Original Article

Subacute Noninfective Inflammatory Encephalopathy: Our Experience and Diagnostic Problems

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ABSTRACT

Introduction: Immune dysregulation associated encephalopathies present with significant psychiatric manifestations and only a few soft neurological and general systemic features. They are generally resistant to treatment with psychiatric medications. Generalized orthostatic myoclonus and faciobrachial dystonic seizures are mistaken as Creutzfeldt-Jakob disease and subacute sclerosing panencephalitis. **Patients and Methods:** Forty-two patients seen during 2010–2015 and diagnosed as noninfective encephalopathy were analyzed. Those patients with infective causes and those who had significant features of systemic manifestations of vasculitis and other disorders of central nervous system were excluded from the study. They were investigated with cerebrospinal fluid imaging, electroencephalogram (EEG), and antibody profile. **Results:** More than 70% patients had psychiatric manifestation as presenting features and reported to psychiatrist. Three patients had paraneoplastic and others N-methyl-D-aspartate, voltage-gated potassium channel, thyroid peroxidase, antinuclear antibody related, and few were due to unknown antibody. **Conclusion:** Serious diagnostic errors are common and early diagnosis is based on high degree suspicion in patients presenting with new-onset refractory psychosis. Soft neurological features should be looked for and EEG serves as a very sensitive tool in establishing organicity.

Key words: *Creutzfeldt-Jakob disease, neuropsychiatric lupus, noninfective encephalopathy, subacute sclerosing panencephalitis*

INTRODUCTION

Immune dysregulation plays an important role in a large spectrum of neurological disease involving both central and peripheral nervous system. Their clinical manifestations also are varied causing delay in onset to treatment initiation by several months making the prognosis grave. With reference to central nervous system, the symptoms evolve over days to weeks, and as limbic structures are especially vulnerable, the

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clinical manifestations are in the neuropsychiatric border zone areas causing some degree of diagnostic problems. The common antibodies involved are N-methyl-D-aspartate receptor (NMDAR), glutamic acid decarboxylase (GAD), voltage-gated potassium channel (VGKC), leucine-rich glioma inactivated 1 (LGI1), gamma-aminobutyric acid receptor–B, contactin associated protein-like 2 (CASPR2). Common clinical features are memory dysfunction, delirium, hallucinations, faciobrachial dystonic seizures, psychosis, etc.[1,2] In these disorders, antibody is pathogenic affecting synaptic transmission and plasticity and there are also paraneoplastic syndromes where the antibody as such is not pathogenic but T-cell response targeting neuronal antigens causes damage. Antibody to intracellular synaptic proteins is seen in GAD65. There are less well-established conditions such as lupus celebrities and acute disseminated encephalomyelitis.

Antibodies directed against brain epitopes occur asymptomatically in nearly 90% of individuals.[3,4] Any measurable symptom produced by these antibodies is probably based on the integrity of blood–brain barrier (BBB). A study involving large number of normal people, psychiatrically ill persons, and neurologically ill using 25 distinct antibodies directed against defined brain antigens revealed that the most prevalent antibody was NMDARI AB. The other 24 screened had a very low prevalence. It was observed that influenza was a major nonspecific autoimmunity triggering agent in the physiological presence of these antibodies. Apolipoprotein E 4 carriers with leaky BBB are likely to develop disease. Moreover, it is also postulated; these antibodies may be modulatory in certain disease states than pathogenic. Immune-mediated encephalopathies can be categorized into (1) those associated with antibody to intracellular antigens such as anti-Hu seen with malignancy. (2) Extracellular epitopes of ion channels, receptors, and associated proteins such as N-methyl-D-aspartate (NMDA). (3) Intracellular synaptic proteins such as GAD65. (4) Syndromes with less clearly established antigens such as SLE.

The common antibodies and postulated disease association

NMDAR subunit NRI extracellular and synaptic substance involved in excitatory glutaminergic synaptic transmission and plasticity. Encephalitis is the postulated disease association. VGKC antibodies are directed against cell surface antigens that form part of VGKC complex. Antigenic target is typically LGI protein-1 associated with limbic encephalitis. Amphiphysin is intracellular synaptic protein involved in vesicle endocytosis. This antibody is reported in associated with stiff person syndrome and limbic encephalitis. (ARHGAP26 GRAF) Rho GTPase activating protein 26 is involved in clathrin-independent endocytosis and associated with subacute inflammatory cerebellar ataxia. CASPR2 is associated with Morvan's syndrome, limbic encephalitis, neuromyotonia, etc., Myelin oligodendrocyte glycoprotein is associated with acute disseminated encephalomyelitis, multiple sclerosis, neuromyelitis optica, etc., GAD65 is associated with stiff-person syndrome epilepsy, limbic encephalitis, cerebellar ataxia, etc., Ma2, Ma1, Yo are unknown proteins associated with limbic encephalitis, cerebellar ataxia, peripheral neuropathy, etc., Thyroid peroxidase (TPO)[4] activated complement in addition to thyroiditis is often associated with Hashimoto encephalitis which is steroid responsive and presents with psychosis, myoclonus, cognitive dysfunction, with or without delirium, and focal deficits occasionally. Paraneoplastic disorders associated with antibodies to intracellular antigens, such as anti-Hu, Ri, Yo, Ma2, CRMP5, and amphiphysin are strongly cancer associated and involve T-cell responses targeting neurons.[5] AK5 acts on intracellular antigens but not cancer associated. VGKC, NMDA, AMPA, GABAb, glycine receptor (PEMR) act on neuronal surface receptors and 40%–60% are paraneoplastic.

Common clinical features are as follows. New-onset nonfamilial psychosis, seizures, myoclonus, unexplained status epilepticus, dystonia chorea syndrome, faciobrachial dystonic seizures, video 1 showing fascio brachial dystonic seizures in one of our patients ataxia, peripheral neuropathy, neuromyotonia, stiff-person syndrome, etc., The diagnostic criteria by Gultekin *et al*. are commonly used for paraneoplastic encephalitis.[6,7] The criteria are as follows: (1) definite if there is pathological confirmation. (2) All of the following (a) symptoms of short-term memory loss, seizures, or psychiatric symptoms. (b) Less than 4 years between the diagnosis of neurological illness and malignancy. (c) Exclusion of infection, metabolic, metastatic, and other causes for encephalopathy. (d) One of the following cerebrospinal fluid (CSF) showing evidence of inflammatory change, magnetic resonance imaging (MRI) changes, and electroencephalogram (EEG) abnormalities

Well-known clinical features with reference to the specific types

The term limbic encephalitis is applied to the following phenotype with the triad of anterograde amnesia, psychiatric features, and seizures. Diencephalic encephalitis indicates somnolence, narcolepsy, hyperthermia, sexual dysfunction and hypothalomopituitory dysfunction, and weight gain. The term brainstem encephalitis is applied when there is dysarthria, dysphagia, ophthalmoplegia, and parkinsonian features and encephalomyelitis when spinal cord is also involved.[8]

PATIENTS AND METHODS

Patients with short-duration encephalopathy and later considered to be immune mediated seen from 2010 to 2015 by the authors were analyzed. Patients with infective, traumatic, prion related, rapid degenerative diseases, and well-established cases of vasculitis were excluded. They were evaluated clinically and investigated with VGKC, NMDA, TPO, vasculitic workup, CSF measles antibody titers, herpes simplex antibody, and routine evaluation EEG, MRI, and neuropsychological symptoms were done in all cases. Paraneoplastic workup done based on affordability and clinical suspicion. Almost all the patients were unsuitable for detailed neuropsychological evaluation and hence not done. Duration of follow-up varied from 1 year to 5 years.

RESULTS

There were a total of 42 patients. Their age group varied from 11 years to 75 years. There were 13 females and 29 males [Figure 1]. Thirty patients reported to psychiatrist first 72%.

Clinical features

Most patients reported malaise, fatigue, low-grade fever, and lack of interest which lasted for a varying period from few days to weeks followed by psychiatric symptoms followed by neurological features and varying periods of recovery. During the initial stage, unexplained anxiety and psychotic features were seen in 69%, panic was reported by 47%, depressive features noted in 21%, overfamiliarity and maniacal features in 14%, occasional social incontinence and wandering in 12% each, unexplained paroxysmal symptoms in 2%, seizures in 45%, myoclonic jerks in 43%, and stroke-like episodes in 7%. Signs were very few. Optic atrophy and mild hemiparesis were seen in 7% each, papilledema in 4%, and ophthalmoplegia in 2%. Minor skin changes such as allergic rashes were reported by two patients and one patient developed malar rash during follow-up. Splenomegaly was seen in one patient and hair loss reported by six patients. Catatonic features were seen in 6 cases.[9] [Figure 2]. Three patients were found to suffer from paraneoplastic syndrome. One female among them developed breast cancer during follow-up, one male had anti-Ri antibody positive, improved with plasmapheresis 1 and 1½ years after the symptom onset was detected to have angiosarcomatous deposit scalp [Figure 3] and another male showed adenocarcinomatous deposit in cervical lymph node.

Laboratory features

Antibody profile could not be done in 7 cases and negative for the tested antibody in 8 cases. Anti-Ri was positive in 1 case, VGKC in 7, VGKC and HIV seropositivity in 1 case, NMDA in 8 cases, measles antibody elevated to 1/625 dilution in 6 cases.[10] TPO elevated more than 3 fold in 3 cases, antinuclear antibody positive in 6 cases [Figure 4]. Imaging showed no abnormality in 6 cases. Imaging no significant abnormality was seen in MRI in 6 cases (13%). One patient showed infiltrating lesions in pons with enhancement suggestive of clippers [Figure 5]. Mesial temporal lobe, cingulum, external capsule cerebellum, basal ganglia, cerebral cortex, or brainstem showed varying degrees of T2 hyperintense lesions which were noncontrast enhancing. Meningeal changes in the optochiasmal and tentorial meningeal regions were seen in one case which turned out to be IGg4-mediated encephalitis on syncytiotrophoblast. Multiple white matter diffusion restricting lesions were seen in patients with lupus encephalitis. One patient with VGKC syndrome who had relapse showed severe atrophy following relapse [Figure 6]. EEG showed abnormality in 97% of cases. Periodic lateralized epileptiform changes were seen in 9%. Diffuse ictal activity in 9%. Mid-positive triphasic waves in 55%. Nonspecific slowing and delta brush in 10%.

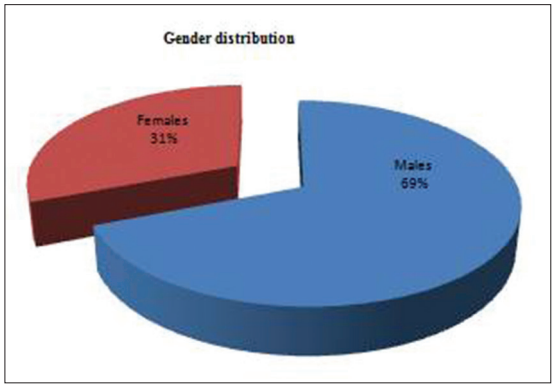

Figure 1: Gender-wise distribution of our patients

Figure 2: Catatonia

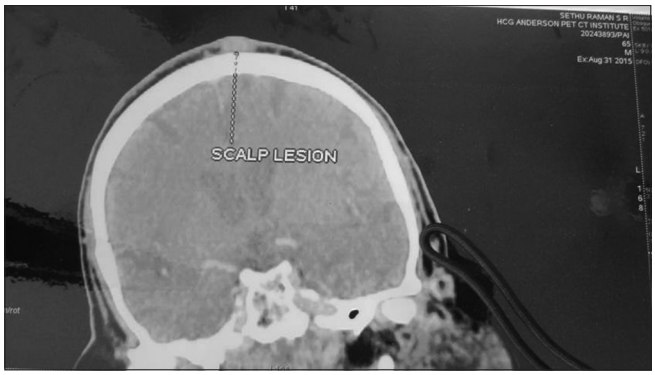

Figure 3: Angiosarcomatous deposit scalp

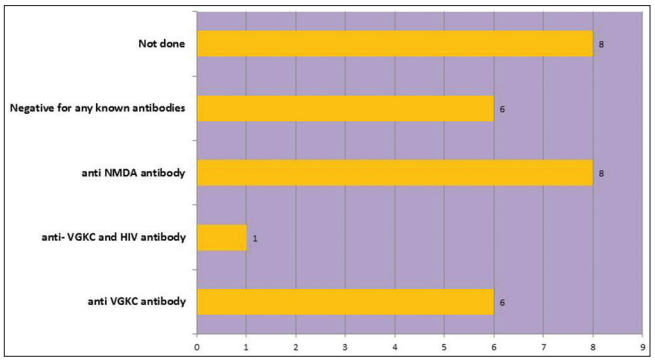

Figure 4: Distribution of antibody

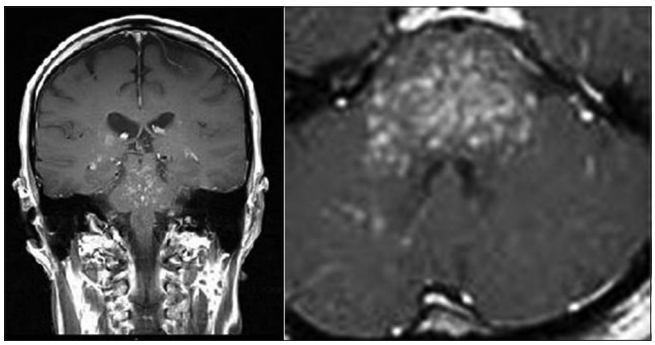

Figure 5: Clippers showing pontine perivascular enhancement

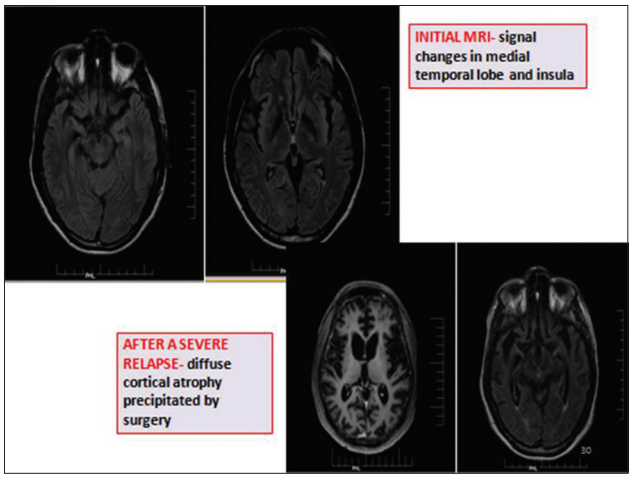

Figure 6: Diffuse severe atrophy seen after severe relapse

Treatment, course, and outcome

Nearly (thirty patients) 70% of patients received psychiatric treatment for varying periods of time. Among these patients, three patients received electroconvulsive therapy before organic cause was suspected. All patients received intravenous methyl prednisolone monthly pulse for 6 months. Patients who did not show satisfactory response received intravenous immunoglobulin, plasmapheresis, cyclophosphamide pulse. Those with lupus-associated encephalopathy received regular azathioprine 1–2 mg/kg. None of our patients received other immunomodulators. Drug-induced side effects were not seen in any case.

Onset to diagnosis delay varied from weeks to 2 years. One female with neuropsychiatric lupus died during pregnancy. Three patients with malignancy initially showed response to plasmapheresis and after the malignancy was identified and referred for appropriate treatment they were lost for follow-up. None of our patients with NMDA associated encephalitis showed malignancy during our follow-up period. One patient who had VGKC antibody-associated encephalopathy had severe relapse following surgery for a fractured hip and left with severe cognitive squeal and brain atrophy. Complete functional recovery was seen in 26 patients. Twelve patients showed very significant morbidity. Major diagnostic errors as Creutzfeldt-Jakob disease (CJD) was seen in 3 cases, subacute sclerosing panencephalitis (SSPE) in 6 cases, catatonia in 6 cases, and psychosis in 5 cases.

DISCUSSION

Conclusion new-onset psychosis in any patient with rapid course and refractory to usual modes of symptomatic treatment needs to be evaluated for immune-mediated encephalopathies. EEG is a cheap screening tool to differentiate organic from pure psychiatric conditions. Catatonia is not uncommon, especially in children with immune-mediated encephalopathy. Orthostatic myoclonus associated with VGKC specific IgG-associated encephalopathy can be mistaken as CJD and faciobrachial dystonic seizures seen in VGKC Lgi1antibody can closely mimic slow myoclonus of SSPE, and therefore, a high degree of suspicion is needed and correlation of the phenotype with EEg, imaging findings, and when indicated immunofixation and microneutralization to establish or exclude the diagnosis of SSPE is lifesaving. Soft systemic symptoms are common and often ignored by patients and inquiry into the same will help in planning appropriate investigations.

CONCLUSION

Immune dysregulation results in a wide spectrum of neurological syndromes and therefore, is a great imitator. High degree of suspicion is needed to plan that right investigations as well as not to ignore soft systemic and neurological signs before labeling them as non organic. Simple tools like EEG is of great use in differentiating organicity so that potentially harmful treatment options are not carried out and the right treatment not denied.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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