Neurotoxicity Research, 2003, Vol. 5 (1-2). pp. 27-34

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Is There a Subtype of Developmental Parkinson´s Disease?

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(Received 22 October 2001; Revised 06 June 2002; In final form 05 December 2002)

Keywords: Parkinson´s disease subtypes; Environmental hypothesis; Developmental disorder; Hypokinetic/hypertone syndrome; Viral infection; Neurodegeneration; Genetic hypothesis

INTRODUCTION

All developmental genes, neurotrophic factors and environmental stress (influenza, other viruses, noise, certain chemicals, severe complications during pregnancy and birth-giving, etc.) may cause malformations in the developing brain, affecting developing of nerve cell body density and growth, fibre targeting, synapse number and plasticity, spine morphology and quality of synaptic contacts. All theses neurodevelopmental changes might (but must not necessarily) lead to neurodegeneration.

HIV / AIDS associated motor disturbances including frequently parkinsonism (even in affected children) is associated with the typical morphological and neurochemical features of Parkinson´s disease (PD). In addition, experimental work clearly demonstrates a close interaction of dopaminergic function and SIV viral expression in macaques.

These studies underline the concepts and clinical as well as neuropathological experimentations in encephalitis lethargica. From all these evidences it seems to be not farfetched to assume that viral infections of the brain can cause a subtype of PD which if this occurs pre-, peri or postnatally may also have detrimental effects on the developing brain in general and regions of interest for parkinsonism in particular.

Seasonal variation with birth peak March-June is compatible with intra-uterine influenza, around 6 months gestation, as the seasonal peak in influenzal activity is usually between January and March (Registrar General England and Wales 1921-1931)

Differences of infection of the developing nervous system is due to the dependence (1) of the selective vulnerability of specific cell populations to different viruses and (2) of the specific stage of development when infection occurred (Becker *et al.*, 1974). However, this statement may be enlarged to other environmental disturbances too.

The early work by Widhalm (1985) demonstrates that hypokinesia / parkinsonism in children occurring after clinically overt problems during pregnancy and at the time of birth-giving may be associated with developmental disturbances of respective brain areas. Therefore it is suggested that infantile and juvenile PD aged about <20 years is a developmental disorder based on environmental and / or genetic origin.

ONTOGENETIC ASPECTS OF CATECHOLAMINERGIC SYSTEMS

It seems evident that the pre-, peri- and postnatal periods are of extensive vulnerability not only to endogenous but also to exogenous (environmental) influences. According to transient phases of increased glutamatergic transmission, Retz *et al.* (1996) discussed the ontogeny of excitatory amino acids (EAAs) and the fetal % variations of monoamines and their metabolites have been detected in the human putamen at three age groups, i.e. 0-9 years, 10-59.9 years and 60 years and older (Konradi *et al.*, 1992). An increase in serotonin (5-HT) levels, decrease in 5-hydroxyindoleacetic acid (5-HIAA) levels and a decrease in the 5-HIAA / 5-HT ratio were observed after the first decade of life. Changes in the dopaminergic system were seen in senescence, with decreasing dopamine (DA) levels and an increase in the HVA / DA ratio (HVA, homovanillic acid). DOPAC/HVA (DOPAC, 3,4-dihydroxyphenylacetic acid) and the DOPAC/DA ratio were unaffected. Noradrenaline (NA) was similar in all groups. There was a strong correlation between the DA ergic and 5-HT ergic systems (Konradi *et al.*, 1992).

Also, maturation of large neurons is evident at week 28-30 of gestation while small neurons become mature at weeks 33-36. In addition, apoptosis in the striatum begins before neuronal maturation and continues during all stages of striatal maturation. However, the analysis of TUNEL-positive cells revealed a different reaction pattern for the various basal ganglia with regard to timing

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ISSN 1029 8428 print/ ISSN 1476-3524 online

TABLE I Development of brain stem

Catecholamine cell groups		Reference
P3:	enzyme system develops TH activity at P3	Clark *et al.,* 1994
	environmental changes temperature nutrition oxygenation	
	stressful conditions (A-, NA-release)	Lagercantz *et al.,* 1992
	delay TH activation	Sessa and Perez, 1975
	open BBB: A and NA pass	
	catecholamines and corticosterone participate in maturation	Slotkin and Seidler, 1988
P14-P21:	further large increase in TH activity (1,3-3,5) fold higher than at adulthood	Coyle and Axelrod, 1972
P15:	cortical sprouting of noradrenergic inputs	Saito *et al.,* 1996
P17-P21:	enzymes involved in metabolism and energy (ATP) reach highest volumes	Clark *et al.,* 1993, 1994
P19-P25:	weaning in the rat	

A, adrenaline; NA, noradrenaline; BBB, blood-brain barrier; TH, tyrosine hydroxylase

and degree of the apoptotic process in regulating cell numbers (Itoh *et al.*, 2001).

Table 1 shows the development of catecholaminergic fibre systems.

Misgeld *et al.* (1986) studied the functional maturation of intrinsic circuitry in the neostriatum by intracellular recording and intracellular staining with Lucifers yellow in slices obtained from rat pups at postnatal days P1-P20 and from adult rats. Interstriatal stimulation elicited inhibitory responses in slices from animals at P1-P6 while the response was excitatory after P10. These authors concluded that maturation of excitatory synapses is the main change during postnatal development. Intracellular staining demonstrated that the changes in postsynaptic potentials were paralleled by the appearance of spines on dendrites around P7. Also it appeared that dendritic conductances had a stronger influence on somatic discharge in the electrically compact young neurons than in adult neurons. Moreover, dopaminergic neurons of the substantia nigra pas compacta (SNPC) undergo natural cell death during development in rats. This developmental P2-P32 cell death, with a morphology of apoptosis, plays a critical role in regulating adult numbers of SNPC neurons (Jackson-Lewis *et al.*, 2000).

Human striatal D_1 and D_2 receptors have been demonstrated to show a significant increase within the first 2-3 years of life, while there was a significant loss of receptor density during the following 3-5 years. Then the loss was about 2-3 % per decade (Seeman *et al.*, 1987). More recent data in Fischer 344 rats, and using detection of D_{1A} and D_2 receptor mRNAs show highest levels at P30 and then decreased by P120 (Xu *et al.*, 1992). These data confirm early work on the development of synaptic densities in the postnatal period (Huttenlocher *et al.*, 1979). These changes support the hypothesis of transient overproduction and subsequent regressive events during human brain development. Widespread reorganization of neuronal circuitries in distinct periods of brain development may be due to trophic factors, variations including neurotransmitters (Mattson, 1988), in gene expression, apoptotic processes and other events. Ontogeny of human brain neurotransmitters and especially of excitatory amino acids (glutamate, aspartate) has been reviewed by Retz *et al.* (1996).

TABLE II Benefit of L-DOPA Therapy

Benefit	RATING (1-10)		
	mild (1-4) N (%)	moderate (4-7) N (%)	severe (7-10) N (%)
very good	26 (90)	14 (50)	—-
good	3 (10)	14 (50)	5 (62)
moderate	—-		2 (25)
no success	—-		1 (13)

Rating: 0-1 normal locomotion • 1-4 mild disturbances • 4-7 moderate parkinsonian signs, • 7-10 severe parkinsonism of akinetic type

Drugs that influence striatal receptor ontogenesis include estradiol. Estradiol (10 mg/kg for three days or 50 mg/kg for six days) did not change D_1-receptor density and affinity at P15, P21, P40 and P120 days in rats of both sexes. In contrast D_2-receptor density showed biphasic behaviour with a loss at low dose and supersensitivity at high doses in 15-day old females (Ferretti *et al.*, 1992).

While neuromelanin in the SN is seen in humans only after about 3-5 years postnatally, with increases thereafter continuously until old age, iron reaches a steady state concentration at around 20-30 years of age (Zecca *et al* 2001).

Whether the number of pigmented cells in relation to unpigmented dopaminergic neurons and the rate of pigmentation in relation to the content of iron plays an etiopathobiological role in PD is not known. Also the total number of pigmented and non-pigmented dopaminergic SN neurons may be a vulnerability factor for PD, i.e. a rather low number may give rise to PD earlier and at lower rates of vulnerability factors, as shown in ^{18}F-L-DOPA-PET (L-DOPA, L-3,4-dihydroxyphenylalanine; PET, positron emission tomography) studies of putamen in PD (Brooks, personal communication).

In addition, apoptosis in the striatum is facilitated by down-regulated bcl-2 expression and by a high density of stem cells.

GENETIC ASPECTS OF JUVENILE PD

Although there is ample evidence for a genetic defect for a PD phenotype in some kindreds with dominantly transmitted PD, recent data obtained from twin studies point to a substantial role for inheritance in sporadic PD (Piccini *et al.*, 1999). Therefore, it is of great interest that mutations in the parkin gene are a major cause of early-onset autosomal recessive familial PD and isolated juvenile-onset PD at or even before the age of 20 years (Lücking *et al.*, 2000).

Recently Lücking *et al.* (2000) reported on the frequency of mutations in the Parkin gene in 100 patients with isolated early-onset PD according to age of onset. In the age group at onset of the disease 20 years or younger, 77% (10/13) were patients with homozygous or heterozygous mutations but only in 2 of 64 patients (3%) with an age at onset of 31 to 45 years. Patients with Parkin mutations were more likely to have dystonia and symmetric signs at onset, as well as hyperreflexia at onset or later, were more likely to have a better response to L-DOPA, but were more likely to have dyskinesia during treatment compared to patients without mutations. The disease progressed slowly in patients with mutations, while dementia was rare. Pathology shows less widespread but rather selective neuronal loss in SN and locus coeruleus. Also Lewy bodies have not been detected in patients with parkin mutations. These mutations are more frequent among patients with autosomal recessive PD. Risk factors during pregnancy were not reported. Therefore, in this PD subgroup a link between genetic disturbances to environmental factors or birth problems cannot be drawn.

Rapid progress is evident in identifying genes controlling nigro-striatal development. Genetic programs regulate processes that control regional specification, morphogenesis, cell type specification, neuronal migration and connectivity.

Recently, a series of 19 cases of essential tremor (ET)

in childhood was described by Louis *et al.* (2001). Although ET is regarded as a disease of the elderly, about 4.6–5.3 % arise during the first two decades of life.Also childhood cases differ from adult forms of ET (e.g. gender distribution, somatotopic organization) to the temporal development of ET. Unfortunately, Louis *et al.* (2001) did not mention any possible clinical features of pre-, peri-, or postnatal environmental difficulties.

HYPOKINESIA DUE TO PRENATAL AND BIRTH-RELATED PROBLEMS

The problem of environmental factors or birth problems was addressed as early as 1985 when genetic studies did not have the impact and methodological backup as they do today. In this context the early work of the late Viennese Sylvester Widhalm (1985) who described a hypokinetic/hypertone syndrome in 65 children aged 4-18 years (11 females, 54 males) may be seminal for the understanding of environmental and birth problems leading to malformations of the developing brain with the phenotype of hypoactivity / hypokinesia. In these children weight was age-related, intelligence at average (*N*=37), below average (*N*=19) and above average in 9 cases. EEG findings were age-related in 12 cases, slightly abnormal (*N*=43) and moderately abnormal (*N*=2).

Potential risk factors during pregnancy consisted of bleeding (*N*=19), uncontrolled vomiting (*N*=18), pyelonephritis with high blood pressure (*N*=10), while there were no organic problems in 18 pregnants.

With regard to the prenatal and birth-related clinical history it is evident that 30 children suffered from asphyxia during birth-giving, another 24 had severe problems pre-or postnatally, while only 11 mothers reported no organic problems.

The severity of symptomology in the hypokinetic-hypertone syndrome was mild (*N*=29), moderate (*N*=28) and severe in 8 cases. L-DOPA plus the peripheral decarboxylase inhibitor benserazide was given in slowly increasing doses for 15-25 months in an age-dependent regime ranging from 125 mg twice a day at age 4-6 years, up to 500 mg t.i.d. for children at age 14-18 years. Dyskinesias were noted as side effect after 8-30 months. Treatment of dyskinesias with neuroleptics worsened the hypokinetic syndrome. In addition to L-DOPA treatment, antidepressants and in some cases anticonvulsants were necessary therapeutic strategies.

The success of L-DOPA therapy is summarized in Table II. After withdrawal of L-DOPA the children developed normally. Follow up observations up to a maximum of 11.5 years did not give evidence for a progressive disorder.

As discussed by Widhalm (1985) there is good evidence that pre- and perinatal anoxias lesion brain stem areas to a greater degree than cortical areas. According to Cammermayer (1958) this is due to the lower metabolic activity of cortical regions shortly after birth. Exact lesion pattern due to asphyxia neonatorum were described as early as 1959 (Ranck and Windie, 1959). Later, Davis *et al.* (1979) reported disturbances of synthesis and storage of catecholamines after only mild neuronal hypoxia. According to Rorke (1982) lesions caused by asphyxias can be differentiated according to the stage of development of the brain.

(1) Asphyxia during the first trimester causes severe disturbances mostly not compatable with survival.
(2) In children born prematurely, diffuse lesions have been verified by neuropathology in the hippocampus, thalamus, subcortical grey structures, especially globus pallidus and white matter.
(3) Perinatal period: basal ganglia, deep grey structures, especially thalamus, hippocampus, cerebellum, periventricular lesions of the white matter.
(4) With improved development and maturity the pattern of lesions will more and more equal lesions of asphyxia of fully developed brain regions.

The observations by Widhalm (1985) clearly demonstrate that pre-, peri- and postnatal environmental and other birth problems may lead to disturbances in brain development and maturation, and that these can be antagonized by pharmacological treatment strategies as far as the time-limited follow up observations demonstrate. Whether or not Widhalm's cases can be regarded as a subtype of early parkinsonism is open for discussion. Also the appearantly low frequency of "hypokinesia" in children (compared to the "hyperkinetic syndrome") is a matter of discussion.

It is important to note that prenatal stress affects the functional development of the offspring (Weinstock *et al.*, 1988). This author clearly states that the development and later behaviour of an immature organism is not only determined by genetic factors and the postnatal environment, but also by the maternal environment during gestation. Therefore, drugs, diseases, nutrition and stressful life events may have effects on the developing brain and its maturation.

Animal studies demonstrate in a variety of experimental designs that this is in fact the case (reviewed by Weinstock *et al.*, 1988). Also, prenatal stress depresses immune function in rats (Kay *et al.*, 1998), alters the reactivity of the hypothalamic-pituitary-adrenal axis-(HPA-) system in female rats (Weinstock *et al.*, 1992), increases anxiety related behaviour, and alters cerebral lateralization of DA activity (Fride and Weinstock, 1988). These authors have also shown that exposure of pregnant

rat to unpredictable (random) noise and light stress resulted in a retardation of early motor development in their offspring (Fride and Weinstock, 1984; 1985) and caused impairment of development of hippocampal function which lasted into adulthood (Fride *et al.*, 1986).

Programmed cell death considered to occur in the form of apoptosis is important for the development of the CNS, by controlling neuronal numbers and adequate synaptic connection. Itoh *et al.* (2001) studied the gestational age of 47 foetuses and newborns ranging from 12 to 40 weeks. In the striatum TUNEL positive neurons were observed around week 12 of gestation followed by a loss of total cell density. Apoptosis increased with advanced gestation and age. The labelling index of apoptotic cells in the globus pallidus increased between week 20 and week 28, and decreased thereafter until week 40.

Near total destruction of rat nigrostriatal DA neurons by intraventricular 6-hydroxydopamine soon after birth resulted in a significant reduction of D_1 receptor density in the rostral neostriatum (22%) but was unchanged in the caudal half and in the SN. In contrast, autoradiography of D_2 receptors showed an increase of binding sites (10-40%) in the neostriatum and a significant 80% reduction in the SN. These findings were in part dissociated from the expression of receptor in RNA levels (Radja *et al.*, 1993).

Drugs like MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which need monoamine-oxidase (MAO) for conversion into toxic metabolites seem not to be dangerous for the offspring after intoxication of pregnant female mice at day 17, due to absence in the embryonal brain of adequately developed MAO-B activity (Melamed *et al.*, 1990)

Golbe *et al.* (1990) describe several factors that are associated with PD: (1) PD is negatively associated with early-life intake of vitamin E-rich foods (2) PD is positively associated with rural experience, i.e. pesticides, insecticides, herbicides. In addition Menza *et al.* (1990) show that PD is associated with stoic, industrious and inflexible personality traits and with less novelty-seeking behaviour!

Whether pre, peri or postnatal environmental stress may result in an increased echogenicity of the SN in 8.6% of 330 healthy volunteers is not known. However, SN hyperechogenicity appears to indicate a functional impairment of the nigro-striatal system even in young adults (Berg *et al.*, 1999).

VIRUS AND DISEASE

A viral hypothesis for PD has been suspected since the pandemic of encephalitis lethargica between 1915 and 1926. There is no doubt that a virus could induce akinesia, rigidity and tremor in postencephalitic PD. Therefore, postencephalitic PD adds to the spectrum of PD despite the fact that many clinical symptoms, neurophathological findings, and respone to treatment with antiparkinsonian medication differs from classical idiopathic PD (Bernheimer *et al.*, 1973).

Reactivation of the viral hypothesis comes from early data demonstrating viral antigens in the brains of patients with postencephalitic PD and the co-expression of chronic virus infections and acute encephalitides and parkinsonism. These reports have not been confirmed by others, as reviewed by Teräväinen *et al.* (1981). However, parkinsonism has been described as a complication of other viral infections including coxsackie, herpes zoster, measles, poliomyelitis, Japaneses B encephalitis, and influenza B, as reviewed by Behan *et al.* (1981). In both Japanese encephalitis and St. Louis encephalitis, lesions of the SN have been reported, as reviewed by Kalita and Misra (2000). However, immunological investigations have revealed no clear evidence of any immune dysfunction, and attempts to transmit the disorder were unsuccessful. Although evidence for viral presence and specific immune response in PD has been negative, Elizan and Casals in their review of 1987 state that "absence of proof is not proof of absence".

Patients with postencephalitic PD were frequently of young age, often in their twenties and thirties at the onset of illness, experienced oculogyric crisis, had more hyperkinesias and had generally a longer time course. This differs from idiopathic PD. In 1988 Mattock *et al.* speculated that intra-uterine influenza may cause PD. They found "that the estimated risk of an individual developing idiopathic PD shows a significant correlation with the crude influenza mortality of the year of his birth, within the range of 1900 an 1930. These authors suggested that intra-uterine influenza may be cytotoxic for the developing foetal substantia nigra and that an affected individual may be born without evident disability but with limited striatal neurochemical reserves and a reduced nigral cell count. Nigral failure may be delayed by many decades as cells are lost and postnatal environmental exposures may modify their rate of decline and hence the interval before overt disease ensues." PD would develop after mildly neurotoxic influenza after a long latent interval, while a particularly toxic influenza with extensive nigral damage would occur after a short latent interval and perhaps before the age of 30.

Interestingly, the human immunodeficiency virus (HIV) infection is frequently associated with parkinsonism (Mirsattari *et al.*, 1998) and seems to be associated with neuronal damage of the SN (Itoh *et al.*, 2000). Motor disorders are attributed to HIV infection *per se*

rather than being associated with opportunistic infections or malignancies (Navia *et al.*, 1986a,b; Mirsattari *et al.*, 1998). Animal models, like the SIV infection of macaques, result in neurological abnormalities that are clinically and pathologically similar to those of HIV-induced dementia and motor abnormalities (Loewenstein and Rubinow, 1987). They show a deficiency of DA in the putamen and SN and an increase in the HVA/DA and DOPAC/DA ratio in both these regions, compared to uninfected control animals (Czub *et al.*, 2001). This corresponds to the human disease in which HIV-positive cells and pathological changes within the gray matter are found primarily in the DA–rich basal ganglia (Berger and Nath, 1997; Lopez *et al.*, 1999). In addition, these regions exhibit an extensive neuronal loss (Masliah and Mucke, 1996) with neuronal damage of the SN (Itoh *et al.*, 2000) and a significant decrease of DA and its metabolites in the CSF, spinal cord and brain of HIV-infected subjects with AIDS (Sofic *et al.*, 1992; Sardar *et al.*, 1996). Calcifications of the basal ganglia were reported in infants and children with HIV infection (Belman *et al.*, 1986).

Furthermore, an interaction of the DA system and viral expression has been demonstrated recently, showing that activation of DA function by dopaminergic drugs like L-dopa or selegiline causes enhanced viral expression (Czub *et al.*, 2001). These data are of some importance because drugs of addiction (cocaine, amphetamine, heroin, etc.), taken frequently by HIV-infected addicts, are enhancing dopaminergic function. In addition, neuropathological examinations of brains at autopsy of patients with HIV / AIDS with or without a history of addiction clearly demonstrate that HIV / AIDS associated with drug abuse has a significantly more severe brain pathology compared to HIV / AIDS patients without drug addiction (Jellinger *et al.*, 2000).

Therefore, treatment of HIV / AIDS associated parkinsonism with antiparkinson medication may be fatal for the progression of the disorder (Czub *et al.*, 2001). These data clearly demonstrate that viral infections of the brain can be associated with the dopaminergic nigro-striatal system and parkinsonism (Koutsilieri *et al.*, 2001). In this regard it is worth mentioning that the antiviral compound amantadine has been shown to prevent uptake of influenza A into cells.

As infection of the basal ganglia in mice is induceable by coronavirus, a primarily respiratory pathogen in humans, Fazzini *et al.* (1992) investigated its possible role in PD. Significant antibody response to four coronavirus antigens suggested an association between coronavirus and PD.

CONCLUSION

Evidence accumulates suggesting that environmental factors including viral and risk factors associated with pregnancy and birth-giving, may increase the incidence of hypokinesia / parkinsonism in early life, or PD in later life. Such environmental pre-, peri- or postnatal stress may lead to disturbances in the developing brain and malformations in regions of particular interest and associated with PD. Genetic predisposition to hypoactivity plus environmental effects may lead to reorganization of brain circuitry including changes in monoaminergic and/or EAA systems, leading to a subtype of PD, i.e. genetic, drug induced, viral, developmental and other possible subtypes. The spectrum disorder of PD is going to be further substantiated into various etiopathologically verifyable subgroups.

Acknowledgement

This work was supported by the National Parkinson Foundation, Miami, USA, SFB 581 and BMBF 01 KI9762/5.

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