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Electroencephalographic findings in anti-*N*-methyl-D-aspartate receptor encephalitis in children: A series of 12 patients

Mirac Yildirim [a,*], Bahadir Konuskan [a], Dilek Yalnizoglu [a], Haluk Topaloglu [a], Ilknur Erol [b], Banu Anlar [a]

[a] Department of Pediatric Neurology, Hacettepe University Hospital, Ankara, Turkey
[b] Department of Pediatric Neurology, Baskent University Hospital, Adana, Turkey

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ABSTRACT

Objective: Anti-*N*-methyl-D-aspartate receptor encephalitis (a-NMDARe) is an acute or subacute encephalopathy where electroencephalogram (EEG) is frequently obtained as part of the workup. Although no diagnostic EEG finding has been described so far, the definition of specific or typical patterns might help to distinguish this group among various encephalopathies of childhood. We examined EEG recordings of our patients with a-NMDARe in order to describe the most frequent findings.

Methods: Clinical and laboratory data and digital EEG recordings of 12 pediatric patients diagnosed with a-NMDARe in two major child neurology centers are evaluated.

Results: We reviewed 43 EEG recordings from 12 children with a-NMDARe and followed their evolution for a median of 6 (range: 1–60) months. Initial EEG was abnormal in 11/12 patients. The most frequent finding was focal or diffuse slowing of the background rhythm. Generalized rhythmic delta activity, brief rhythmic discharges (BRDs), and occipital intermittent rhythmic delta activity (OIRDA) were seen in two patients each. Diffuse excess beta frequency activity was seen in three patients. Extreme delta brushes were observed in 5/12 (41.7%) patients, disappeared in 4–6 months (two patients), or persisted at 10–17 months (two patients). Epileptic activity was seen in seven patients (58%) and lateralized periodic discharges in one. On follow-up EEGs, most epileptic activity disappeared in a median of 8 months.

Conclusions: A normal EEG is rare in a-NMDARe. Focal or diffuse slowing, epileptic activity, and extreme delta brush are common findings. Epileptic activity in early EEGs do not persists in most patients. Severe diffuse slowing may predict neurological impairment if confirmed in larger series.

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1. Introduction

A significant proportion of children and adolescents presenting with altered consciousness, seizures, or behavioral abnormalities have autoimmune encephalitis associated with antibodies against anti-*N*-methyl-D-aspartate receptor (a-NMDARe). Presenting symptoms consist of cognitive, psychiatric, motor disturbances, and seizures [1,2]. Electroencephalogram (EEG) is frequently reported to be abnormal with slow background activity or epileptic discharges; however, EEG has not been studied systematically in pediatric a-NMDARe. As this disorder can mimic or overlap with acute viral encephalitis and other acute or subacute central nervous system disorders, paraclinical markers can be helpful in differential diagnosis. We retrospectively examined our series' EEG recordings in order to describe the frequent EEG findings and their evolution in children with a-NMDARe.

2. Methods

Clinical and laboratory data and digital EEG recordings of patients diagnosed with a-NMDARe in the departments of Pediatric Neurology, Hacettepe University Hospital, Ankara (n = 11) and Baskent University Hospital, Adana (n = 1) were retrieved from medical records. Serum antibodies against *N*-methyl-D-aspartate receptor (NMDAR) had been detected in all patients by commercially available cell-based test (Euroimmun AG, Germany).

All EEGs were obtained according to the international 10–20 system with sleep and awake states, photic stimulation in all patients, and eye closure and hyperventilation according to patients' cooperation; EEG was recorded for at least 30 min. All EEG recordings were evaluated retrospectively by a pediatric epileptologist (DY) with knowledge of the age and diagnosis, but not of the clinical state, symptoms, or signs of the patient. Data from EEG were grouped as follows:

Background rhythm: normal (age-appropriate frequency), focal, or diffuse slowing which was graded as follows: mild signifying theta interspersed with some alpha rhythm, moderate: predominantly theta, and severe: predominantly delta activity.

* Corresponding author at: Department of Pediatric Neurology, Hacettepe University İhsan Dogramacı Children Hospital, 06100 Sihhiye, Ankara, Turkey.
E-mail addresses: miracyildirim@hacettepe.edu.tr (M. Yildirim), dileky@hacettepe.edu.tr (D. Yalnizoglu), htopalog@hacettepe.edu.tr (H. Topaloglu), banlar@hacettepe.edu.tr (B. Anlar).

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Paroxysmal sharp or spike activity was described for localization and pattern. "Extreme theta brush" was defined by analogy to "extreme delta brush", high-voltage 20- to 30-Hz beta activity superposed on a frontally maximal rhythmic theta wave in the absence of benzodiazepine or barbiturate effect.

"Brief rhythmic discharges" (BRDs) are paroxysms of rhythmic electrographic activity with an amplitude of >2 μV and a duration of <10 s. This study included only retrospective clinical information and the Ethics Committee of our institution approved the study.

3. Results

There were a total of 12 serologically proven patients (ages 6 months to 14 years, median: 8 years; 7 girls, 5 boys) (Table 1). Initial EEGs were obtained 4–30 days (median: 22 days) after the onset of symptoms. All patients except one had at least one follow-up EEG obtained 3–60 months after the initial EEG.

The initial symptoms were acute or subacute alterations in consciousness, mostly somnolence-sleepiness (n = 9), behavioral changes, abnormal movements, and fever. All patients except one (Case 12) had seizures before or during hospitalization (11/12, or 91%). Seizure types were generalized (n = 6) or focal and secondarily generalized (n = 5). Underlying conditions were present in 3 patients: mediastinal teratoma (Case 9), herpes simplex virus (HSV) encephalitis one month ago (Case 2), and postvaccinal encephalitis 8 years ago (Case 3).

Immunomodulatory treatment with intravenous immunoglobulin (IVIg) and intravenous pulse methylprednisolone (PMP) was given to all but one patient, followed by rituximab, cyclophosphamide, or plasmapheresis in case there was no response. Seven patients had complete recovery; one relapsed. Five patients had cognitive and psychiatric impairment, including those with a history of HSV encephalitis and postvaccinal encephalitis. Three developed epilepsy, two of them with seizure control under antiepileptic therapy and one with intractable seizures.

The EEG findings (Figs. 1 and 2) are as follows: 11/12 patients had abnormal EEG findings on initial EEG with the normal EEG belonging to Case 9 with mediastinal teratoma whose neurological symptoms subsided after surgical and rapid immunomodulatory treatment. The most frequent EEG finding was focal or diffuse slowing of the background rhythm (n = 9). Diffuse slowing was present in 6 patients (50%); it was severe in 3 patients, moderate in 2, and mild in 1. Three/12 (25%) patients had focal slowing of the background; 2 were occipital, and 1

Table 1
Demographic, clinical features, initial EEG findings and outcome of 12 children with anti-*N*-methyl-D-aspartate receptor encephalitis.

Case	Age at diagnosis (years)	Sex	Onset acute/subacute	Seizure type	Clinic presentations	Initial EEG findings	Outcome
1	9,5	F	Subacute	Generalized and dyscognitive	Sleepiness Dyskinesia Hallucination	Bilateral occipital slowing, excess beta frequency activity (F-C), epileptic activity (L O)	Recovery
2	0,5	F	Acute	Generalized	Sleepiness Fever	Generalized rhythmic delta frequency without extreme delta brush, extreme delta brushes, epileptic activity (R O and T)	Cognitive and motor impairment, no seizure with AED
3	9	M	Subacute	Generalized tonic–clonic and dyscognitive	Sleepiness Chorea Lethargy Irritability	Severe polymorphic diffuse slowing, epileptic activity (bil. O), OIRDA, attenuation periods (<1.5 s), delta brush	Cognitive and motor impairment, no seizure with AED
4	6	M	Subacute	Focal, secondarily generalized tonic–clonic	Sleepiness Lethargy Fever	Moderate polymorphic diffuse slowing (L T predominant), epileptic activity (L F-T), BRDs (frontal-10 s.)	Cognitive and motor impairment
5	2,5	F	Subacute	Focal tonic	Sleepiness Agitation Aphasia Hallucination Behavioral alteration	Mild polymorphic diffuse slowing, OIRDA (R), epileptic activity (R T–P), extreme delta brushes, attenuation period (<1 s)	Relapse then recovery
6	14	M	Subacute	Focal and secondarily generalized tonic–clonic	Sleepiness Agitation Irritability Ataxia	Asymmetric focal slowing (L O), excess beta frequency activity (F-C) (1-month EEG: Extreme delta brushes +)	Recovery
7	14	M	Acute	Focal, secondarily generalized tonic–clonic and dyscognitive	Sleepiness Agitation Fever Vertigo	Excess beta frequency activity (F), photic entrainment	Cognitive and psychiatric impairment
8	7	F	Subacute	Generalized	Irritability Dystonia	Severe polymorphic diffuse slowing, epileptic activity (L F-T)	Cognitive and psychiatric impairment, intractable seizures
9	12	F	Acute	Generalized	Sleepiness Dyskinesia	Normal	Recovery
10	13	F	Subacute	Generalized	Behavioral alteration Agitation	Moderate polymorphic diffuse slowing, extreme delta brushes, PLED (R T)	Recovery
11	5	M	Subacute	Focal and clonic, generalized	Sleepiness Lethargy Agitation Aphasia	Severe polymorphic diffuse slowing (bil. F predominant), generalized rhythmic delta frequency without extreme delta brush, excess beta frequency activity (diffuse) {1-month EEG: Extreme delta brushes and BRDs (frontal, <10 s)}	Recovery
12	6,5	F	Subacute	No seizure	Agitation Emotional lability	Asymmetric focal slowing (severe: R hemispheric, moderate: L-F)	Recovery

OIRDA: occipital intermittent rhythmic delta activity.
BRDs: brief rhythmic discharges.
PLED: periodic lateralized epileptiform discharges.
AED: antiepileptic drug.
0: occipital, C: central, F: frontal, T: temporal.

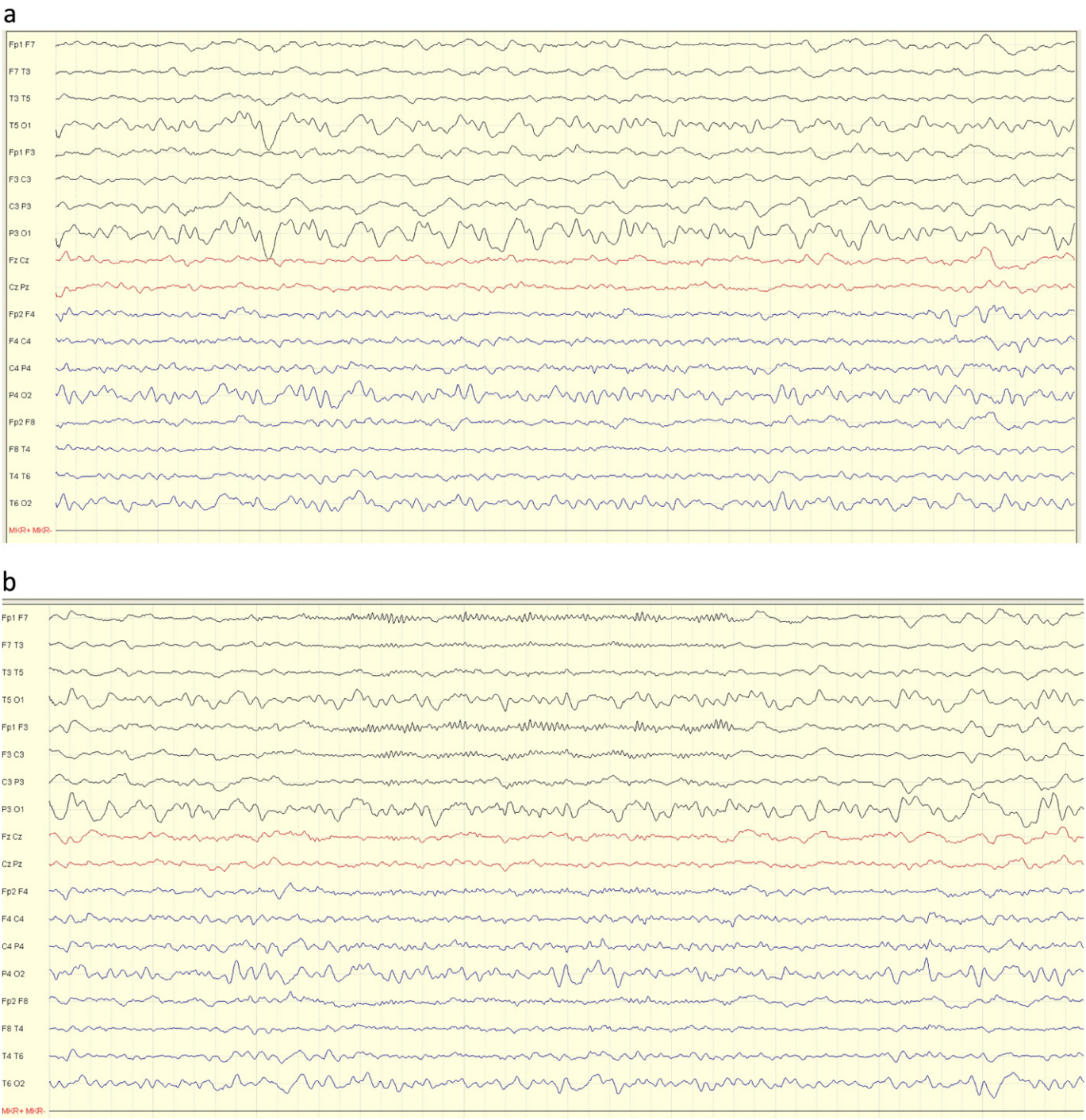

Fig. 1. Case 6. a. Asymmetric focal slowing. b. Excess beta activity.

was right hemispheric. Generalized rhythmic delta activity, BRDs, and occipital intermittent rhythmic delta activity (OIRDA) were seen in two patients each. The BRDs were recorded in frontal electrodes. Two cases had repetitive attenuation periods (<1.5 s) during EEG recording.

Excess beta frequency activity was seen in four patients; one was receiving benzodiazepine. Excessive fast rhythms were frontocentral or frontal in three patients and diffuse in one. Extreme delta brushes were observed in 5 patients' (41.7%) first and second EEG recordings (Cases 2, 5, 6, 10, and 11); they disappeared in four and six months in two patients (Cases 10 and 5 respectively) and persisted at 10 and 17 months in the other two (Cases 2 and 6). The remaining case (Case 11) had no appropriate EEG follow-up.

In 4 cases, clinical seizures were noted during EEG recordings, all of them obtained in the first 6 months after onset. Epileptic activity was seen in 7/12 (58.3%) patients. Three involved occipital and others, temporal areas. One case had localized periodic epileptiform discharges which disappeared after the first month.

Ten of 12 patients had more than one (mean: 4) EEG recordings, 6/10 becoming normal (Table 2). On follow-up EEGs, most epileptic activity disappeared in 6–18 months (median: 8 months). Excessive fast rhythms

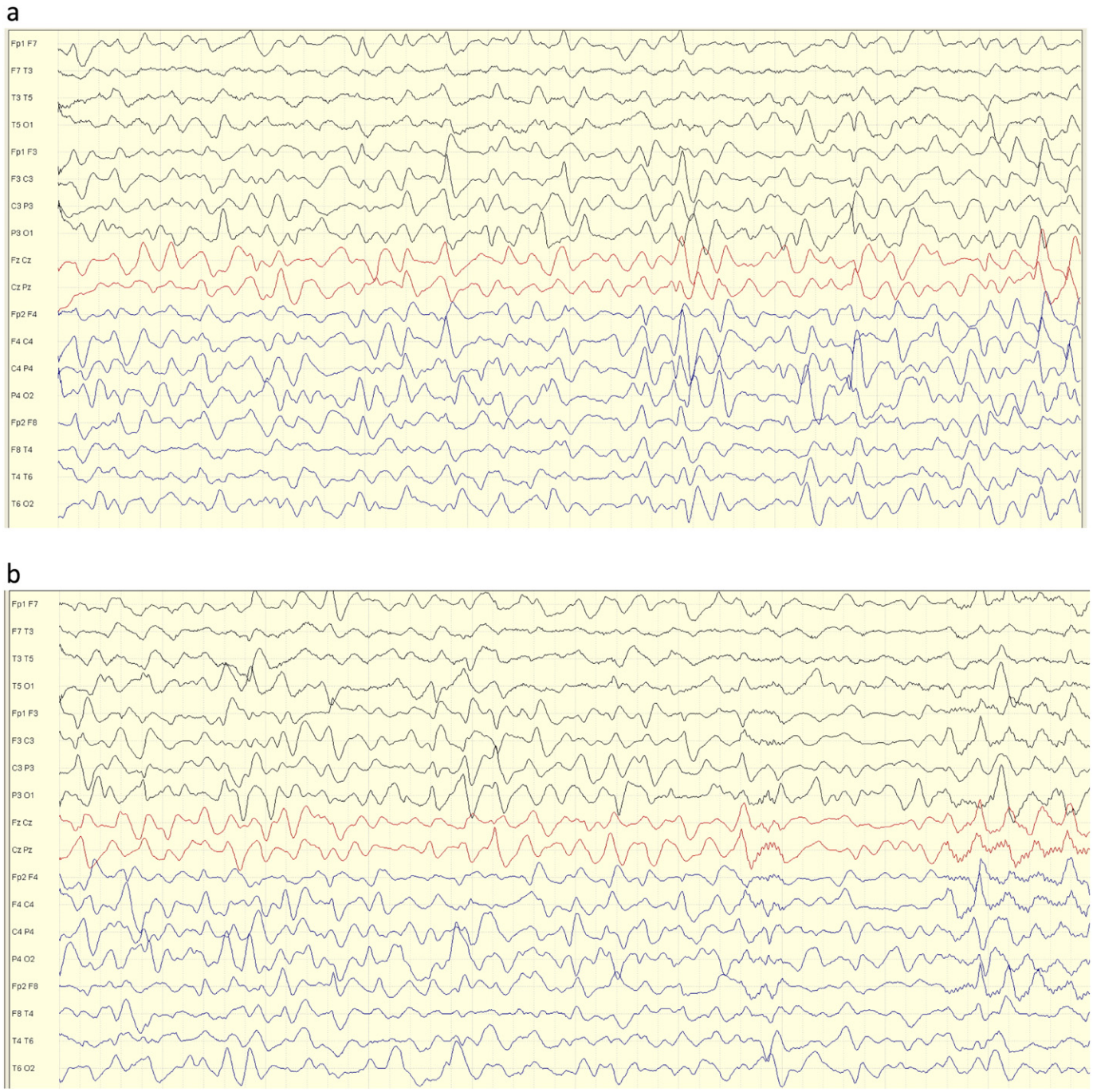

Fig. 2. Case 3. a. Bilateral occipital severe polymorphic diffuse slowing, epileptic activity, occipital intermittent rhythmic delta activity. b. With delta brushes.

and extreme delta brushes were not observed after 18 months, and BRDs were not observed after 6 months of disease. However, epileptic activities, generalized slowing, and OIRDA persisted in certain cases; one patient's EEG showed slow background rhythm and epileptic activity at 38 months (Table 2).

There was little correlation between clinical, magnetic resonance imaging (MRI), and EEG findings. Severe EEG findings could be associated with abnormal (Cases 2, 3, 4) or normal MRI (Cases 8, 11). On the other hand, the presence of normal, focal, mild, or moderate findings on EEG was accompanied by normal or local findings on MRI (Cases 1, 5, 6, 7, 9, 10, 12). Regarding outcome, two patients who had antecedent encephalitis developed neurological impairment, as did patients with severe slowing on EEG, while those with focal slowing recovered (Cases 1, 6, 12). The titer of a-NMDARe antibody titer was not correlated with the clinical picture, degree of EEG abnormality, course, or outcome. Three patients were retested serologically; all were found negative including one post-HSV encephalitis case with severe neurological impairment (Case 3).

4. Discussion

The diagnosis of a-NMDARe is based on clinical suspicion and confirmed by the demonstration of antibodies in the serum or, more sensitively, the cerebrospinal fluid. Common EEG abnormalities have been described as focal or diffuse background slowing, rhythmic theta or

Table 2
Characteristics of follow up EEG recordings.

	EEG time (month) after symptom onset					
	0–1 m	3–6 m	7–12 m	13–18 m	19–24 m	25–60 m
EEG (n)	12	14	5	5	2	5
Patient (n)	12	8	3	5	2	3
Finding						
Normal	1	2	1	4	2	2
Abnormal	11	12	4	1	–	3
Background activity						
Focal slowing	3	3	1	–	–	–
Frontal	–	–	–	–	–	–
Frontocentral	–	1	–	–	–	–
Temporal	–	1	–	–	–	–
Temporoparietal	–	–	1	–	–	–
Occipital	2	1	–	–	–	–
Hemispheric	1	–	–	–	–	–
Generalized slowing	6	9	1	–	–	3
Mild	1	1	1	–	–	–
Moderate	2	4	–	–	–	–
Severe	3	4	–	–	–	3
Excess beta frequency activity	4	2	2	1	–	–
Frontal	1	–	–	1	–	–
Frontocentral	2	2	2	–	–	–
Diffuse	1	–	–	–	–	–
Occipital intermittent rhythmic delta	2	–	–	–	–	1
Generalized rhythmic delta activity w/o extreme delta brush	2	1	1	–	–	–
Extreme delta brush	3	5	1	1	–	–
Photic entrainment	1	2	–	–	–	–
Localized periodic epileptiform discharges	1	–	–	–	–	–
Epileptic activity	7	10	1	–	–	3
Right	3	2	1	–	–	–
Left	3	4	–	–	–	–
Bilateral	1	4	–	–	–	3
Clinical seizure	–	4	–	–	–	–
Status epilepticus	–	–	–	–	–	–
Brief rhythmic discharges	1	2	–	–	–	–
Attenuation period	2	–	–	–	–	3

delta activity, and epileptic, namely, spike and wave discharges [3]. Recent studies reported "extreme delta brush" [4], "extreme beta brush" [5], and "brief rhythmic discharge" [6] as novel EEG findings in a-NMDARe; however, their specificity and sensitivity is unclear especially in children, as knowledge on EEG abnormalities associated with a-NMDARe is based on case reports or small series reported to date. Within the limitations of a retrospective study, we describe the initial EEG findings and could follow their evolution in time, up to a median of 6 months in the majority of our patients.

A recent series of 33 adolescent and adult cases collected in China demonstrated that first EEGs were normal or slightly abnormal in 39%; 54.5% were markedly abnormal, about half showing diffuse or localized slow waves [7]. Typical epileptiform discharges were rare, and only 9% had paroxysmal discharges. Our results show a higher rate of EEG abnormalities, suggesting EEG more likely to be abnormal in children and adolescents compared to adults. The most frequent finding, diffuse or focal slowing of the background activity, might carry clinical or prognostic implications according to its distribution and severity, although the small number of patients in this study prevents any conclusion. All initial (<1 month) EEGs were abnormal except for the patient with mediastinal teratoma. The resection of a germ cell tumor correlates with good outcome, but most such cases are diagnosed and treated late [2,8].

Extreme delta brush has been proposed as typical for a-NMDARe in adults and related to beta activity accompanied by slow rhythm due to pathological activation of a-NMDARe. In recent studies extreme delta brushes have been described in 30.4% [4] and 33.3% [9] of adult patients with a-NMDARe, while others did not observe delta brushes in five and ten pediatric cases [10,11]. This finding was relatively frequent in our series. Interestingly, two patients had no extreme delta brush in initial EEG recordings but only one month later, which persisted even 10 and 17 months after onset. This EEG pattern has been shown to continue 4 months after presentation in an adult case, correlated with more protracted course and more abnormalities on MRI in adult patients [4,12]. Our three patients with extreme delta brush did not display a more severe outcome.

Brief rhythmic discharges (BRDs) suggest a risk of developing seizures [6]. Our two cases who had BRDs also had clinical seizures; however, seizures were frequent in our patients with or without BRDs.

Localized epileptiform discharges were observed in the initial EEG of only one patient. This might be helpful in the differentiation from HSV encephalitis where up to 75% have been reported to demonstrate such discharges [13].

Unlike most studies where no EEG follow-up is reported or the intervals between EEGs are not described, we could follow the evolution of EEG findings in the majority of our patients until 12 months and describe changes over time. In general, abnormalities tended to subside in our patients. The EEGs that are normal at 7–12 months tend to remain normal, while EEG abnormalities persisting at 7–12 months after onset tended to continue until 18 or 24 months. These cases may turn into autoimmune epilepsy, suggesting that some patients diagnosed with autoimmune epilepsy can be suffering consequences of autoimmune encephalitis whose initial encephalitic phase had been subclinical or undiagnosed. However, in the absence of past medical history of encephalitis, the interchangeable utilization of the terms "autoimmune encephalitis" and "autoimmune epilepsy" can be confusing for the readership [14,15,16].

Anti-*N*-methyl-D-aspartate receptor encephalitis can relapse. The rate of relapse, described as 25% of adult cases [2,17] is probably lower in children [18,19] and subject to change with earlier recognition and treatment. In our series, only one patient experienced a neurological relapse after a normal interval, while all others are free from immunotherapy for at least 14 months at the time of this review.

Regarding neurological deficit, etiology appeared to make a difference because those cognitively impaired included those with HSV encephalitis and postvaccinal encephalitis. When EEG findings are examined in relation with outcome, neurologically impaired cases had severe polymorphic diffuse slowing on their initial EEGs. Pillai et al. found a low risk of evolution to epilepsy and drug-resistant epilepsy in a-NMDARe (none of 9 cases); our three/12 cases (25%) represent a higher probability [20].

Most patients had only one anti-NMDAR antibody test, preventing any serological–clinical–EEG correlation. Another limitation of this retrospective study is that the EEG findings are reflecting a certain point in time. Continuous video-EEG monitoring is more likely to detect particular patterns in each patient, or the appearance of all patterns in most patients over time. However, a-NMDARe often has a protracted course, and long monitoring is not feasible in most, even specialized clinics. Therefore, the systematic examination of sleep and awake recordings, done in all our patients, and the evaluation performed by a single epileptologist blinded from the clinical state of the patient appear as strong points of our study.

We conclude that EEG abnormalities are frequent in a-NMDARe, a normal EEG being only occasionally encountered; certain EEG findings like extreme delta brushes, BRDs, and OIRDAs, although uncommon, can be suggestive whenever present. The most frequent finding, nonspecific slowing of the cerebral bioelectric activity, may be related to outcome when severe and diffuse if confirmed in larger studies.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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