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Case Report

Transient extreme spindles in a young child with anti-NMDAR encephalitis: A case report

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Abstract

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a type of immune-mediated encephalitis, which is a new category of treatment-responsive paraneoplastic encephalitis. In patients with this disease, electroencephalography (EEG) shows non-specific findings, but recently, a unique EEG pattern, named the extreme delta brush, was detected in 40% of adult patients and was suggested to be specific to this type of encephalitis. Here, we describe a two-year-old boy with anti-NMDAR encephalitis, who presented with speech arrest and disturbances of gait and cognition several weeks after developing febrile convulsions. In the early stages of the disease, EEG showed 14–16 Hz, continuous, fast waves characterized by a high amplitude (200–500 ÂμV), very diffuse spreading, and a sharp morphology, during light sleep only, which was compatible with extreme spindles. As the patient's symptoms worsened, this finding was replaced by rhythmic, diffuse, high-voltage, slow waves. Immediately after immunomodulatory therapies, including intravenous methylprednisolone and immunoglobulin, his clinical manifestations and EEG abnormalities appeared to improve. We propose that although the extreme spindle is a non-specific finding of this type of encephalitis, early EEG monitoring might be necessary to detect not only the extreme delta brush pattern, but also non-specific findings, including extreme spindles, which would aid early diagnosis and treatment.

Keywords: Anti-NMDAR encephalitis; Extreme spindle; Extreme delta brush; Electroencephalogram; Immune-mediated encephalitis

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a type of immune-mediated encephalitis, which is a new category of treatment-responsive paraneoplastic encephalitis that was first reported by Dalmau in 2005 [1]. Since the first report, a number of other investigators have examined the condition. Now, this type of encephalitis constitutes one of the most common causes of encephalitis in children and adolescents. In patients with anti-NMDAR encephalitis, electroencephalography (EEG) shows non-specific findings, including focal or diffuse, polymorphic, slow-waves and disorganized background activity. Recently, Schmitt et al. reported that a unique EEG pattern, named the extreme delta brush (EDB), was detected in 40% of adult anti-NMDAR encephalitis patients [2]. The EDB is characterized by a near-continuous combination of generalized diffuse delta activity and superimposed fast beta-range activity, and is considered to be highly specific to anti-NMDAR encephalitis. Here, we report

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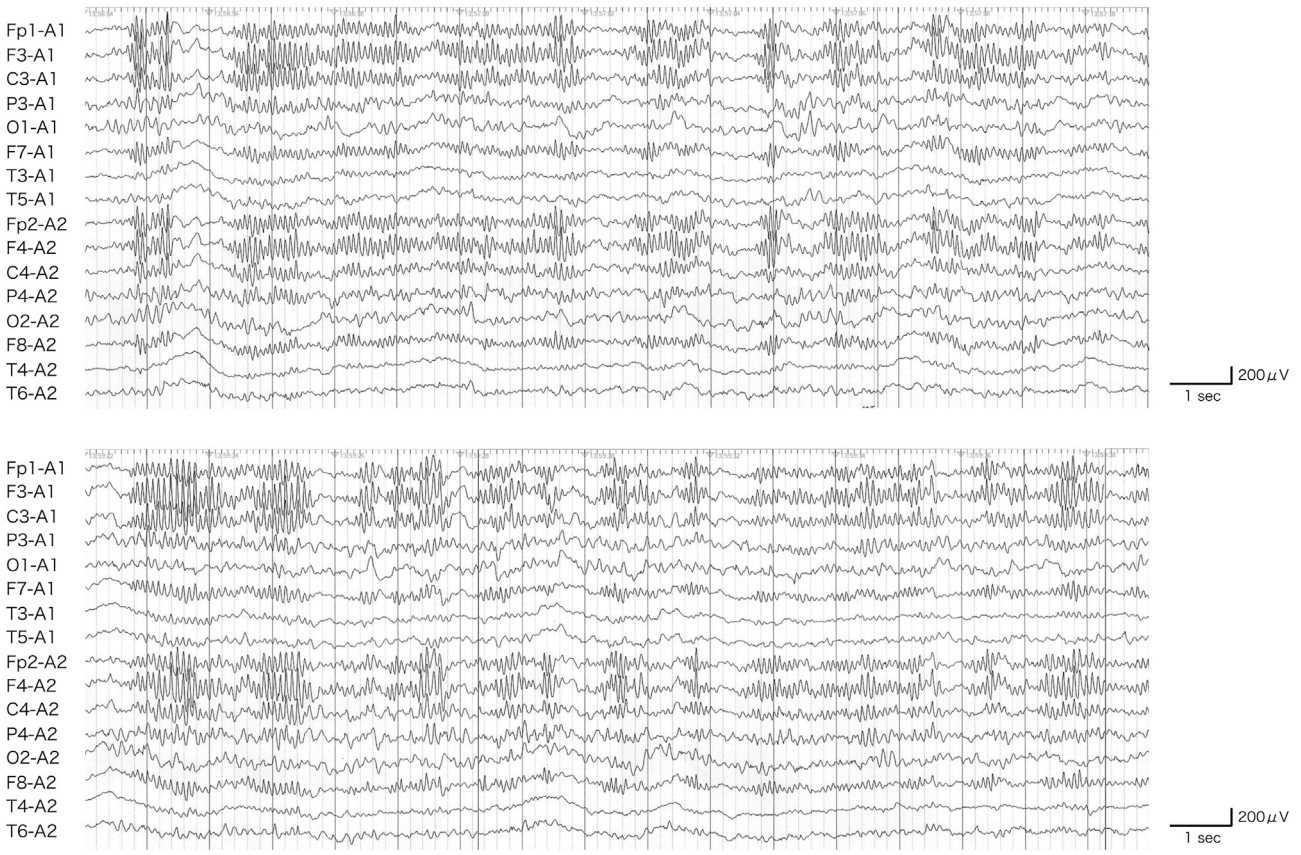

Fig. 1. Sleep electroencephalography (EEG) recorded over the maximum bilateral frontal region when the patient first started speaking less. The traces show 12–14 Hz continuous, high amplitude (150–400 ÂμV) waves and diffuse spreading spindles.

a two-year-old boy with anti-NMDAR encephalitis, who presented with disturbances of gait and cognition and developed speech arrest several weeks after suffering febrile convulsions. Interestingly, in this case, EEG showed extreme spindles, but not the EBD, during the early stages of the patient's condition.

2. Case

The patient, a developmentally normal two-year-old boy, was admitted to our hospital after experiencing his first febrile seizure, which started with vomiting and impaired consciousness, followed by a secondary generalized seizure. Blood examination revealed no abnormalities, but cerebral spinal fluid (CSF) analysis demonstrated mild lymphocytic pleocytosis (cell count: 23 cells/μL). The patient's consciousness became clear the next day. Seven days later, he developed an afebrile generalized seizure. A neurological examination and head magnetic resonance imaging (MRI) did not show any abnormal findings. EEG showed no distinct epileptic discharges, and normal spindles. We made a diagnosis of focal epilepsy and started treatment with levetiracetam. At discharge, the patient was healthy and had no sequelae.

Since two weeks following discharge, the patient evidenced a gradual reduction in speech and motor activity. EEG showed continuous, 12–14 Hz, fast waves that were characterized by high amplitude (150–400 ÂμV), very diffuse spreading, and a sharp morphology, during light sleep (Fig. 1). This unique EEG pattern is compatible with the extreme spindles pattern described by Gibbs EL and Gibbs FA [3]. The patient was urgently readmitted to our hospital for further investigation and treatment. Soon after his second admission, the patient stopped speaking, was unable to perform fine upper-limb movements, exhibited cognitive dysfunction, and spent most of the day in bed. No abnormalities were detected by head MRI or CSF analysis. EEG showed obvious, rhythmic, diffuse, high-voltage slow waves, and the extreme spindles were scattered and fragmented (Fig. 2A–C). We considered that the patient had developed subacute encephalitis, specifically autoimmune encephalitis, which includes anti-NMDAR encephalitis, and he was treated with immunomodulatory therapies, including intravenous methylprednisolone (30 mg/kg/day × 3 days, 3 courses) and immunoglobulin (400 mg/kg × 5 days).

There was a gradual improvement in behavior and cognitive function. One week after completion of thera-

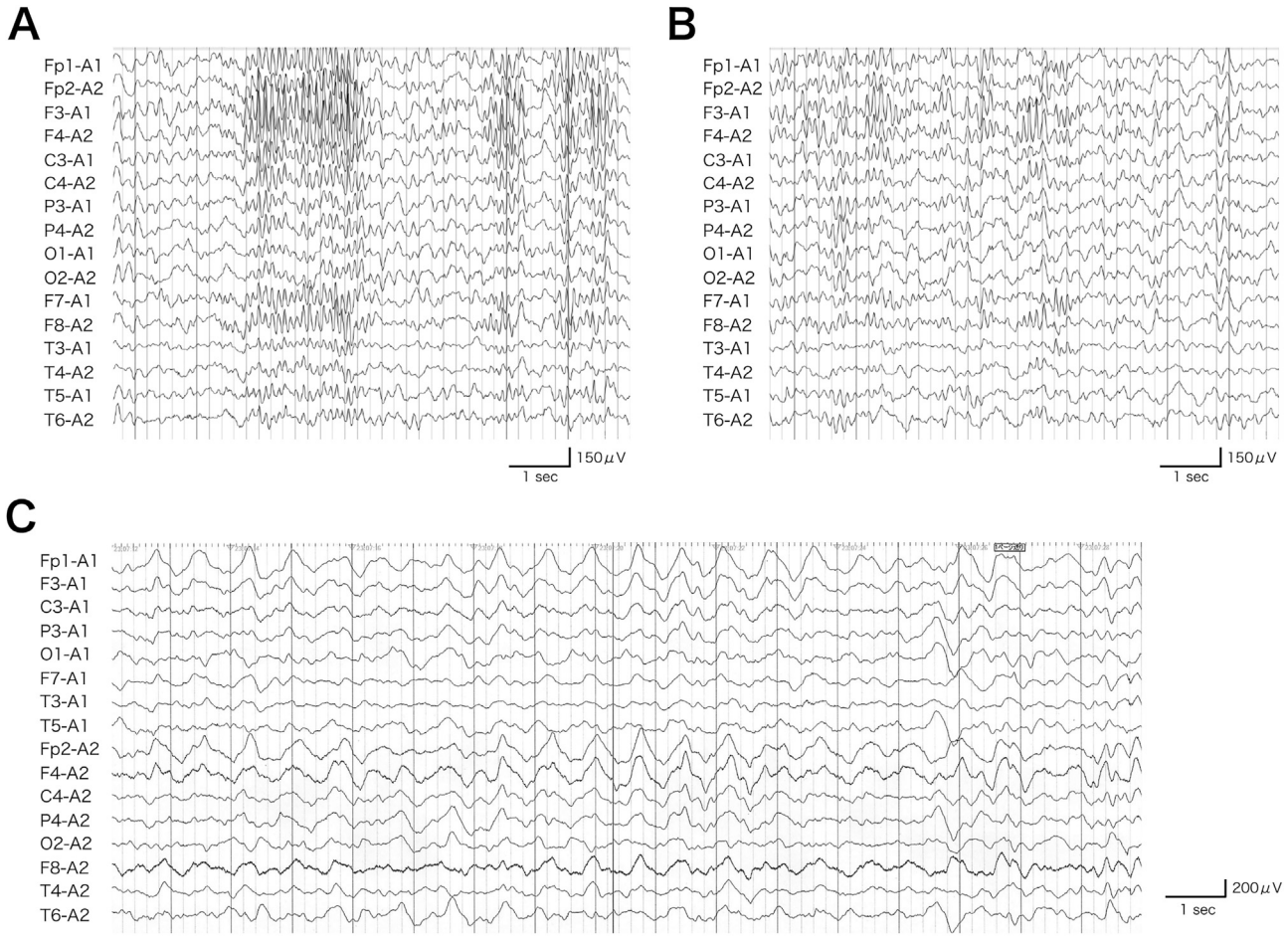

Fig. 2. The traces show that the extreme spindles had become fragmented (A) and scattered (B) and rhythmic, diffuse, high-voltage slow waves had become obvious (C).

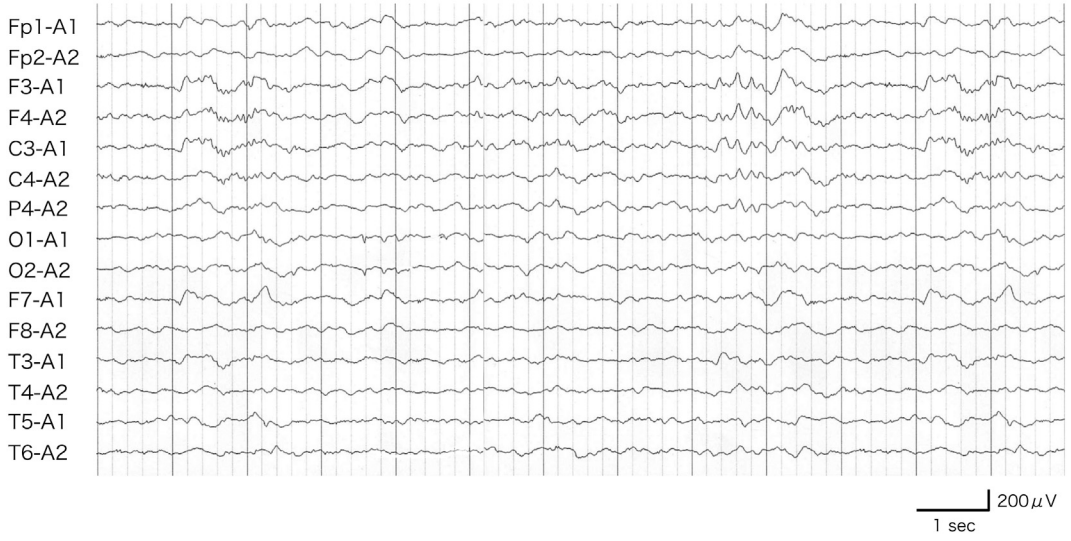

Fig. 3. Sleep EEG performed one week after immunomodulatory therapy. The traces show normal spindles without any distinct seizure discharges.

pies, the patient was discharged from hospital. At discharge, EEG showed no distinct seizure discharges with normal background activity and spindles (Fig. 3), and he could speak many words and walk without support.

Four months after his initial presentations, the patient was completely recovered without neuropsychiatric sequelae. The diagnosis of anti-NMDAR encephalitis was made based on the clinical manifestation and the EEG findings, which suggested localized autoimmune encephalitis, and the detection of anti-NMDAR antibody in the CSF using a cell-based assay. MRI of the abdomen and pelvis was performed, but no tumors were detected.

3. Discussion

Here, we reported a two-year-old boy with anti-NMDAR encephalitis, whose EEG showed extreme spindles, during the early phase of the condition. Gibbs EL and Gibbs FA first reported the presence of extreme spindles in children with intellectual disabilities in 1962 [3]. This EEG finding is characterized by diffuse expression, a high amplitude (200–400 ÂμV), and continuous occurrence, which is compatible with the EEG finding seen in our case. As the EEG performed after the patient's first seizure showed normal sleep spindles, the encephalitis was considered to have caused the extreme spindles.

Most EEG findings obtained in patients with anti-NMDAR encephalitis are non-specific. Recently, Schmitt et al. reported that the EDB pattern was detected in 40% of adult anti-NMDAR encephalitis patients, and they considered this EEG pattern to be specific to anti-NMDAR encephalitis [2]. The EDB pattern is not affected by sleep-wake cycles, stimulation, or the level of arousal, and is present continuously from the earliest available EEG. In our case, this unique EEG pattern was only transiently present during light sleep in the early stages of the disease. As the patient's symptoms worsened, it was replaced by rhythmic, diffuse, high-voltage, slow waves. These were suggestive of increased sleep spindle activity and were different from the EDB pattern.

In previous studies, extreme spindles were reported in children with mental retardation; cerebral palsy, and several neurodevelopmental disorders [3,4]. Spindle frequency is determined by interplay between the interconnected GABAergic inhibitory neurons of the reticular nucleus and thalamocortical neurons. It is influenced by the intrinsic properties of these neurons and by cortical and brainstem inputs. It has been speculated that extreme spindles are caused by the disruption of regulatory mechanisms, including GABAergic inhibitory circuits [5], but the exact mechanism responsible for extreme spindles is unknown. Previous studies provide evidence for preferential disruption of GABAergic circuits in the context of NMDAR hypo-activity states such as anti-NMDAR encephalitis [6,7]. Based on these reports, we consider that extreme spindles might be a characteristic finding in the early stage of anti-NMDAR encephalitis, before more extensive brain dysfunctions occurs. In support of our speculation, Mohammad et al. studied 119 children with encephalitis (including 11 children with anti-NMDAR encephalitis) and detected extreme spindles in four patients (4/11 children with anti-NMDAR encephalitis and 4/119 children with encephalitis) [8]. Shibazaki et al. reported that mature sleep spindle bursts are present by 3 months and are similar to those seen in adults [9]. They also noted that extreme spindles might be due to lesions in structures of the cerebral cortex or thalamus. Thus, we do not consider that extreme spindles have a close relationship with the age of onset.

Anti-NMDAR encephalitis is one of the most common types of encephalitis in children. Early diagnosis and treatment can improve the neuropsychiatric prognosis of patients with this condition. However, in young children the condition can initially present with vague symptoms, including disrupted speech and sleep patterns, and motor dysfunction; therefore, diagnosis and treatment are often delayed [10]. We propose that early EEG monitoring of this type of encephalitis might be necessary to detect not only the EDB pattern, but also non-specific findings, including extreme spindles.

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