

Spectrum of Anti-NMDA Receptor Antibody Encephalitis: Clinical Profile, Management and Outcomes

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Abstract

Background: Anti-N-methyl D-aspartate receptor (anti NMDAR) antibody encephalitis is an immune-mediated entity characterised by a constellation of neuro-psychiatric symptoms. **Objective:** To describe clinical profile and treatment outcomes of patients with anti NMDAR antibody encephalitis. **Settings and Design:** Subjects were selected by screening for all patients satisfying Graus *et al.*'s criteria for probable anti NMDAR antibody encephalitis, admitted in neurology department of a tertiary care centre in Eastern India. **Materials and Methods:** A prospective, longitudinal study was conducted by identifying 25 patients with anti NMDAR antibodies in CSF and or serum, between September 2018 to February 2020. **Statistical Analysis:** Chi square test was used to compare variables. **Results:** Out of 98 patients screened, 25 subjects (14 females: 11 male) were positive for anti NMDAR autoantibodies, with a mean age of 17 years. 13 subjects belonged to paediatric age group. Most common presenting feature was memory/learning deficit (88%) followed by behavioural abnormalities (84%) and seizures (68%). 11 patients (44%) patients needed escalation to second line therapy, rituximab. Seven (28%) and twelve (48%) patients underwent complete (mRS 0-1) and partial recovery (mRS 2-3) respectively, while 4 (16%) became disabled (mRS 4-5). Mortality was 8%. Paediatric population had a better outcome in terms of disability ($p = 0.043$). **Conclusion:** Anti NMDAR-Ab encephalitis is the most common cause of antibody positive autoimmune encephalitis worldwide. There are important clinical markers and investigational profiles which carry prognostic significance.

Keywords: Anti NMDAR, autoimmune, encephalitis, immunotherapy

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first described in 2007 by Dalmau and colleagues.^[1] It is associated with cerebrospinal fluid (CSF) IgG antibodies against the GluN1 subunit of the NMDA receptor.^[2] It is a rare disease, with an estimated incidence of 1.5 per million population per year.^[3] Epidemiological studies suggest that anti NMDAR encephalitis may be the most common cause of autoimmune encephalitis after acute demyelinating encephalitis.^[4] Between September 2007 and February 2011, the California Encephalitis Project examined referrals of 761 patients presenting with encephalitis.^[5] Of the cases of identified aetiology, anti NMDAR encephalitis was the leading entity (32 of 79 cases) within the cohort. In a previous multicentric observational study of 577 patients, this entity was seen to affect younger individuals more commonly, with a female sex predominance of 4:1.^[6] It was also shown in this study that in comparison to teenagers and adults, children tend to present more commonly with abnormal movements and seizures. Teenagers and adults, on the other hand, present more commonly with abnormal behaviour, insomnia, followed by speech dysfunction, autonomic instability and memory deficit.^[2,7] A position paper by Graus *et al.*, 2016, outlines the criteria that permits diagnosis on clinical grounds^[7] [Table 1]. Patients who fulfil these criteria partially, should be tested for antibodies, in both CSF and serum, since a risk of false negative or false positive exists if only serum is tested.^[8]

The antibodies are broadly two types: neuronal cell surface and intracellular.^[9] The neuronal surface group comprises of antibodies to surface receptors and protein complexes such as NMDAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), contactin-associated protein-like 2 (CASPR2), leucine-rich glioma inactivated 1 (LGI-1) and gamma-aminobutyric acid receptor-B and A (GABABR and GABAAR). The intracellular group (classic paraneoplastic antibodies), consists of antibodies against intracellular antigens such as, Hu, Ri, Yo, Amphiphysin, collapsin response mediator protein 5 (CRMP5).

In a record-based study of the population of India from 1978 to 2011, there were 125,030 cases of Acute Encephalitis

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Table 1: Diagnostic criteria for anti NMDAR antibody autoimmune encephalitis

Probable anti-NMDA receptor encephalitis* Diagnosis can be made when all three of the following criteria have been met

1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:

Abnormal (psychiatric) behaviour or cognitive dysfunction

Speech dysfunction (pressured speech, verbal reduction, mutism)

Seizures

Movement disorders, dyskinesias or rigidity/abnormal postures

Decreased level of consciousness

Autonomic dysfunction or central hypoventilation

2. At least one of the following laboratory study results:

Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)

CSF with pleocytosis or oligoclonal bands

3. Reasonable exclusion of other disorders

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis* Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies, † after reasonable exclusion of other disorders

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (e.g., live neurons or tissue immunohistochemistry, in addition to cell-based assay).

Syndrome (AES) in which the cause was unknown in 68-75%.^[10] Reliable epidemiological data regarding incidence and prevalence of antibody mediated encephalitis is scarce from our country, particularly in the state of West Bengal. We aimed to explore the epidemiological and clinical spectrum of a subset of such patients as well as their outcomes of treatment at a tertiary care neurology referral centre of Eastern India.

MATERIALS AND METHODS

Study setting

A hospital based prospective observational study was conducted at the Department of Neurology of Bangur Institute of Neurosciences (BIN), Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata, over a period of one and half years between September 2018 to February 2020.

Patients

The study was approved by the Institutional Ethics Committee and informed consent was obtained from the study participants and their parents or legal guardians. All patients admitted in paediatric and adult neurology wards of this department, with subacute onset of memory/cognitive deficits, decreased levels of consciousness, behavioural/psychiatric symptoms, seizures, abnormal movements/dyskinesias and autonomic dysfunction/central hypoventilation were assessed for eligibility for inclusion. These six groups of symptoms were as per criteria for probable anti NMDAR antibody encephalitis by Graus *et al.*,^[7] [Table 1].

Every patient underwent detailed clinical evaluation and investigations including 3 Tesla (T) magnetic resonance imaging (MRI) of brain on a Siemens Magnetom Verio 3-T MRI scanner. Sixteen channel electroencephalography (EEG) with longitudinal bipolar montage was done for all patients. Patients underwent ultrasonography (USG) and contrast

enhanced computerized tomography (CECT) scans of abdomen and thorax and positron emission tomography (PET) scans, as indicated.

A total of 98 patients were screened for specific set of six autoantibodies to cell surface or synaptic antigens in CSF and serum samples: anti-NMDAR, anti-AMPA, anti-CASPR2, anti-LGI-1, anti GABA-B, GABA-A. They were determined by indirect immunofluorescence (IIF) cell-based assay using EUROIMMUN® (Germany). Inclusion in our study mandated demonstration of anti NMDAR antibody positivity in CSF. Positivity in serum samples alone were excluded, because of chances of false positive results.^[8] Blood and CSF sampling of all patients were done in acute phase of illness.

Patients of age less than two years were excluded from the study (in view of difficulty obtaining clinical history and adequate blood and CSF samples), as were those with history of birth asphyxia, structural central nervous system (CNS) lesions, evidence of CNS infections and primary CNS demyelination. Those with low CSF glucose were excluded as well as those with evidence of collagen vascular disease (lupus, Sjogren's, vasculitis). For all included patients, clinical and epidemiological information were procured using a semi-structured pre-designed questionnaire. Memory/learning deficits were defined as learning/concentration difficulties, regression of milestones, working memory, short term memory deficits. Assessment of these deficits were done in the convalescent stage after treatment with first line therapeutic agent(s). In young children, in whom formal cognitive assessment could not be done, "regression of milestones" was considered equivalent to inclusion criteria of memory/learning deficits. Psychopathological features in our study were defined in accordance with a study by Al Diwani., 2019.^[11] "Abnormal behaviour" included agitation, aggression, disorganisation, incoherent speech, violence, inappropriate laughter/crying, disinhibition, impulsivity, and self-talking.

As per our institutional protocol and based on previous published reports,^[12] all patients were treated with intravenous methyl prednisolone during acute attacks, followed by either intravenous immunoglobulin (0.4 g/kg/day for five days) or plasmapheresis (PLEX). In patients with a relapsing course, second line non-steroidal immunosuppressants, rituximab (375 mg/m², weekly X 4 weeks) and/or injection cyclophosphamide (intravenous) 750 mg/m², were used. All patients were followed up till end of study period or at least 6 months, whichever was longer. Assessment of disability was done at admission, discharge and follow-up using modified Rankin scale (mRS).^[13]

Statistical analysis was done using IBM SPSS Statistics version 23.0 (IBM Corporation, NY, USA). Chi-square test was utilized for comparison of variables. *P* value of less than 0.05 was considered significant.

RESULTS

Epidemiological/Demographic features

Amongst the 98 patients screened, 25 (14 females: 11 male) found to be positive for anti NMDAR autoantibodies (in either CSF or both serum and CSF), aged between 3 and 60 years, were included in the study. No other antibodies were found to be positive. A solitary patient was positive for anti NMDAR antibody in serum alone and was excluded from our cohort.

Ethnicity of all 25 patients was Bengali. The median age of presentation for the study population was 17 years. 13 subjects (52%) belonged to paediatric age group (below 18 years of age).

Clinical features at onset

The most common clinical feature was memory/learning deficit, being present in twenty-two patients (88%), followed by abnormal (psychiatric) behaviour in 21 (84%) and seizures in 17 patients (68%). Abnormal movements/dyskinesias were noted in 10 patients (40%). Extrapyramidal features (dystonia/parkinsonism) were a presentation in 6 patients (24%) whereas ataxia was a feature of 4 (16%). Features of memory/learning deficit (92.3% vs 82.3%, *P* = 0.593), movement disorders (46.2% vs 33.3%, *P* = 0.688), seizures (76.9% vs 58.3%, *P* = 0.411) and abnormal behaviour (92.3% vs 75%, *P* = 0.322) were more common in the paediatric age group while extra-pyramidal features (23.1% vs 25%, *P* = 1.000) were more common in adults. Ataxia (0.0% vs 33.3%, *P* = 0.03) was exclusively seen in the adult age groups [Figure 1]. Four patients had features of dysautonomia (16%) (15.4 vs 16.7, *P* = 1.000). 24 patients (96%) presented with two or more clinical features. The mean interval from onset of symptoms to admission was 2.68 weeks (standard deviation 1.796, standard error of mean 0.359).

Most common seizure type was focal with impaired awareness (47.1%) followed by generalized tonic-clonic type (GTCS) (29.4%). Four (23.5%) patients had combination

of both GTCS and focal seizures. Of the seventeen patients presenting with seizures, only two had a solitary seizure (11.8%), ten patients (58.8%) had repetitive seizures while five (29.4%) had status epilepticus.

Ancillary investigations

CSF examination was abnormal in 20 patients (80%). Amongst them, 8 patients (40%) had only pleocytosis, five (25%) patients had only raised protein concentration, seven (35%) had both pleocytosis and raised protein levels in CSF. MRI was abnormal in 13 patients (52%), which included abnormal signals in insula/peri-sylvian cortex, basal ganglia, mesial temporal lobe, juxta-cortical and deep white matter, as well as cortical and cerebellar atrophy. EEG was abnormal in 20 patients (80%), most common pattern being focal slowing, present in 12 patients (60%). None of the patients exhibited characteristic "extreme delta brush pattern" on EEG. None of the patients had feature of systemic malignancy or ovarian teratoma, as evidenced by normal CT/USG scans.

Treatment and follow-up

All patients were initially treated with a 5-day course of intravenous methylprednisolone (IVMP) (20-30 mg/kg, maximum of 1 gram/day). In 20 patients (80%), IVMP was followed by immunoglobulin (IVIg) (0.4 g/kg/day) for 5 days. Remaining five patients (20%) received plasmapheresis (PLEX). There was no significant difference in outcome in the two groups. 5 patients (20%) needed to be shifted to intensive care unit (ICU) following admission, of whom 2 succumbed during ICU stay. Reason for ICU transfer was status epilepticus and autonomic instability. 11 patients (44%) needed escalation to second line therapy, i.e., rituximab (375 mg/m²), following a downhill course despite first line therapy (IVMP + IVIg or IVMP + PLEX) at time of first admission. The median mRS score at time of discharge was 2, whereas that during admission was 4. All patients were discharged with tapering dose of oral steroids. Median duration of hospital stay was 55 days (15-98 days). Median duration of follow-up was 7 months (5-12 months).

Five patients (20%), relapsed following discharge, while on tapering dose of steroids and re-required re-hospitalization within two months of discharge. All these patients were adults. Following admission, search for systemic malignancy was undertaken with help of pertinent investigations, like that in the first-time during admission. However, none showed any evidence of neoplasm. Four (out of five) patients were treated with routine first line therapy followed by rituximab, while one additionally received cyclophosphamide (intravenous) 750 mg/m² for 3 months. Cyclophosphamide was not administered routinely as second line agent owing to unfavourable side effect profile. Barring one subject, all patients who had relapsed following discharge became progressively disabled (mRS 4-5) despite therapy with second line agent. By the time of last follow-up, seven (28%) patients had completely recovered (mRS 0-1), twelve (48%) patients had partially recovered (mRS 2-3) and four (16%) patients were

disabled (mRS 4-5) [Figure 2]. Paediatric patients had better outcomes at end of follow-up period ($P = 0.043$) [Figure 3]. 2 patients (8%) succumbed during admission.

DISCUSSION

Previous studies have revealed anti NMDAR encephalitis to be the most common cause of autoimmune encephalitis, and that early diagnosis and treatment decreases the likelihood of morbidity and mortality.^[14-17] We attempted to analyse the clinical features, ancillary examination results and treatment outcomes in Indian patients with anti NMDAR encephalitis.

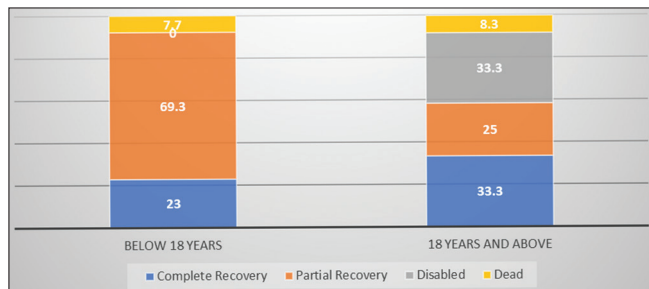


Figure 1: Bar chart showing distribution of clinical features in paediatric adult age groups

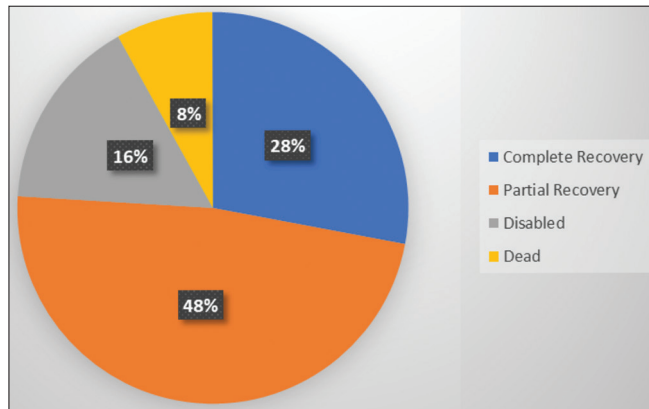


Figure 2: Pie chart showing distribution of outcomes of patients

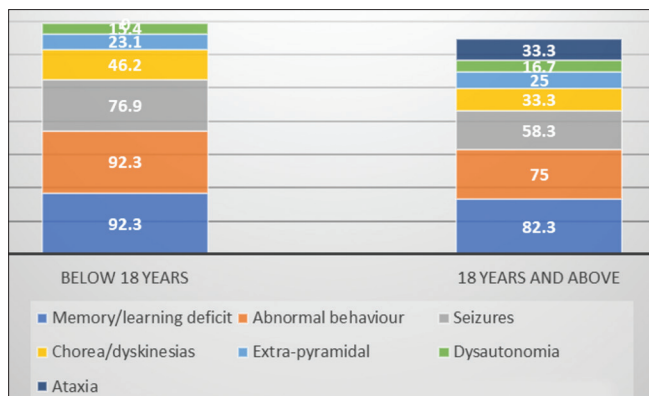


Figure 3: Bar chart showing distribution of outcome amongst adult and paediatric patients

25 patients were included in the present study, 56% being females. A study from the National Institute of Mental Health and Neurological Sciences (NIMHANS), Bengaluru, India, by Chandra SR *et al.*,^[18] showed an overwhelming female predilection, with only 3 out of 29 (10.3%) patients being male. The median age of onset of symptoms for patients in our study was 17 years (11-30 years), which was in accordance with the study done by Chandra SR *et al.*,^[18] Paediatric patients comprised of 52% of our cohort which was significantly higher in proportion as compared to a meta-analysis by L Zhang *et al.*^[19]

The clinical phenotype of anti NMDAR encephalitis may be dependent on the age of presentation. As compared to adult patients, in our study, abnormal (psychiatric) behaviour was more commonly seen in paediatric age group. This was in contrast to study by L Zhang *et al.*,^[19] which showed higher ratio of seizures to psychiatric symptoms in adult patients (31:36 vs 33:111, $P = 0.0012$). Memory/learning deficits were slightly more common in the paediatric age group (92.3% vs 82.3%, $P = 0.593$) in our study. In a previous study by Titulaer MJ *et al.*,^[6] psychosis, abnormal behaviour and memory/learning deficits were demonstrated to be more common in adults, which contrasted with our study. However, movement disorders were more common in paediatric population in our study, a finding reminiscent of Titulaer MJ *et al.*^[6] Atypical symptoms like ataxia was found exclusively in adults, whereas previously, it has been described more commonly in children.^[6] Only one case of adult onset anti NMDAR encephalitis presenting with ataxia has been reported so far from Korea.^[20] In a study by Wang W *et al.*,^[21] a solitary patient exhibited ataxia, without any seizures or psychiatric manifestations. Similarly, one adult patient in our study presented with subacute onset, progressive extra-pyramidal signs, and symptoms, which has previously not been reported, even though extra-pyramidal symptoms have previously been described in children.^[22,23] Table 2 shows a comparative analysis of clinico-demographic features between our cohort and three other large scale studies.

Seizures are a common presentation of anti-NMDAR encephalitis in children and young men,^[6,24,25] in concurrence with findings reported by Wang W *et al.*^[21] However, most common seizure type in our cohort was focal seizure with impaired awareness followed by GTCS. Previous studies^[20,23] have revealed difference in presentation of first symptom between sexes which may have been attributed to hormonal factors, however, no such differences were noted in our study.

About 70% of patients are admitted to intensive care unit for airway obstruction, dyskinesia, persistent dysautonomia, fluctuating level of consciousness and breathing dysfunction.^[6,26] Previously, Wang W *et al.*^[21] and Zhang L *et al.*^[19] reported autonomic dysfunction in 14% and 3% of patients respectively. We came across similar observations in our study.

Proportion of MRI abnormalities were much higher in comparison to other large-scale studies^[6,20,21] [Table 3]. The study by Chandra SR *et al.*,^[18] showed a higher proportion of

Table 2: Comparison of epidemiological and clinical features amongst different studies

Epidemiological and clinical features	Wang, 2015 ^[21] (n = 51)	Zhang L, 2016 ^[19] (n = 432)	Chandra SR, 2018 ^[18] (n = 29)	Present study (n = 25)
Male (%)	37	32	10.3	44
Female (%)	63	68	89.7	56
Median/Mean age of onset (Range, in years)	21.6 (9-39)	22.0 (0.6-84)	17 (3-31)	17 (11-30)
Dysautonomia (%)	28	3	Not reported	16
Abnormal behaviour (%)	90	65	100.0	84
Dyskinesias/abnormal movement (%)	57	3	10.3	40
Seizures (%)	84	28	72.4	68
Memory/learning deficit (%)	31	8	100.0	88

Table 3: Comparison of ancillary examination findings across different studies

	Titulaer, 2013 ^[6] (n = 577)	Wang, 2015 ^[21] (n = 51)	Zhang L, 2016 ^[19] (n = 432)	Chandra SR, 2018 ^[18] (n = 29)	Present study (n = 25)
Abnormal MRI (Percentage)	33	40	40	75.9	52
Abnormal EEG (Percentage)	90	86	85	Not reported	80
Abnormal CSF (Percentage)	79	63	58	Not reported	80

Table 4: Comparison of duration of follow-up and relapses between studies

	Irani SR, 2010 ^[28] (n = 44)	Gabilondo, I, 2011 ^[29] (n = 25)	Titulaer, 2013 ^[6] (n = 577)	Present study (n = 25)
Median duration of follow-up (months)	16	20	24	7
Relapses (%)	23	24	12	20

Table 5: Comparison of variables between patients with good and bad outcome

Patient Attributes	Good Outcome (mRS 0-3) (n = 19)	Bad Outcome (mRS 4-6) (n = 6)	P value*
Age <18 years (n = 13)	92.3%	7.7%	0.043
Female (n = 14)	78.6%	21.4%	0.588
Memory/learning deficit (n = 22)	77.2%	22.6%	0.069
Abnormal Behaviour (n = 21)	76.2%	23.8	0.305
Seizures (n = 17)	76.4%	23.4%	0.740
Chorea/dyskinesias (n = 10)	80.0%	20.0%	0.757
Extra pyramidal (Dystonia/parkinsonism) (n = 6)	57.1%	42.9%	0.539
Ataxia (n = 4)	50.0%	50.0%	0.347
Dysautonomia (n = 4)	75.0%	25.0%	0.959
Abnormal MRI (n = 13)	76.9%	23.1%	0.505
Abnormal EEG (n = 13)	85.7%	14.3%	0.293
Abnormal CSF (n = 20)	80.0%	20.0%	0.348

*Fischer exact *t* test; *p* value <0.005 considered significant

MRI abnormalities, which was in accordance with our study. Despite these findings, no definite patterns could be identified which might provide a diagnostic clue. Previous research,^[27] has indicated that abnormal MRI results do not affect prognosis as reflected by mRS scores; study by Zhang L *et al.*^[19] failed to reveal prognostic significance of abnormal EEG patterns with respect to outcome. These findings were in concordance with our study (*P* = 0.505).

An interesting finding in our study was the absence of systemic malignancy and/or ovarian tumour. However, this may be due

to the younger age of patients in our cohort since association with tumour increases with age as shown previously by Dalmau *et al.*,^[2] Ethnicity might be another contributing factor as a previous study from South India by Chandra SR *et al.*,^[18] also showed a relatively low prevalence of tumours.

There is no definite consensus regarding differences in outcome among various immunotherapies. A multi-institutional study by Irani SR *et al.*^[28] suggested that patients treated with second line immunotherapy during first episode of encephalitis had lower chances of relapse. These findings were not reflected in

subsequent studies by Zhang L *et al.*^[19] In accordance with the latter, we did not find any significant difference in treatment outcomes between groups who received only first line therapy versus those that received second line therapy following first line ($P = 0.468$). Frequency of relapses in our study (20%) were slightly lower than those reported previously by Irani SR *et al.*^[28] and Gabilondo I *et al.*^[29]; however, this might be attributed to lower median duration of follow-up in our study [Table 4].

Two independent predictors of outcome suggested previously,^[6] were lower severity of symptoms at presentation and early initiation of immunotherapy. However, we did not find any significant correlation between time of initiation of therapy and outcome ($P = 0.779$). In a comparison of outcome amongst patients in our cohort and different clinico-radiological and epidemiological parameters, it was found that paediatric patients did significantly better ($P = 0.043$) [Table 5]. Zhang L *et al.*^[19] had previously demonstrated higher rate of full recovery in paediatric age group compared to adults (51% vs 40%).

LIMITATIONS OF THE STUDY

Our study is limited by its small sample size and lack of long-term follow-up. All the patients received first line immunotherapy, hence efficacy of first line and second line therapies could not be compared head to head. CSF study was not done on follow up and titre of anti NMDAR antibodies were not assessed by our laboratory assays; therefore, the role of antibody titres in disease monitoring is a domain that needs future exploration. A small sample size also made comparison of clinical parameters difficult amongst categories of patients (adult and paediatric in our case). Subsequent studies with larger sample size are desirable. Since the treatment was not randomized, no definite analysis could be done.

CONCLUSION

Anti NMDAR antibody encephalitis is a heterogenous disease entity. We aimed to provide some insight into some of its clinical features which may aid in diagnosis as well as identification of prognostic markers. However, considering the above limitations, further clinical studies with larger populations, based on strict design, would be necessary to confirm the findings of our study.

Compliance with Ethical standards

We would like to state that our study was approved by appropriate Ethics Committee according to the International standards and we declare no authors did any intervention involving animals here.

Informed Consent

Written informed consent has been taken from the patients for participation in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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