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Autoimmune encephalitis: an observational study from South India

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Abstract

Background Ever since AE was acknowledged as a potentially treatable cause of encephalitis, it has been increasingly recognised worldwide. Data suggests that these disorders are under-recognized, which calls for an increased awareness of the varying clinical, laboratory, electrophysiological and radiological presentations of the different types of autoimmune encephalitis. This cross-sectional observational study included all patients diagnosed with AE, who presented to a tertiary care centre from June 2016 to January 2021. Data were collected including patient's demography, clinical, laboratory, radiological and electrophysiology studies, management and outcomes.

Results 31 study participants were included, of which 13 patients were anti-NMDA antibody positive, 12 patients were anti-LGI1 antibody positive, 2 patients were anti-CASPR2 antibody positive, 2 were positive for dual positive status (anti-LGi1 and anti-CASPR2), and one each for anti-GABA-B and anti-GAD 65. There was a marginal male predilection with overall seizures being the most common symptom (68%) followed by behavioural disturbance (64.5%), and impairment of consciousness (32.3%). Patients with Anti-NMDA encephalitis were likely to be young females, with CSF pleocytosis, a more protracted hospital course with more chances of relapse and residual disease, while the patients with anti-Lgi1 encephalitis were likely to be older males with a shorter, less severe hospital course.

Conclusion The present study detailed the demographic, clinical, imaging, laboratory and EEG characteristics of 31 AE patients from a tertiary centre. The findings concurred with the literature and demonstrate the diverse spectrum of clinical manifestations of patients with AE, present with.

Keywords Autoimmune encephalitis, Anti-NMDA encephalitis, Anti-Lgi1 encephalitis

Background

Encephalitis, which translates to inflammation of the brain, has a range of causes and is held to be immune-mediated when caused by antibodies directed against autoantigens [1]. Immune-mediated encephalitis can be broadly further subclassified into autoimmune encephalitis (AE), when the autoantibodies are directed against cell surface antigens and paraneoplastic encephalitis, when they are directed against intracellular antigens [1]. The distinction between these two entities is important as antibodies against cell surface cause reversible neuronal dysfunction [1, 2].

Encephalitis per se has an estimated annual incidence of around 5 to 8 cases per 100,000, and further analysis shows that amongst the identified causes AE accounts for the third most common cause after viral encephalitis and post-infectious [3, 4]. Amongst any individual cause of encephalitis, a type of AE associated with antibodies against the N-methyl-d-aspartate receptor (NMDAR) was the most common cause more than any individual viral aetiology [3, 4]. Furthermore, the diagnosis of AE,

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which was infrequent earlier, is being more commonly recognized in the present years and this is attributable to improved antibody detection [5]. Being potentially reversible, it is important that AE is considered at the bedside, or that the clinician operates with a high index of suspicion for AE, as data suggests that these disorders are under-recognized. A review of data at the US National prion disease pathology surveillance centre has revealed that nearly 7% of the cases, labelled as progressive and untreatable prion diseases, have turned out to be AE after autopsy [6]. Analysis of patients treated for AE, also showed that around 35% had been previously diagnosed with an incurable neurodegenerative disease [7]. The epidemiology of AE in India is unknown. This calls for an increased awareness of the varying clinical, laboratory, electrophysiological and radiological presentations of the different types of autoimmune encephalitis. Apart from identifying a potentially different diagnosis, this has profound therapeutic and prognostic implications.

Methods

This was an ambispective observational cohort study, which included all patients diagnosed with AE, who presented to a tertiary care centre from June 2016 to January 2021. Diagnosis of AE was made when the patients were positive for at least one of the neuronal cell surface autoantibodies in their sera and/or cerebrospinal fluid in the context of an appropriate clinical setting. The patients were reviewed by a member of the neurology team during their inpatient stay or outpatient consult, and data was collected. This study employed the following Exclusion criteria: (a) Patients who did not consent to the study (b) Patients with neuronal intra-cellular antigen-mediated encephalitis (Paraneoplastic encephalitis) and (c) Patients with incomplete medical records.

The presence of antibodies to cell surface antigens was investigated using indirect immunofluorescence using cell-based assays, which contained human embryonic kidney (HEK) 293 cells transfected with plasmids encoding: antigens: N-methyl-D-aspartate receptor (NMDAR), leucine-rich, glioma-inactivated protein 1 (LGI1), contactin-associated protein-like 2 (CASPR2), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR; GluR1 and GluR2 subunits), γ-aminobutyric acid B receptor (GABABR; B1 and B2 subunits).

Magnetic resonance imaging (MRI) was performed using GE Signa HDXT 1.5 Tesla machine to obtain T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences with 1.5T field intensity in axial, coronal and sagittal planes, with or without gadolinium enhancement. Tumour screening was done using chest X-ray, ultrasound abdomen and in select cases mammogram, apart from blood markers. Inter-ictal electroencephalogram (EEG) studies were done using Nihon Kohden, JE-921A, 2007 (Japan) machine, for all patients, and the results were categorised as normal, generalised/focal slowing, and generalised/focal epileptiform abnormalities. Cerebrospinal Fluid (CSF) analysis was done to quantify proteins, sugars, total white blood cells (WBC), differential counts, and red blood cells (RBC), whenever CSF samples were available. Other routine investigations included a complete hemogram and renal and liver function tests including electrolytes.

Demographic, laboratory, radiological and EEG characteristics of each patient were obtained from the patients by the neurology team during admission, Outpatient visit or medical records. Clinical data including the spectrum of manifestations, type of seizures, treatment given, outcomes, recurrences, and relapses were collected. History of cancer and previous infections were also collected. Acute treatment included intravenous prednisolone (IVMP 1 g daily for 5 days), intravenous immunoglobulin (IVIG 2 g/kg over 5 days) or plasma exchange (250 mL/kg). Rituximab (1 g twice 2 weeks apart) was considered for refractory cases. Long-term immunosuppression was administered by using azathioprine or mycophenolate mofetil.

Data were entered using Microsoft excel and were analysed using Statistical Package for Social Sciences (SPSS) version 16.0, (IBM Canada). Categorical data was represented in the form of frequencies and proportions. For qualitative data, the Chi-square test was used as a test of significance. Continuous data were represented as means and standard deviation. An independent t-test was used as a test of significance to identify the mean difference between two quantitative variables. The strength of association between different variables will be assessed within 95% confidence intervals and a p-value of less than 0.05 was considered statistically significant.

Results

This study included 31 study participants, of which 13 patients were Anti-NMDAR antibody positive, and 16 patients were positive for one of the Anti-VGKC antibodies (12 patients were Anti-LGI1 antibody positive, 2 patients were Anti-CASPR2 antibody positive, and 2 were positive for dual antibody positive status (Anti-LGI1 and Anti-CASPR2). Apart from the above, one patient was found to be Anti-GABA-B antibody positive and one for Anti-GAD 65 antibody. Table 1 shows demographic, clinico-investigative, management and outcome data comparisons for the Anti-NMDAR and the Anti-VGKC subgroups, which comprise the majority of the study population.

The overall mean age was 43.26 years (SD-21.43), with a minimum age of 7 years and maximum age of

Table 1 Demography, Clinical features, Investigations, management patterns and outcomes in AE ($n=31$) and subgroup comparison between Anti-NMDAR Encephalitis ($n=13$) and Anti-VGKC Encephalitis

	Total $n=31$	**Anti-NMDAR AE** $n=13$	**Anti-VGKC AE** $n=16$
Gender female (%)	9 (29)	7 (53.8)	1 (6.2)
Mean age (± SD) (years)	44.37 ± 9.89	34.84 ± 11.77	52.12 ± 10.39
Clinical manifestations			
Cognitive/Behavioural disturbances (%)	20 (64.5)	10 (76.9)	10 (62.5)
Seizures (%)	21 (67.7)	11 (84.6)	9 (56.2)
GTCS (%)	15 (48.3)	11 (84.6)	3 (18.7)
FBDS (%)	6 (19.3)	Nil	6 (37.5)
Sleep disturbances (%)	5 (19.3)	5 (38.4)	1 (6.2)
Memory disturbances (%)	5 (16.1)	3 (23)	2 (12.5)
Language disturbances (%)	5 (16.1)	5 (38.4)	Nil
Decreased level of consiousness (%)	10 (32.2)	8 (61.5)	1 (6.2)
Visual Hallucination (%)	4 (12.9)	2 (15.3)	2 (12.5)
Movement disorders (%)	3 (9.6)	1 (7.6)	2 (12.5)
Neuromyotonia (%)	3 (9.6)	Nil	3 (18.7)
Autonomic disturbances (%)	2 (6.4)	1 (7.6)	1 (6.2)
Ataxia and cerebellar signs (%)	2 (6.4)	Nil	2 (12.5)
Fasciculations (%)	2 (6.4)	Nil	2 (12.5)
Tongue Atrophy (%)	1 (3.2)	Nil	1 (6.2)
EEG findings			
Generalized slowing (%)	7 (22.5)	3 (23)	3 (18.7)
Generalized spike-and-wave (%)	6 (19.3)	5 (38.4)	1 (6.2)
Normal (%)	18 (58)	5 (38.4)	12 (75)
MRI findings			
Normal (%)	24 (77.4)	10 (76.9)	13 (81.2)
CSF findings			
Pleocytosis ° (%)	13/25 (52)	9/12 (75)	2/13 (15.3)
Mean protein concentration (± SD)	43.30 (± 20.46)	45.72 (± 20.3)	49.63 (± 21.36)
Preceding infection (%)	5 (16.1)	5 (38.4)	Nil
Treatment			
Pulse steroids (%)	29 (93.5)	13 (100)	15 (93.7)
IVIG (%)	13 (41.9)	6 (46.1)	6 (37.5)
Plasmapharesis (%)	2 (6.40	2 (15.3)	Nil
Rituximab (%)	3 (9.6)	3 (23)	Nil
Outcomes			
Replases (%)	2 (6.4)	1 (7.6)	1 (6.2)
Residual deficits (%)	3 (9.7)	3 (23)	Nil

AE Autoimmune Encephalitis, *CSF* Cerebrospinal Fluid, *EEG* Electroencephalogram, *FBDS* Faciobrachial Dystonic Seizures, *GTCS* Generalised Tonic Clonic Seizures; *IVIG* Intravenous Immunoglobulin; *MRI* Magnetic Resonance Imaging, *NMDA* N-methyl-D-aspartate, *SD* Standard Deviation, *VGKC* Voltage-gated potassium channels

78 years. With regards to the AE subgroups in our study, in the anti-NMDAR antibody encephalitis subgroup, the mean age was 34.84 ± 11.77 years, and in the Anti-LGI1 encephalitis subgroup, the mean age was 54 ± 9.32 years. The Anti-CASPR2 encephalitis patients were each 34 and 58 years old. The Anti-LGI1 + Anti-CASPR2 patients were 66 and 28 years old. The one Anti-GABA-B encephalitis patient was 47 years old and the Anti-GAD65 encephalitis patient was 7 years old.

Out of the study population of 31 patients, 22 (71%) were males and 9 (29%) were females. With regards to subgroup analysis, the incidence of anti-NMDAR antibody encephalitis, was marginally more in the female gender ($n=7$, 53.84%). In the Anti-LGI1 autoantibodies,

subgroup majority of them were of male gender ($n=11$, 91.6%) in our study. Both the Anti-CASPR2 patients and patients with Anti-LGi1 + CASPR2 antibodies were male. The Single patient with the Anti-GABA B antibody was female and the patient with the Anti-GAD65 antibody was male.

In our study when the entire study population was analysed, ($n=20$) 64.5% of the study population had behavioural change abnormality and ($n=21$) 67.7% of the study population had seizures. Apart from these symptoms, language disturbances were seen in ($n=5$)16% of the patients, visual hallucinations in ($n=4$) 13%, sleep disturbances in ($n=5$) 19%, memory disturbances in ($n=5$)16%, disorders of the level of consciousness in ($n=10$) 32.2% and autonomic disturbances in ($n=2$) 6% of patients. Two patients had ataxia and two had hyperphagia, with tongue atrophy and low backache seen in one patient each. With regards to movement disorders, one patient had dystonia (Anti-LGI1), and two had chorea (One Anti-LGI1 and one Anti-NMDAR encephalitis). Three patients had neuro-myotonia (One participant had antibodies against Anti-LGI1 and 2 had antibodies against Anti-LgI1 + CASPR2). Two participants who had fasciculations were positive for Anti-CASPR2 antibodies. The distribution of the prevalent clinical features amongst various AE subgroups is represented in Fig. 1.

Apart from this non-specifically, 6.5% ($n=2$) of the participants had ataxia (Both were Anti-CASPR2 antibody positive) and hyperphagia (in Anti-NMDAR encephalitis). Similarly, low backache and tongue atrophy was each seen in the patients with the Anti-LGI1 + Anti-CASPR2 subgroup.

In our study ($n=5$) 16% had historical or laboratory evidence of preceding infection. Two patients had positive preceding samples for HSV encephalitis, and three patients had a history of fever in the last month. All 5 patients belonged to the Anti-NMDA subgroup.

The analysis of the distribution of autoantibodies between CSF and serum could not be done as both samples were not sent to all patients due to cost, unwillingness, or a positive result in the first sample sent. Among the different subgroups, Anti-NMDA antibodies were sampled only in CSF for 9 patients, only in serum for 1 patient, and both samples were sent for 3 patients in which 2 had dual positivity and one had positive results in CSF only. In the Anti-LGI1 subgroup, Anti-LGI1 antibodies were sent only in CSF for 2 patients, serum only for 4 patients, and both samples were sent for 6 patients, out of which both were positive in 2 patients and serum only was positive in 4 patients. In the Anti-CASPR2 encephalitis subgroup, both samples were sent for both patients in which one had positive antibodies in CSF and one patient had positive antibodies in Serum. In the Anti-CASPR2 + Anti-LGI1 dual positive subgroup both samples were sent for both patients and antibodies were found only in serum in both patients. Both the Anti-GABA-B and Anti-GAD positivity was seen in CSF samples, which was the only sample sent. A total of 5 patients (1 Anti-NMDAR encephalitis and 4 Anti-LGI1 encephalitis) did not undergo CSF analysis due to unwillingness or a positive result in the serum sample sent. The distribution of antibodies across the samples sent is represented in Fig. 2.

Among the 31 study participants, 23% ($n=7$) had an abnormal MRI Brain report, and 77% ($n=24$) had a normal MRI report. Out of the abnormal MRIs, T2/FLAIR Hyperintense lesion in the medial temporal region was the most common abnormality detected, and other abnormalities include hyperintense lesions in basal ganglia regions, thalamus, basal ganglia, and hippocampus. One patient had sub-acute cerebrovascular disease, and one patient had a thrombus in the superior sagittal sinus and right transverse sinus thrombosis. With regards to subgroups, ($n=10$) 76.9% of Anti-NMDA encephalitis and ($n=9$) 75% of Anti-LGI1 encephalitis had normal MRI Brain.

25/31 of the study population underwent CSF analysis. The mean CSF protein was detected to be 45.36 mg/dl (SD-20.46 mg/dl), CSF glucose to be 51 mg/dl (SD-19.84 mg/dl) among our study population and 48.38% had a pleocytosis. The mean protein level in patients with Anti-NMDA encephalitis was 45.7 mg/dl and the mean protein level in patients with Anti-LGI1 encephalitis was 49.6 mg/dl. The mean sugar levels were also not significantly different in these two groups. With regards to the presence of a significant number of White Blood Cells in the CSF samples, defined as more than 5 cells/cubic mm, in the Anti-NMDA subgroup, 75% (9/12) of patients for whom CSF analysis was done had a significant number of cells, with mean WBC number at 44.75 cells/cubic mm. In the Anti-LGI1 subgroup 25% (2/8) for whom CSF analysis was done had a significant number of WBCs with a mean WBC number of 11 cells/cubic mm. In the Anti-NMDAR encephalitis subgroup, out of the 9 patients with a significant number of cells in CSF analysis, 44.4% ($n=4$) had polymorph predominance, whereas 55.5% ($n=5$) patients had lymphocyte predominance. In the Anti-LGI1 subgroup one patient had polymorph predominance, whereas one patient had lymphocyte predominance. The patient with Anti-GAD65 positivity had protein levels of 71 mg/dl with no cells. The patients with Anti-CASP2, Anti-LGi1 + Anti-CASPR2 and Anti-GABA-B antibodies did not have significant numbers of WBC detected.

In our study, ($n=13$) 41.9% had an abnormal EEG, out of which ($n=6$) 46.1% was epileptiform activity

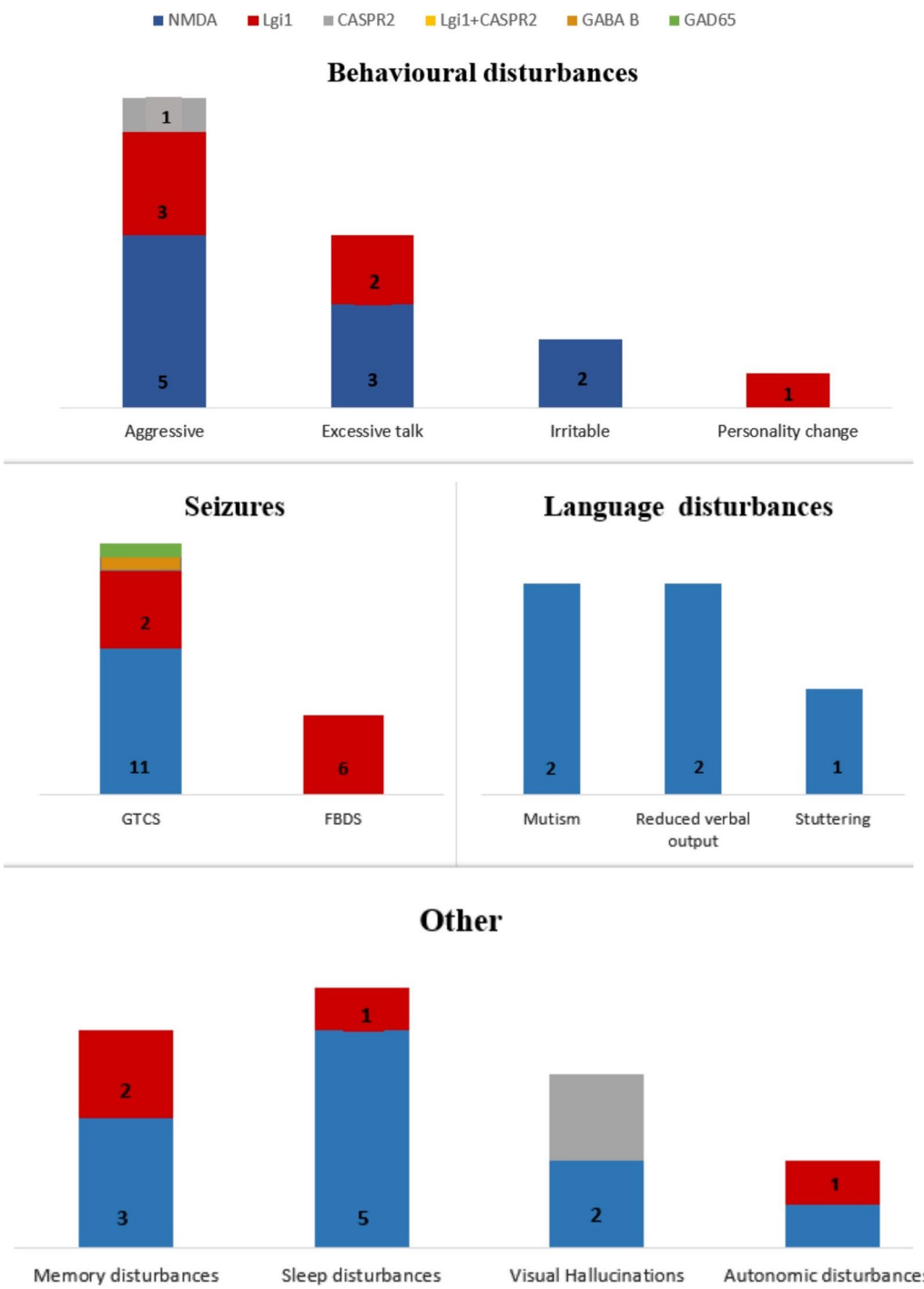

Fig. 1 Distribution of clinical features amongst the AE subgroups

and ($n=7$) 53.8% was abnormal background slowing. The characteristic extreme delta brush sign was seen in just one Anti-NMDAR antibody encephalitis patient. Amongst subgroups, ($n=8$) 61.5% of the Anti-NMDAR antibody encephalitis cohort had EEG abnormalities, and ($n=4$) 25% of the Anti-LGI1 antibody patients had abnormal EEG. Of the two patterns of abnormality seen, epileptiform activity was seen in 6 patients (Anti NMDAR Encephalitis 5, Anti-LgI1 encephalitis 1). Diffuse slowing activity was seen equally distributed among participants with Anti-NMDA and Anti-LGI1 antibodies (3 each) and in one other patient with anti-GAD65

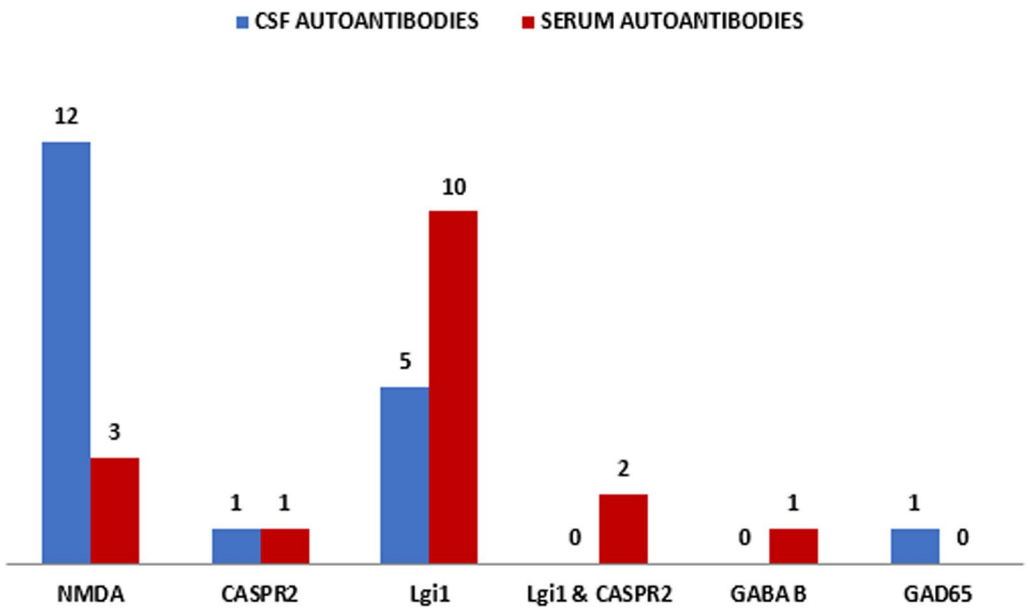

Fig. 2 Auto-antibody distribution in CSF and serum samples for AE subgroups

antibodies but was not seen in those with other antibodies (Fig. 3).

Pulse steroid therapy was the initial treatment attempted in most of our AE patients and according to our study, ($n=29$) 93.5% of the patients received pulse steroid therapy. The two patients who did not receive pulse steroids were the Anti-GABAR antibodies positive patient, who did not have any further symptoms and one of the Anti-LGI1 + CASPR2 antibodies patients. Second-line immunotherapy was reserved for non- responders, and patients with severe symptoms at presentation. In our study, ($n=13$) 41.9% of patients required IVIG, 2 patients required plasmapheresis, and 3 patients required rituximab (one of them had required both IVIG and during follow-up had attempted plasmapheresis). Most of the patients were not on any follow-up medications,

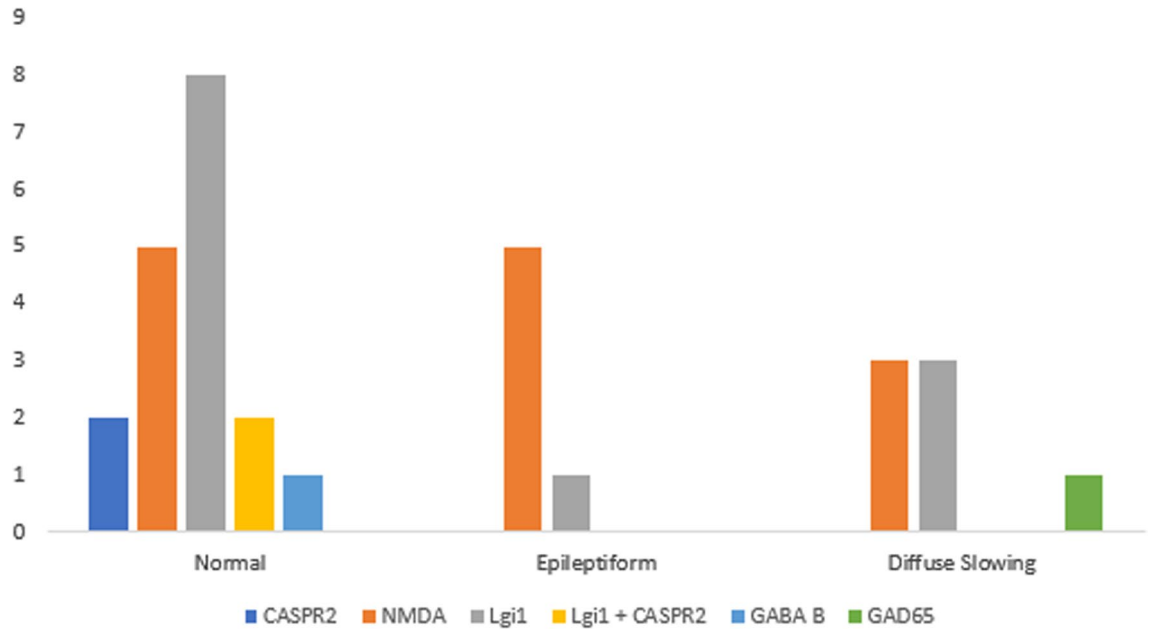

Fig. 3 EEG Findings in AE subgroups

with two patients requiring a prolonged tapering regimen of oral steroids and one patient requiring long-term azathioprine.

With regards to the second-line immunotherapy requirement (IVIG/plasmapheresis), amongst subgroups, 13 Anti-NMDAR encephalitis patients required IVIG, and 2 patients required plasmapheresis. In the Anti-LGI1 encephalitis sub-group required 5 patients required IVIG. One Anti-LgI1 + CASPR2 subgroup patient and the Anti-GAD65 antibody-positive patient required IVIG.

In our study, ($n=28$) 90.3% of the patients improved with good outcomes, with the treatment given, with three patients having residual deficits (behavioural abnormality). Similarly, 6.5% ($n=2$) had a relapse during the follow-up observation in the form of seizures and there was no mortality. The mean duration of hospital stay was 19.94 days and ($n=5$) 16.1% of the patients required mechanical ventilation. Follow-up was done for 12 months after disease onset.

In our study, ($n=10$) 76.92% of patients with Anti-NMDAR antibody encephalitis had a complete recovery and ($n=3$) 23.07% developed residual behavioural abnormality. The relapse rate in the present study was ($n=2$) 7.70% for Anti-NMDAR antibody encephalitis when followed up for one year. 31% ($n=4$) of the Anti-NMDAR encephalitis patients required mechanical ventilation with the mean duration of hospital stay being 27.1 days. In our study, none of the patients in the anti-LGI1 cohort had any residual deficit or relapses of the disease, the mean duration of hospital stay was 14.5 days for the Anti-LGI1 subgroup, with none of the patients requiring mechanical ventilation.

In our study population evidence of tumour was not detected during the time of admission and the immediate follow-up period of up to 6 months.

Discussion

Ever since AE was acknowledged as a prevalent and potentially treatable cause of Encephalitis, it has been increasingly recognised worldwide. Cross-sectional studies and several Ambi-spective cohorts from India are emerging showing the prevalence of this condition here [8–16]. After a review of the literature, the studies published from India have been tabulated in Table 2 after excluding individual case reports and cohorts from centres with overlapping timelines. The present study included 31 study subjects. There was a marginal male predilection, possibly due to a higher number of Anti-VGKC encephalitis patients in our study. Overall Seizures were the most common symptom (68%) followed by behavioural disturbance (64.5%), impairment of consciousness (32.3%), sleep disturbances (19%), language disturbance (16%), memory disturbance (16%), visual hallucinations (13%), autonomic disturbance (6%), with a few patients having low-backache and tongue atrophy as a part of the presenting symptoms.

Laboratory evaluation showed that apart from normal routine investigations, MRI Brain was normal in 77% of the patients, which was concurrent with results from published literature [17, 18]. Furthermore, EEG was only abnormal in 41.9% of the patients. The possible explanation for the lesser EEG abnormalities could be because of the timing of EEG which was usually done on day 3 or 4 after stabilisation, and after AED initiation, and the distribution of more Anti-LGI1 patients with FBDS in our cohort, which is less likely to have EEG abnormalities. With predominant imaging and EEG being normal, diagnosis of definite AE by criteria is less likely [19]. CSF analysis showed a mean protein of 43.30 mg/dl and CSF pleocytosis in 52%. Taking into account the percentage of EEG and MRI abnormalities along with the CSF abnormality percentage, diagnosis of even possible AE

Table 2 Studies from India with AE cohorts

S. No	Investigators and year	Place	AE number	Antibody distribution
1	Cyril and colleagues [8], 2009–2013	Trivandrum	14	14 NMDA
2	Kamble and colleagues [9], 2011–2015	Bangalore	16	10 NMDA, 4 anti-TPO, 2 Lgi1
3	Sudan and colleagues [10], 2011–2014	Kochi	13	13 NMDA
4	Dash and colleagues [11], 2013–2016	Delhi	41	24 NMDA, 12 LGi1; 5 GAD
5	Kannoth and colleagues [12], 2013–2016	Kochi	54	34 Lgi1; 13 CASPR2; 7 Both
6	Chandra and colleagues [13], 2013–2018	Bangalore	29	29 NMDA
7	Shivaraman and colleagues [14], 2014–2020	Bangalore	16	16 CASPR2
8	Raja and colleagues [15], 2018–2020	Bangalore	28	28 NMDA
9	Datta and colleagues [16] 2018–2020	Kolkatta	25	25 NMDA

AE – Autoimmune Encephalitis; CASPR2 – Contactin-associated protein-like 2; GAD – Glutamic acid decarboxylase; LGi1 – Leucine-rich glioma inactivated NMDA – N-Methyl-D Aspartate Receptor; TPO—thyroid peroxidase VGKC – Voltage-gated potassium channels

becomes dependent on the presence of seizures, which is again not seen in 1/3 of patients. A high index of suspicion hence has to be maintained to diagnose AE early.

With regards to subgroup analysis, comparative data was collected, but the interferential analysis was done mainly between the Anti- NMDAR encephalitis subgroup and the Anti-LGI1 subgroups, considering the sample size. The Anti-NMDAR encephalitis subgroup was likely to be younger with a median age of 23 years, while the Anti-LGI1 subgroup had a median age of 57.5 years. Patients aged below 40 years had 8 times more odds of developing Anti-NMDA receptor encephalitis in our study and were more likely to be female ($p < 0.05$). This correlates with results from several other studies as well. The Anti-NMDAR encephalitis subgroup was more likely to have behavioural, language, GCTS type of seizure ($p = 0.02$), and impairment of consciousness ($p < 0.05$) while the Anti-LGI1 subgroup was more likely to present with movement disorder/spontaneous activity ($p < 0.05$), and facio-brachial dystonic type of seizure ($p = 0.02$). Evidence of preceding infection was seen only in the Anti-NMDAR encephalitis subgroup (5/31). CSF WBC count of more than 5 cells had a 9 times greater association with anti-NMDA antibodies than with Anti-LGI1 antibodies and the association was statistically significant ($p < 0.05$). This concurs with the study by Blinder and colleagues which reported that Anti-NMDAR antibody encephalitis was found to be associated with more inflammatory changes in the CSF (evidenced by either higher protein, cells or OCB) when compared to Anti-LGI1 encephalitis, whose CSF was normal. 61.5% of the Anti-NMDAR encephalitis subgroup had EEG abnormalities, whereas 33.3% of the Anti-LGI1 subgroup had an abnormal EEG, with epileptiform abnormalities seen more in Anti-NMDA encephalitis.

In our study, three Anti-NMDAR antibody encephalitis developed residual behavioural abnormality. The relapse rate in the present study was 7.70% for Anti-NMDAR antibody encephalitis, while none of the patients in the Anti-LGI1 cohort had any residual deficit or relapses. None of the patients in either subgroup had any tumour incidence, which correlates with a good recovery. This is also consistent with published literature [12, 18, 20, 21].

To summarise, between subgroups, Anti-NMDAR encephalitis patients were likely to be younger females, and more likely to present with behavioural abnormalities, GTCS, language disturbances, and impairment of consciousness. They have predominantly normal MRI brains, are more likely to have epileptiform abnormalities in EEG if abnormal, and are significantly more likely to have pleocytosis in CSF fluid. They seem to have a longer mean duration of hospital stay, are more likely to require mechanical ventilation, and have relapses and residual deficits. The Anti-LgI1 subgroup patients were likely to be older males, and more likely to present with movement disorder/spontaneous movements and FBDS. They predominantly have normal MRI and normal CSF analysis. They seem to require a shorter hospital stay with less chance for relapses and residual disease activity.

The present study is limited by small sample size, and the trends observed cannot be generalised. All patients did not undergo CSF analysis and autoantibody samples were not sent in both serum and CSF samples for all patients, due to various factors. Long-term follow-up data related to relapse could not be obtained. The tumour workup could not be repeated in the follow-up. Large prospective cohorts are required to completely assess the efficacy of the treatment, long-term outcomes and the requirement of additional therapy in patients with AE.

Conclusion

The present study detailed the demographic, clinical, imaging, laboratory and EEG characteristics of 31 AE from a tertiary centre in Chennai, India. The finding concurred with the literature and demonstrate the diverse spectrum of clinical manifestations of patients with AE present. Moreover considering the robust response to treatment, when the condition is identified and promptly initiated, it becomes pertinent to be aware of the local prevalence. Large prospective cohorts are required to completely assess the efficacy of the treatment, long-term outcomes and the requirement of additional therapy in patients with AE.

Abbreviations

AE	Autoimmune encephalitis
AED	Anti epileptic drugs
AMPA	Alpha-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
CASPR2	Contactin-associated protein-like 2
CNS	Central nervous system
CSF	Cerebrospinal fluid
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
GAD	Glutamic acid decarboxylase
GE HEK	Human embryonic kidney
HSV	Herpes simplex virus
LGi1	Leucine-rich glioma inactivated 1
IG	Immunoglobulin
IVIG	Intravenous immunoglobulin
MRI	Magnetic resonance imaging
NMDAR	N-methyl-d-aspartate receptor
OCB	Oligoclonal bands
PLEX	Plasma exchange
SPSS	Statistical package for social sciences
VGKC	Voltage-gated potassium channels

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Author contributions

RR—Conception and design, data acquisition, interpretation, drafting, revision and Given final approval. PH—Data acquisition, drafting and revising it for

critical intellectual content. SV—Interpretation of data and Final approval. SS—Data acquisition, final approval. VP—Data Acquisition, final approval. SP—Conception, data acquisition, interpretation and final approval. PR—Design, and final approval. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from the institutional ethics committee of Sri Ramachandra Institute of Higher Education and Research. [REF: CSP-MED/20/JAN/58/31] prior to study initiation. Informed consent was obtained from all the study participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Dalmau J, Graus F. Antibody-mediated encephalitis. N Engl J Med. 2018;378(9):840–51.
2. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. Physiol Rev. 2017;97:839–87.
3. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10:835–44.
4. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral aetiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012;54:899–904.
5. Dubey. D, Pittock, S.J, Kelly. C.R, McKeon. A, Lopez-Chiriboga. A.S, Lennon et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018; 83: 166–177.
6. Chitravas N, Jung RS, Kofskey DM, Blevins JE, Gambetti P, Leigh RJ, et al. Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. Ann Neurol. 2011;70(3):437–44.
7. Flanagan EP, McKeon A, Lennon VA, Boeve BF, Trenerry MR, Tan KM, et al. Autoimmune dementia: clinical course and predictors of immunotherapy response. Mayo Clin Proc. 2010;85(10):881–97.
8. Cyril AC, Nair SS, Mathai A, Kannoth S, Thomas SV. Autoimmune encephalitis: Clinical diagnosis versus antibody confirmation. Ann Indian Acad Neurol. 2015;18(4):408–11.
9. Kamble N, Netravathi M, Saini J, Mahadevan A, Yadav R, Nalini A, et al. Clinical and imaging characteristics of 16 patients with autoimmune neuronal synaptic encephalitis. Neurol India. 2015;63:687–96.
10. Sudan YS, Vinayan KP, Roy AG, Wagh A, Kannoth S, Patil S. Clinical Characteristics and Follow-up of South Indian Children with Autoimmune Encephalopathy. Indian J Pediatr. 2016;83(12–13):1367–73.
11. Dash D, Ihtisham K, Tripathi M, Tripathi M. Proportion and spectrum of movement disorders in adolescent and adult patients of autoimmune encephalitis of non-neoplastic aetiology. J Clin Neurosci. 2019;59:185–9.
12. Kannoth S, Nambiar V, Gopinath S, Anandakuttan A, Mathai A, Rajan PK. Expanding spectrum of contactin-associated protein 2 (CASPR2) autoimmunity-syndrome of parkinsonism and ataxia. Neurol Sci. 2018;39(3):455–60.
13. Chandra SR, Padmanabha H, Koti N, KalyaVyasaraj K, Mailankody P, Pai AR. N-Methyl-D-Aspartate Encephalitis our Experience with Diagnostic Dilemmas, Clinical Features, and Outcome. J Pediatr Neurosci. 2018;13(4):423–8.
14. Shivaram S, Nagappa M, Seshagiri DV, Mahadevan A, Gangadhar Y, Sathyaprabha TN, et al. Clinical profile and treatment response in patients with CASPR2 antibody-associated neurological disease. Ann Indian Acad Neurol. 2021;24(2):178–85.
15. Raja P, Shamick B, Nitish LK, Holla VV, Pal PK, Mahadevan A, et al. Clinical characteristics, treatment and long-term prognosis in patients with anti-NMDAR encephalitis. Neurol Sci. 2021;42(11):4683–96.
16. Datta AK, Pandit A, Biswas S, Biswas A, Roy BK, Gangopaddhyay G. Spectrum of anti-NMDA receptor antibody encephalitis: clinical profile, management and outcomes. Ann Indian Acad Neurol. 2021;24(3):383–9.
17. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain. 2010;133:1655–67.
18. Saraya AW, Worachotsueptrakun K, Vutipongsatorn K, Sonpee C, Hemachudha T. Differences and diversity of autoimmune encephalitis in 77 cases from a single tertiary care center. BMC Neurol. 2019;19(1):273.
19. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404.
20. Gu Y, Zhong M, He L, Li W, Huang Y, Liu J, et al. Epidemiology of antibody-positive autoimmune encephalitis in Southwest China: a multicenter study. Front Immunol. 2019;10:2611.
21. Li W, Wu S, Meng Q, Zhang X, Guo Y, Cong L, et al. Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study. BMC Neurol. 2018;18(1):96.

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