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

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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.

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.

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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.