Original Article

Antibody Negative Autoimmune Encephalitis- Does it Differ from Definite One?

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Abstract

Context: Autoimmune encephalitis (AE) is an emerging cause of non-infective encephalitis, presentations of which vary widely. Traditionally the diagnosis of AE is based on detection of antibodies in a patient with clinical picture suggestive of AE. **Aim:** To evaluate the clinical characteristics and response to immunotherapy in patients with antibody negative autoimmune encephalitis and to compare them with definite cases. **Settings and Design:** A prospective follow-up study was done in patients presenting with presumptive symptoms of AE from January 2017 to January 2019. The study was done in a tertiary care institute of Northern India. **Patients and Methods:** Demographic and clinical parameters were noted and relevant investigations for management were done according to well-defined protocol. The patients were treated with immunomodulatory therapy in the form of steroids and/or intravenous immunoglobulins (IVIg). They were followed up for treatment response and relapse at 2 monthly intervals. **Statistical Analysis Used:** The data was expressed as either proportions or mean/median. Chi-square test/Independent T test was used to compare antibody positive and antibody negative group. **Results:** Out of 31 patients with presumptive AE, 16 patients tested positive for autoimmune antibodies (definite AE). Incidences of seizure, behavioral abnormalities, dementia and altered sensorium were similar between the 2 groups ($p > 0.05$). Complete or partial response was seen in all treated patients in both groups with no significant difference (p 0.716). CSF protein concentration and cellularity were higher in the definite group although only high protein concentration could reach statistical significance (p 0.002). Malignancy could be confirmed after extensive search in 2 out of 16 patients with definite AE and in 1 out of 15 antibody negative AE patients. **Conclusions:** Clinical presentation of antibody negative cases does not differ significantly from definite ones. Since treatment response is also similar in both the groups, starting immunotherapy in a patient presenting with presumptive symptoms of AE, while ruling out other common mimickers, seems to be the need of the hour in the management of this evolving entity.

Keywords: Autoimmune, definite, encephalitis, immunotherapy

Introduction

The last decade has seen the emergence of autoimmune encephalitis as a major cause of non-infectious encephalitis. Infectious causes such as herpes simplex encephalitis, malignancies such as carcinoma lung, thymoma etc., or any autoimmune disease, such as systemic lupus erythematous can predispose to the development of autoantibodies against cell-surface, synaptic or intracellular antigens.[1-3] Sometimes, it becomes difficult to ascertain whether the clinical presentations are due to the premorbid disease, it's relapse or due to the subsequently triggered auto-antibodies. Moreover, the clinical presentation of different causes of AE are more or less overlapping, leaving very few of them to be called as specific for a particular disease. The presentations in neonates and children remain all the more ambiguous because of their non-specificity.[4] All these issues make the diagnosis of AE confusing.

In fact, the guidelines for diagnosis suggest that a complete antibody panel consisting of antibodies against intracellular, surface antigen and ion channels should be done in a case of suspected AE.[5] In the recent years, with the advancement of knowledge about this disease, the overlap in diagnostic and management nuances is so much that the antibody- based diagnosis has gradually shifted to predominantly clinical symptomatology.[5] These criteria of probable, possible and definite AE, although were introduced to bring more clinically suspected patients of AE within the ambit of the disease spectrum so as to ensure early treatment, are not easy to apply in suspected AE patients. The clinical utility of this division of AE into various subtypes particularly in the management of AE is still not proven. We have already emphasized in our earlier report that probable and possible AE could be merged to make a antibody negative group.[6] As this group also responds to immunotherapy, we proposed to institute immunotherapy as a presumptive therapy irrespective of the antibody status. Other studies from India have also supported the use of immunotherapy in seronegative AE.[7] Therefore, in the present

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paper, we tried to look for any clinical or therapeutic difference in antibody positive (definite) and antibody negative AE.

Methods

A prospective follow-up of 31 cases of presumptive AE based on sub-acute onset of well-known symptomatology of AE[5,8,9] was done during the study period of January 2017 to January 2019. The cases were followed up every 2 months till the composition of manuscript or death of the patient (2 patients died in follow-up), whichever was earlier. The patients were only included if they had a minimum follow-up of 2 months. The maximum follow-up duration was 36 months in our study. The consent form was signed by all of the patients before enrolment in the study.

Demographic and clinical parameters were noted after thorough history taking and clinical examination. Cerebrospinal fluid (CSF) analysis, electroencephalographic examination and magnetic resonance imaging of the brain were done at baseline. CSF samples were sent for autoimmune antibody panel consisting of NMDA-NR1, AMPA-GluR1 and GluR2, GABA- A and B, VGKC (LGI1 and CASPR2) and GAD antibodies. If this panel was negative, paraneoplastic antibody panel consisting of anti- Hu, anti- Ri, anti Yo, anti CV2/CRMP-5, anti-amphiphysin was done from CSF. Antibody (IgG) was detected by indirect immunofluorescence in 1:10 sample screening dilution in tranfected HEK cells. In case of patient's refusal to get CSF examination conducted, we resorted to checking antibodies in serum sample of those patients (a total of 11 patients). Antibodies from both serum and CSF samples were not done due to financial constraints.

Routine hemato-chemistry, thyroid stimulating hormone (TSH) levels with anti- thyroid peroxidase and anti- thyroglobulin antibodies, vasculitis profile (antinuclear antibody, anti- neutrophilic antibody, antibodies against extractable nuclear antigen, anti-cardiolipin antibodies), CSF angiotensin converting enzyme (ACE) levels, radiographs of the chest, ultrasound abdomen, serum electrophoresis (in >50 years old), prostate specific antigen in elderly male (>50 years) and carcino-embryonic antigen in elderly female (>50 years) were done to rule out other mimickers of autoimmune encephalitis. Positron emission tomography as a part of the malignancy evaluation workup could be done only in 2 patients due to financial constraints and technical issues. Part B and C of Figure 1 shows PET abnormalities detected in them. Treatment received by patients (steroids, IVIg, or both) and response to treatment was noted. The selection between IVIg and steroids were based on relative contraindication of the other agent and financial status of the patient. Response was noted as complete (if the patient was completely asymptomatic at discharge or in follow-up), partial (in case of partial/incomplete resolution of the presenting symptoms in follow-up) or relapse (in case of reappearance of symptoms in the follow-up period after the patient has been declared symptom-free once). Only change in clinical parameters was taken into consideration in the follow-up. Investigations could not be repeated in most of the patients due to financial constraints.

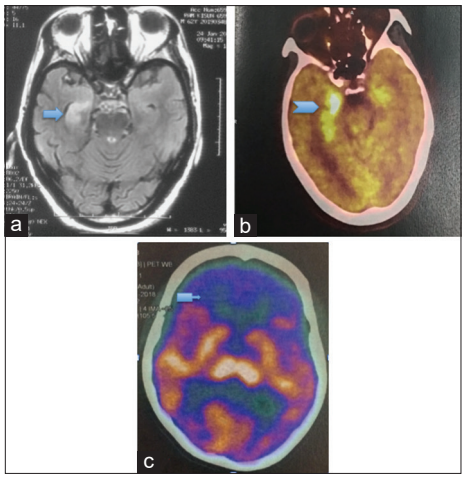

Figure 1: T2 Flair right medial temporal lobe hyper intensity (arrow in Figure a) in MRI brain and right medial temporal lobe hyper metabolism (notched arrow in Figure b) in PET scan of a CASPR2 antibody positive AE patient. Frontal hypo metabolism (arrow callout in Figure c) in PET scan of a NMDAR antibody positive AE patient

Data were expressed as median with IQR for continuous variables and number (percentage) for categorical variables. Data was analyzed after recording in Statistical Package for Social Sciences-23 for MAC, OS. Chi- square test/Independent T test was used to look for differences between the 2 groups.

Ethical approval: All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (IEC: 2018-213-IP-EXP-4) and with the 1964 Helsinki declaration and its later amendments.

Results

Out of 31 patients with presumptive autoimmune encephalitis, 16 had antibody positivity. The most common antibodies detected were anti NMDAR in 5 patients (16.1%) and whole VGKC complex in 4 patients (12.9%). LGI1 antibody was present in 2 patients (6.5%), while there was 1 patient each of CASPR2, mGluR1, GABA-B, GAD and Yo antibody. Complete response was seen in 9 (56.3%) patients while partial response in 7 (43.8%) patients. 15 patients who had negative antibody panel were treated with immunotherapy, of which 10 (66.7%) had complete response while the remaining 5 (33.3%) had partial response. Response was comparable between the antibody-positive and antibody-negative group (p 0.716). 12 patients of definite group and 13 patients of antibody-negative group could do their daily activities independently after therapy, which was also comparable (p 0.654).

6 patients in definite group and 8 patients in antibody-negative group received only steroids. 2 patients in either group received

only IVIg (4-5 courses). The rest of the patients (8 in definite group and 5 in antibody-negative group received 3 courses of IVIg initially followed by tapering dose of steroids. There was no significant difference (p 0.623) in the type of treatment in either group. So, comparable treatment response may be due to early and timely treatment in 2 groups rather than type of treatment received.

Seizures were present in 9 (56.3%) patients of antibody positive group and 7 (46.6%) patients of antibody-negative group. Irritable/apathetic/psychotic behavior was present in 9 (56.3%) patients of definite group and 7 (46.7%) patients of antibody-negative group. Incidences of dementia in the 2 groups were almost similar (7 in definite group and 6 in antibody-negative group). Three patients of definite group and five patients of antibody-negative group had altered sensorium. There was no significant difference between the two groups in any of the common clinical parameters ($p > 0.05$).

CSF examination could be done in 11 patients of definite group and 9 patients of antibody-negative group. CSF protein was significantly higher (p 0.002) in definite group (65.55 ± 15.62 mg/dl) when compared to antibody-negative group (37.20 ± 20.46 mg/dl). CSF sugar and CSF cellularity were not significantly different between the 2 groups. The results are shown in Table 1.

EEG abnormality was seen in 13 out of 15 patients (86.6%) in antibody-negative group while the same was seen in 13 out of 16 patients (81.3%) in definite group. The difference was insignificant (p 0.585). Both the groups had similar pattern of EEG abnormalities like delta brush, focal slowing in any leads, generalized theta-delta slowing, intermittent generalized slowing or tri phasic waves.

Typical MRI abnormality of unilateral or bilateral medial temporal lobe hyperintensity was found in 4 (25%) patients of definite group and 1 (6.6%) patient of antibody-negative group. 4 patients of definite group and seven patients of antibody-negative group had non-specific MRI abnormalities. The difference in MRI patterns between the 2 groups was not significant (p 0.41) [Table 1]. Part A of Figure 1 shows unilateral medial temporal lobe hyperintensity in MRI brain of a CASPR2 antibody positive patient. Abnormal PET scan of 2 antibody positive AE patients are shown in part B and C of Figure 1.

Malignancy was found in 2 patients in definite group and 1 patient in antibody-negative group on follow-up. One patient having GAD antibody positivity died of sepsis after initial improvement while one with cutaneous lymphoma and negative antibody panel died in the follow-up period.

The clinical characteristics of both groups of patients are tabulated in Tables 2 and 3.

Table 1: Comparison between antibody positive and antibody negative autoimmune encephalitis patients

Parameters	Antibody positive (Definite) $n=16$	Antibody negative $n=15$	p
Male, *n* (%)	10 (62.5)	12 (80)	0.43
Duration of illness before presentation (in months) mean±SD	3.63±2.19	3.07±2.79	0.54
Altered sensorium, *n* (%)	3 (18.8)	5 (33.3)	0.43
Seizures, *n* (%)	9 (56.3)	7 (46.7)	0.72
Behavioral abnormalities, *n* (%)	9 (56.3)	7 (46.7)	0.65
Forgetfulness, *n* (%)	7 (43.8)	6 (40.0)	0.83
Extrapyramidal signs, *n* (%)	5 (31.2)	6 (40)	0.53
Cerebellar dysfunction, *n* (%)	2 (12.5)	5 (33.3)	0.30
CSF pleocytosis, mean±SD	20.82±41.26	3.89±3.37	0.24
CSF protein elevation, mean±SD	65.55±15.62	37.20±20.46	0.002
Abnormal MRI, *n* (%)	8 (53.3)	8 (50.0)	0.41
Abnormal EEG, *n* (%)	13 (86.6)	13 (81.3)	0.87
Treatment, *n* (%)			
IVIg	2 (12.5)	2 (13.3)	
Steroids	6 (37.5)	8 (53.3)	
IVIg+Steroids	8 (50.0)	5 (33.3)	0.62
Response, *n* (%)			
Complete	9 (56.3)	10 (66.7)	0.716
Partial	7 (43.8)	5 (33.3)	

CSF- Cerebrospinal fluid, IVIg- Intravenous immunoglobulin, MRI- Magnetic resonance imaging, EEG- Electroencephalogram

Discussion

We had a prospective observational cohort of 31 patients with presumed autoimmune encephalitis. As a part of our treatment protocol, we initiated first line immunotherapy in them pending autoimmune encephalitis panel report and after ruling out common mimickers. This is in conformation with the recent guidelines regarding treatment of patients with AE. Sixteen of them had antibody positivity, reports of which were available during the second week of hospital stay. We considered AE cases as definite if they had positive antibody panel. The remaining 15 patients had negative autoimmune panel reports. All of the patients had either complete or partial response to first line therapy. We could see that there was no significant difference in treatment response between the definite and presumptive AE group. This is in line with other recent studies that have shown that patients with antibody negative autoimmune encephalitis may also respond to immunotherapy.[10]

Clinical-criteria-based syndromic diagnosis has been given precedence by some authors over other approaches of treatment in AE which include clinical features, CSF, EEG and MRI findings and response to immunotherapy.[11] Each approach has its own merits and demerits. Response to immunotherapy can only be ascertained in retrospective analysis. Antibodies can be negative in half of the AE cases while in some of the cases, they can just be a by-stander.[12,13] The logistic issues of these antibody panels starting with

Table 2: Demographic, clinical and laboratory characteristics of antibody positive (definite) autoimmune encephalitis patients

-	Antibody	Age/Gender	Duration (months)	Symptoms (subacute onset)/ Signs	CSF findings	MRI findings	EEG findings	Treatment modality (response)	Follow-up		Sequential improvement in symptoms
									Duration in months	Relapse/ Death	
1	NMDA	30/F	3	GTCS, irritable behavior, slurring of speech, disoriented to person and time	P=70, G=55, C=140	Normal	Delta brush	Steroids (Partial)	6	-	Irritable behavior by 1 week, GTCS by 4 weeks, disorientation in 6 weeks
2	NMDA	12/F	6	Focal seizures with bilateral tonic clonic seizures, vomiting, persistent laughter, psychotic behaviour	-	Bifrontal diffusion restriction	Triphasic waves	Steroids followed by IVIG (Complete)	24	-	Seizures by 4 weeks, psychotic behavior by 3 months
3	NMDA	5/M	1	Facio-brachial seizures, apathetic behaviour	P=64, G=13, C=5 (100)	Left high parietal T2/ FLAIR hyperintensity	Focal left parietal slowing	Steroids followed by IVIg (Complete)	8	-	Seizures by 2 weeks, behavioral change by 2 months
4	NMDA	10/F	4	Facio-brachial seizures, psychotic behaviour	P=58, G=87, C=10 (100)	Bifrontal diffusion restriction	Triphasic wave	Steroid followed by IVIg (Complete)	18	-	Seizures by 3 weeks, behavioral change by 3 months
5	NMDA	2/F	4	Extensor spasms, developmental regression	-	Gross cortical atrophy	Normal	IVIg followed by Steroids (Partial response)	12	-	Extensor spasms by 1 month, stable development after 3 months with no deterioration
6	CASPR2	62/M	4	Bilateral tonic clonic seizures, irritability, RBD, forgetfulness, altered sensorium, parkinsonian features, autonomic features	P=84, G=62, L=4	Bilateral media temporal lobe hyperintensity	Generalized slowing	Steroids followed by IVIg (Partial response)	4	-	Autonomic features by 1 week, Seizures by 3 weeks, behavioral change by 4 months
7	LGI1	74/M	6	Bilateral tonic clonic seizures, irritable behavior, visual hallucinations, RBD, facial myokymia, hyponatremia, parkinsonian features, delirium	P=86, G=85, C=5	Normal	Intermittent generalized slowing	IVIg (Partial response)	6	Ca rectum with scapular metastasis	Seizures by 2 weeks, delirium by 1 week, visual hallucinations by 3 weeks
8	LGI1	60/M	4	Myoclonic jerks, focal seizures with bilateral tonic clonic , forgetfulness, fatigue, parkinsonian features, hyponatremia,	P=84, G=56, C=5	Unilateral medial temporal lobe hyperintensity	Focal slowing	Steroids (Complete)	12	-	Seizures by 2 weeks, forgetfulness in 1 week, parkinsonian features by 3 months

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Table 2: Contd...

-	Antibody	Age/Gender	Duration (months)	Symptoms (subacute onset)/ Signs	CSF findings	MRI findings	EEG findings	Treatment modality (response)	Follow-up		Sequential improvement in symptoms
									Duration in months	Relapse/ Death	
9	VGKC	64/F	7	RBD, irritable behavior, auditory hallucinations, altered sensorium, paranoid delusions, bilateral rigidity, bilateral frontal release signs present	-	Normal	Focal slowing	Steroids Partial response)	6	-	Altered sensorium by 1 week, behavioral abnormalities by 4 months, rigidity resolved by 5 months
10	VGKC	60/M	2	REM sleep movement disorder, irritability, forgetfulness	P=42, G=66, C=40	Bilateral medial temporal lobe hyperintensity	Triphasic waves	IVIg (Complete)	8	-	RBD and behavioral disturbance by 5 month, forgetfulness by 7 months
11	VGKC	53/M	2	Episodic and working memory loss	P=68, G=54, C=20	Bilateral medial temporal lobe hyperintensity	Triphasic waves	IVIG followed by steroids (Complete)	11	-	Memory loss by 5 months
12	VGKC	40/M	1	RBD, irritability, facial myokymia, proximal>distal weakness in all 4 limbs		Normal	Normal	IVIG followed by Steroids (Partial response)	6	-	RBD and behavioral disturbance by 3 months, myokymia resolved partially by 5 months
13	GAD	67/M	2	Forgetfulness, LMN type paraparesis with myokymia in lower limbs	P=66, G=272, C=0	Normal	Triphasic waves	Steroids followed by IVIg (Partial response)	2	Death following sepsis after 3 months	Partial improvement in memory by 6 weeks
14	mGLUR-1	40/M	3	Slowness of all daily activities, forgetfulness, cogwheel rigidity in bilateral upper limbs	P=59, G=57, C=0	Normal	Triphasic waves	Steroids (Complete)	6	-	Parkinsonian symptoms by 4 months, forgetfulness resolved by 5th month
15	GABA-B	75/M	1	Bilateral tonic clonic seizures, imbalance while walking with syncopal attacks, autonomic dysfunction		Normal	Normal	Steroids (Complete)	4	-	Autonomic dysfunction by 1 week, seizures by 8 weeks
16	Anti-Yo	48/F	8	RBD, imbalance while walking, bilateral cerebellar signs	P=40, G=75, C=0	Normal	Normal	Steroids (Partial)	4	Carcinoma lung	Improvement in cerebellar signs by 6 weeks

NMDA- N- methyl-D- aspartate, CASPR2- Contactin Associated Protein 2, LGI1- Leucine rich glioma inactivated 1, VGKC- Voltage gated potassium channel, GAD- Glutamic acid decarboxylase, mGLUR1- Metabotrophic glutamate receptor 1, GABA- B-Gamma- aminobutyric acid- B receptor, M-Male, F- Female, RBD- REM sleep behavior disorder, CSF- Cerebrospinal fluid, MRI – Magnetic resonance imaging, EEG- Electroencephalogram, P-Protein, G- Glucose, C- Cells

their availability, methods used for detection, long latency of reports are things that need to be sorted out. The syndrome-based approach can help in making an idea about the presence of AE and its sub-types, but the overlapping clinical features among the various sub-types with new symptoms being reported with this entity quite frequently make it a rather tedious job to divide these patients initially into possible and then to various types of probable AE as advised by some authors.[5]

The presence of facio-brachial seizures, which has been reported till now only with LGI1 encephalitis[14] were observed in 2 patients with NMDA-r encephalitis and 1 patient with negative antibody panel, highlighting the overlapping pattern

Table 3: Demographic, clinical and laboratory characteristics of antibody negative autoimmune encephalitis patients

Case	Age/Gender	Duration (months)	Symptoms (subacute onset)/ signs	CSF findings	MRI findings	EEG findings	Treatment modality (response)	Follow-up		Sequential improvement in symptoms
								Duration in months	Relapse/ Malignancy/Death	
1	61/M	2	Visual hallucinations, delirium, forgetfulness, resting tremors in both upper limbs, gait ataxia	-	Non specific T2/FLAIR white matter hyperintensities	Intermittent slowing	Steroids (Complete)	8	-	Behavioral symptoms by 4 weeks, tremors and gait ataxia by 4 months
2	32/M	2	Bilateral tonic clonic seizures, REM sleep movement disorder parkinsonian features, bilateral cerebellar signs	-	Bilateral Medial temporal lobe hyperintensity	Triphasic waves	IVIg (Complete)	6	-	Seizures by 3 weeks, RBD and parkinsonian symptoms by 3 months
3	9/M	1	Focal with bilateral tonic clonic, altered sensorium dystonia of all 4 limbs	P=33, G=55, C=5 (80%)	Normal	Generalsied theta-delta slowing	Steroids followed by IVIg (Complete)	36	-	Seizures by 3 weeks, dystonia by 6 months
4	3/M	2	Irritability, hyperactive behaviour-	P=21, G=63, C=0	Normal	Triphasic waves	IVIg (Complete)	28	-	Behavioral improvement by 4 weeks and complete resolution by 3 months
5	1/F	2	Facio-brachial seizures, milestone regression truncal ataxia	P=43, G=89, C=5	Normal	Delta-brush	Steroids followed by IVIg (Complete)	24	-	Seizures by 2 weeks, milestones stabilized and started improving by 5 months
6	50/F	1	Decreased speech output akinetic mutism	P=36, G=62, C=5	Non specific T2/FLAIR white matter hyperintensities	Triphasic waves	Steroids (Partial response)	2	Cutaneous lymphoma, Died after 2 months due to sepsis	Mild improvement in speech output by 1 month
7	71/M	4	Irritable behavior, forgetfulness psychosis	P=86, G=74, C=10	Normal	Triphasic waves	Steroids (Complete)	6	-	Behavioral changes improved by 2 months
8	61/M	2	Visual hallucinations, delirium, forgetfulness, imbalance while doing daily activities, intermittent sleepiness, parkinsonian features, bilateral cerebellar signs (appendicular >axial)	-	Gross cerebral atrophy	Triphasic waves	Steroids (Complete)	10	-	Behavioral and sleep disturbances improved by 1 month, parkinsonian symptoms by 4 months, cerebellar symptoms by 6 months
9	3/M	4	Persistent irritability with hyperactive behavior after a febrile episode of 5 days	P=21, G=63, C=0	Normal	Focal right parietal spikes	Steroids followed by IVIg (Complete)	8	-	Behavioral changes by 8 weeks

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Table 3: Contd...

Case	Age/Gender	Duration (months)	Symptoms (subacute onset)/ signs	CSF findings	MRI findings	EEG findings	Treatment modality (response)	Follow-up		Sequential improvement in symptoms
								Duration in months	Relapse/ Malignancy/Death	
10	30/M	3	Visual hallucinations, right UL and LL weakness and loss of dexterity, word finding difficulty, slowed thought process right left disorientation	-	Left posterior parietal atrophy	Left focal slowing	Steroids (partial resolution)	4	Lost to follow-up after 4 months	Dexterity improved by 3 months
11	73/M	9	Visual hallucinations, forgetfulness psychotic behavior, rigidity in all four limbs, slow saccades, broken pursuits	-	Normal	Triphasic waves	Steroids (partial resolution)	12	-	Behavioral changes by 3 months
12	52/F	2	Myoclonic jerks, irritable behavior, intermittent altered sensorium, generalized rigidity, forgetfulness, bilateral cerebellar signs	P=29, G=100, C=0	Bilateral diffusion restriction in basal ganglia and thalamus	Normal	Steroids (Partial response)	18	-	Altered sensorium by 2 weeks, improvement in myoclonic jerks by 2 weeks, memory by 3 months
13	9/M	1	Myoclonic jerks, focal seizures with impaired awareness, faciobrachial seizures, intellectual deterioration, not recognizing relatives athetosis of hands, occasional choreoform movements of both upper limbs	P=21, G=72. C=0	Bilateral basifrontal/ parietal white matter hyperintensity	Generalized theta-delta slowing	Steroids (complete)	24	-	Seizures by 6 weeks, movement disorders by 2 months, memory improvement by 3 months
14	25/M	1	Bilateral tonic clonic seizure psychotic behaviour	-	Right temporo -parietal T2/FLAIR white matter hyperintensity, right frontal cortex diffusion restriction	Normal	Steroids followed by IVIg (Partial response)	16	-	Seizures by 4 weeks, mild improvement in behavior by 4 months
15	9/M	10	Bilateral tonic clonic seizure, irritable behavior, not able to learn new things, eating non edible things, hyperorality, recurrent falls truncal ataxia	P=45, G=65, C=6 (100)	Normal	Triphasic waves	Steroids followed by IVIg (complete)	8	-	Seizures by 1 month, byperorality by 2 months, cerebellar signs by 5 months

CSF- Cerebrospinal fluid, MRI – Magnetic resonance imaging, EEG- Electroencephalogram, M-Male, F- Female, P-Protein, G- Glucose, C- Cells

of symptoms in AE. Predominant symptom of orthostatic hypotension due to autonomic dysfunction in GABA-B receptor encephalitis as in one of our patient with definite AE, is not known in literature. Hyperactive and irritable behavior in a child persisting for 2 months after a prodromal illness or persistent dystonia after the control of initial seizures in a premorbidly normal child getting resolved with immunotherapy, may point towards a form of autoimmune phenomena against cell surface/synaptic antigens of the brain. So, for the time being, it seems quite logical to treat all potential

cases of autoimmune encephalitis with first line immunotherapy pending other investigations. Ruling out mimickers like herpes simplex encephalitis, vasculitis, sarcoidosis, mitochondrial diseases and CNS lymphoma with readily available tests in a patient with unexplained neurological deficits may be kept as the only prerequisite before starting immunotherapy. The facts that more than half of the AE patients are antibody negative[15] and early immunotherapy improves outcome[16,17] further support this view. All of our patients responded partially or completely during the variable period of follow-up with no relapse. 2 patients died after 2-3 months due to sepsis, which may be related or unrelated to steroid therapy used for immunosuppression in these patients. Reports of antibody panel, when available, will of course guide us for escalation of immunotherapy in fulminant cases and also for prognostication. However, it is worth noting that an expensive therapy such as IVIg, which is not free of serious adverse effects in specific situations, need to be used judiciously.

In that context, this needs to be emphasized that a thorough investigative workup is mandatory to rule out all the mimics before presuming the patient to be suffering from AE. To that effect, this will act as a safeguard against the possible misuse of IVIg.

When we compared the clinical characteristics and laboratory parameters between the two groups (definite and presumptive) of AE, we could find certain differences between them. The presumptive group had more non-specific MRI features (46.7% vs 25.0%), less CSF cellularity and protein levels although only CSF protein concentration could attain significance (p 0.002) between the 2 groups. The subtle differences in the CSF and MRI findings of the 2 groups had so much of overlap in individual cases that they may not predict antibody status of a particular patient. However, this forms the basis for more observations in future to predict the same.

Studies on patients with antibody negative limbic encephalitis responding to initial immunotherapy have shown development of malignancy in upto 58.3% of the cases on follow-up.[18] Although only 1 out of our 15 patients in presumptive group developed cutaneous lymphoma on follow-up, this suggests that the presumptive AE patients may also require stringent longitudinal follow-up to look for any other emerging clinical features that may change their management.

This is the first study comparing clinical characteristics and treatment response in antibody negative and definite AE cases. We could not do PET imaging as a part of malignancy workup in all of the patients. The variable follow-up period and immunotherapy modality in our cohort is also a limitation.

Conclusion

Since antibody negative AE has more or less similar clinical features and treatment response as definite AE, it's better to start immunotherapy in suspected patients of AE based on presumptive symptoms, thereby simplifying the management of this evolving entity.

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Conflicts of interest

There are no conflicts of interest.

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