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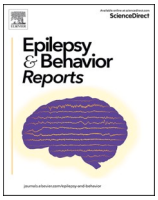

Abnormal theta-band rhythm: EEG abnormality as potential biomarkers for disease severity in pediatric anti-NMDAR encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children often requires early immunosuppressive therapy before antibody detection. While various electroencephalogram (EEG) patterns, including extreme delta brushes (EDBs), have been reported in adults, pediatric EEG characteristics remain understudied. This study aims to assist clinicians in identifying severe cases early, potentially improving treatment outcomes through prompt intervention. This retrospective case series examined EEG features influenced by disease severity in children with anti-NMDAR encephalitis. We evaluated six children (1–13 years old; four females, two males) treated at Tokyo Metropolitan Neurological Hospital from January 2007 to January 2023. The severity of autoimmune encephalitis in our patients was assessed using the Clinical Assessment Scale in Autoimmune Encephalitis (CASE). The literature proposes a severity classification for the CASE score, wherein scores of 0–8 points are categorized as mild, 9–18 points as moderate, and 19–27 points as severe. In our patients, CASE scores ranged from 4 to 25 (median:19). We reviewed acute-phase EEG recordings, including 13 long-term videos and 58 conventional recordings. None of the patients maintained a normal posterior-dominant rhythm, and only one exhibited EDBs. Notably, three patients with higher CASE scores (≥15) displayed abnormal theta-band rhythm during non-REM sleep and prolonged EEG recovery times. Our findings suggest that abnormal theta-band rhythms may serve as a potential acute-phase EEG biomarker for severe anti-NMDAR encephalitis in children.

1. Introduction

Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterized by a wide range of symptoms, including neuropsychiatric manifestations, seizures, hypoventilation, involuntary movements, and sleep disturbances [1]. The diagnosis of this condition in pediatric patients can be challenging owing to the non-specific or atypical presentation of symptoms. Early diagnosis is crucial because early treatment has been associated with better outcomes. [2]. Although the detection of anti-NMDAR antibodies in cerebrospinal fluid (CSF) is necessary for a definitive diagnosis, results from cell-based assays can take several days to weeks. In many countries this situation is considered the same [3]. The diagnostic criteria for probable anti-NMDAR encephalitis [3], which do not require antibody tests, are reliable in determining the initiation of first-line treatment in both adults and children. However, the prevalence of antibodies among children who meet these criteria is only 31.7 % [4]. Hence, there is a pressing need for an appropriate biomarker to guide the early diagnosis and aggressive treatment decisions in pediatric patients with anti-NMDAR encephalitis.

Several studies have highlighted the utility of EEG in the diagnosis of anti-NMDAR encephalitis [5,6]. While some EEG patterns, such as extreme delta brushes (EDBs), have been reported as characteristics of anti-NMDAR encephalitis in adult patients [7], there are limited reports of EDB in childhood cases. A previous study suggested that abnormal theta and alpha rhythms, collectively termed “theta-alpha-band rhythms,” are EEG patterns suggestive of anti-NMDAR encephalitis in children [8]. High-amplitude diffuse alpha and theta rhythm (5–10 Hz)

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characterize this EEG feature during the non-rapid eye movement (REM) sleep stage. However, the characteristic EEG features of children with severe anti-NMDAR encephalitis have not been adequately reported. The primary objective of this study was to identify specific EEG features in the initial stages of severe anti-NMDAR encephalitis in pediatric patients.

2. Patients and methods

2.1. Study patients

This retrospective case series included children with confirmed anti-NMDAR encephalitis treated at Tokyo Metropolitan Neurological Hospital from January 2007 to January 2023. We also included cases from 2001 to 2006 initially diagnosed as encephalitis of unknown etiology but later confirmed as anti-NMDAR encephalitis when testing became available. The inclusion criteria were a definitive diagnosis of anti-NMDAR encephalitis based on the criteria proposed by Graus et al. [3] and the availability of clinical course data for more than 3 years. The diagnostic criteria for probable anti-NMDAR encephalitis require three criteria: 1) rapid onset (less than 3 months) of at least four of the six major symptom groups, 2) at least one of the specified laboratory study results, and 3) reasonable exclusion of other disorders. A definitive diagnosis of anti-NMDAR encephalitis can be made in the presence of one or more of the six major symptom groups and CSF IgG anti-GluN1 antibodies following the exclusion of other disorders. NMDAR antibodies in the CSF were measured using a commercially available immunocytochemical assay kit (Autoimmune Encephalitis Mosaic 1; Euroimmune, Lübeck, Germany) at the Tokyo Metropolitan Institute of Medical Science.

2.2. Clinical and EEG findings

The collected patient data included age, sex, psychiatric and neurological symptoms, seizures, involuntary movements, autonomic symptoms, antiepileptic drugs, immunological treatment, prognosis, EEG and MRI findings, and length of hospital stay. The severity of autoimmune encephalitis was evaluated using the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) [9]. EEG findings were assessed for background activity, posterior dominant rhythm (PDR), theta-band rhythms, abnormal slowing, EDB, interictal discharges, and ictal events. EDB was defined as a rhythmic delta activity (1–3 Hz) with superimposed bursts of rhythmic beta-frequency activity. Abnormal theta-band rhythms were defined as continuous high-amplitude diffuse theta rhythms (4–7 Hz) occurring in more than 30 % of the non-REM sleep stage. EEG data were independently reviewed by the first author and two specialists in epilepsy and pediatric neurology.

Outcome measures included the modified Rankin Scale (mRS) score at discharge and at 1 year follow-up, and duration of hospital stay.

3. Results

3.1. Clinical information of patients

Six patients (four females and two males) with a median age of onset of 4.1 years (range: 1.3–13.5 years) were included in the study. All patients had a history of psychiatric changes, and five of the six patients had involuntary movements and autonomic disabilities. Clinical seizures were observed in three patients who required antiseizure medications. Each patient's total CASE score is described in Supplementary Table S1, and details of clinical examination results can be found in Table 1. All patients had anti-NMDAR antibodies in the CSF, five had oligoclonal bands, and four had pleocytosis. One patient (Patient 3) was positive for both anti-NMDAR and anti-MOG antibodies. This patient met the definitive criteria for anti-NMDAR encephalitis and exhibited clinical features consistent with this diagnosis.

Three patients had MRI abnormalities. All patients received immunotherapy, including high-dose intravenous methylprednisolone (6/6), immunoglobulin therapy (5/6), plasma exchange (3/6), intravenous rituximab (4/6), and oral mycophenolate mofetil (3/6) (Table 1).

3.2. EEG findings

Thirteen long-term videos and 58 conventional EEG recordings were reviewed. All EEGs were performed without sedatives. All patients exhibited continuous slow waves during their awake state, with varying delta-wave localization. None of the patients had a normal PDR in the awake state during the acute stage, and it took more than 6 months for normal PDR to be restored in three patients. The patient with the highest CASE score (Patient 4, CASE score 25) was the only one to exhibit extreme delta brush pattern on EEG (Fig. 1a). No ictal events were recorded during the EEG recordings.

An abnormal theta-band rhythm was observed in three patients (Fig. 1 b, c, and d), characterized by a continuous 4–8 Hz frequency rhythm during sleep from the acute stage to the recovery stage. These rhythms persisted even after the restoration of the PDR and were mainly composed of a theta band rhythm. The three patients with abnormal theta-band rhythms had higher CASE scores, slower recovery of normal PDR and worse clinical prognoses than the other three patients (Table 1). Patients with abnormal theta-band rhythms had longer

Table 1
Clinical information, Laboratory, and EEG Findings in Pediatric Patients with Anti-NMDAR Encephalitis.

Pt	Age Sex	CASE score	CSF Ab	OCB	Pleo	MRI changes	ATBR(Appearance location: period)	EDB	Time to normal PDR	Key Symptoms	Treatment	Hospital stay	Outcome (mRS scale) Notes
1	2y3mM	15	+	−	−	+	+ (F, C: 2w–7 m)	−	9 *m*	Chorea, dystonia	IS, IG, Rx	11 *m*	2
2	6y7mF	8	+	+	−	−	−	−	1 *m*	Myoclonus, ballism	IS, IG, PE	1 *m*	0
3	13y7mM	4	+	+	+	+	−	−	2 w	Mild psychiatric symptom	IS, PS	1 *m*	0 MOG Ab+
4	2y8mF	25	+	+	+	+	+ (F, C, P: 2w–1 m)	+	3y4m	Ballism, seizures	IS, IG, Rx, MM, PE	3y6m	5
5	1y3mF	23	+	+	+	−	+ (F, C, P: 3w–3y5m)	−	8 *m*	Dyskinesia, apnea	IS, IG, Rx, MM, PE	4 *m*	4
6	5y4mF	23	+	+	+	−	−	−	3 *m*	Dyskinesia, tachycardia	IS, IG, Rx, MM	3 *m*	0

Pt: Patient; CASE: Clinical Assessment Scale in Autoimmune Encephalitis; CSF Ab: CSF Anti-NMDAR Antibody; OCB: Oligoclonal Bands; Pleo: Pleocytosis; ATBR: Abnormal Theta-Band Rhythm; EDB: Extreme Delta Brush; PDR: Posterior Dominant Rhythm; IS: IV Steroid; IG: IV Immunoglobulin; Rx: Rituximab; PE: Plasma Exchange; PS: Prednisolone; MM: Mycophenolate Mofetil; m: months; w: weeks; y: years.

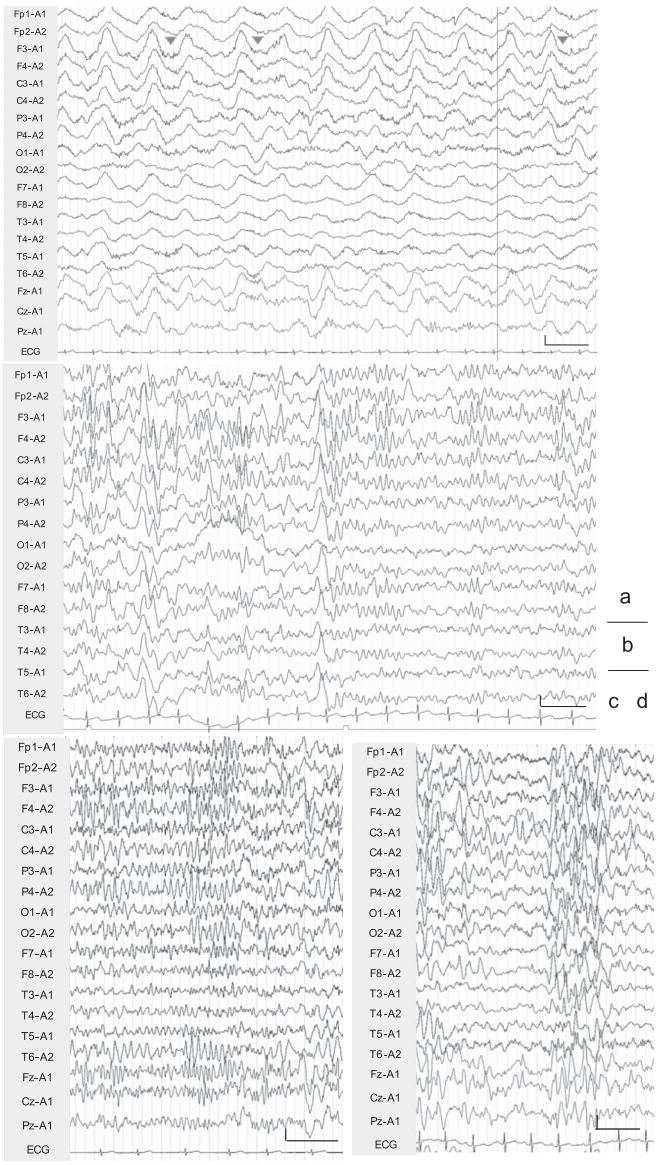

Fig. 1. Electroencephalographic records of patients. (a) Extreme delta brushes (▼) in Patient 4. Theta-band rhythms on sleep recording in (b) Patient 1, (c) Patient 4, and (d) Patient 5. Horizontal and vertical bars indicate 1 and 50 μV, respectively.

hospital stays (mean 127 days vs. 35 days) and higher mRS scores at discharge (mean 3.67 vs. 0) compared to those without these EEG findings.

4. Discussion

The major EEG findings in anti-NMDAR encephalitis are generally non-specific encephalopathic changes, such as a lack of PDR, generalized slow waves, and paroxysmal activities. Although EDB is a characteristic feature of anti-NMDAR encephalitis, its prevalence varies among studies and is insufficient for diagnosing severe cases, particularly in pediatric patients [10,11]. In this study, only one of the six patients had EDB, highlighting the need for additional prognostic EEG biomarker for anti-NMDAR encephalitis.

Half of the patients in this study had an abnormal theta-band rhythm, consistent with a previous report where six of nine children with anti-NMDAR encephalitis exhibited theta-alpha band rhythms [8]. Patients with abnormal theta-band rhythms exhibited delayed recovery to normal PDRs and had worse outcomes than patients without this finding. The alpha-band rhythm component of theta-alpha-band rhythms may be indistinguishable from extreme spindles, a nonspecific EEG pattern associated with various pathological conditions. Therefore, abnormal theta-band rhythms may be a more appropriate biomarker for anti-NMDAR encephalitis than theta- and alpha-band rhythms combined. The presence of abnormal theta-band rhythms in severe anti-NMDAR encephalitis may reflect underlying pathophysiological mechanisms. NMDAR dysfunction can lead to altered thalamocortical circuits, which are crucial for generating normal sleep rhythms [12]. The persistence of theta rhythms during sleep might indicate a disruption in the normal transition between wake and sleep states due to NMDAR hypofunction. Furthermore, these rhythms may represent a compensatory mechanism in response to reduced NMDAR-mediated excitatory neurotransmission.

We posit that abnormal theta-band rhythms observed in our study may be specific to anti-NMDAR encephalitis. This hypothesis is based on two key observations. Firstly, to the best of our knowledge, such rhythms have not been previously reported in other forms of autoimmune encephalitis (AE). Secondly, the emergence of these abnormalities specifically during non-REM sleep stages appears to be a unique characteristic of anti-NMDAR antibody-mediated pathology.

The specificity of EEG patterns in different types of AE has been a subject of ongoing research. While certain EEG findings have been associated with particular forms of AE, such as extreme delta brush in anti-NMDAR encephalitis, the identification of specific sleep-related EEG abnormalities is novel. The presence of abnormal theta-band rhythms during non-REM sleep of anti-NMDAR encephalitis patients suggests a distinct pathophysiological mechanism that may be directly related to NMDAR dysfunction.

This observation warrants further investigation to establish its sensitivity and specificity as a potential biomarker for anti-NMDAR encephalitis. Future studies comparing EEG findings across different types of AE, with particular attention to sleep-stage specific abnormalities, could help validate this hypothesis and potentially provide a new diagnostic tool for clinicians.

The limitations of this study include the small sample size, and one patient being double-positive for anti-NMDAR and anti-MOG antibodies. However, the patient fulfilled the definitive criteria for anti-NMDAR encephalitis, and prior studies have indicated no significant differences in clinical features between the coexistence of anti-NMDAR and MOG antibody-associated encephalitis and anti-NMDAR encephalitis alone [13].

In conclusion, abnormal theta-band rhythms during sleep may be a potential acute-phase EEG biomarker for severe anti-NMDAR encephalitis in children. Further large-scale studies are required to clarify the features and clinical correlations of these abnormal theta-band rhythms in pediatric patients with anti-NMDAR encephalitis.

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Declaration of Generative AI and AI-assisted technologies in the writing process

We did not use generative AI in the writing process.

CRediT authorship contribution statement

Yumie Tamura: Writing – original draft, Data curation, Conceptualization. **Mitsumasa Fukuda:** Writing – review & editing, Funding acquisition, Data curation. **Akihiko Ishiyama:** Writing – review & editing, Data curation. **Hiroya Nishida:** Writing – review & editing, Data curation. **Hirofumi Kashii:** Data curation. **Hideaki Mashimoa:**

Data curation. **Kenji Inoue:** Data curation. **Hiroshi Sakuma:** Writing – review & editing. **Satoko Kumada:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical statement

We confirm that this report is consistent with the journal guidelines.

This study, including the data, was approved by the institutional review board of Tokyo Metropolitan Neurological Hospital (approval number, TS-R02-052) and Tokyo Metropolitan Institute of Medical Science (18-3 and 21-2).

The data that support the findings of this study are available on request from the corresponding author, YT. The data are not publicly available because of their containing information that could compromise the privacy of participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100704.

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