Autoimmune encephalitis: A potentially reversible cause of status epilepticus, epilepsy, and cognitive decline

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Abstract

Objectives: To review clinical characteristics and response to immunomodulation therapy in autoimmune encephalitis presenting with status epilepticus (SE), epilepsy, and cognitive decline. **Design:** Observational, prospective case series. **Setting:** All India Institute of Medical Sciences, New Delhi, India. **Materials and Methods:** Prospective analysis of 15 patients, who presented with SE, epilepsy, cognitive decline, and other neurological symptoms with positive autoantibodies. Demographic and clinical characteristics were recorded. Brain magnetic resonance imaging (MRI), cerebrospinal-fluid analysis (CSF), and tumor screening were done periodically. Treatment received and responses (categorized as per patients and treating doctor's information) were noted. **Results:** There were 15 (males = 10) patients of autoimmune encephalitis. The mean age of presentation was 24 years (range: 2-64 years). The most common onset was subacute (64%) and four (29%) patients presented as SE. Predominant clinical presentations were seizures (100%) almost of every semiology. CSF was done in 10 patients; it was normal in 60%. Brain MRI was done in all patients, in six (40%) it was normal, six (40%) showed T2W and FLAIR hyperintensities in bilateral limbic areas. Antibodies found were the N-methyl-D-aspartate receptor antibody in seven (50%), voltage-gated potassium channel antibody in five (36%), two of antiglutamic acid decarboxylase, and one patient with double stranded DNA (dsDNA) antibodies. None showed evidence of malignancy. Patients received immunotherapy, either steroids, intravenous immunoglobulin, or both. Follow-up showed significant improvement in majority of cases, neither further seizures nor relapse in nine (67%) cases. One death occurred, due to delayed presentation. **Conclusions:** Uncommon but potentially reversible causes of SE, epilepsy, and cognitive decline may be immune-related and high index of suspicion will prevent missing the diagnosis.

Key Words

Autoimmune encephalitis, cognitive decline, drug refractory epilepsy, seizures, status epilepticus

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Introduction

Seizures clusters and status epilepticus (SE) are common medical emergencies. They have to be identified early and treated at the earliest. Common causes of SE are acute events (brain injury, stroke, infection, tumor, or childhood febrile SE) or occur in patients with a prior history of epilepsy. A smaller proportion of patients with or without seizures due to epilepsy and SE are likely to be due to intercurrent illness such as systemic infections or metabolic disturbances or changes in antiepileptic medication or some remote symptomatic etiology. There is an emergence in the recognition of immune-mediated epilepsy of paraneoplastic or nonparaneoplastic etiology with or without encephalitis.[1,2] Some of these immune-mediated encephalitis have identified antibodies and others are associated with syndromes having yet unidentified/unknown antibodies. Autoantibodies of paraneoplastic limbic encephalitis include antineuronal nuclear antibody type 1, collapsin response-mediator protein 5 (CRMP-5), and Ma2. Voltage-gated potassium channel (VGKC) complex and glutamic acid decarboxylase 65 antibodies, often nonparaneoplastic in etiology, have been reported in patients with limbic encephalitis[3-6] and idiopathic epilepsy with anti epileptic drug (AED)-resistant seizures.[7-12] Newly identified autoantibody specificities that strongly correlate with clinical seizures include N-methyl-D-aspartate (NMDA),[13] gamma aminobutyric acid B,[14] and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.[15] Identification of immune-mediated mechanisms in SE, epilepsy, cognitive decline, and other neurological symptoms is important to provide patients a benefit of immunomudulatory therapy, which may albeit be slow, but

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potentially completely reverse the epilepsy and other associated neurological manifestations. The antibodies are mainly of two types targeting neuronal cell surface antigen and the other targeting intracellular antigens. Antineuronal antibodies affect the neuronal signaling or synaptic transmission, the evidence to this is supported by benefit of immunomodulation and *in vitro* studies.[13,15-18] The intracellular antibodies mediated by cytotoxic T cell, is supported by autopsies showing inflammatory infiltrates of mononuclear cells, including CD4 and CD8 cells, which predominate in symptomatic areas of the nervous system.[19-21] These onconeural antibodies can be absent or be present in variable titers in patients with or without cancers.[22-25] Presence of antibodies, therefore, should not be the only defining feature of neurologic syndromes of autoimmune encephalitis. If an antibody present is usually associated with the particular neurologic syndrome of the patient, then the patient should be evaluated for said symptoms and treated.[26,27]

We describe herewith 15 cases of immune-mediated encephalitis all having antibodies positivity and presenting with seizures. The intention of this article is to raise awareness of immune-mediated epilepsy as a potentially reversible cause of drug refractory epilepsy and SE.

Materials and Methods

A prospective detection and follow-up of 15 patients was done (December 2011-June 2013). These patients presented with seizures and other neurological symptoms with positive autoantibodies [Figure 1]. Demographic and clinical characteristics (seizure types, clinical course, and associated symptoms) were recorded. Neuroimaging [brain magnetic resonance imaging (MRI)], cerebrospinal fluid analysis (CSF), and tumor screening was done periodically. All patients underwent thorough clinical examination along with skeletal survey (X-rays), chest and abdomen and pelvis computed tomography scan, positron emission tomography (PET) whole body, prostate-specific antigen in male patients more than 50 years, carcinoembryonic antigen 125 in all women, complete blood count, liver, renal function test, and serum electrophoresis. Serum electrophoresis was done in elderly patients (>50 years). None of the patients showed any evidence of malignancy either at baseline or in annual follow-up with whole body PET scan.

Anti-NMDA antibody was measured by radioimmunoassay. Enzyme immunoassay for anti-VGKC antibody and anti-GAD antibodies was done. These were tested in 1:10 dilution. Serum levels of anti-NMDA antibodies were ranging between 1:800 and 3200 either positive or negative in that dilution. Anti-VGKC antibody ranged from 197 to 2800 (>100pM/mL is positive) and anti-GAD antibody 105 to 200 (normal range: 0-10 U/Ml) antinuclear antibodies (ANA), anti-dsDNA, and anti-Ro antibody also had to be significant in titer of >1:40 (immunofluorescence), 65 (normal range: 0-50 IU/mLby ELISA; enzyme-linked immunosorbent assay technique) and 106 U/mL (normal <8 U/mL by ELISA), respectively. Treatment received by patients and response to the treatment was noted. Response to immunotherapy was categorized as per patients and treating doctors information (regarding seizure free/control and other neurological symptom improvement).

Data were expressed as median (range and interquartile range) for continuous variables and counts (percentages) for categorical variables. Detailed statistical analyses was done following entry of data in Microsoft excel 2011.

Results

There were 15 (males = 10 and females = 5) patients recorded of autoimmune encephalitis. The mean age of presentation was 24 years (age range: 2-64 years). Onset of disease most commonly was subacute (62%) followed by chronic, none of the patients presented with an acute onset. All patients had seizures (100%) and these were of various semiology [Tables 1 and 2]. Other associated clinical features were recorded, as mentioned in Tables 1 and 2. CSF was done in 10 patients and was normal in six (6 of 10; 60%), in the rest of CSF showed variable findings from mild raised protein (75-150 mg/dL) to raised cell counts (10-20/cu mm). CSF was more likely to be done in those who presented with SE and encephalitis like presentation rather than drug refractory epilepsy. Neuroimaging (brain MRI) was done in all patients, six (40%) were normal, six (40%) showed T2W and FLAIR hyperintensities in bilateral limbic areas, one had bilateral basal ganglia atrophy with periventricular hyperintensity on T2W and FLAIR images, one had diffuse cerebral and cerebellar atrophy, and one had right insular cortex hyperintensities with atrophy of the right hippocampus. Some of other abnormalities observed were bilateral perisylvian and bilateral posterior hyperintensities in one [Figure 2a] and another patient showing bilateral hyperintense swollen hippocampus [Figure 2b]. Antibodies were tested in all patients as these patients had no known cause for their seizures and encephalopathy (infective, herpes, malignant, metabolic, etc.) and were basically categorized as unknown etiology of status, epilepsy, and encephalopathy depending on their clinical manifestations. NMDA receptor antibody positivity was found in seven (50%) patients, VGKC antibody in five (36%) patients, and two patients had anti-GAD and in another anti-dsDNA antibodies were found. None of the patients showed any evidence of malignancy in the periodic tumor screening done. Each of patients received treatment in form of immunotherapy, steroid, intravenous immunoglobulin (IVIg), or both. There was a significant improvement in majority of cases, that is, no further seizures or relapse in 10 (67%) of 15 cases. There was one death (case 1), she presented very late, after almost 5 years of duration of illness without receiving any specific treatment and being misdiagnosed with a psychiatric diagnosis. On diagnosis, she received aggressive immunomodulation (steroids, rituximab, immunoglobulin) but developed drug-induced pancytopenia and died of severe sepsis. In case 4, initial workup (concordant clinical, video electroencephalography, MRI brain, and substraction ictal single photon emission computed tomography (SPECT) coregistred with interictal SPECT (SISCOS) study) was concluded as mesial temporal sclerosis of the right side. He was operated upon, but did not show any change in seizures, reevaluation showed his as having NMDA receptor antibody positivity and he showed a dramatic response to oral steroids, earlier his seizure frequency was 25 to 30 per month to the frequency post steroids of 1 to 2 per month. Case 6 had a presentation of seizures clusters, cognitive decline and was almost in a mute state she turned out to be NMDA positive, she was initiated on IVIg followed by pulse steroids and plasmapharesis. But had poor recovery after

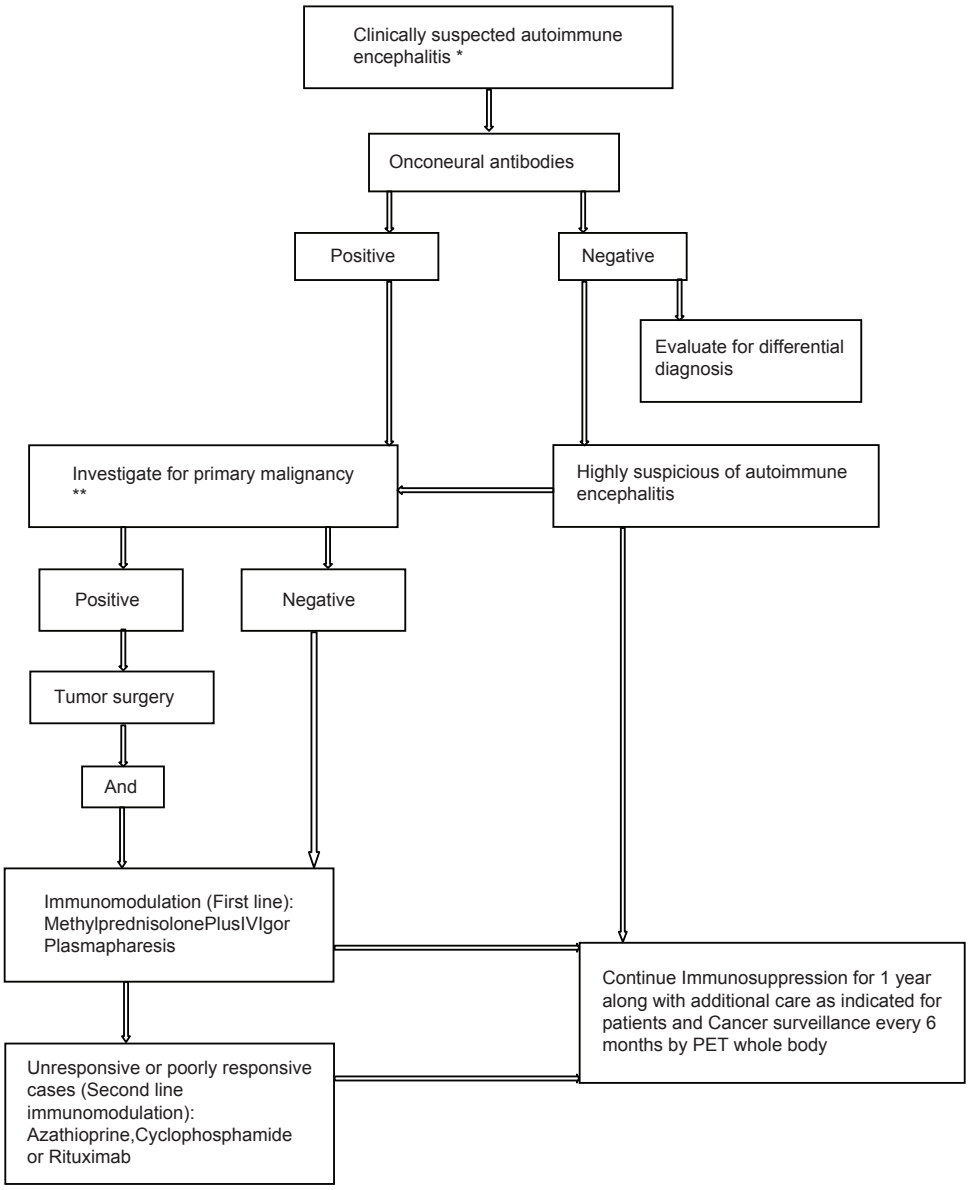

Figure 1: *Acute, Subacute (more commonly), chronic rapidly progressive neurological deficit, exclude alternate differential diagnosis.Thorough clinical examination along with skeletal survey (X rays), chest and abdomen and pelvis CT (Computed tomography) scan, positron emission tomography (PET) whole body, prostate-specific antigen (PSA) in male patients more than 50 years, carcinoembryonic antigen 125 (CEA-125) in all women, serum electrophoresis was done in elderly patients more than 50 years**

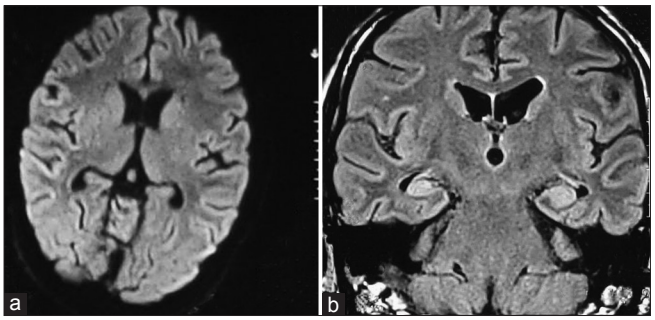

Figure 2: (a) Bilateral posterior parietal cortical hyperintensity on FLAIR magnetic resonance imaging (anti-sN-methyl-D-aspartate antibody positive) (b) Bilateral hyper intense swollen hippocampus (antivoltage-gated potassium channel antibody)

2 weeks of immunomodulation, she was initiated upon pulse cyclophosphamide and rituximab. She is gradually recovering in the most recent follow-up. She is able to communicate and has no seizures. Case 14, continued having seizures, although frequency and intensity had reduced, as compared with previous by 70%.

Discussion

Our study is prospective observation of 15 persons of suspected and subsequently confirmed autoimmune encephalitis. Seizures were the predominant and main presenting clinical feature present in all the cases (100%). We could find a very significant, no relapse and complete seizure freedom in

Table 1: Clinical, treatment, and follow-up profile of patients

Antibody	Case	Age; years/ Gender	Duration	Typical clinical feature(s)	Type(s) of seizure	CSF All Negative for HSV	Neuroimaging (MRI Brain)	Treatment received	Follow-up		
									Duration in months and (mRS)	On immunomodulation	Relapse (Yes/No)
NMDA	1	22/F	5 years	Vomiting, seizures, memory impairment, dystonia	GTCS, myoclonic jerks (cortical), Status epilepticus	Normal	Basal ganglia atrophy and periventricular hyper intensity. Bilateral cortical hyperintense [Figure 2a].	Pulse methylprednisolone followed by oral prednisolone. Rituximab	12 (6)	-	Died
	2	10/M	4 weeks	Seizures, declining scholastic performance	Atonic seizures	Normal	Normal study	2 pulses of IVIg and steroids	16 (1)	+	No
	3	18/M	8 weeks	Seizures, dystonia, memory impairment	Myoclonic jerks (cortical), GTCS, CPS, status epilepticus	TLC 20 cells/cu mm with normal glucose and raised protein (75 mg/dl).	T2W and FLAIR hyper intensity in bilateral limbic area	IVIg, pulse steroids followed by oral steroids	12 (1)	+Tapering steroids	No
	4	12/M	4 years	Focal seizures (Drug refractory 3-5/ days)	Focal seizures, secondary generalized seizures	-	? Right insular cortex focal cortical dysplasia and right mesial temporal sclerosis	ECoG guided right temporal amygdalohippocampectomy (26.02.10), Oral steroid (25.01.12)	Since 2006 (2)	+Tapering steroids	Reduced seizure frequency (1-2/ month by 80%)
	5	14/M	12 weeks	Behavior changes, cognitive decline, seizures	Complex partial seizures	Acellular with raised protein (150 mg/dl) and normal glucose.	Normal study	IV steroids followed by IVIg and oral steroids	8 (1)	+Tapering steroids	No
	6	10/F	12 weeks	Seizures, right upper limb followed by generalized choreoathetoid movements, cognitive decline	GTCS, Myoclonic jerks and status epilepticus	Normal	Normal study	IV Steroids, IVIg, Plasmapharesis, pulse cyclophosphamide and rituximab	6 (3)	+Steroids	No seizures and choreoathetoid movements and also cognition improvement.
	7	15/F	24 weeks	Seizures brief focal, cognitive decline	Focal motor seizures	Normal	Normal study	IVIG, IV MPS and Plasmapharesis	6 (1)	+Steroids	No seizures

Table 2: Details of case series

Antibody	Case	Age; years/ Gender	Duration	Typical clinical feature(s)	Type(s) of seizure	CSF All Negative for HSV	Neuroimaging (MRI Brain)	Treatment received	Follow-up		
									Duration in months and (mRS)	On immunomodulation	Relapse (Yes/No)
VGKC	8	27/F	12 weeks	Seizures, confusional state and memory impairment	Complex partial seizures -refractory	TLC 10 cells/cu mm, lymphocytic and normal glucose and protein	Bilateral temporal lobe, hippocampus hyper intensity on FLAIR with mild diffusion restriction	IVIg, prednisolone	15 (0)	+ Tapering steroids	No
	9	64/M	12 weeks	Seizures, chorea and memory impairment	GTCS, right focal seizures	Acellular with normal glucose and protein.	T2W and FLAIR hyper intensity bilateral limbic area. Bilateral swollen hippocampus [Figure 2b]	Prednisolone	24 (2)	+Tapering steroids	No
	10	21/F	24 weeks	Seizures, memory impairment	GTCS, status epilepticus	Acellular with raised protein (110 mg/dl) and normal glucose. Negative for HSV	T2W and FLAIR hyper intensity in bilateral limbic area	IVIg followed by oral steroids	24 (1)	+Oof steroids on AEDs	No
	11	60/M	1 year	Behavior changes, cognitive impairment and seizures	GTCS	Acellular with normal glucose and protein. Negative for HSV	T2W and FLAIR hyper intensity in bilateral temporal lobes	IVIg followed by oral steroids	14 (1)	+Tapering steroids	No
	12	62/M	12 weeks	Seizures, cognitive decline	Myoclonic jerks, GTCS	-	T2W and FLAIR hyperintensity bilateral limbic area	IV steroids	24 (2)	+Tapering steroids	No
Anti-GAD	13	02/M	1 week	Focal seizures (right and left)	Focal seizures	-	Normal study	IV steroids	12 (mRS not applied), ambulatory and independent	+	No
	14	12/M	1 year	Focal seizures (right and left)	Focal seizures	-	Normal study	IV steroids	12 (2)	+	No
ANA, dsDNA, Anti Ro	15	15/M	18 weeks	Focal seizures (B/L frontal), polyarthritis	Focal seizures	-	Cortical and cerebellar atrophy	IVIg, Steroids and Methotrexate	12 (2)	+	Seizures reduced by 70%

Most patients were given antiepileptic drugs. After immunosuppression, it was possible to reduce and taper from polytherapy to monotherapy

67% cases and overall there was significant improvement in the neurological status in 94% of our patients. Our series reflects that the diagnosis of autoimmune etiology should be considered in all persons with an unknown etiology of status, encephalopathy, cognitive, and behavior changes when other common causes have been ruled out. Our series is similar to previous observations on autoimmune encephalitis.[8-11,28-30]

An autoimmune etiology is identified most readily in patients who present with the full syndrome of limbic encephalitis, characterized by subacute memory impairment with affective changes and temporal lobe seizures. The diagnosis of autoimmune limbic encephalitis is aided by detection of neural autoantibodies with radiological or pathological evidence of temporomedial inflammation and in some cases a history of neoplasia in the preceding 5 years.[31]

One of our patients had undergone temporal lobectomy with a misdiagnosis of hippocampal sclerosis; this has also been observed by previous authors reporting limbic encephalitis to be an antecedent in adult onset temporal lobe epilepsy.[32,33] Another of our patient reached late to us, a psychiatric diagnosis of catatonia, drug-induced movement disorder, seizures and schizophrenia had been made. Other series too have a variation in diagnosis, for example, adult onset temporal lobe epilepsy in anti-NMDA receptor antibodies.[32]

The diagnosis of autoimmune encephalitis presenting as SE, epilepsy, cognitive impairment, and other neurological symptoms, requires a high index of suspicion at initial evaluation.[34] The clinical presentations in our patients were heterogeneous, but some general observations can be made. Very brief frequent seizures, faciobrachial seizures, tonic seizures associated with movement disorder and behavioral changes. Data from the current cohort suggest that autoimmune investigation should be considered in the presence of one or more of the following: Subacute onset of neurological symptoms (epilepsy, movement disorder, behavioral changes, and cognitive decline), an unusually high seizure frequency, very brief seizures, faciobrachial seizures, intra individual seizure variability with seizure clusters or multifocality, antiepileptic drug resistance with a nonsurgical substrate, personal or family history of autoimmunity [either organ-specific (e.g., thyroid disease, diabetes mellitus, pernicious anemia, or celiac disease) or nonorgan-specific (rheumatoid arthritis or systemic lupus erythematosus)], or recent or past neoplasia. Serological testing is increasingly valuable as an aid to establishing the diagnosis of an autoimmune etiology.

Half (7 of 15; 47%) of our patients were anti-NMDA receptor antibody positive with mean age of 14 years (range: 10-22 years), having seizures both focal (2) and myoclonic jerks (1) in three of seven patients with memory impairment, dystonia, choreoathetoid movements, reduced scholastic performance, behavioral changes, and vomiting. In comparison to a series of 100 patients[13] our observation varied having mean age lesser (14 years), as compared to 23 years in Dalmau's series, a contrast in gender preponderance was also observed. Clinical features observed in anti-NMDA receptor encephalitis were similar to other series which have reported; seizures of any type in 76%, dystonia and choreoathetoid movement in 47% each, additional neuropsychiatric manifestations, autonomic instability and central hypoventilation. Dalmau (2008) also observed prodromal symptoms, that is, viral-like symptoms in 72 of 84 patients. A total of six of our patients had undergone CSF study which was normal in half, rest half showed raised protein and one together with mild lymphocytic pleocytosis. In Dalmau's series 95 CSF studies were abnormal, but main abnormalities were similar, in form of raised protein and lymphocytic pleocytosis. We had only three (43%) abnormal MRIs and four (57%) normal MRIs in anti-NMDA receptor antibody positive cases. Whereas Dalmau's series about 55% had abnormal MRIs. The abnormalities we observed were basal ganglia atrophy, periventricular hyperintensities, and bilateral limbic region hyperintensity on T2 and FLAIR images. One case showed features of mesial temporal sclerosis. Normal MRI brain is not unusual for autoimmune epilepsies. We had no patients with tumor on screening at baseline or till now- all having 1 year of follow up with sequential whole body PET and ultrasound abdomen and pelvis.

We had five patients of autoimmune epilepsy with anti-VGKC antibody positivity with male preponderance (60%) and mean age of 47 years (range: 21-64 years). All these patients had seizures and memory impairment. Few patients had additional confusional state, behavioral changes, and chorea. In a series of 51 cases by Tan *et al*.,[35] which had a predominant female distribution (73%) the mean age at diagnosis was 66 years. Our observation differed in gender distribution, although the age distribution was nearly similar. Predominant clinical features[35] observed were cognitive impairment in 71%, seizures (faciobrachial) in 58%, autonomic instability in 33%, myoclonus in 29%, sleep disturbances in 26%, and extrapyramidal features in 21% (chorea in 4% cases) cases. Also noted were hyponatremia (36%), cranial nerve or brainstem involvement (19%), peripheral nerve hyperexcitability (17%), neuropathy (14%), headache (6%), cerebellar features (8%), and Morvan syndrome (3%). Our patients were similar in clinical findings. Our patients had CSF (two of four cases) abnormality in form of raised protein in one case and mild lymphocytic pleocytosis in one. However, magnetic resonance of the brain was abnormal in all the cases. In the series of Tan *et al*., 57% CSF (27 of 47 available CSF studies) and 54% (26 of 48 available MRIs) of MRIs were abnormal. None of our patients had a tumor at baseline or followup.

We had two children with anti-GAD antibody positivity these children were in their first decade with refractory focal epilepsy. They had a normal brain MRI and had a very excellent response to steroids, and had complete seizure freedom. Only one case of autoimmune epilepsy had ANA, anti-dsDNA, and anti-Ro positive, he was a 15 years boy with recurrent focal seizures and polyarthritis.

Our study shows excellent prognosis of being seizure-free and no further relapse of symptoms along with resolution of associated neurological deficits in 70%. As noted in 22 of 27 (81%) patients the immunomodulation therapy led to favorable outcome ($P < 0.05$).[36] In a recent observation of anti-NMDA encephalitis;[37] various immunotherapies used were steroids as first line, IVIg, and plasmapharesis, regarding second-line therapy cyclophosphamide and rituximab was used. There is a significant benefit in the use of both first-line and second-line immunotherapy, although this study was not

a randomized trial. Hence, it is advisable for such patients to get immunomodulation in form of IVIg or MPS; however, future relapses may occur and if there is no improvement more aggressive immunomodulation with cyclophosphamide and rituximab is warranted. There have been no placebo-controlled clinical trials; the treatment is based on few prospective series that have been reported in literature.

On follow-up of antibody levels, three had reduced titers and these were absent in two cases at 6 months of follow-up and absent levels in five cases at 12 months of follow-up (one case had reduced levels at 6 months had absent levels at 12 months). It was not possible to repeat titers more frequently, as it would increase costs of management.

To conclude, rare causes of SE, epilepsy, and cognitive decline may be immune-related and a high index of suspicion should be kept, as these are reversible in many cases. The clinical accompaniments in these patients of seizures associated with movement disorders; cognitive, behavioral features will help us making an early diagnosis and prevent neurological morbidity.

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