Original Article

Spectrum and Evolution of EEG Changes in Anti-NMDAR Encephalitis

Lakshminarayanapuram Gopal Viswanathan, Shreedhara A. Siddappa, Madhu Nagappa, Anita Mahadevan[1], Shishir Duble, Parayil S Bindu, Arun B Taly, Sanjib Sinha

Departments of Neurology, [1]Neuropathology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India

Abstract

Background: NMDA receptor encephalitis (NMDARE) is the most prevalent autoimmune encephalitis and it encompasses a spectrum of clinical features. It is most commonly associated with alteration in consciousness, seizures, neuro-psychiatric symptoms, and movement disorders. Electroencephalography (EEG) plays a vital role and can give clues to diagnosis in a subset of patients. **Methods:** We retrospectively characterized the clinical and EEG findings in our NMDARE patients (n = 48). A total of 131 EEGs were analyzed. **Results:** We observed that patients with seizures had a younger age of onset ($p < 0.001$). The most common EEG pattern that was noted was diffuse slowing (n = 20) followed by generalized rhythmic delta activity (n = 9), focal spikes and slowing (n = 8 each). Delta brush pattern was seen in only 3 EEGs. Focal ictal rhythms were seen in 3 EEGs. There was no significant difference in outcomes such as seizure recurrence, modified Rankin score (mRS) at follow up/discharge or relapse between groups of patients who had EEG abnormalities in the first EEG and with those who did not. **Conclusions:** NMDARE has varied EEG findings, most of them being non-specific. When combined with clinical presentation, EEG is a useful tool in the diagnosis and management of NMDARE.

Keywords: Autoimmune encephalitis, EEG, NMDA receptor encephalitis

Introduction

Anti-NMDAR encephalitis (NMDARE) was first described in 2007[1] and since then, has been the most prevalent autoimmune encephalitis (AIE) in the community. The disease has varied presentations and most common being a constellation of seizures, movement disorders, psychiatric disturbances, and alterations in the level of sensorium and cognition. Seizures are usually focal with secondary generalization and can have variable frequencies. Rarely, these patients can also have refractory status epilepticus. Even in patients who do not have seizures, electroencephalographic (EEG) changes have been described. Many EEG biomarkers have been proposed for the diagnosis of NMDARE, some of which are poorly sensitive or specific or both. The aim of this paper was to describe the EEG findings in a cohort of NMDARE and to study their evolution in serial EEGs during the course of illness.

Patients and Methods

This is a retrospective analysis carried out at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Patients (n = 48) who were diagnosed to have NMDARE and evaluated and followed up in a single neurology unit between 2013 and 2017 were included. The study was approved by the Institute Ethics Committee (IEC) (NIMHANS/DO/94TH IEC/2014, dated November 25, 2014).

The diagnosis was based on the presence of monophasic or relapsing-remitting neuropsychiatric illness and the presence antibodies against NR1 subunit of NMDAR in serum and/or cerebrospinal fluid (CSF).[2] Clinical data regarding the age at onset, duration and course of illness, nature of symptoms, imaging findings and treatment were recorded. The modified Rankin Scale (mRS) scores were recorded at first admission, discharge, and at last follow up.

Scalp EEGs were recorded using the standard international 10-20 system and 21 cup electrodes. Activation procedures were used whenever the patient was cooperative and these included hyperventilation, post hyperventilation for up to 2 min and intermittent photic stimulation. Photic stimulation was carried out using a stroboscope placed 30 cm in front of the subjects face and recording with eyes closed at frequency of 1, 2, 3, 6, 9, 12, and 30 Hz for five seconds each. EEGs were analyzed by three authors who are trained epileptologists (LGV, AS, SS). The parameters assessed included background activity, inter-ictal epileptiform discharges (IEDs) and ictal discharges (if any). The EEGs recorded during follow up were similarly analyzed.

Data were entered in a predesigned proforma and was analyzed in IBM SPSS Statistics for MacOS version 24 (IBM Corp.

Address for correspondence: Dr. Sanjib Sinha, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore - 560 029, Karnataka, India.
E-mail: sanjib_sinha2004@yahoo.co.in

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Armonk, N.Y., USA). The EEGs were classified as normal or abnormal. If abnormal, the type and location of abnormality i.e., focal slowing, focal spikes, ictal discharges, generalized rhythmic delta, delta brush, etc., were recorded. Fisher's exact test was used to determine whether the mRS and seizure recurrence were significantly different between patients who had abnormal or normal EEGs at the time of first evaluation. Independent samples t-test was used to compare means.

Results

Female preponderance was observed (n = 39, 81%). The median age at presentation was 14.5 years (range: 3-55 years). The mean duration of symptoms at time of presentation was 66.7 ± 12.3 (S.E.) days. Four patients (8%) had NMDA antibody positivity in CSF, but not in serum. The median time to testing for NMDA antibodies from onset of symptoms was one month (range: 10 days to 12 months). The most common presenting symptom was seizures (n = 40, 82%) followed by behavioral abnormalities (n = 39, 81%). Patients who had a younger age of onset were more likely to be affected by seizures (mean age of patients with seizures: 13.8 ± 1.2; mean age of patients without seizures: 28.6 ± 7.4, $P < 0.001$). Other clinical features included altered sensorium (n = 36, 75%), hallucinations (n = 11, 23%), choreoathetosis (n = 35, 73%), stereotyped movements (n = 22, 46%), myoclonus (n = 5, 10%), cranio-facial dystonia (n = 13, 27%), limb dystonia (n = 17, 35%), akinesia (n = 7, 14%), and ataxia (n = 5, 10%). None of the patients had underlying malignancy. MRI of brain was abnormal in 12 (25%). Abnormalities included medial temporal lobe hyperintensities (n = 8), cingulate hyperintensities (n = 1), subcortical white matter hyperintensities (n = 1), gliosis in the right parieto-occipito-temporal regions (n = 1), and basal ganglia bleed (n = 1).

A total of 131 EEGs were analyzed. In 41 patients the first EEG was done within one month of diagnosis. The first EEG was done two months and three months after the diagnosis in six and one patient respectively. The first EEG was normal in 10 patients. In 15 patients, follow up EEGs done within 3 months of illness normalized. In all of these patients, subsequent EEG continued to remain normal except in one patient who relapsed after 5 years and EEG showed focal slowing. There was no significant difference between abnormal and normal EEG groups and the duration of symptoms before the first EEG (p = 0.89). Various types of abnormalities were identified which are listed in Table 1 and Figure 1.

The most common abnormality which was observed was diffuse slowing (n = 21, 16%). Generalized rhythmic delta activity (GRDA) and delta brush pattern were seen in nine and three EEGs respectively. Focal spikes were seen most commonly in the temporal and centrotemporal region (n = 11). Other regions where IEDs were observed included the centroparietal (n = 2), posterior head region (n = 1) and frontal region (n = 1). Spikes in more than one location were seen only in two EEGs. Focal slowing was also most commonly seen in the posterior quadrant (n = 6) followed by temporal regions (n = 4). Frontal intermittent rhythmic delta activity (FIRDA) was seen in only two EEGs. At first follow up (12 ± 7.8 months), NMDAR antibody testing was done for 41 subjects (7 lost for follow-up) of which 18 (44%) were found to be positive. Eleven of the 18 cases had normal EEGs despite persistence of presence of NMDAR antibodies in serum.

All patients were treated with steroids in the form of intravenous methylprednisolone which was given as monthly pulses for 5 days for at least 6 months and then tapered according to clinical and serological response. During the acute period or during relapse, addition IVIg was given in 20 patients and 5-7 plasma exchange was administered for 36 cases. All patients were followed up and mRS scores were documented at follow up visits [Figure 2]. The mean duration of follow up was 27 ± 14 months. At last follow-up, 37 patients had mRS scores < 2. Over the course of illness, 7 patients suffered from clinical relapses. Four of them had a single relapse and one each had 2, 3, and 4 relapses. Time to first relapse varied from 6 months to 3 years from first symptom. Two patients with frequent relapses received rituximab. There was no statistically significant difference in the mRS, recurrence of seizures or relapses between groups of patients who had a first normal and abnormal EEG at first discharge or last follow up. There was also no difference in EEG findings between patients who had CSF abnormalities (either pleocytosis/elevated protein)/MRI abnormalities and those who did not [Table 2].

Discussion

The AIE is a syndrome characterized by a constellation of symptoms, the most prominent of those being psychosis, behavioral disturbances, and seizures.[1,2] They are most commonly seen in young women; however, males and females of any age group can be affected. In our study of 48 patients, there was a 4:1 preponderance. This is in accordance with other large studies pertaining to NMDARE.[3] Overall, the median age at onset was 14.5 years which is lesser than what is commonly reported (23 years).[1] Reason could be referral bias, non-consecutive inclusion, retrospective study etc., Additionally, patients who had seizures in our cohort were significantly younger than those who did not have seizures during their illness. The diagnosis is confirmed by testing for antibodies in the serum or CSF which are available commercially as panels that test a wide range of antibodies. Four patients were negative for antibodies in serum; however, they were positive for NMDAR antibodies in cerebrospinal fluid.[4] This finding emphasizes the need for CSF testing when clinical suspicion is high.

EEG was done in all patients and was initially normal in 10% of cases which is comparable to other studies and reviews.[5,6] The most common abnormality that was seen in EEGs done within three months of diagnosis was slowing (diffuse as well as focal), mostly in the theta range, indicating a diffuse encephalopathy and is not specific to autoimmune encephalitis.

Table 1: Summary of EEG abnormalities (n=131) in 48 patients with NMDARE in the present cohort

EEG observations	<3 m	4-12 m	12-24 m	<24 m	Total
Normal	20	17	27	6	70
Focal spikes	8	5	0	2	15
Focal slowing	8	2	1	1	12
Intermittent background slowing	6	1	0	0	7
Frontal intermittent rhythmic delta activity	2	0	0	0	2
Focal ictal onset	3	0	0	0	3
Diffuse slowing	20	1	0	0	21
Generalized rhythmic delta activity (GRDA)	9	1	0	0	10
Delta brush	3	0	0	0	3

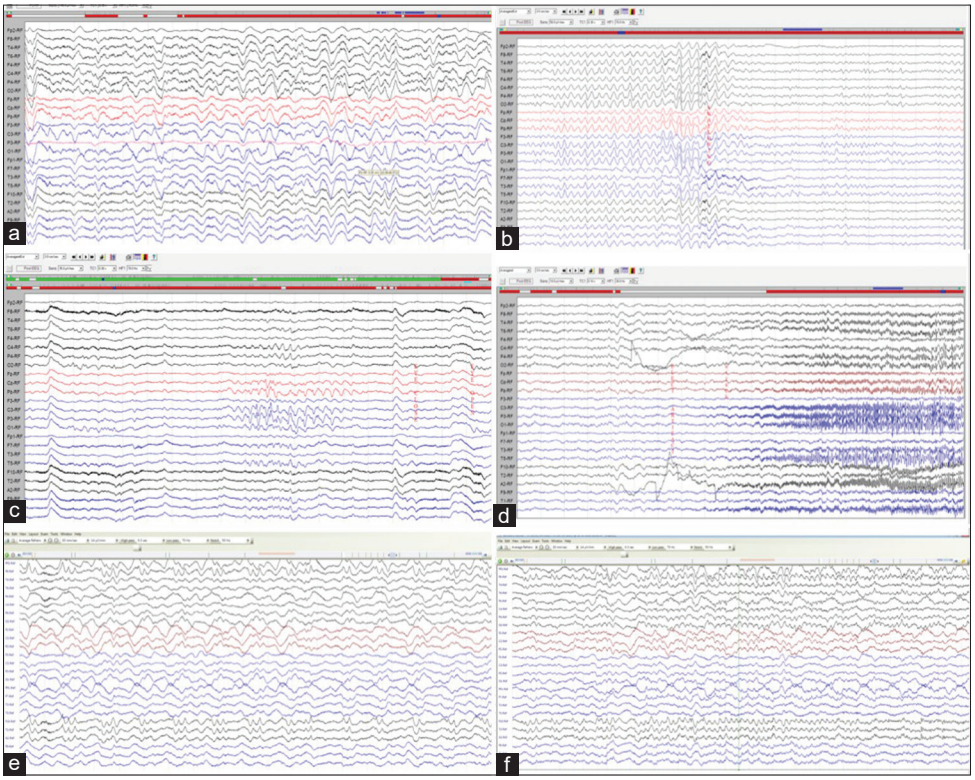

Figure 1: EEG findings in NMDARE: (a) Extreme delta brush (b) Generalized rhythmic delta activity (c) Left frontal spikes (d) Ictal onset from the left centroparietal region - rhythmic fast activity (e) Right temporal PLEDs (f) Evolution of PLEDs into an ictal rhythm in the right temporal leads

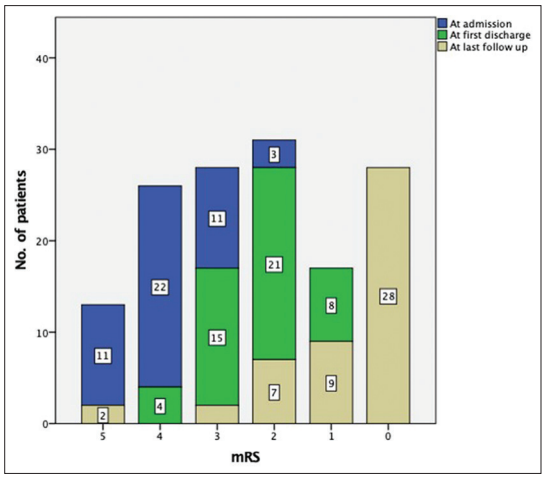

Figure 2: mRS outcomes at various time points

Extreme delta brush (EDB) pattern, wherein there is beta activity over-riding delta slowing was seen in only 4% of cases (3 EEGs). The prevalence of this pattern is variable, ranging from 5-33% across different studies.[5,7] Though it is a relatively specific abnormality it is not quite common. It must also be highlighted that EDB has been found in other conditions as well, such as hypoxic encephalopathy, metabolic derangements, and stroke.[8] Both patients who had EDB in our study presented with alteration in consciousness and subsequently improved with treatment. After 6 months of treatment, both were asymptomatic. Prognostic value of EDB is unclear but there are studies that suggest that it carries a poor prognosis and may entail care in the intensive care unit during the course of illness.[9] One must exercise caution when interpreting EEGs when sedative medications have been used or when patient is on benzodiazepines or barbiturates.

Table 2: Correlation of outcomes of patients with NMDARE and first EEG findings

Groups	First EEG		*P*
	Normal	Abnormal	
mRS <2 at first discharge			
Yes	2	6	0.66
No	8	32	
mRS <2 at last follow up			
Yes	9	28	0.41
No	1	10	
Seizure recurrence			
Yes	0	6	0.57
No	9	32	
Relapse			
Yes	1	6	>0.99
No	9	32	

The drug-induced fast activity could be wrongly interpreted to be a part of an EDB when it is intermixed with slowing of the background. Ictal rhythms are seen frequently in AIE and rarely patients can present in non-convulsive or convulsive status epilepticus. In our cohort, focal ictal onset patterns were seen in 3 patients from different areas in the brain. All events commenced with buildup of rhythmic beta fast activity. When these patterns last less than ten seconds, they are referred to as Brief potentially ictal rhythmic discharges (B (I) RDs). This pattern has been described in NMDARE but was not found in our group of patients. Continuous EEG monitoring is ideal in NMDARE, especially when patient has an altered level of consciousness.[10] GRDA is monomorphic, repetitive waveforms with constant frequency which has been described in patients who are comatose due to varied causes.[11] In NMDARE this pattern has been linked to non-convulsive status epilepticus[12] and movement disorders.[7] On the contrary, due to lack of change in EEG after administration of the anti-seizure medication, this pattern has been regarded as non-epileptic by some.[13,14] Better understanding of this pattern is necessary, so that needless administration of benzodiazepines and other medications to 'stop seizures' can be avoided. Due their association with involuntary non-epileptic movement disorders, it is hypothesized that this rhythm may have its origins from the basal ganglia[7] but conclusive evidence to back this plausibility is lacking. NMDARE progresses, signs shift from cortical origins (seizures, neuropsychiatric symptoms and hallucinations) which are seen in the first 10-20 days of the illness to more central and deeper structures (changes in tone, movement disorders, dysautonomia and changes in level of consciousness). Intuitively, EEG changes may also reflect the same. Early in the course of illness; spiking activity, delta brushes and ictal rhythms may be more common. But as disease progresses, slowing (both focal and generalized) may ensue.[15] In our group of patients, EEG patterns normalized within the first 3-12 months of disease detection and only focal spikes/slowing was seen in EEGs done after 12-24 months, probably due to permanent brain damage that has supervened after the acute illness. Beta-delta power ratio is a recently detected EEG marker which is significantly more prevalent in NMDARE groups than non-NMDARE groups.[16] In spite of a multitude of studies, a highly specific and sensitive EEG marker for this illness is still lacking. In a nation-wide cohort study in The Netherlands, the authors had observed that normal background in the posterior quadrants predicted a better clinical outcome and grossly abnormal EEGs foretold poor prognosis.[17] However, our study failed to identify any significant difference in outcome, seizure recurrence or relapses between patients who had normal and abnormal EEGs at the time of diagnosis.

The limitations were retrospective study and since cEEG was not employed, the abnormalities could be under-reported. Since EEG was not carried prior to initiating AEDs, decreased occurrence of the EEG abnormalities in this study cannot be excluded. Larger prospective studies are required to describe an EEG biomarker that can precisely diagnose and prognosticate patients with NMDARE. In the revised diagnostic criteria for NMDARE, Dalmau *et al*. emphasize the need for CSF antibody testing to rule out false positives/negatives.[18] CSF antibody testing results were not available for all patients in this study. To conclude NMDARE has varied EEG changes albeit none of them are specific or sensitive by themselves. Delta brushes were rare in our study and brief rhythms such as BIRDs were not found. That said, EEG plays a crucial role in suspecting the diagnosis when combined with clinical presentation. Longer duration of EEG recording, preferably continuous can help identify more abnormalities and in some cases, NCSE.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, *et al*. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8.
2. 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;15:391-404.
3. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, *et al*. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol 2013;12:157-65.
4. Damato V. Diagnostic algorithms in autoimmune encephalitis. Neuroimmunol Neuroinflamm 2016;3:93-7.
5. Gillinder L, Warren N, Hartel G, Dionisio S, O'Gorman C. EEG findings in NMDA encephalitis – A systematic review. Seizure 2019;65:20-4.
6. Zhang Y, Liu G, Jiang MD, Li LP, Su YY. Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitis patients in China. Clin Neurophysiol 2017;128:1227-33.
7. Jeannin-Mayer S, André-Obadia N, Rosenberg S, Boutet C, Honnorat J, Antoine JC, *et al*. EEG analysis in anti-NMDA receptor encephalitis: Description of typical patterns. Clin Neurophysiol. 2019;130:289-96.
8. Baykan B, Gungor Tuncer O, Vanli-Yavuz EN, Kirac LB, Gundogdu G, Bebek N, *et al*. Delta brush pattern is not unique to NMDAR encephalitis: Evaluation of two independent long-term EEG cohorts. Clin EEG Neurosci 2018;49:278-84.
9. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D.

Extreme delta brush: A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79:1094-1100.
10. da Silva-Júnior FP, Castro LHM, Andrade JQ, Bastos CG, Moreira CH, Valério RMF, *et al*. Serial and prolonged EEG monitoring in anti-N-Methyl-d-Aspartate receptor encephalitis. Clin Neurophysiol. 2014;125:1541-4.
11. Trinka E, Leitinger M. Which EEG patterns in coma are nonconvulsive status epilepticus? Epilepsy Behav 2015;49:203-22.
12. Gataullina S, Plouin P, Vincent A, Scalais E, Nuttin C, Dulac O. Paroxysmal EEG pattern in a child with N-methyl-d-aspartate receptor antibody encephalitis: Case report. Dev Med Child Neurol 2011;53:764-7.
13. Probasco JC, Benavides DR, Ciarallo A, Sanin BW, Wabulya A, Bergey GK, *et al*. Electroencephalographic and fluorodeoxyglucose-positron emission tomography correlates in anti-N-methyl-d-aspartate receptor autoimmune encephalitis. Epilepsy Behav Case Rep 2014;2:174-8.
14. Chanson E, Bicilli É, Lauxerois M, Kauffmann S, Chabanne R, Ducray F, *et al*. Anti-NMDA-R encephalitis: Should we consider extreme delta brush as electrical status epilepticus? Clin Neurophysiol 2016;46:17-25.
15. 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.
16. Foff EP, Taplinger D, Suski J, Lopes MBS, Quigg M. EEG findings may serve as a potential biomarker for Anti–NMDA receptor encephalitis. Clin EEG Neurosci 2017;48:48-53.
17. van Sonderen A, Arends S, Tavy DLJ, Bastiaansen AEM, de Bruijn MAAM, Schreurs MWJ, *et al*. Predictive value of electroencephalography in anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 2018;89:1101-6.
18. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, *et al*. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: Mechanisms and models. Lancet Neurol 2019;18:1045-57.