Mycoplasma pneumoniae (M. pneumoniae) infections, but the cause of the specific susceptibility of the myelon is unknown. Contradictory reports exist about the extent and the reversibility of this myelitis: While some authors have reported MRI imaging of the spinal cord to be normal (Albucher et al. 1995), also asymptomatic spinal cord lesions have been described. To elucidate the role of spinal MRI we studied the clinical course and MRI longterm follow up of two patients with extensive myelitis associated with M. pneumoniae infections. Both patients (P1=patient 1, P2=patient 2) developed a severe paraparesis with urinary retention and a sensory level following a pulmonary infection. The CSF contained a pleocytosis (P1: 123 cells/ul),P2: 352 cells/ul) with elevated protein and oligoclonal bands. Antibody titers specific for M. pneumoniae were elevated in both the serum (P1: 1:10240; P2: 1: 1280) and the CSF (P1:1: 64; P2: 1:128). In the CSF of patient 2 DNA of M. pneumoniae was detectable by PCR amplification. MR imaging showed widespread hyperintense T2 signals of the spinal cord in both cases, covering almost the entire cord below the Th2 or C4 level, respectively. Along with the clinical improvement under antibiotic treatment, follow up studies of spinal MR imaging up to one year showed remarkable reversibility of the inflammatory lesions resulting in a complete restitutio ad integrum from an imaging point of view, clinically minor residual symptoms persisted. This is the first report of follow up spinal MRI imaging of M. pneumoniae associated myelitis showing extensive lesions covering almost the entire spinal cord with complete reversibility under therapy. In contrast to previous reports, lesions in both patients were symptomatic and the reversibility of the pathological MR signals preceded clinical improvement.

P857
THE CLINICAL ROLE OF ENTEROVIRUS PCR IN MENINGITIS. Biran I[1], Karni A[1], Abramsky O[1], Morag A[2]. Departments of Neurology[1] and Virology[2], Hadassah University Hospital, Jerusalem, Israël

Enteroviruses (EV) are a frequent cause of meningitis. Diagnosis of EV meningitis using viral cultures and serology is problematic due to low sensitivity and delayed results. We examined the role of a rapid RT-PCR (reversed transcriptase-PCR) assay in early diagnosis and management of enterovirus meningitis. Methods: A retrospective study of patients admitted to Hadassah University Hospital between 5/96 to 8/98 who had meningitis and were tested by a PCR assay for enteroviruses (Amplicor®, Roche®). Clinical impression, treatment given and length of hospital stay were recorded. Since in most cases the PCR results were not used clinically, we tried to determine whether those results could have changed the management of the patients. Results: There were 72 patients who met our criteria. Positive PCR was found in 55(79%). However, only 18(33%) were managed as viral meningitis. The rest (37,67%) were given IV antibiotics as if suffering from a bacterial infection. 8(14%) as partially treated meningitis and 29(53%) with the initial suspicion of bacterial meningitis. In all those treated with antibiotics the initial diagnosis was changed, based on negative cultures, to viral meningitis. The average hospital stay was 5.2 days for those treated with antibiotics compared with 4.2 days for those managed initially as viral meningitis. Discussion: A large proportion of patients with EV meningitis are managed as patients with bacterial meningitis due to lack of early diagnosis. The RT-PCR can detect those patients and prevent unnecessary treatment with antibiotics as well as prolonged hospital stay.

P858
PRIMARY HUMAN HERPESVIRUS 6 (HHV-6) INFECTION PRESENTED AS MIELOMENINGOENCEPHALITIS IN AN IMMUNOCOMPETENT ADULT PATIENT: CASE REPORT. A.Costa, S.Sacconi, G. Alborini, E. Merelli. Department of Neurology - University of Modena - Italy

A 33-year-old woman, immunocompetent and HIV negative, was admitted to the Neurological Department for headache and fever from 20 days and bilateral visual loss from 6 days. She presented bilateral papilledema, meningeal signs with mild left hemiparesis, cerebellar signs and right sixth cranial nerve paralisis. Cerebral and spinal MRI showed foci of abnormal T1- and T2-weighted signal in left lenticular nucleus and the medulla with multifocal leptomeningeal enhancement after gadolinium (GD) administration. HHV-6 IgM antibodies tested with ELISA (Genuclin-Medical System 1997), were strongly positive in serum and CSF, while IgG were negative in both the tissues. On the day of admission she began Aciclovir 1500 mg for 7 days, Cefotaxime 9 g for 10 days and Dexamethasone 8 mg for 10 days followed by tapering per os. Three months after the onset of the disease, neurological examination was normal and cerebral and spinal MRI did not revealed foci of abnormal signal before and after GD administration. HHV-6 IgM serum antibodies were still weakly positive while IgG became positive at medium titer. Up to now very few cases of HHV-

6 meningoencephalitis in immunocompetent adults are reported and generally attributed to viral reactivation; we suggest that this case of mielomeningoencephalitis do not represent a reactivation, but a primary infection of the virus.

P859
CRYPTOCOCCAL MENINGITIS AS A CAUSE OF CHRONIC LYMPHOCYTIC MENINGITIS IN PATIENTS WITH LYMPHOMA. Navarro V, Adams D, Rérat K, Nahum L, Bourée P, Said G. Le Kremlin-Bicêtre, France.

Prevalence of cryptococcal meningitis (CM), which affects immunosuppressed patients, has notably increased since the AIDS epidemic. Its diagnosis is based on detection of cryptococcal antigen (CA) and India ink preparation (IIP) in CSF. We report 2 cases of CM in patients with lymphoma and stress the possible diagnostic difficulties. Patient 1, a 38-year-old man with a relapsing Hodgkin's disease developed a chronic lymphocytic meningitis with low glucose content, revealed by headache and pain in lower limbs 18 months ago. He was treated for tuberculosis after negative exhaustive investigations including biology for Cryptococcus neoformans and meningeal biopsy 4 months later. On examination, he had tendon reflex abolished in the lower limbs. On a new CSF examined, culture on Sabouraud's agar isolated Cryptococcus neoformans while CA's titre was limit (1/4) and IIP negative. Patient 2, a 60-year-old woman, with a history of lymphoma, developed transient febrile and behavioural changes at the end of a course of chemotherapy for a relapse. One month later, a lymphocytic meningitis with low glucose content was detected on a systematic lumbar puncture. She complained of headache but clinical examination was normal. CM was diagnosed on a new CSF examined with positive CA in CSF (titre: 1/18) and culture on Sabouraud's agar medium while IIP was negative. Both patients were successfully treated by fluconazole. Patients were HIV-negative with CD4 + cell count of 221 and 332 µL. We conclude that cryptococcal meningitis can have a protracted course in immunodepressed patients and should have appropriate investigations including culture on Sabouraud's agar.

P860
HERPES SIMPLEX VIRUS ENCEPHALITIS AND MRI APPROACH. I. Ivanovic., S. Stefan*, D. Kozic, M. Lucic, M. Prvulovic, J. Jovanovic*. Imaging diagnostic Center, Sremska Kamenica, Yugoslavia - *University Clinic for infectology, Novi Sad, Yugoslavia

Herpes simplex (HSV) encephalitis is the commonest and gravest form of acute encephalitis which comprise about 10 percent of all cases of encephalitis. Early diagnosis is crucial because of significant mortality rate, high incidence of sequele, and poor efficiency of antiviral drugs, in the late stage of disease. Purpose: To correlate the clinical signs with CT and MRI findings of brain involvement in herpetic encephalitis. Material and methods: Twelve patient with clinical and serologic confirmation of the HSV encephalitis with diferent simptoms like fever, headache, seizures, confusion, stupor and coma underwent CT brain examination and consequently MRI brain examination. Results: CT findings were positive in only 3/12 (25%) patients, while MRI was positive in all 12 patients. MRI examination revealed bilateral distibution in 8/12 (66,6%) patients., and typical involvement of temporal, frontal and insular region in all patients wuth present giral enhancement after administration of paramegnetic contrast agent (Gd DTPA). Basal ganglia were involved in 2/12 (16,6%) patients. Petechial hemorrhage were present in 3/12 (25%) patients. Early phase involvement of the medial temporal and inferior frontal lobus unilateraly were detected in 3/12 (25%) patients only by MRI. Hemorage/necrotic changes were detected in 5/12 (41,6%) patients. Conclusion: Our result indicate that MRI is superior imaging modality in examination of the patients with HSV encephalitis than CT, especially in the early phase of disease.

Multiple sclerosis

P861
DYSREGULATION OF THE HYPOTHALAMO-PITUITARY-ADRENAL AXIS IS RELATED TO THE CLINICAL COURSE OF MULTIPLE SCLEROSIS.Florian Then Bergh, Tania Kümpfel, Claudia Trenkwalder, Rainer Rupprecht, and Florian Holsboer. Max-Planck-Insitut fuer Psychiatrie, Neurology, D-80804 Muenchen, Germany

As the immune system is under the influence of hormones, neuroendocrine regulation has been studied in multiple sclerosis (MS), with emphasis on the hypothalamo-pituitary-adrenal (HPA) axis. We investigated a total of sixty MS patients with the combined dexamethasone-corticotropin releasing hormone test (Dex-CRH test). In addition, the short ACTH test was performed in thirty-three consecutive patients. All patients were in active disease, and none were treated with glucocorticoids, immunosuppressants or beta-interferon. As compared to twenty-nine healthy controls, patients had an exaggerated rise in plasma cortisol concentrations in the Dex-CRH test ($p < 0.05$), indicating activation of the HPA system. The degree of activation was moderate in relapsing-remitting MS (n=38; area under the time-course curve for cortisol, AUC-Cort, 226.2 ± 38.9 arbitrary units, meanSEM), intermediate in secondary chronic progressive MS (n=16; AUC-Cort 286.8 ± 60.2), and marked in primary chronic progressive MS (n=6, AUC-Cort 670.6 ± 148.6). These differences were statistically significant between the three patient groups ($p < 0.005$), and between controls (n=29, AUC-Cort 150.8 ± 34.1) and each patient group. Parameters of HPA axis activation correlated with neurological disability (Kurtzke's EDSS), but not with the duration of the disease, number of previous relapses or previous corticosteroid treatments, or depressed mood (Hamilton Depression Score). The ACTH test was normal in 31 of the 33 patients. These data show that HPA axis activation in MS is related to the clinical type of disease, and suggest increasing HPA activation with disease progression.

P862

A POPULATION-BASED STUDY ON THE EPIDEMIOLOGY OF MULTIPLE SCLEROSIS IN JERUSALEM COUNTY.Kami, E. Kahana, N. Zilber, D. Karussis, and 0. Abramsky, Jerusalem, Israel

Objective: To compare the prevalence rate (PR) of multiple sclerosis (MS) between Israeli natives and immigrants Jews, and Moslem Arabs. Background: Previous epidemiological study of MS in Jerusalem used old diagnostic criteria which does not include MRI findings, and did not calculate PR for Arab populations. Methods: 276 patients with definite/probable MS from Jerusalem county (December 31 1995) were identified in a review of Hadassah Hospital medical records and the national MS registry. Patient groups comprised: native-born Jews of European/American (I-E/A) and Asian/African (IA/A) origin, immigrant Jews from Europe/America (E/A) and Asia/Africa (A/A), and Moslem Arabs (MA). Jerusalem county population data was obtained from the Israeli Central Bureau of Statistics. The PR are age-adjusted and are expressed per 105 inhabitants. Results: A significant lower PR was found among A/A (22.11) vs. IA/A (52.06) and among the latter vs. IE/A (63.47). No significant difference was found between I-E/A and E/A (64.26). Among MA, PR (23.28) was significantly lower than in native born Jews, but was similar to A/A_ Conclusion: The PR of MS among Israeli Jews is higher than previously described. Since A/A patients have a similar genetic susceptibility to MS as I-A/A, their lower PR is probably due to environmental factors. The similarity in PR between E/A and IE/A does not support the effect of latitude on the disease. The narrowed differences in the PR in the second generations (IE/A and I-A/A) is due to the increase of the PR among I-A/A_ MA do not seem to differ from A/A in the susceptibility to MS.

P863
THYROID DISORDERS IN MULTIPLE SCLEROSIS PATIENTS. Amon Karm, MD, Oded Abramsky, MD, PhD, Jerusalem, Israel.

Objectives. To determine whether thyroid disorders are found with increased frequency in patients with multiple sclerosis (MS). Methods. A controlled prospective survey was conducted on a cohort of patients with MS derived from the hospitalized and outpatients clinic patients. A control group with similar demographic features was generated from the same sources and included subjects with headache or low back pain but without inflammatory diseases. Consecutive patients were evaluated over a period of 30 months. The evaluation included a complete history, physical and neurological examination, determination of serum triiodathyroxine and thyroid stimulating hormone. Results. Of the 245 women with MS, 32 (13, 1%) had evidence of primary thyroid disorder compared with the 4 (4.3%) of 93 female controls (p=0.03). The excess thyroid disorders is mainly due to hypothyroidism (p=0.04) and was independent of age, MS onset age and disease course. Conclusion. Thyroid disorder is seen more often in women with MS than m women with similar demographic features with headache or low back pain but without inflammatory diseases. This is account mainly to the excess hypothyroidism among female with MS. Both MS and hypothyroidism can cause proximal muscular weakness and fatigue. Therefore it is important to perform thyroid function tests m MS patients whenever these symptoms occur, since hormonal replacement ther-

apy may improve such complaints. Since interferon therapy for MS may worsen autoimmune thyroid disorders, it is important to consider this effect when choosing preventive treatment for MS and to monitor carefully the thyroid hormone level whenever such therapy is implemented m MS patients with thyroid disorders. As hypothyroidism is usually due to Hashimoto's thyroiditis, its association with MS may support the autoimmune hypothesis of MS etiology.

P864
MEASUREMENT OF FATIGUE IN MULTIPLE SCLEROSIS. Merkelbach S, Kölmel C, [1]Sittinger H, [2]Georg T, Müller M.Departments of Neurology and [1]Psychiatry and [2]Institute of Medical Biometrics, Epidemiology and Medical Informatics, University hospital, D-66421 Homburg/Saar, Germany

Fatigue is reported as a frequent and disabling symptom in Multiple Sclerosis (MS) and has been associated with pyramidal tract lesions. To evaluate different aspects of fatigue, we compared four questionnaires with one another and with clinical data. Patients and methods: Sixty-one patients (46 women, mean age 40 years) with definit MS were evaluated using the Fatigue Severity Scale (FSS), Chronic fatigue Scale (CFS), Fatigue Scale (FS), CIS-R, and Beck-Depression-Index (BDI). Additionally, all patients were scored using the Kurtzke Scale and funktional systems were classified. Results: Median Score values were: FSS=4.3; CFS=8; FS=33; CIS-R=3; EDSS=3.5. The scales were related to one another with coefficients ranging from 0.5716 to 0.7914. There was no correlation of any scale to EDSS and only weakly significant correlations between fatigue scores and predominantely cerebral functions (r=0.32 to 0.42) or cerebellar function (r=0.40), respectively. A highly significant relationship was found between depression and all fatigue scales. Neither age nor duration of disease were correlated to fatigue. Conclusion: The frequency of fatigue in MS depends on the assessment instrument used. The scales seem to depict different aspects of fatigue. With respect to basic MS data, fatigue might be subposed to EDSS measured disease severity throughout the duration of the disease.

P865
THE CHIETI EXPERIENCE WITH INTERFERON β1b (IFNβ1b) DURING THE FIRST 2 YEARS: EFFICACY. F. Marzoli, D. Farina, C. Iarlori, G. De Luca, L. Bonanni, A. Di Iorio, A. Lugaresi, D. Gambi. Chieti, Italy

IFN1b is available for treatment of RR-MS in Italy since February 1996. Aim of this study was to assess the efficacy of IFN1b in the first 30 patients treated at our MS Center. Relapses decreased from 3.4±1.0 in the 2 yrs before treatment to 0.84±0.6/yr at 2 yrs. Mean EDSS was 2.8±0.7 before treatment, 2.7±0.9 at 1 yr and 3.2±1.5 at 2 yrs. Treatment failure occurred in 6 pts: in 1 (positive for NAB) at 1 yr; 5 others experienced sustained progression without increased number of relapses at 18-24 mo.s. Of these pts 3/6 have interrupted treatment, 1 has switched to IFN1a for 6 months without further relapses or progression, 2 are being tested for NAB. Of the remaining 24 pts 2 have discontinued treatment for personal reasons, 3 have switched to IFN1a for practical reasons and 2 because of side effects. At 24 months 17/30 pts are still treated and doing well. MRI performed before treatment and at yr 1 and 2 has remained unchanged in responders. The only predictor of relapses in the second yr of treatment was a high number of relapses (> 2/yr) pre-treatment (O.R.=5.4). Our results are in very good agreement with findings of the North-American Study and confirm the efficacy of IFN1b in RR-MS.

P866
THE CHIETI EXPERIENCE WITH INTERFERON β1b (IFNβ1b) DURING THE FIRST 2 YEARS: SIDE EFFECTS. D. Farina, F. Marzoli, C. Iarlori, G. De Luca, L. Bonanni, A. Lugaresi, D. Gambi. Chieti, Italy

Aim of this study was to assess tolerability and safety of IFNβ1b. Pts underwent physical examination and laboratory tests (blood cell count, liver enzymes, thyroid enzymes, organ and non-organ-specific autoantibodies) monthly for the first 3 months and every 3 months subsequently. The local reaction was mild to moderate in all cases. Flu-like symptoms subsided in all pts after 3 months, but occasionally reappear. Depression was treated successfully, without need of interrupting treatment in 5 pts. Worsening of MS symptoms related to IFNβ1b administration was limited to spasticity and fatigue and in 1 case caused shift to IFNβ1a. In one pt psoriasis worsened during treatment, she just shifted to IFNβ1a. Laboratory abnormalities included increased liver enzymes (AST and ALT) (5 pts), leukopenia (4 pts, persistent in 1), presence of autoantibodies (non-organ specific, 3, already present in 1, ACA, 6, already present in 1, anti-thyroid, 9, already present in 4); in all cases titers were fluctuating in time and never symptomatic. In conclusion IFNβ1b was well tolerated in the majority of pts. Administration schedule induced 3 pts to shift to IFNβ1a or stop treatment (1 pt). One further pt discontinued all treatment to have a baby. In conclusion our results, in agreement with the North American Study, confirm the good safety profile of IFNβ1b.

P867
CHEMOKINES ARE MODULATED BY INTERFERON BETA1B (IFN-BETA1B) IN RELAPSING-REMITTING MULTIPLE SCLEROSIS (RR-MS). C. Iarlori, M. Reale, G. De Luca, L. Bonanni, D. Farina, F. Marzoli, A. Di Iorio, A. Lugaresi, P. Conti, D. Gambi. Chieti, Italy

Chemokines are involved in leukocyte migration into the CNS during immune mediated inflammation. Migration into the CNS can be decreased in vitro by IFNbeta through reduction in MMP-9 production. Aim of this study was to evaluate whether chemokine production by adherent monocytes from RR-MS is modified in vivo by IFNbeta1b. Adherent monocytes were obtained from 28 RR-MS (19 in relapse and 9 in remission) and 22 RR-MS treated with IFNbeta1b for at least 1 year (4 in relapse, 18 in remission). MCP-1 and RANTES levels in 24-h supernatants from unstimulated and PHA-stimulated mononuclear cell cultures were measured with commercially available ELISA kits. In RR-MS treated with IFNbeta1b, RANTES and MCP-1 production were decreased compared to RR-MS in basal conditions (RANTES: 5.4±1.8 vs 8.4±1.6, p=0.04; MCP-1: 4.6±0.4 vs 6.3±0.6, p=0.009). IFNbeta1b modulated RANTES, but not MCP-1 production in the presence of PHA (RANTES: 11.9±3.0 vs 15.2±1.4, p=0.02; MCP-1: 11.7±1.3 vs 11.6±1.0, n.s.). A linear correlation existed between RANTES and MCP-1 both in basal conditions (Spearman sign=0.002) and in the presence of PHA (sign=0.04). The increase in RANTES and MCP-1 levels in the presence of PHA was present and comparable both in relapse and remission. Our results suggest that IFNbeta1b might favourably modulate chemokine production, and therefore the inflammatory process in RR-MS.

P868
SEROLOGICAL INDICATION OF AN INCREASED CORONA VIRUS INFECTIONS IN DUTCH MULTIPLE SCLEROSIS PATIENTS. D. Buljevac[1], J. Groen[2], P.A. van Doorn[1], A.D.M.E. Osterhaus[2] and F.G.A. van der Meché[1], Dpts. of Neurology[1] and Virology[2], Erasmus University Medical Centre, Rotterdam, The Netherlands.

Aim: To study the relation between common infections and the relapses in MS we have set up a longitudinal prospective study with a cohort of 60 definite relapsing-remitting MS patients for a duration of 24 months. Method: Blood sampling is performed every two months. Additional blood samples and material for direct virus isolation are collected at infection or relapse and 3 weeks afterwords. Serology is performed in mostly paired serum for: EBV, CMV, HSV, HHV 6 *(IgG and IgM)*; M.Pnaeumoniae *(IgM)*; Adenoviruses, RSV and Parainfluenza 1, 2 and 3 *(IgG)*; Coronaviruses *(IgA)*. Virus isolation and direct antigen detection are performed on throat-swab, urine and faeces specimens. Results: In the initial group of tested serum samples, collected at baseline and during the first infections (n = 99) we have seen a positive serology for Coronaviruses in 27 % (15/54) of patients, which is slightly more then the average 20 % positivity in the peak season for Coronaviruses in the Dutch population. With the exeption of Coronaviruses, no serological evidence was found against any of the above members of the Herpesviridae and respiratory viruses. Likewise, no viral antigens or viruses could be detected in 200 tested specimens from these patients. Conclusions: Our results indicate that corona viruses may play a more prominent role in multiple sclerosis then other ubiquitous pathogens.

P869
UPREGULATION OF sICAM-1 DURING CLINICAL INFECTIONS IN MULTIPLE SCLEROSIS (MS). D. Buljevac[1], H. Savelkoul[2], P.A. van Doorn[1], D. Hijdra[2] and F.G.A. van der Meché[1], Dpts. of Neurology[1] and Immunology[2], Erasmus University Medical Centre, Rotterdam, The Netherlands.

Aim: To study the effect of infections on cytokine and adhesion molecule levels in relapsing-remitting MS in relation to the clinical course. Method: A longitudinal, prospective study with 60 relapsing-remitting MS patients

and expected duration of 24 months is initiated. Blood samples and PBMCs are collected every 2 months. Additional samples are collected at the time of clinical infection or relapse and 3 weeks later. Cytokines are measured in plasma using quantitative ELISA method. Results: Until now, we observed 30 infections in 26/28 patients. In 18/30 (62 %) cases an increase in sICAM-1 concentration was measured at the moment of clinically evident infection. 6/30 (20 %) infections were time-related to a relapse. No significant association between sICAM-1 increase and relapses was observed. Increase in sICAM-1 was associated with a decrease in the TNF-α concentration (Fisher's exact P=0.009). Conclusions: The increase in sICAM-1 during infections in MS follows a non-specific immunological upregulation after the contact with the pathogen and is probably not related to relapses. On the basis of observed simultaneous decrease of TNF- we hypothesize that: (1) TNF-α and ICAM-1 have different kinetics and (2) upregulation of TNF-α precedes the release of ICAM-1.

P870
OPTIC NEURITIS AND MULTIPLE SCLEROSIS. M Eraksoy, G Demir, N Gozum M Guler, E Tfiziin, S Tinaz, H Ozcan, C Ozdemir Istanbul Faculty of Medicine, Departments of Neurology and Ophthalmology*, Istanbul, Turkey.

The objective of this study was to determine the incidence, clinical characteristics and outcome of monosymptomatic optic neuritis in patients who were managed at our multiple sclerosis (MS) unit between 1997 and 1998. We reviewed the records of all patients with optic neuritis (ON) in our MS unit. This series consisted of 1624 suspected MS patients, and 1156 out of 1624 were clinically definite (CDMS), laboratory-supported definite (LSDMS), and probable (CPMS) MS patients. Of 1624, 264 patients (16%) presented with monosymptomatic unilateral ON or bilateral optic neuritis. At the time of last follow-up, 169 of the 264 patients (64 %) had MS. Of 264, 131 patients (49.6 %) had CDMS, 28 (10.6 %) and 10 (3.7 %) had LSDMS and CPMS, respectively. In 72 of 264 patients (27.2 %), other causes were identified or reaching a precise diagnosis could not be possible. The remaining of the patients (n=23, 8.7 %) were lost to follow-up. Of 1156 patients, 169 (14.6 %) presented with ON. In CDMS group, there were 94 females and 3 7 males (2.5: 1). The mean age at onset of ON was 25.2 years. In this cohort, 53 patients (40.4 %) had left eye involvement, and 51 (38.9 %) had right eye involvement. Twenty- seven patients (20.6 %) had bilateral involvement within 15 days. In most of the patients (% 81), visual acuity improved spontaneously or with steroid therapy in a month. The mean interval from diagnosis of ON to the development of the diagnosis of MS was 3.7 years. Seyerity per cent of patients converted from ON to CDMS within five years. The average follow-up period was 6.5 years and the disease duration was 13.6 years. In other two groups of patients with MS presented with isolated brainstem and sensory manifestations, the mean intevals from diagnosis of these symptoms to the development of MS were determined and were compared with ON, no significant difference was observed. This study revealed that the development of MS following monosymptomatic ON, most commonly occured within the first five years (70%) in Turkish patients. There was no significant difference between the mean intervals front diagnosis of monosymptomatic ON, brainstem and sensory symptoms to the development of MS.

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MOVEMENT-RELATED DESYNCHRONIZATION/SYNCHRONIZATION OF THE ELECTROENCEPHALOGRAM IN MULTIPLE SCLEROSIS PATIENTS COMPLAINING OF FATIGUE.[1]L.Leocani, [2]B. Colombo, [1,2]G. Magnani, [2]F. Martinelli, [2]P. Rossi, [2]V. Martinelli, [1]S. Mennea, [1,2]G. Comi.Department of [1]Neurophysiology and [2]Neurology, MS Centre, Scientific Institute Hospital San Raffaele, Milan, Italy.

Patients with Multiple Sclerosis (MS) often complain of fatigue, even in the initial phases of the disease. The mechanism of this phenomenon is not completely understood. Event-related desynchronization (ERD) of the alpha and beta rhythms of the electroencephalogram (EEG), observed over the sensorimotor cortex during preparation and execution of self-paced movements and is considered an indicator of cortical activation. Beta band synchronization (ERS) over the sensorimotor areas occurring after movement execution is considered a sign of cortical inhibition. We studied cortical activation, using ERD/ERS analysis of the alpha and beta rhythms in a self-paced movement paradigm, in a group of MS patients complaining of fatigue (n=11), and compared them to a group of patients without fatigue (n=12) and to a group of normal controls of similar age. Patients with EDSS exceeding 1.5 were not included. ERD to movement preparation and execution was similar in all three groups. Post-movement beta ERS was significantly reduced both in MS patients with and without fatigue compared to normal controls. However, the decrease of beta ERS was also significant in the fatigue group compared to the non-fatigue group. We conclude that reduced activity of cortical inhibitory circuits after movement termination may at least partially account for the mechanism underlying fatigue in Multiple Sclerosis.

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Abstract withdrawn by author

P873
INTERLEUKIN-6 EXPRESSION IN EARLY MULTIPLE SCLEROSIS LESIONS. L. M. Schönrock[1,2], G. Gawlowski[1] and W. Brück[1].[1]Dept. of Neuropathology, University of Göttingen, Germany and [2]Dept. of Neurology, University of Würzburg, Germany

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system leading to selective destruction of myelin sheaths and/or oligodendrocytes. The mechanisms behind activation or recruitment of the inflammatory cells, astrogliosis, myelin destruction and repair are poorly understood. Interleukin-6 (IL-6) is a pleiotropic cytokine involved in the dynamics of MS. We investigated the expression of IL-6 protein in steretactic brain biopsy material of 36 patients with early chronic MS in correlation to the disease activity, clinical course and the heterogenous pattern of oligodendrocyte pathology. IL-6 positive and negative cases were observed; we identified IL-6 expressing subpopulations of astrocytes (approximately 10 to 17 %) and macrophages (up to 2%). Highest numbers of IL-6 positive cells were found in inactive demyelinating lesions without statistic significance. Early remyelinating lesions but also late active lesions showed significantly increased numbers of IL-6 expressing macrophages compared to periplaque white matter. In periplaque white matter, statistically significant more IL-6 positive astrocytes than macrophages were detected. Highest numbers of IL-6 positive cells (statistically very significant: astrocytes) were found in tissue with oligodendrocyte preservation, whereas absence of IL-6 expression correlated with oligodendrocyte loss and might thus indicate a possible important role for IL-6 in oligodendrocyte protection and survival as a beneficial cytokine in myelin repair.

P874
MEASUREMENT OF MAGNETISATION TRANSFER, N-ACETYL ASPARTATE AND MOTOR IMPAIRMENT IN MULTIPLE SCLEROSIS AND STROKE. M A Lee, S T Pendlebury, A M Blamire, P Styles and P M Matthews, Oxford, U.K.

Magnetic resonance techniques allow in vivo examination of pathology within the CNS. Matrix disruption and myelin loss is associated with a reduction in the magnetisation transfer ratio (MTR). Reductions in N-acetyl aspartate (NAA) occur in regions of axonal or neuronal damage. We have examined the relationship between axonal injury and matrix disruption, as measured by NAA and MTR, from ithin the same regions of the posterior limb of the internal capsule, and motor deficit in 12 patients with MS and 18 patients with stroke. Results: A significant correlation was found between motor deficit and reduction in NAA both in stroke ($p < 0.001$) and MS ($p=0.02$) patients. In stroke, a significant correlation was also found between MTR and motor deficit ($p < 0.001$) and between MTR and NAA ($p=0.03$). This relationship was not seen in patients with MS although MTR was significantly reduced compared to controls. Nearly all MS patients, and a significant proportion of stroke patients, had no evidence of lesion within the voxel of interest. Conclusions: Findings are consistent with the hypothesis that axonal integrity is an important determinant of impairment in stroke and MS and that functionally significant changes may occur remote from areas of focal damage in both conditions. The poor relationship between MTR and impairment found in MS suggests demyelination and gliosis may occur independently of axonal damage in MS and are less closely linked with functional impairment.

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PHASE II RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF THE ORALLY ACTIVE PLATELET ACTIVATING FACTOR INHIBITOR, LEXIPAFANT, IN PATIENTS WITH MULTIPLE SCLEROSIS. M A Lee, S Adams, A Cavey, J Palace

There is growing evidence to suggest that platelet activating factor (PAF) may play an important role in inflammatory CNS pathology. PAF is produced by a variety of cells and causes neutrophil activation, increased blood brain barrier permeability and neuronal cytotoxicity. PAF inhibitors have demonstrated disease attenuation in animals with EAE. We report the results of the first randomised double-blind placebo controlled cross-over phase II study of orally active PAF inhibitor, Lexipafant, in 23 patients with relapsing/remitting multiple sclerosis. Methods: Patients were treated with oral Lexipafant or placebo twice daily for 16 weeks, switching to alternative treatment after one month washout. Primary outcome measures assessed were the number and volume of gadolinium-enhancing (Gd) T1 lesions seen on monthly scans. The study was designed to detect a 50% reduction in lesion frequency (= 0.05, power = 0.8). Results: Cross-over analysis revealed no statistically significant difference in the number (p=0.43) or volume (p=0.77) of Gd T1 lesions seen between treatment periods. Whilst more patients had a reduction in the number of Gd T1 lesions on treatment (37%) than on placebo (21%) alone, an appreciable proportion (42%) showed no reduction. No difference in relapse rates between treatment periods was found. Conclusions: No statistically significant effect of Lexipafant on MRI activity was demonstrated.

P876
NEUROPSYCHOLOGICAL ASSESSMENT IN MS. O. Santiago Rolanía, G. Martín Ozaeta, J.J. Hernçndez Regadera, A. Martinez Yélamos, Tx. Arbizu Urdiain. Unidad de Esclerosis Mútiple. Servicio de Neurología. Hospital Princeps d'Espanya. CSUB. L'Hospitalet de Llobregat. Barcelona, Spain

Although changes in cognitive function in patients with multiple sclerosis (MS) have been reported, these changes have been traditionally associeted with the later stages of the disease.Objective. To assess cognitive performance of MS patiens in whom the disease progression was relatively mild.Methods. 35 definite MS patients and 20 controls matched for age and education were submited to a neuropsychological test battery. Both groups were examined for anxiety and depression.Results. MS patients performed worse than controls on learning t=7.66 (t=3.64,.001), verbal memory t=5.75 (t=3.64,.001), visual memory t=9.26 (t=3.64,.001) attention t=4.72 (t=3.64,.001) and information processing t=4.54 (t=2.87,.001) Cognitive deficits were not related to abnormal emotional states. Conclusions. Changes in cognitive function can occur in the mild stages of the disease.

P877
LARGE FOCAL DEMYELINATING LESIONS IN MULTIPLE SCLEROSIS (MS). A CLINICAL AND MAGNETIC RESONANCE IMAGING (MRI) FOLLOW UP STUDY OF TWO PATIENTS. J.M. Guglielmi (1), V. Ganthier (2), P. Davous (1). Service de neurologie (1) et radiologie (2). Hôpital d'Argenteuil, France.

It is known that MS can present as an intracranial tumor. MRI is an important tool to identify MS lesion and monitor the activity of the disease. We report two patients with defined MS. Patient 1 is a 29 year-old female with history of regressive paraparesis. She developped right hemiplegia and aphasia lasting four months. Duration of follow-up was eleven months. Patient condition improved after steroid treatment. Sequential MRI disclosed a tumor-like lesion measuring 4 cm in diameter located in the left fronto-parietal region with Gd enhancement. In spite of clinical recovery MRI worsened. Patient 2 is a 23 year-old male presenting initially right facial central palsy. Over a period of 4 years he has three well documented exacerbations characterized by right hemiparesis. He responded to intermittent course of steroids. Sequential MRI showed a persistent 2 cm focal area in the left centrum semi-ovale with no Gd enhancement. Over the period study no additionnal signal abnormality was shown. In conclusion large focal lesions in MS can have a monophasic clinical course, they can also recur in one or more instances. Although MRI show good correlation between the location of lesions and clinical symptomatology no correlation between disability and size of lesion was found.

P878
BETAFERON^{R}: EFFICIENCY AND SIDE EFFECTS. Kreisler A, Duval L, Bour Binauld N, Louchart P, De Seze J, Stojkovic T, Vermersh P, Gallois P, Hautecoeur P, France.

INFβ1b (Betaferon^{R}) is used in France since august 1996 to reduce the frequency of relapses in multiple sclerosis. The aim of the study was to assess side effects and long-term follow-up of patients treated with Betaferon^{R}. Sixty-seven patients were included. The Expanded Disability Status Scale (EDSS), the frequency of relapses, side effects and reasons of treatment disruption were noticed. The treatment was stopped in 36 patients, because of: (1) side effects (seven cutaneous damages including three necrosis; five depressions; two leucopenia; two flu-like syndromes; one hepatic disorder; one dysmenorrhoea; one dizziness), (2) disease progression (EDSS superior to 5.5 in six patients; frequent relapses in five patients), (3) a discomfort related to the frequency of injections (four patients), (4) a pregnancy (two patients). Twenty patients have been followed at least 24 months. In thirteen, the EDSS did not change (n=9) or became lower (n=4). In eighteen, the frequency of relapses was the same (n=1) or lower (n=17) than during the two previous years; five patients presented no relapse. INFβ1b seems to have stabilised the disease in a significant number of patients; this result has to be considered with care in the absence of placebo group. However, this treatment had to be stopped in 54 % of the patients, mainly because of side effects, which is more than in previous studies.

P879
THE IMPACT OF BETA-INTERFERON (IFN) IN THE TREATMENT OF RR-MULTIPLE SCLEROSIS (RR-MS): RESULTS OF A QUESTIONNAIRE TO ITALIAN NEUROLOGISTS. A. Ghezzi, M. Zaffaroni, G. Comi*. Centro Studi SM (Gallarate) and (*) MS Centre H.S. Raffaele (Milan), Italy

Objective: a questionnaire was sent to neurologists of Italian MS centres in order to assess the opinion on the therapy of the RR-MS. Neurologists were asked to give their opinion about the treatment of MS in different clinical cases, 66 questionnaires were collected. Results. The choice of the drug in different clinical cases is reported below: Typical RR-MS: IFN=84.5%, COP1=1.5%, AZA=4.5%, no therapy=6%, other treatments= 3.0%; RR-MS with mild signs: IFN=42.5%, COP1=4.5%, AZA=7.5%, no therapy 42.5%, other treatments =3.0%; Benign MS followed by RR course: IFN=72.7%, COP1=3.0%, AZA=3.0%, no therapy 19.8%, other treatments=1.5%; RR-MS with short duration: IFN=45.5%, COP1=6.0%, AZA=6.0%, no therapy 39.5%, other treatments =3.0%; RR-MS with anti-thyroid-antibodies: IFN=31.8%, COP1=33.3%, AZA=15.2%, no therapy= 15.2%, other treatments=4.5%; Case as above, with further RR course: IFN=47.0%, COP1=25.8%, AZA=16.7%, no therapy 1.5%. No neurologist advised females against a pregnancy before starting any therapy. Seven neurologists stopped IFN after the development of depression, 46 associated antidepressants, 6 reduced IFN dose, 7 changed the type of IFN. Fourteen neurologists replaced IFN with other immunosuppressants after the development of frequent relapses. The development of anti-thyroid antibodies induced 17 physicians to withdraw IFN. Most neurologists decided to continue the IFN administration in relapse-free cases during a 3 year treatment. Avonex was prescribed more frequently than Betaferon (62 % vs. 38%).

P880
THE PROGNOSIS OF MULTIPLE SCLEROSIS WITH ONSET ≤ 15 YEARS. A. Ghezzi, L. M. Gherardi, M. Liguori, MG. Marrosu, N. Milani, C. Milanese, C. Pozzilli, I. Simone, M. Zaffaroni. Gallarate, Bari, Cagliari, Milan, Rome (ITALY)

Objective: to evaluate the prognosis of multiple sclerosis (MS) in subjects with age of onset < 15 years prospectively studied. Subjects: 54 patients with clinically definite MS, f/m ratio=2, mean age of onset 12.6 ± 2.1 years, mean follow up duration 11.1 ± 5.6 years. Disability was measured by the Expanded Disability Status Scale (EDSS). The onset was monosymptomatic in 29 cases, polysymptomatic in 25 cases. Brainstem dysfunction was observed in 20 cases, pyramidal involvement in 17, sensory involvement in 11, optic nerve involvement in 9, cerebellar involvement in 9 cases. Follow up results: the EDSS was 2.2 at onset, 1.3 after 1 year, 2.1 after 4 years, 3.5 after 8 years, 3.8 after 10 years. After 8 years, the EDSS score was ≤ 3.5 in 25 subjects (69.5%), between 4 and 6 in 3 subjects (8.3%), ≥ 6.5 in 8 subjects (22.2%). The EDSS after 8 years was highly predicted by: the EDSS in the first year, the relapse rate in the first to years. Gender, symptoms and age at onset were not correlated with disability at the end of the follow up.

P881
IL-1 IN CEREBROSPINAL FLUID AND PLASMA OF MULTIPLE SCLEROSIS PATIENTS DURING ONE YEAR COPAXONE® FOL-

LOW-UP TREATMENT. Dordevic D, Jovicic A, Vojvodic D*, Raicevic R, Dincic E, Popovic P*Department of Neurology, Department of experimental medicine*, Military Medical Academy, Belgrade, Yugoslavia

Copaxone® is a new immunomodulatory drug that probably influence T helper and T suppressor functions and can modulate the immune response in multiple sclerosis (MS). The aim of the study was IL-10 follow-up in cerebrospinal fluid (CSF) and plasma of MS patients during one year Copaxone treatment. Among 12 patients (7 females/ 5 males, age 25-45 years, average EDSS 3.5), 9 were remitent-relapse form of (RR), 2 secondary progressive (SP) and 1 primary progressive (PP) form MS. CSF and plasma samples were taken before the therapy, 3, 6, and 12 months during the treatment. Concentrations of IL-10 were measured by ELISA method. Results: in 7 RR patients and 1 PP, CSF IL-1 levels decreased during therapy; 2 patients in remission had initially decreased and afterwards increased levels of IL-1 in CSF (6. And 12. month). In 1 SP patient, the increase of IL-1 CSF levels was found while in other SP patients tendency of mild decrease of IL-1 and than raise in the 12th month was noted. In 9 patients (7 RR and 2 SP) plasma levels of IL-1 were lower than start values, in 1 RR patient plasma IL-1 level increased at 6th month, and in 1 PP patient, IL-1 was detected for the first time at 6th month. Conclusion: Copaxone has decreased the CSF levels of IL-1 in MS patients, especially in those with clinically milder form of disease.

P882
A GENE THERAPY WITH NAKED DNA ENCONDING FOR PLP IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS. Agata Walczak, Czeslawa Kowal*, Jolanta Pentela, Cedric S. Raine* and Krzysztof Selmaj; Lodz, Poland and *New York, U.S.A.

The therapeutic effect of vaccination with naked DNA upon the outcome of later sensitization for autoimmune demyelinating disease was tested using a DNA construct encoding proteolipid protein (pRc/CMV-PLP) in combination with a model of actively-induced experimental autoimmune encephalomyelitis (EAE) induced in SJL mice with PLP 139-151 peptide in adjuvant. Intramuscular naked DNA vaccination led to expression of PLP gene in local muscle tissue. Sensitization for EAE 4 weeks after DNA vaccination predisposed recipient mice to a severe, exacerbated form of EAE (in comparison to control EAE mice), while sensitization for EAE 10 weeks after DNA vaccination resulted in a milder, ameliorated form. Mechanistically, pRc/CMV-PLP vaccination led to a transient Th1-type cytokine response. In mice sensitized later (10 weeks) for EAE it led to peripheral tolerance as evidenced by a decrease in T cell proliferation and CTL response, no Th2 response, and no increase in apoptosis. The ability of DNA vaccination to differentially and beneficially modulate the course of EAE may have therapeutic implications for multiple sclerosis and a number of autoimmune conditions.

P883
THE EDMUS GRADING SCALE Grimaud J, Amato MP, Confavreux Ch, for the EVALUED Study Group. (The EVALUED Study Group. Amato MP, Bartolozzi ML, Florence-Italy. Confavreux Ch, Cortinovis P, Hours M, Adeleine P, Lyon-France. Hartung HP, Morrisey S, Flachenecker P, Würzburg-Germany. Kappos L, Huber S, Lechner-Scott J, Basel - Switzerland. Livrea P, Trojano M, Avolio C, Bari - Italy. Thompson AJ, Hobart J, Grimaud J, London-UK.)

The EDMUS Grading Scale (EDMUS-GS)[1] is adapted from Kurtzke's DSS scale, based mainly on symptoms and walking abilities. It is suitable for daily practice and epidemiological studies. Retrospective use is also possible. Method: 12 neurologists working in pairs from 6 European centres (Bari, Basel, Florence, London, Lyon, Wurzburg) scored 30 patients independently according to EDSS[3] and EGS scales at the same patient visit. The variations in scores was reported. Results: In most cases the score is the same regardless of the scale used. Inter-rater agreement is higher for EDMUS-GS than EDSS scale. Agreement within 0 point was 59% for EDSS and 78% for EGS. Agreement within 1.0 point was 93% for EDSS and 97% for EGS, and within 2.0 point 99% for both scales. Conclusion: The EGS classifies the patients in the same way as the EDSS. But It is quicker and easier to use, even to a non specialist. References [1] *Confavreux Ch.* et al. JNNP1992,*55:671-676.* [2] Kurtzke JF. *Neurology 1983*,33:1444-1452.

P884
CHANGING FREQUENCY OF MULTIPLE SCLEROSIS (MS) IN ENNA, SICILY. L.M.E. Grimaldi, A. Rizzo, G. Salemi, R. Marziolo, C. Lo Presti, D. Maimone, V. Romano, F. Fazzi, G. Grimaldi, G. Savettieri. Milan, Enna, Palermo, Catania, Troina, Italy.

Since the survey by Dean et al. (1979), the city of Enna has been considered a high risk area for MS with a prevalence of $53/10^5$. Recent surveys have found an increase of MS prevalence throughout Sicily with the highest rate ($73/10^5$) in Monreale City. We reevaluated the prevalence of MS in Enna, a mountain city of central Sicily (altitude 986 meters), at January 1, 1996. A search of MS patients was made among the residents in Enna (N = 28,386) throughout the following sources: Italian MS Centers; survey of general practitioners; hospital databases; MS charities. Patients were classified according to Poser's criteria. The score at the Kurtzke expanded disability status scale (EDSS) was determined. We identified 32 patients with definite/probable MS (20 female, 16 male). Prevalence was $112/10^5$ (CI 77-159). Thirteen patients had onset during 1988-95 generating an average incidence of $5.7/10^5$/year. The primary progressive form was found in 18.7% of patients, a benign course in 20% of them. Mean EDSS score was 3.1. In conclusion, we found a rise of MS prevalence in Enna by more than 2 times in a 20-year period and a brisk annual incidence rate which makes Enna the city with the highest prevalence of MS so far reported in Italy. Explanations include increased awareness of the disease among the general population and attending physicians, improved diagnostic methodologies, or the occurrence of an ongoing epidemic.

P885
MULTIPLE SCLEROSIS IN KUWAIT - THE LOCAL SCENE. Dr Khan R A, Dr Hussein J M, Dr Shubaili A F -Ibin Sina Hospital, Kuwait.

Multiple Sclerosis is a chronic neurologic disability predominantly affecting young adults during their most productive years. Almost 70% of the patients manifest their symptoms between 20-40 years of age. Like other immune mediated diseases, females are more affected than males. Worldwide studies have shown that M.S is unequally distributed. While it is more common in persons of Scandinavian decent, it is less common in the near & Middle Eastern regions according to published prevalence rate data. Both genetic & environmental factors have been postulated to influence the disease frequency. Ibin Sina hospital Neurology Services is the only tertiary referral center for the entire State of Kuwait. According to the hospital records until Dec. 1988, there were 201 registered M.S patients. Kuwaitis were only 51 among them. These figures have shown a sudden jump over the next 9 years. Until Dec. 1998, the total no: of M.S patients reached 325. The Kuwaitis comprising 227 - a four-fold increase. This is far higher than the known prevalence of the disease in the neighboring countries. The clinical presentation, neurological findings and other supportive diagnostic data in our M.S cases does not differ very much from those of the neighboring and other western countries. There is no known curative treatment for M.S. Interferons are successively used to reduce frequency and severity of relapses. "Epidemics " of Multiple Sclerosis have been reported to occur in world literature, but whether such a phenomenon is happening in Kuwait is yet to be understood and explained. The contribution of the Gulf war in this "epidemic" cannot be disregarded. However, it is worth mentioning that specific "point agents" in other such incidences around the world have not been identified.

P886
CYTOKINE LEVELS IN SERA FROM PATIENTS WITH NEUROIMMUNE DISEASES. P Bongioanni, R Ricciardi, MR Metelli, M Tararê, R Catalani, E Mariotti, G Marra, G Marcacci, B Rossi, Pisa & Livorno, Italy

Cytokines have pleiotropic effects on the neuroimmune system: some of them are able to enhance immune mechanisms, whereas others can act as negative immunoregulators. Recently, attention has been focused on cytokines produced by the two T-helper (T_h) subsets: T_{h1}-type cytokines (interleukin(IL)-2, IL-12, interferon(IFN)-γ, tumor necrosis factor (TNF)-α and β), regulating the delayed type hypersensitivity response and inflammation; and T_{h2}-type cytokines (IL-4, IL-5, IL-6 and IL-10), modulating B-cell growth and differentiation, and counterregulating T_{h1} cells. The aim of the present work was to assay serum T_{h1}-type and T_{h2}-type cytokine levels in patients with multiple sclerosis (MS) or myasthenia gravis (MG), two typical neuroimmune diseases. In both diseases, we observed increased levels of IL-6, soluble IL-6 receptors (sIL-6R), TNF-α and IL-12, and inconstantly decreased levels of IL-10. Immunosuppressive treatment reduced sIL-6R levels in both MG and MS, and TNF-α amounts in MG patients only. Such findings further support the immunological role of cytokines in MS and MG, and may have some therapeutic implications.

P887
1,25-D3 TREATMENT IN MULTIPLE SCLEROSIS. Achiron, MD, PhD, Y. Barak, MD, S. Miron, MD, PhD, Y. Izhak*, MD, M. Faibel*, MD, S. Edelstein#, PhD. Neuroimmunology Unit and *Department of Radiology, Sheba Medical Center, Tel-Hashomer, #Department of Biocemistry, The Weizmann Institute of Science, Rehovot, Israel.

1,25-dihydroxyvitamin D3 has recently been reported to beneficially affect experimental autoimmune encephalomyelitis through intervention in cytokine mediated immune processes. In the present study five patients suffering from relapsing-remitting multiple sclerosis were treated by 1,25-dihydroxyvitamin D3 at a dose of 1.5 mgr for a period of 6 months. No side effects or adverse events were recorded during the trial period. Compliance was ascertained through repeated measurements of 1,25-D3 serum levels. Clinical and brain MR imaging demonstrated no deterioration in patients status. Thus, 1,25-D3 is safe and should be further investigated as a potential immunomodulatory compound for patients suffering from multiple sclerosis

P888
MRI OF MULTIPLE SCLEROSIS SIMULATING TUMOR. Pappa, N. Bontozoglou, A. Tavernarakis, H. Koutra, C. Potagas, N. Balakas. Athens, Greece

Multiple sclerosis may rarely present as a solitary lesion with the clinical and radiological features of a tumor. We describe one patient with definite and two patients with possible multiple sclerosis with large focal lesions in the brainstem (2) and the cervical cord (1). In one case the lesion was gadolinium enhancing while in the others a new MRI showed an enlargement of the lesions suggesting a tumoral process. In all cases follow-up MRI revealed complete regression of the lesions by the time of clinical recovery. These cases illustrate the fact that demyelinating disease can mimic tumor even in MR imaging. They furthermore indicate that the clinical course and the serial MRI studies may rule out the diagnosis of tumor in suspected MS presenting as a single lesion without the need of surgical verification.

P889
EVALUATION OF LONG-TERM SAFETY AND CLINICAL EFFICACY OF COPAXONE (GLATIRAMER ACETATE, FORMERLY KNOWN AS COP 1) IN MULTIPLE SCLEROSIS. La Mantia L., Milanese C., Pieri E*, Salmaggi A, Palumbo R.Istituto Nazionale Neurologico "C. Besta", Milan -Italy* TEVA Pharma Italia S.r.l. Milano Italy.

Cop 1 has been approved for treatment of Multiple Sclerosis (MS) on the basis of the results of two placebo controlled trials, confirmed at the extension study at 29 months. The aim of the project was to evaluate the long-term (more than 2 years) efficacy and safety of Cop 1 in MS. The patients,previous informed consent, were enrolled in Protocol 1140, an open phase III trial, involving 14 Italian Centres. In our Center the study duration was three years; at the end the patients continued therapy within the "Copaxone Compassionate Use Protocol". 28 patients were enrolled, 18 with Relapsing-Remitting and 10 Secondary Progressive MS, EDSS 3.2 ±1.3; Pre-trial relapse frequency 2.5 ± 1.06. The mean treatment duration was 2.6 ± 1.26 years: 21 patients were treated for 2 years, 15 for 3 and 6 for four years. Relapse rate decreased of 68% and 78% at 2 and 3 years respectively. The mean time to first exacerbation was 7.74 months. At 3 years 87% were stable. The treament was well tolerated, local and systemic reaction occuring in 43% and 14% of cases. These preliminary data suggest that Cop 1 is effective and safe after two years of therapy.

P890
IL-10 IN CEREBROSPINAL FLUID AND PLASMA OF MULTIPLE SCLEROSIS PATIENTS DURING ONE YEAR COPAXONE® FOLLOW-UP TREATMENT. Dordevic D, Jovicic A, Vojvodic D*, Raicevic R, Dincic E, Lepic T, Obradovic S.Department of Neurology, Department of experimental medicine*, Military Medical Academy, Belgrade, Yugoslavia

Copaxone® is a new immunomodulatory drug in multiple sclerosis (MS) treatment. It is assumed that changes of T helper and T suppressor lymphocytes function may modify autodestructive immune response and prevent clinical flares of the disease. The aim of the study was IL-10 follow-up in cerebrospinal fluid (CSF) and plasma of MS patients during one year Copaxone treatment. Among 12 patients (7 females/ 5 males, age 25-45 years, average EDSS 3.5), 9 were remittent-relapse form (RR), 2 secondary progressive (SP) and 1 primary progressive (PP) form of MS. CSF and plasma samples were taken before the therapy, 3, 6, and 12 months during the treatment. Concentrations of IL-10 were measured by ELISA method. Results: in 7 RR patients CSF levels of IL-10 increased during treatment, while in 2 decreased, which corresponded to clinical deterioration (3. and 6. month). In 1 SP patient CSF IL-10 was detectable only before the therapy and in other 2 patients (1 SP and 1 PP) IL-10 was not detected. Plasma levels of IL-10 were increased in 5 RR patients, however, in all others it decreased during therapy. Conclusion: Copaxone caused increase of CSF IL-10 levels during therapy which corresponded to clinical remission of MS, however, the plasma concentration were the part of systemic response and underlie to other mechanisms of regulation.

P891
EARLY DIAGNOSIS OF TIBIAL MUSCULAR DYSTROPHY: INTEREST OF MUSCULAR IMAGING. J. de Seze, T. Stojkovic, B. Udd, A. Salhi, H. Haravuori, N. Boutry, P. Vermersch. Lille, France; Vasa, Finland

Background: We recently described the first European tibial muscular dystrophy (TMD) family outside the Finnish population (de Seze et al., 1998). TMD is a late onset distal leg myopathy with an autosomal dominant transmission. Diagnosis is difficult to assess at the onset of the disease. Objective: The aim of this study was to evaluate the interest of imaging (CT or MRI scan) at the early stage of the disease and to compare radiological findings in other neuromuscular diseases with distal leg impairment (scapuloperoneal muscular dystrophy, Charcot-Marie-Tooth disease.). Patients and methods: We performed CT scan or MRI in 11 patients of our large TMD familyand in patients with other distal leg neuromuscular disorders. We correlated imaging with molecular genetic on chromosome 2 to confirm the diagnosis. Results: Three of our 11 patients were clinically involved. One asymptomatic patient was detected by CT and MRI scan and confirmed by molecular genetic. All of the TMD patients had a specific radiological pattern with a focal abnormality (hypointensity on CT-scan and hypersignal on T1 weighted MRI) concerning only the tibial anterior muscle. None of the controls showed the same pattern. Conclusion: Imaging is a very useful tool for the diagnosis of distal neuromuscular disorders especially for TMD showing a specific impairment of tibial anterior muscle.

Muscle Disorders

P892
CLINICAL FINDINGS IN RICKER'S DISEASE (PROMM): ANALYSIS OF 11 SPANISH PATIENTS. J. Gçmez, L. Martorell, C. Navarro, JM. Martínez, C. Cervera. Servicio Neurologia Hospital Gral. Universitario Vall d'Hebron. Barcelona, Spain.

Ricker's disease or PROMM is a multisystemic hereditary disorder with autosomal dominant transmission. Its features are similar to but distinct from Myotonic Dystrophy (MD). The clinical characteristics, initially described, were: myotonia, proximal muscle weakness and cataracts. From those symptoms, the term PROMM (proximal myotonic myopathy) was coined. The presence of myalgias was recently incorporated to this triad as a core symptom. Some authors have reported the presence of other findings: cardiac arrhythmias, insulin resistance, tremor, hypogonadism, increased CK/GGT, fasciculations, and white matter lesions. To date, none of the patients with PROMM have shown changes in mental state, hypersomnia, gastrointestinal hypomotility, hypersomnia or other problems typical of MD. The presence of congenital forms has not been observed. Objective: To evaluate the different clinical and paraclinical findings of 11 patients affected with Ricker's disease. Methods: We studied 11 patients belonging to 4 different families (5 males/6 females). The presence of the pathologic CTG expansion of the chromosome 19q13.3 was discarded in all patients. Muscular biopsy was performed on five patients. Results: Myotonia was present in 81% of patients, proximal weakness in 63%, cataracts in 36%, and myalgia in 72% and cardiac arrhythmia in 27%. CK and GGT were increased in 45%. Conclusions: In 36% of patients the classic tetrad was present, while the majority of patients only showed 2 or three characteristic PROMM findings. In this subgroup of patients, diagnosis can be difficult. Only the discovery of the genetic error causing this disease would help to detect these paucisymptomatic patients.

P893
MAGNESIUM AND MITOCHONDRIAL DISEASE REVISITED. AJ Larner, C Williamson, NS Ward, JF Acheson, S Robinson, SF Farmer. St

Mary's Hospital, London; and National Hospital for Neurology and Neurosurgery, Queen Square, London, U.K.

There have been occasional reports of patients with chronic hypomagnesaemia of congenital or drug-induced origin who developed mitochondrial disease, manifest as proximal limb weakness, cardiomyopathy and seizures, with ragged red fibres in muscle biopsies. It has been suggested that this rare association may be pathogenetic: since magnesium ions are essential for the function of some mitochondrial enzymes, hypomagnesaemia may contribute to the development of mitochondrial dysfunction. We present a patient with a congenital magnesium-losing nephropathy who, despite adequate replacement therapy, developed seizures, myoclonus, and pigmentary retinopathy in his teenage years; there was no ophthalmoplegia. Investigations showed increased blood and cerebrospinal fluid lactate, cerebellar atrophy on magnetic resonance imaging, cortical hyperexcitability on somatosensory evoked potential studies, and abnormal electroretinograms. All these features may be part of the phenotype of mitochondrial disease. However, electromyography, aerobic lactate test, muscle biopsy, and mitochondrial DNA analysis of blood were all normal, excluding this diagnosis. In the light of these findings, we suggest the proposed role of hypomagnesaemia in the pathogenesis of mitochondrial dysfunction requires re-examination; the few cases reported may represent chance concurrence.

P894

Abstract withdrawn by author

P895

MIXED TOXIC MYOPATHY.Vilchez JJ, SevillaT, Dobùn I, Baquero M, Mayordomo F. Valencia, Spain.

Toxic myopathies (TM) are quite common. It is important to recognize them because patients usually recover after drug suppression. Objective: To present a colchicine toxic myopathy that progressed toward a fatal outcome in spite of the drug retrieval. Case Report: Male, 69 years, with chronic renal insufficiency treated with kidney transplantation in 1980. He had been receiving immunosuppression with low doses of prednisone and azatioprine, as well as -blockers for hypertension and colchicine for gout arthritis. During the last seven months he had been complaining of progressive proximal muscle weakness and symptoms of cardiac failure. Laboratory findings included creatinine level of 1.96 mg/dl (1,4) and serum creatine kinase of 65 I.U./l. (< 165). An electromyography showed fibrillations, positive sharp waves and motor-unit potentials of short amplitude and duration that was interpreted as "polymyositis". Prednisone was raised to 60 mg. daily. After the suppression of colchicine the patient not only did not improve but required mechanical ventilation and finally died. Results: In muscle biopsy appeared loss of myosin thick filaments in addition to a vacuolar myopathy. Conclusions: The muscle biopsy discovered features of a chronic colchicine toxicity and acute corticoid impairment. We interpreted that a potentiation effect of both drugs would lead to the severe myopathy.

P896

CLINICAL AND MRI-FINDINGS IN SYMPTOMATIC AND PRESYMPTOMATIC CASES OF DISTAL MYOPATHY OF MIYOSHI TYPE.1D. Knorpp, 1U. Knirsch, 2R. Tomczak, 1H. Schreiber, 1Dept. of Neurology, University of Ulm, RKU Hospital, Ulm, Germany, 2Dept. of Diagnostic Radiology, University of Ulm

Miyoshi distal myopathy is characterized by progressive muscular weakness and atrophy beginning in posterior compartment of lower extremities at second or third decade of life. The inheritance pattern is autosomal-recessive. Linkage to chromosome 2p 12-14 has been found, consanguinity is often reported. Whereas it is well known that elevated serum creatine kinase (CK) may precede clinical affection, it is not known yet, whether MRI may be able to detect preclinical, laboratory and MRI-findings. Methods: From 2 families three patients (aged 17-23 years) with the typical presentation of Miyoshi myopathy and 3 to date unaffected siblings (aged 7-13 years) were identified. One family consisted of Turkish consanguin parents and 4 children: One 20year old male, clinically affected, two 13year old female dizygotc twins, without clinical sympoms but higly elevated serum-CK and one 17year old male without pathological clinical or laboratory findings. In the other family no consanguinity was found between the two German parents: the 23 year old daughter was severely affected, the 18 year old daughter was slightly affected. The 7 year old son showed no clinical symptoms to date, but had already slightly elevated serum-CK. Muscle biopsy was performed in two patients. M. quadriceps demonstrated a mild myopathic pattern. Results: MRI (T2 weighted axial plane) of the lower limb demonstrated an increased signal intensity pattern of dorsal calf muscels, e.g. soleus an gastrocnemius muscle in clinically affected persons. In presymptomatic family members with elevated serum-CK MRI (T2 weighted axial plane with fat saturation) of the lower limb, also showed increased signal intensity of the medial portion of the gastrocnemius muscles. However members without any pathologic clinical or laboratory findings, MRI of the lower extremities revealed normal signal intensity of the muscles. Discussion: Cupler et al (1998) has recently found that presymptomatic siblings of Miyoshi patients with elevated serum-CK had normal MRI-findings, whereas we observed correlations of severity of MRI alteration and elevated serum-CK even in clinically not yet affected patients. We conclude that MRI-alterations may precede the onset of clinical symptoms in distal Miyoshi mopathy as well as elevated CK-levels. So routine use of MRI in patients suspected to suffer from Miyoshi myopathy is recommended.

P897

EXPRESSION OF UBIQUITIN AND TNFα IN NEUROGENIC TARGET FIBERS. Feki I, Chazaud B, Eliezer-Vanerot MC, Poron F, Gheradi RK, Authier FJ. Groupe d'Etudes et de Recherches sur le Muscle et le Nerf (GERMEN), EA 2347, Université Paris-XII Val de Marne, Creteil, France.

Histological features of neurogenic muscle involvement include myofiber atrophy, type-grouping and target fibers. Neurogenic muscle atrophy and target fibers are characterized by myofilament breakdown, mainly due to ubiquitin-ATP-dependent proteolysis. Signals for enhanced ubiquitin gene expression included the proinflammatory cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)α. We previously showed that muscle fibers undergoing neurogenic changes expressed IL-1, specially most atrophic and target fibers [Authier FJ et al. Acta Neuropathol 1997; 94: 272-279]. In the present study, we evaluated the myofiber expression of IL-6, TNFα and ubiquitin in peroneus brevis muscle biopsy samples from 5 patients with peripheral neuropathies, using immunohistochemistry and immunoblot. Controls were 5 histologically normal muscles. Immunohistochemical expression of ubiquitin was onserved only in target fibers (mean of positive fibers: 50.7%). Immunohistochemical expression of TNFα was observed in both atrophic and target fibers (mean of positive fibers: 28.8%) and confirmed by immunoblot. In target fibers, immunoreactivities for TNFα and for ubiquitin were localized at the ring level. Statistical analysis showed a positive correlation between the percentages of ubiquitin-positive and TNFα-positive target fibers ($r = 0.879$). Subsarcolemmal immunohistochemical expression of IL-6 was observed in both normal and neurogenic muscles, but was not confirmed by immunoblot. We conclude that human myofibers express both TNFα and ubiquitin during denervating processes, and that TNFα may act in combination with IL-1 for triggering ubiquitin expression in neurogenic target fibers.

P898

DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER TRIAL OF CREATINE MONOHYDRATE IN MITOCHONDRIAL MYOPATHIES. Thomas Klopstock, Veronika Schlamp, Folkart Schmidt, Florian Gekeler, Manfred Hartard, Thomas Gasser, Dieter Pongratz, Marianne Dieterich, Andreas Straube and Wolfgang Müller-Felber; München, Germany

Mitochondrial diseases are due to a defect of aerobic energy metabolism, and depletion of adenosine triphosphate (ATP) leads to increased dephosphorylation of phosphocreatine (PCr). Supplemental creatine (Cr) ingestion results in an increase of muscle Cr and PCr in healthy subjects and may increase maximal power output up to 20%. Thus, Cr supplementation may benefit patients with mitochondrial diseases by increasing intramuscular Cr and PCr and improving ATP resynthesis. After approval from the Ethics Committee, 16 patients suffering from chronic progressive external ophthalmoplegia (CPEO), CPEO plus or mitochondrial myopathy (MM) participated in a randomized, double-blind, placebo-controlled cross-over trial. Cr or placebo were given orally in a dose of 20g/day for 4 weeks, and were tolerated without side effects. Measurements of therapeutic efficacy, however, showed no significant effects of Cr as compared to placebo with regard to several neuromuscular scores, quantitative torque and performance analysis, aerobic cycle ergometry with pre- and post-exercise lactate analysis, neuroorthoptic examination, and analysis of saccade velocity

measured by an infrared reflection device. In conclusion, Cr is safe, but does not have major therapeutic effects in CPEO and MM.

P899
PERSISTENT HYPERCKEMIA: FINAL REPORT OF A STUDY ON A LARGE POPULATION OF ASYMPTOMATIC OR PAUCISYMPTOMATIC PATIENTS. Prelle A., Tancredi L., Chiveri L., Comi G.P., Sciacco M., Battistel A., Ciscato P., Bordoni A., Fortunato F., Napoli L., Scarlato G. and Moggio M., Milan, Italy.

Persistently increased serum CK levels (hyperCKemia) is occasionally encountered in otherwise healthy patients. We made a retrospective evaluation of 120 asymptomatic or paucisymptomatic patients who came to our observation in the last years because of occasional, but persistent hyperCKemia. Last year we showed preliminary results of our study whose objective is to verify whether these patients are affected with subclinical myopathy or idiopathic hyperCKemia. All patients underwent clinical evaluation of muscle strenght (MRC scale), routine blood examination, EMG, EKG, Munsat test, exercise testing, urine aminoacids and organic acids and, finally, muscle biopsy. We performed routine morphological muscle examination along with reactions for myoadenilate deaminase (MAD), myophosphorilase, phosphofruktokinase and immunoistochemistry for dystrophin. Proper immunohistochemical, ultrastructural, biochemical and genetic studies were also performed. Our investigations allowed us to make a definite diagnosis in 25 patients: 8 dystrophinopathies, 5 cases of increased susceptibility to malignant hyperthemia, 4 partial CPT deficiencies, 2 desminopathies, 1 mitochondriopathy, 1 MAD deficiency, 1 tubular aggregate myopathy, 1 fluctuans myotonia, 1 central core myopathy, 1 mild limb girdle dystrophy. Further 35 patients presented some pathological changes at muscle biopsy whereas 60 biopsies were completely normal. In conclusion our studies allowed us to make an established diagnosis in 21 % of patients.

P900
MYASTHENIA GRAVIS WITH INFLAMMATORY FEATURES AT MUSCLE BIOPSY. Chiveri L., Prelle A., Sciacco M., Bazzi P., Conti E., Pesenti A., Scarlato G., Moggio M. Milan, Italy

We report the case of a 41 y.o. woman with a two month history of spontaneous and exercise-induced muscle aching and proximal weakness followed by episodic diplopia in all gaze directions. First neurological evaluation showed weakness of three oculomotor muscles plus moderate limb weakness. Serum CK, autoantibodies and basal lactate were normal. EMG studies showed diffuse proximal myogenic signs, ripetitive stimulation and jitter being negative. At muscle biopsy we found moderate fiber size variability, fiber necroses with mononuclear cellular infiltrates, and positivity for anti-HLA I antibodies in a perifascicular distribution. These findings indicated an inflammatory myopathy, but, considering the clinical manifestations, we measured anti acetylcholine receptor antibodies whose titre was higher than normal, therefore suggesting an end-plate disorder. Therapy with pyridostigmine was started and followed by dramatic clinical improvement. Four months later, though chest MRI was normal, she underwent thymectomy which disclosed a large thymic gland with an adipose involution. Corticosteroid therapy had been associated a few weeks before thymectomy and continued afterwards. After thymectomy she referred further improvement of limb weakness. The term "Myasthenic myopathy" is used to designate several phenomena where the diagnosis of MG is questioned by incongruous clinical, therapeutic, neurophysiologic or histologic criteria. Our patient had a clinical history compatible with myasthenia, but the bioptic pattern was consistent with myositis.

P901
MITOCHONDRIAL ENCEPHALOMYOPATHIES: APOPTOTIC MECHANISM IN OXIDATIVE DEFICIENT MUSCLE FIBRE. Bazzi P, Fagiolari G, Lamperti C,, Prelle A, Sciacco M, Messina S, Chiveri L, Scarlato G and Moggio M. Milano, Italy.

Mitochondrial encephalomyopathies are a heterogeneous group of multisystem disorders caused either by mtDNA mutations or nuclear gene alteration, leading to oxidative mitochondrial defect. Mitochondria have been shown to partecipate in the regulation of apoptotic nuclear disintegration and their imparment may alter this control. For these reasons, we studied 29 muscle biopsies from patients affected with mitochondrial encephalomyopathies, using TUNEL reaction. Ultrastructural examination was performed in all muscle biopsies, especially at ragged red fibre level. Normal and pathologic muscles were used as controls. Twelve patients were affected with CPEO and genetic analysis showed large mitochondrial deletions.The percentage of deleted genomes varied from 26.3% to 77.8%. Ten patients had MELAS/MERRF fenotype and genetic analysis showed mitochondrial point mutations.Six patient had multiple deletions. One patient had mDNA depletion. In all muscle biopsies results were similar: no apoptosis was found either in COX positive or negative muscle fibers, but in a few ragged red fibers.

P902
ROLE OF APOPTOSIS IN INCLUSION BODY MYOSITIS. Lamperti C, Fagiolari G, Bazzi P, Prelle A, Tancredi L, Baron PL, Conti E, Ciscato P, Scarlato and Moggio M.Milano, Italy.

Inflammatory myopathies are disorders in which muscle necrosis is mediated by T cells through vasculitic or perforin-cytotoxic mechanism. So far, cell injury does not seem to be caused by apoptosis. Nevertheless Beherens et al. found muscle expression of both pro (Fas/Fas-ligand) and inhibiting apoptotic factors (bcl2) in these diseases. Conversely, Tews and Goebel did not find these factors in muscle fibers. To clarify the role of these proteins, we studied muscle biopsies from 5 patients affected with either polymyositis (PM), dermatomyositis (DM) or inclusion body myositis (IBM), using TUNEL reaction and antibodies against Bcl-2 and Fas proteins. We confirm the absence of significant TUNEL positivity in all biopsies. We do not find Bcl-2 and Fas expression in PM and DM. Otherwise, some muscle fibers (mean=6%) both normal and hypotrophic, show Fas and bcl2 positivity in IBM. The majority of muscle fibers coexpresses these two proteins. Rare muscle fibers with TUNEL-positive nuclei do not show Fas and Bcl-2 positivity. The significance of apoptotic factors in IBM is not clear and needs to be further elucidated before ruling out apoptotic mechanisms in this disease.

P903
OXYGEN CONSUMPTION AND MUSCLE FATIGUE IN MITOCHONDRIAL ENCEPHALOMYOPATHIES. T. Müller, W. Schulte-Mattler, F.N. Gellerich, M. Deschauer, S. Zierz.Klinik und Poliklinik für Neurologie, Martin-Luther-Universität Halle-Wittenberg, Germany

Muscle weakness and abnormal muscle fatigue are common symptoms of mitochondrial encephalo-myopathies. The metabolic impairment can lead to decreased oxygen consumption of working muscle. We measured simultaneously changes of concentration of deoxyhemoglobin (deoxy-Hb) using near-infrared spectroscopy (NIRS) and force of paced dorsiflexors of the lower leg by an incorporated strain gauge to measure isometric torque in 12 patients with mitochondrial encephalomyopathies (8 CPEO [chronic progressive external ophthalmoplegia], 2 MELAS [mito-chondrial encephalomyopathy with lactic acidosis and stroke like episodes], 2 other mitochondrial myopathies) and in 20 healthy controls. The diagnosis based on clinical, biochemical (lactic acidosis, decreased enzyme activities), histological (ragged red fibers) and genetic (5/12 single deletions and 2/12 A3243G mitochondrial mutation) findings. To induce isometrics of ankle dorsiflexors supramaximally stimulations of the common peroneal nerve at rates of stimulations of 0.2; 0.5; 1; 2; 3 and 5/sec. for 1 minute followed by a break of 2 minutes were done. We found both abnormal fatigue and decreased amounts of deoxy-Hb ($p < 0.001$) in 8/12 of patients compared with our controls. 3/12 patients were in normal range of fatigue and oxygen consumption, 1/12 patient showed decreased deoxy-Hb and no fatigue. The data suggest a positive correlation of metabolic impairment represented by decreased deoxy-Hb production and fatigue of muscle.

P904
THE LARGE SPECTRUM OF STIFF-PERSON SYNDROME: EVIDENCE FOR A FOCAL FORM. R. Marconi, E. Martino, K. Plewnia, C. Paradiso - Divisione di Neurologia, Grosseto (Italy).

Stiff-Person Syndrome (SPS) is characterized by progressive muscle stiffness, axial rigidity and action-induced painful spasms, that, generally, affects trunk or proximal limb muscles. The term "Stiff leg Syndrome" (SLS) has been coined for patients with stiffness and spasms confined to one or both legs (Brown P et al, JNNP 1997;62;31-37). Positive serum anti-glutamic acid decarboxylase (GAD) antibodies are detected very uncommonly (Saiz A et al, Ann Neurol 1998;43:400-403). We report on a 69-year-old woman with a two-year history of diabetes mellitus, atypical cramps and progressive stiffening of the right leg. Neurologic examination revealed abnormal posturing of the right leg with knee extension and an-

kle plantar flexion. There was no sign of pyramidal tract or sensory dysfunction. Cerebral and spinal MRI examinations were normal. Hyperglicemia and high titers of GAD, islet cell - ICA - and IA2 autoantibodies, were detected in serum. Electromyography showed continuous motor unit activity. Prazepam (20 mg/die), baclofen (30 mg/die), levodopa (500 mg/die) or gabapentin (900 mg/die) reduced cramps and stiffness. Our findings confirm that the clinical spectrum of GAD antibody-positive SPS includes focal forms presenting as the Stiff leg Syndrome.

P905
UPREGULATION OF CATHEPSINS BY IFN-γ: IMPLICATIONS IN DERMATOMYOSITIS. E. Gallardo, C. Serrano, R. Rojas, I. Illa. Barcelona, Spain.

Objective: To study if molecules which might be implicated in muscle fibers degeneration become activated by IFN-γ. Background: Cytokines have been recognized in the muscle tissue from polymyositis (PM) and dermatomyositis (DM) patients, but their functional in situ role has not been identified. We have demonstrated (Amer J Pathol 1997, 151(1):81-88) that STAT1 is specifically activated by IFN-γ in human muscle cultures and present in perifascicular degenerating fibers of DM patients, indicating a role for IFN-γ in perifascicular atrophy. Methods: The upregulation of Cathepsin B, and L and Calpain was studied in stablished primary muscle cultures stimulated with IFN-γ using semiquantitative PCR(sPCR) and Western-Blot(WB). Other molecules were used as controls including proteins known to become activated by IFN-γ in muscle or other tissues (Bclx-l, p21, MHC-I) and molecules that remain unchanged with IFN-γ (STAT3, -actin). Results: Upregulation of Cathepsin B and L was demonstrated by sPCR and WB. Calpain did not show quantitative changes after IFN- stimulation. We observed,as expected, upregulation of Bclx-l, p21 and MHC-I, whereas STAT3 and β-actin remained unchanged. Conclusions: The demonstration of increased expression of the lysosomal proteolitic enzymes cathepsin L and B after IFN-γ stimulation in muscle fibers further supports our previous studies with IFN-γ/STAT1 and indicate their implication in the perifascicular muscle fiber degeneration in DM. *Supported by Fiss 96/2190[E]*

P906
DRAMATIC MITOCHONDRIAL MYOPATHY IN A PATIENT WITH FAMILIAL COX DEFICIENCY AND ZIDOVUDINE THERAPY. C. Lacroix, V. Planté-Bordeneuve, A. Slama, P. Reynier, C Bouchard, L. Gérard, J. Mikol. Paris. France.

High doses of zidovudine (AZT) were responsible for myopathy in patients with HIV infection. The assumed mechanism of the muscle involvement was a Cytochrome C Oxydase (COX)-deficiency. We report a 27-year-old man, who presented a severe facial and upper limb myopathy after 1 year of AZT therapy. A mitochondrial cytopathy was previously diagnosed in his grandmother and mother. The patient had a past history of cataract operated at age 3. HIV infection was detected in 1991 and was treated with AZT since January 1995 without information on his family history. Four months later, he complained of weakness in hands, dysphagia and dysphonia. The symptoms were slowly progressive until AZT was stopped after 1 year. On examination, then, he had facial and distal upper limbs wasting and weakness, ptosis, dysphonic voice and swallowing difficulties. CK levels were 6000 UI. Muscle biopsy demonstrated necrotic fibres and 60 % COX-negative fibres, numerous giant mitochondria with paracristallin and filamentous inclusions. After treatment withdrawal, neurological signs improved slowly. Eleven months later, CK were normal. A second muscle biopsy showed no necrosis, but as many COX-negative fibres. Important reduction of complex I, III and IV of the respiratory chain was found. Southern-blot and PCR detected multiple deletions of muscle mtDNA in both, the patient and his mother. This observation further illustrates the AZT muscle toxicity through a worsening of the respiratory chain dysfunction induced by mtDNA deletions.

P907
HETEROGENEITY OF CLINICAL PRESENTATION IN FACIO-SCAPULO-HUMERAL MUSCULAR DYSTROPHY. Verdelho A*, Carvalho M*, Evangelista T*, Vieira LM**. *Neurology Department, Hospital Santa Maria, Lisboa,**Genetic Laboratory, H Ponta Delgada, Ponta Delgada, Portugal.

Background: Scapulo-peroneal and facio-scapulo-humeral (FSHD) muscular dystrophies were believed to be part of a continuum spectre of muscle disorders, before genetic investigation settled a different classification. Objective: To report a family whose proband presented scapulo-peroneal weakness, with no facial involvement. The proband's daughter had mild facial and proximal upper limb paresis. Materials and Methods: Electrophysiologic, pathologic and genetic evaluation was performed. Results and conclusions: The proband developed slowly progressive (over 45 years) asymetric limb weakness, mainly of the upper limbs proximal muscles and of the lower limbs distal muscles, where foot steppage was seen. EMG identified muscle dystrophy. Muscle byopsy has confirmed this fact. The 21-year-old daugther had bilateral facial and proximal limb weakness, noticed 2 years before. EMG showed myopathic motor units. Genetic evaluation was performed in the two patients. The proband has also 2 other healthy sons, who refused medical investigations. DNA studies of proband and his daughter showed linkage to the 4q35 FSHD locus. Proband study showed a genetic mosaic presentation. Therefore, his disease probably expresses a new genetic mutation. This study presents a case of facio-scapulo-humeral muscular dystrophy with no facial involvement and reminds the continuity of clinical expression in diseases with genetic distinction.

P908
EXTENSION OF CLINICAL SPECTRUM OF FACIOSCAPULO-HUMERAL MUSCULAR DYSTROPHY (FSHD) DUE TO AVAILABILITY OF DNA-TEST. M.C. Visser[1], A.J. van der Kooi[2], N.R. Rosenberg[2], R.M. van den Berg-Vos [1], J.H.J. Wokke [1], M. de Visser[2].1. Department of Neuromuscular Diseases, University Medical Centre Utrecht, Utrecht, 2. Department of Neuromuscular diseases, Amsterdam Medical Centre, University of Amsterdam, the Netherlands.

Diagnostic criteria for FSHD are onset of the disease in facial or shoulder girdle muscles, facial weakness in more than 50% of affected family members, autosomal dominant inheritance in familial cases, and evidence of myopathic diseases in at least one affected member without biopsy features specific to alternative diagnoses. Recently six patients were seen in our out clinic who did not meet these criteria but were diagnosed as FSHD with DNA testing, showing specific abnormalities on chromosome 4 (test specificity 99%). We present the histories, symptoms and clinical signs, and auxiliary investigations of these patients. Two had dropping feet, one proximal leg weakness, one unilateral calf weakness, one presented with an elevated creatinine kinase, and muscle pain, and one was diagnosed at first as having a polyneuropathy. None of them had apparent facial weakness, none of them complained of weakness in the shoulders, none of them had a positive family history. Physical examination however showed scapular winging on one or both sides in all patients, raising suspicion of FSHD. Creatinine kinase levels were normal or slightly elevated. DNA testing confirmed the diagnosis of FSHD. We argue that the clinical spectrum of FSHD is much broader than has been previously acknowledged. Furthermore, every clinical suspicion of FSHD, especially a winging scapula, should be tested with a DNA-test.

P909

Abstract withdrawn by author

P910
FAMILIAL OCULOPHARYNGEAL MUSCULAR DYSTROPHY WITH TWO TYPES OF TUBULOFILAMENTOUS INCLUSIONS IN SKELETAL MUSCLE FIBERS.Anna Kaminska, Anna Fidzianska. Department of Neurology, The Medical University of Warsaw, and Neuromuscular Unit Polish Academy of Sciences, Warsaw, Poland

Oculopharyngeal muscular dystrophy (OPMD) is a rare autosomal dominant muscle disease of late onset, characterized by progressive ptosis and dysphagia followed by trunk and limb muscle weakness. Unique intranuclear inclusions (INI) in skeletal muscle fibers, not reported in any other normal or pathologic condition, are the pathologic hallmark of the disease. Presence of inclusion body myositis (IBM) – like filaments located mostly in cytoplasm is also reported in some cases of OPMD. Here we describe two Polish female siblings who developed late-onset, slowly progressive ptosis, dysphagia, and limb muscle weakness. There was no family history of neuromuscular disease. Both parents died early and were nonconsanguineous. Muscle biopsy findings were identical in both cases and consisted of variability in fiber size, presence of small angulated fibers and vacuolation involving less than 1% of fibers. Vacuoles, single or multiple were located subsarcolemmally or in the center and were rimmed by ba-

sophilic material. At ultrastructural level two types of inclusions were found: 1) INI composed of tubular filaments, organised in palisades and tangles, about 8.5 nm in outer diameter, characteristic for OPMD and 2) IBM-like cytoplasmic filaments 16-20 nm in outer diameter arranged in bundles, located near cellular debris and myelin figures. Possible associations between these two types of inclusions remain unclear. The degenerative process involved in inclusion formation may share a common pathogenic mechanism or, as has been proposed previously, INI may play role in generation of IBM-like filaments.

P911
MUTATION SCREENING IN 79 HYPOKALEMIC PERIODIC PARALYSIS FAMILIES. Jurkat-Rott K, Hang C, Scherr S, Lehmann-Horn F. Dept. of Applied Physiology, Ulm, Germany

Familial hypokalemic periodic paralysis is associated with mutations in the 1 subunit of the dihydropyridine receptor encoded by the CACNA1S gene. Typically, clinical diagnosis is made by the detection of hypokalemia during episodic attacks of flaccid weakness that affected individuals experience upon provocation by exercise and carbohydrate intake. The amelioration of symptoms by oral potassium administration is also considered to be indicative. We performed mutation screening in CACNA1S in 79 families fulfilling these criteria. Of the three known mutations, we found the R528H in 14 families, the R1239H in 10 families and the R1239G in 4 families, last of which also occured as a de novo mutation excluding the possibility of a founder effect for this formerly only in a single individual reported mutation. In the remaining 51 families, we performed single strand conformation analysis on the 25 exons encoding the highly conserved transmembrane segments of the channel. No new mutations, but several polymorphisms were detected, among others substituting highly conserved residues in the putative pore region of the channel. Remarkably, with four exceptions, the cases without known mutations were either sporadic or no information about family history was available. For one of the exceptions only, linkage to CACNA1S could be excluded. This makes a second major locus rather unlikely, but could indicate some polymorphisms to contribute to disease pathogenesis which require additional factors for development of clinical symptoms.

P912
EXPLORING SEGMENT IV/S6 OF THE HUMAN SKELETAL MUSCLE SODIUM CHANNEL AS A RECEPTOR SITE FOR THE INACTIVATION GATE. Alekov, E. Derra, N. Mitrovic, F. Lehmann-Horn and H. Lerche.Depts. of Neurology and Applied Physiology, University of Ulm, D-89069 Ulm, Germany

Na^+-channelopathies are caused by various point mutations in the gene encoding the -subunit of the human muscle Na^+ channel. Two mutations causing either hyperkalemic periodic paralysis or K^+-aggravated myotonia are located at the intracellular side of segment S6 in the fourth domain (IV/S6: M1592V and V1589M). Both mutations show inactivation defects in form of an increased persistent Na^+ current. A current model for the molecular mechansim of fast Na^+ channel inactivation proposes that a cluster of three amino acids (IFM) within the cytoplasmic III-IV linker occludes the channel pore in a hinged-lid fashion. We explored the possibility that IV/S6 serves as a receptor site for IFM by the cysteine mutagenesis and accessibility method. Four cysteine mutations (F1586C, V1589C, M1592C, I1596C) and a double mutation (F1586C/I1596C) were introduced, expressed in tsA201 cells and studied using whole cell patch clamping and the thiolreagent MTSES. Whereas all four mutations on its own did only show minor defects of inactivation, the double mutant showed a persistent current of 122% of peak current, that increased slowly up to 665% upon application of MTSES. This removal of fast inactivation was strongly voltage-dependent. When the holding potential was set to 0 mV, the reaction rate was on average 0.9 ms^{-1} compared to 6 ms^{-1} at –80mV. The voltage dependence of this reaction is very similar to steady-state inactivation of the double mutant indicating that the exposure of IV/S6 to the cytoplasm goes along with fast inactivation of the channel. We conclude that this region may participate to a receptor site for the IFM-motif.

P913
CHRONIC LIMB-GIRDLE MYASTHENIA GRAVIS: CLINICAL, ELECTROPHYSIOLOGICAL AND MORPHOLOGICAL FEATURES. Rodolico, A. Toscano, M. Autunno, C. Nicolosi, M. Laurê, P. Girlanda, G. Vita, C. Messina. Messina, Italy

We report herein 5 patients (4 M, 1 F; age range: 23-55 yrs) affected by myasthenia gravis, with an exclusive limb-girdle muscles impairment without ocular muscles weakness or muscle fatigability. The disease was familial in two and sporadic in three. Two patients had increased CK blood levels. CNEMG with a quantitative analysis of motor unit potentials showed a myopathic pattern. So far, we performed muscle biopsy in every patient that evidenced tubular aggregates in familial cases and myopathic changes (splitting, centralized nuclei, increased perimisial and endomisial connective tissue, atrophic fibers) in the other three patients. At follow-up we studied neuromuscular trasmission using single fiber electromyography and repetitive stimulation of a proximal muscle, and we found a condition compatible with a diagnosis of myasthenia in each patient. Acetylcholine receptor antibodies were positive in one patient and thymoma was detected in two patients. A diagnosis of chronic limb-girdle myasthenia gravis was made in our patients. Familial cases responded to acetylcholinesterase inhibitors; one patient underwent, successfully, steroid therapy. Diagnosis of limb-girdle myasthenia requires a strong index of suspicion as it has therapeutic implications.

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INTRAVENOUS IMMUNOGLOBULIN THERAPY IN POLYMYOSITIS. Zeki GOKCIL, Fatih Ozdag, Seref Demirkaya, Zeki Odabasi, Okay Vural. Department Of Neurology, Gulhane Medical School, Ankara, Turkey

Many possible interventions are available to treat the patients with polymyositis (PM): steroids, immunosupressive agents, and plasmapheresis. Intravenous immunoglobulin (IVIG) therapy is a new modality to treat for patients with PM who have become unresponsive to conventional therapies. We report five patients (4 men, 1 woman, mean age 24.2 years) with PM treated with IVIG, two of whom had been on steroid treatment. None had PM associated with connective tissue disease.The average duration of PM before IVIG therapy was 16.8 months. Diagnosis was based on proximal muscle weakness, elevated CK levels, myopathic changes on EMG, and muscle biopsy changes. All patients were treated with IVIG therapy. The treatment regimen consisted of 0.4g/kg/day during five days. The course was repeated at one-month intervals, up to 4 or 5 times. Clinical evaluation was performed before and after IVIG therapies. Muscle strength in two patients before and after IVIG therapy was slightly improved. Three patients remained unchanged in which one patient showed a significant decrease of CK levels during IVIG therapy. VIG therapy may be a useful therapeutic modality for some patients especially with subacute or chronic PM who have resistance to conventional therapies. However, further controlled clinical trials are needed to determine the efficacy of IVIG therapy in the treatment of PM.

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EXPRESSION OF $GABA_B$ RECEPTOR 1 mRNA IN DIFFERENT REGIONS OF THE HUMAN BRAIN. A. Berthele, S. Platzer, S.Weis, W. Zieglgänsberger, B.Conrad, TR.Tölle. Munich, Magdeburg; Germany.

The metabotropic $GABA_B$ receptor is known to be functionally involved in several neurological disorders, e.g. epilepsy or hyperalgesia. Using in situ hybridization we investigated the regional distribution of the principal $GABA_B$ receptor 1 ($GABA_BR1$, all splice variants) in the human brain. Tissues (N=4) were obtained at autopsy from patients with no history of neurological or psychiatric disease. In the cerebellum, $GABA_BR1$ mRNA was expressed in Purkinje cells in very high amounts. A moderate signal along the Purkinje cell layer indicated transcript expression in Bergmann glia. The signal was high in granule cells and Golgi cells and low to moderate in stellate/basket cells; mRNA was further detectable in the dentate nucleus. In the hippocampus, $GABA_BR1$ mRNA was detected in high amounts in granule cells of the dentate gyrus. The signal in hippocampal pyramidal cells was lower indicating moderate to high mRNA expression. In the subiculum, the mRNA was expressed in moderate amounts. In human basal ganglia, $GABA_BR1$ mRNA was detectable in the caudate-putamen in moderate amounts, the signal in the globus pallidus was low. In frontal cortex, $GABA_BR1$ mRNA was expressed throughout all laminae in moderate (lamina I-II) to high (lamina III-VI) amounts. In summary, the human $GABA_B$ receptor 1 transcript is widely expressed in different regions of the human brain. Moreover, its expression pattern seems to be highly conserved between corresponding structures of the rat and human brain.

Additional abstracts

THROMBOLYSIS IN ACUTE STROKE. Werner Hacke MD, Department of Neurology; Ruprecht-Karls-Universitat Heidelberg. Im Neuenheimer Feld 400; D69120 HEIDELBERG; Germany

Introduction

Large-scale trials have shown that thrombolytic therapy reduces mortality and preserves left ventricular function in patients with acute myocardial infarction. As most ischemic strokes are thromboembolic in origin (1) there appears to be a rationale for the use of thrombolysis in ischemic stroke.

Thrombolysic therapy in stroke

We will focus here on the use of thrombolytics in acute ischemic stroke. Other rare indications for the use of thrombolytic substances in cewrebrovascular disorders such as intraventricular application of tPA following intraventricular hemorrhage, stereotyctic clot lysis in spontaneous hypertensive intracerebral hemorrhage or intraoperative topical application of lytic substances into the subarachnoid space following subarachnoid hemorrhage are experimental procedures and can not be considered standard indications.

Early angiographic studies in acute ischemic stroke show that a high proportion of patients with hyperacute ischemic stroke have a corresponding cerebral artery occlusion. Some strokes may result from occlusion of vessels too small to be detected by angiography (2 3). Early thrombolytic therapy during ischemic stroke may restore perfusion to the affected area. However, CT is necessary to identify patients whose stroke is hemorrhagic, rather than ischemic before treatment can begin. Recently, it has been shown that signs of early edema afer ischemic stroke is also an important factor in assessing patients for suitability of thrombolytic therapy (4).

The timing of thrombolytic therapy is important. Following occlusion of a cerebral artery, the infarct is surrounded by an expanding area of poorly perfused tissue (the ischemic penumbra), which can be salvaged if perfusion is restored within a critical time period (2). Studies in animals suggest that this period lasts no more than 1-3 hours. It has been discussed that the dura tion in humans may be a little bit longer. Thrombolytic therapy is, therefore, rarely started aher 6 hours and should begin as early as possible (2 3).

Intracerebral hemorrhage is a recognized complication of thrombolytic treatment aher acute myocardial infarction (MI), and although the incidence is low, it is fatal in over 50% of patients, and causes serious disability in approximately 25%.1 The lowest incidence of cerebral hemorrhage in AMI patients is seen with streptokinase (approxi mately 0.2%), and the highest with rt-PA (approximately 0.6%). Data from open uncontrolled trials of thrombolysis in stroke report the occurrence of hemorrhage as between 0-1 8%.5~6 In view of the risk of intracerebral hemorrhage associated with thrombolytic drugs, CT is advisable to exclude bleeding, and identify patients with major infarcts or hemispheric ischemia who appear to be at increased risk of hemorrhagic complications (3-7)

Intra-arterial treatment

Several case series have shown that local intra-arterial application of lytic drugs leads to improved outcome in patients with a rare, but extremely dangerous cerebral vessel occlusion, the thrombosis of the basilar artery (5). There have also been case series concerning local thrombolytic therapy in hemispheric vessel occlusion. Currently we are waiting for the results of a randomized trial comparing intraarterial pro-Urokinase and i.v. heparin (PROACT II).

Intra-venous treatment

Data from open and small placebo-controlled trials show a relationship between partial or complete thrombolysis and a better clinical outcome (3-10). A placebo-controlled trial by Mori et al. of intravenous 20 MU or 30 MU duteplase (two-chain rt-PA), found that the highest patency rates occurred where there was occlusion of distal vessels. Also placebo-controlled, a trial by Yamaguchi et al. found that clinical outcome was significantly better in rt-PA-treated than in placebo-treated patients. Interestingly though, this diffe ence was only evident in patients treated up to 4 hours after symptom onset. The value of thrombolysis in ischemic stroke has further been evaluated in several randomized controlled trials which have recently been completed (7, 11-15)

Studies with streptokinase

Three large trials have examined the effect of streptokinase treat ment (12-14). Two of these - the *Multicentre Acute Stroke Trial Europe (MAST-E,* 12) and the *Australian Streptokinase Trial (ASK,* 14) were terminated prematurely because of an increased incidence of adverse outcomes in streptokinase-treated patients. In MAST-E, patients were randomized to receive either streptokinase, 1.5 MU, or placebo within 6 hours of the onset of stroke. The trial was terminated after 270 patients had been recruited because of significant increases in short-term (within 10 days) and long-term (6 months) mortality, and an almost six-fold higher incidence of symptomatic intracranial hemorrhage in streptokinase-treated patients. In the ASK study, which had a similar design to MAST-E, an interim analysis showed that the risk of death or poor outcome at 3 months was significantly higher in patients treated more than 3 hours aher the onset of stroke than in those treated earlier, who had a trend towards better autcome.

The *Multicentre Acute Stroke Trial Italy (MAST-I,* 13) involved 622 patients who were randomized to receive streptokinase, 1.5 MU, or aspirin, 300 mg/day for 10 days, streptokinase plus aspirin, or neither. All treatment was started within 6 hours of the onset of stroke. Streptokinase, alone or in combination with aspirin, was associated with a significant increase in mortality at 10 days, compared with patients who received neither drug (27% versus 12%, respectively, $P < 0.00001$. There was a slight reduction in the incidence of death or severe disability at 6 months among streptokinase-treated patients, but this was not statistically significant. In summary, streptokinase should no longer be used to treat acute ischemic stroke.

Recent studies with rt-PA

The *European Cooperative Acute Stroke Study (ECASS I)* studied 620 patients who were treated with either intravenous rt-PA, 1.1 mg/kg, or placebo within 6 hours of the onset of stroke (7). An intention-to-treat analysis showed no significant difference in functional outcome (Barthel Index and Modified Rankin Scale) after 90 days in patients treated with rt-PA, although a significant improvement was seen in a target population analysis which excluded patients with protocol violations. In addition, functional neurological recovery (combined Barthel-Rankin), speed of neurological recovery (Scandinavian Stroke Scale) and duration of hospital stay were significantly better for rt-PA-treated patients, both in the total, and target population analysis. There was no significant difference in the total incidence of intracerebral hemorrhages between the two groups, but significantly more large parenchymal hemorrhages occurred in patients receiving intravenous rt-PA (62 vs 20, $P < 0.001$). Mortality at 30 days was not significantly different, but at 90 days, in the total population analysis mortality was higher in rt-PA-treated patients, and was highest among those with CT inclusion criteria violations.

In the *National Institute of Neurological Disorders and Stroke (NINDS) Stroke Study,* 624 patients were treated with rt-PA, 0.9 mg/kg, or placebo within 3 hours of the onset of symptoms (half of the patients were treated within 90 minutes). There was no significant difference in early clinical effect, as indicated by either an improvement of four points on the National Institutes of Health Stroke Scale (NIHSS) or resolution of the neurological deficit within 24 hours, but there was a significant improvement in median NIHSS. Most importantly, there was a significant improvement in outcome after 3 months in patients treated with rt-PA; this group were at least 30% more likely to show no disability (12% absolute increase), as measured by the Barthel Index, Modified Rankin Scale, Glasgow Coma Score and NIHSS. This benefit was seen in all stroke subtypes and in both time strata. Symptomatic intracerebral hemorrhages occurred within 36 hours in 6.4% of patients receiving rt-PA, compared with only 0.6% of placebo-treated patients ($P < 0.001$), but there was no significant difference in 3-month mortality between the groups.

The *second European cooperative acute stroke study, ECASS II* was launched to determine the safety and efficacy of intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA, 0.9 mg/kg body weight) in a 6-hour time window after onset of symptoms (15). ECASS II was a non-angiographic, randomized, double-blind, placebo-controlled trial evaluating the use of rt-PA for acute ischaemic stroke in 800 patients at 108 centres in 14 European countries, Austrialia and New Zealand. Patients were randomised in a stratified manner to receive treatment 0-3 hours or >3-6 hours after onset of symptoms. The primary end-point was the modified Rankin Scale (mRS) at 90 days after treatment, dichotomised for favourable (score 0,1) and unfavourable (score 2-6) outcome. Additionally, the dichotomization for independent (mRS 0-2) vs dependent or dead (3-6) was calculated. Secondary end-points were the change from baseline in the National Institutes of Health Stroke Scale (NIHSS) score at 30 days and the combined Barthel Index (BI)/Rankin Scale at 90 days and. Safety measures included mortality, the occurrence of intracranial haemorrhages (ICHs), and serious adverse events.

There was a non-significant 3.7% absolute difference (10% relative difference) in the primary end-point in favour of rt-PA treatment ($p=0.28$). The increase of independent patients (+8.3%) was significant. A trend towards a more favourable outcome under rt-PA was observed in the combined BI/mRS end-point ($p=0.098$), and the NIHSS score at 30 days was significantly improved ($p=0.035$). An unexpectedly high placebo response (mRS=36.6% favourable outcome) rendered the overall efficacy evalua-

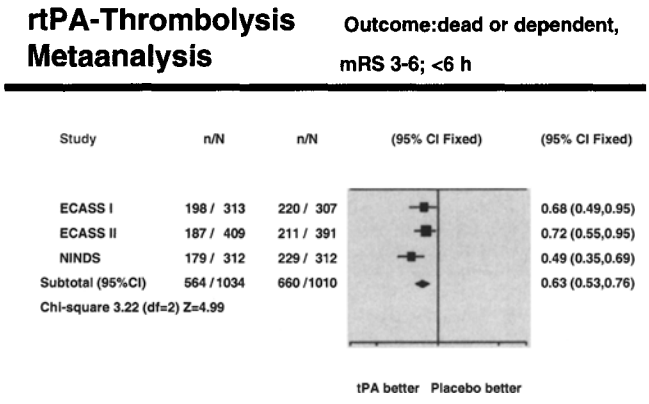

Fig. 1

tion inconclusive. The absolute treatment differences were very similar in those patients treated with rt-PA within 3 hours of stroke onset compared to those treated within >3–6 hours. In total, 83 patients died by day 90 (42 rt-PA patients and 41 placebo patients). Most deaths in both groups occurred before day 7. There were slightly more ICHs in the rt-PA-treated patients (48.4%, 197 patients) than the placebo patients (40.2%, 155 patients). However, symptomatic parenchymal haematomas were four times more frequent in the rt-PA-treated patients than in the placebo group, however (8.1%, 33 patients vs 0.8%, 3 patients, respectively). This difference did not lead to an excess in morbidity or mortality in the rt-PA group.

The high placebo response observed in ECASS II is probably a consequence of both better management of stroke patients in general, and the inclusion of patients with less severe strokes than those in earlier trials (median NIHSS at baseline=11 compared with 12/23 respectively in ECASS I). Mortality rates were substantially lower than those seen in other trials evaluating rt-PA therapy, which cannot be solely attributed to the 1-2 point less severe stroke syndrome at inclusion in the trial.

Recent *metaanalyses* including data of all 3 thrombolysis trials (fig. 1) show an odds ratio for death and disability of 0.67 (95%CI .56; 0.8). The number needed to treat to prevent one death or disability is 11 in a 6 hour time window and 7 in a 3 hour time window. These are impressive numbers that are rarely found in other areas of internal or neurological medicine: For example, the NNT to prevent one death in thrombolysis in MI is about 30!.

Practical considerations

rt-PA is only approved in the US, and it remains to be hoped, that the European authorities will allow the use of rt-PA in a 3 hour time window. But what about the 6 hour time window?. ECASS II failed to show the efficacy difference expected for the predefined primary endpoint. The study was not powered to prove an efficacy difference of about 4%. On the other hand, in the alternate dichotomization for independency, a frequently used endpoint that many researchers believe to be superior to the one, the ECASS steering committee had agreed upon under the impression of the NINDS trial and ECASS I post hoc analyses, reveals an impressive, statistically significant result in favour of rtPA treatment. In addition, one of the two secondary endpoints was statistically significant and the other showed a statistical trend, both in favor of rt-PA treatment. In addition, meta-analyses of the 3 large rtPA-trials for both, the overall time window and the 3 hour cohorts show a consistent and robust advantage for rtPA without increased morbidity or mortality. So we may conclude, that rt-PA at a dose of 0.9 mg/kg is a safe and efficacious treatment for AIS in carefully selected patients in a 6 hour time window, provided that it is used together with the best medical standard therapy. ECASS II confirms the safety of rt-PA relative to placebo shown in the NINDS trial within an extended (6-hour) time window and in a much broader clinical setting. With statistically significant better outcome in the alternate dichotomization for the primary endpoint and the neurological status at 30 days, as well as consistent trends towards improved outcomes in the primary and secondary endpoints, it also provides supportive evidence of the efficacy shown in NINDS. The observed 3.7%-8% absolute increase in the number of patients with no or minimal functional deficit, or independency, respectively - over and above the best stroke unit management - is a substantial and clinically very meaningful benefit.

In clinical practice, the use of rt-PA may vary largely from country to country: Where it is approved, patients may (or should?) be treated if they arrive in time to be treated within 3 hours after stroke onset. Some physicians may choose to be carefull and withhold the treatment from those patients known to be at great risk for complications. Although the earlier the treatment starts, the better the results may be expected, I personally do not have any reluctancy concerning the use in a 6 hour time window, even without official approval. I feel comfortable with the accumulated evidence from randomized trials, including metaanalyses. ECASS II has demonstrated, that the treatment can b performed safe.

In some countries without approval for rt-PA in a 3 hour time window, physicians are allowed to use the substance for individual patients based upon doctors decisions, in other countries, the legal system would not allow this procedure. In Germany and few other countries, doctors may use rt-PA even with a longer time window for selected patients. However they have to make clear to patients and their relatives, that this is an unproven treatment and experimentally, but that there are good reasons to expect that outcome can be improved. Ethical committee approval is advisable.

Thrombolysis remains the only effective treatment for stroke up to now, and after the failure of the neuroprotection trials and the heparin-studies, it is the only specific treatment we have to offer. The results from the ECASS II placebo arm indicate, that general treatment has improved significantly. Still, rt-PA enhances outcome Lets work on even better and faster treatment delivery and test combination therapies, that include best medical treatment, neuroprotectants and thrombolysis. We need to convince our peers and the regulatory agencies, that the observed benefit is important for a disease, in which therapies are so poorly develpoped. We have something to offer and we should work on improving it rather than calling the study neutral and conclude, that there is nothing to treat if an acute stroke occurs.

Conclusions

Thrombolytic treatment may have an important role in the management of acute stroke, but the studies to-date highlight the importance of early intervention and careful patient selection. In the NINDS trial, treatment within 3 hours was associated with an improved functional outcome without an increase in mortality. In ECASS, treatment of eligible patients resulted in improved neurologic and functional outcome. In the MAST-E and ASK trials, later intervention was associated with an increased risk of cerebral hemorrhage and poor outcome. Successful use of thrombolytic therapy, therefore, depends on rapid assessment to exclude patients with hemorrhagic stroke or those at risk of hemorrhagic complications. At present, though thrombolysis cannot be recommended for all patients with acute stroke, it has been shown to be beneficial in patients treated within 3 hours who conform to the strict inclusion and exclusion criteria of the NINDS trial. After the results of ECASS II, however, and the recent meta-analyses of all three major rtPA trials, it seems that with strict selection criteria, expert CT-reading, adherence to the protocols and a stroke unit type approach, the time window for thrombolysis may be as long as 6 hours in selected patients.

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NEW ANTIEPILEPTIC DRUGS. J.W. Sander, MD PhD Institute of Neurology, Queen Square, London WC1N 3BG, UK.

New antiepileptic drugs (AEDs) are necessary for patients with chronic epilepsy and for improving upon established AEDs as first line therapy. Eight novel AEDs have been released worldwide in the last decade (vigabatrin, lamotrigine, gabapentin, topiramate, tigabine, oxcarbazepine, zonisamide and felbamate). Complete freedom from seizures with the absence of side effects should be the ultimate aim for AED treatment and the new drugs have not entirely lived up to expectations. Only a small number of patients with chronic epilepsy have been rendered seizure-free by the addition of new AEDs. Despite claims to the contrary, the safety profile of the new drugs is only slightly more favourable when compared with the profile of the established drugs. The chronic side-effect profile for the new drugs has not yet been fully established.

Vigabatrin (GVG)

GVG increases GABA levels by irreversible inhibition of GABA-aminotransferase. GVG is a second line treatment for patients with partial seizures and first line treatment for infantile spasms particularly those associated with tuberous sclerosis. It has no use primary generalised epilepsy and it may worsen myoclonic seizures. Tolerance may develop in up to a third of responders.

Sedation, dizziness and headache are the most commonly reported acute adverse effects. Allergic skin rashes are extremely rare. Up to 10% of patients taking GVG develop a change in mood, commonly agitation, ill temper and disturbed behaviour, depression or more rarely paranoid and psychotic symptoms. Visual field defects have recently been associated with long term treatment with GVG and this may limit the use of the drug to those cases were potential benefit outweighs risk.

Lamotrigine (LTG)

LTG was originally developed for its antifolic activity following suggestions of the existence of a relationship between folate antagonism and antiepileptic action. Its mode of action, however, is due to its potential to modulate sodium channels and to block the release of glutamate.

LTG is licensed as first line drug for patients with partial seizures, with or without secondarily generalisation and in tonic clonic convulsions and as a second line drug for refractory epilepsy.

Headaches, drowsiness, ataxia, diplopia usually transient are the most common acute adverse effects. A skin rash is the commonest idiosyncratic effect of this drug and affects up to 3% of patients. The incidence is higher if larger initial doses of LTG are used or in combination with sodium valproate.

Gabapentin (GBT)

GBT is a structural analogue of GABA and was originally designed a GABA-mimetic. Subsequent, however, it was shown that GBT is inactive at GABA receptors. Recent studies have shown that GBT interacts with a specific high affinity binding site in the brain that has is not yet been identified functionally. It appears, however, to be associated with a Leucin transporter system across neuronal cell membranes. GBT is used mainly as second line treatment of partial seizures with or without secondarily generalisation. It is of no use in other seizure types. GBT is usually well tolerated and its side effects are mainly related to the CNS. The most frequently reported side effect is drowsiness; others include dizziness, diplopia, ataxia and headache. GBT treatment has not been associated with any serious idiosyncratic reaction to date.

Topiramate (TPM)

TPM is a sulphurated fructose and to date five possible mechanisms of action have been identified. It is a strong blocker of voltage-activated sodium channels and it has an effect on Gaba-a receptors. In addition, it blocks the kainate/AMPA type of glutamate receptors, modulates calcium channels and is a weak inhibitor of carbonic anhydrase but it is not clear if this is relevant to its antiepileptic action.

It is used as a second line drug for patients with partial seizures and refractory generalised seizure disorders. Most of acute side effects of TPM are CNS-related. These include dizziness, drowsiness, headaches, irritability, cognitive slowing and speech impairment. These are mostly transient and in some patients seem to be related to rate of titration. Parasthesias and nephrolitiasis have also been reported. Patients starting TPM should increase their fluid intake to reduce the risk of kidney stones. Initial weight loss is seen in up to 40% of patients and is usually not problematic. No idiosyncratic side-effects have yet been described.

*Tiagabine (TGB)**

TGB increases GABA via inhibition of GABA's reuptake in glial cells.

TGB is a second line drug for partial seizures with or without secondarily generalisation.

TGB side effects are primarily central nervous system related and are more common during drug titration; the main side effects being sedation, headache, tiredness and dizziness. Tremor, diarrhoea, irritability, confusion and depression have also been reported.

Felbamate (FBM)

FBM is a di-carbamate closely related to mebrobamate. Its exact mechanism of action is not known but appears to prevent seizure spread by both increasing seizure threshold and inhibiting seizure spread. It is an effective drug with a broad spectrum of action but due to it safety profile it is used as a drug of last resort in patients with intractable epilepsy, particularly in patients with the Lennox Gastaut syndrome. FBM exhibits significant PKI with phenytoin, carbamazepine and valproic acid.

The most frequently reported side effects during FBM therapy have been neurological (diplopia, insomnia, dizziness, headache and ataxia), and gastrointestinal (anorexia, nausea and vomiting). A major use-limiting problem is its potential to cause aplastic anaemia and liver failure affecting as many as 1/4,000 patients exposed. Hence, it seems prudent to limit its use to severe intractable cases where potential benefit outweighs the risk.

OXCARBAZEPINE (OXC)

OXB has a similar mechanism of action to carbamazepine. Its indications are also very similar to that of carbamazepine: effective in partial seizures; may worsen absences and myoclonic seizures. One difference between the two is that OXC does not induce hepatic enzymes, and so is likely to have fewer interactions than carbamazepine. OXC does not alter the metabolism of other AEDs. It safety profile is very similar to that of carbamazepine apart from hyponatraemia which is more pronounced with OXC and allergic skin reactions which are less common with OXC. Cross sensitivity is seen in less than a third of patients hypersensitive to carbamazepine.

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LOSS OF VELOCITY STORAGE AS AN EXPLANATION FOR THE 'IMBALANCE OF THE ELDERLY. Martin Gizzi, MD, PhD, Robert Clarke, PhD, Ming-Jia Dai, PhD, Theodore Raphan, PhD and Bernard Cohen, MD. Edison, NJ and New York, NY, USA.

Modeling has shown the, the vestibulo-ocular reflex can be considered to have two components. The shorter component, attributable to activity in the eighth nerve has a time constant of ~4 sec in monkeys and in humans. The slower component has been referred to as "velocity storage." The time constant of velocity storage in humans is typically 10–15 sec. We studied 20 older subjects complaining of isolated imbalance who had normal vestibular gains, but time constants below 6 seconds. Double-exponential fits to velocity step data demonstrated only a (normal) eighth nerve response with no velocity storage component. Consistent with this, when these subjects are rotated in light at a constant velocity and stopped in darkness, they had vestibular afternystagmus. In normals, optokinetic afternystagmus cancels vestibular afternystagmus and there is no net nystagmus on stopping. We studied ocular motor function, audiometry and posturography in these subjects and found only mild high-frequency sensorineural hearing loss Consistent with age and postural abnormalities consistent with vestibular deficits. CT or MR imaging showed only E occasional, scattered small-vessel white matter disease. We have identified a (D population of patients complaining of imbalance who appear to have only a loss of 4- central velocity storage. Loss of velocity storage may explain at least some cases of "imbalance of the elderly" referred to in the literature.