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Extreme delta brush guides to the diagnosis of anti-NMDAR encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatable but often misdiagnosed autoimmune encephalitis. Diagnosis depends on NMDAR antibody testing, which may not be readily available. Alternatively, the electroencephalogram (EEG) extreme delta brush pattern may provide a valuable immediate indicator for the diagnosis of anti-NMDAR encephalitis. A 32-year-old female (case 1) presented with fever, headache, behavioral changes, confusion, intractable seizures, central hypoventilation, dysautonomia, facial and limb dyskinesias, and comorbid ovarian teratoma. Cerebral spinal fluid (CSF) testing revealed mild lymphocytic pleocytosis while brain MRI results were normal. A 45-year-old male (case 2) presented with major behavioral changes and rare seizures. Results of routine CSF testing and brain MRI scanning were unremarkable. In both cases, EEG initially revealed the extreme delta brush (EDB) pattern of beta bursting on the peaks and/or the troughs of delta waves, which led to subsequent NMDAR antibody testing and the confirmative diagnosis. Thus, EDB may be a readily accessible sign for suspected anti-NMDAR encephalitis.

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1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disease associated with serum antibodies against functional NMDA receptors. It is characterized by prodromal symptoms of a flu-like disease, and may progress to psychosis, memory deficits, seizures, dyskinesia, autonomic and breathing instability, and decreased consciousness. The disorder predominantly affects children and young adults with or without tumor (usually an ovarian teratoma in women) [1,2]. The disorder is often misdiagnosed as viral encephalitis, neuroleptic malignant syndrome, or psychosis. Despite the severity of the disorder, patients often respond well to tumor removal and immunotherapy [1]. Prompt diagnosis and treatment of anti-NMDAR encephalitis will improve outcome.

The electroencephalogram (EEG) may be useful for diagnosis of anti-NMDAR encephalitis. In many patients, EEG shows non-specific, slow, and disorganized background activity [1,2]. However, in 2012 the "extreme delta brush" (EDB) pattern, characterized by beta bursts riding on delta waves, was recognized as a unique EEG pattern in some patients with anti-NMDAR encephalitis [3]. Since the original seven patients reported by Schmitt et al. [3], a few more cases have been reported with EEG showing EDB, with beta bursts not only riding on the peaks but also on the troughs of delta waves [4–7]. Recently, we obtained EEG recordings from two Chinese patients showing EDB, both of whom were subsequently shown to have anti-NMDAR encephalitis by antibody testing.

2. Case presentations

2.1. Case 1

A 32-year-old female was admitted with headache, fever, and behavioral changes of five days' duration. On admission, temperature was 38.9 °C and she was mentally confused. Motor examination revealed withdrawal of all extremities from noxious stimuli. Other reflexes were also normal, plantar responses were flexor, and meningeal signs were negative. Results of brain magnetic resonance imaging (MRI) examinations, including T1-weighted, T2-weighted, DWI, and FLAIR imaging, were normal with no visible enhancements. On lumbar puncture, cerebral spinal fluid (CSF) pressure was 160 mm H_2O. Examination of CSF revealed a white blood cell count of 50/μL (mild pleocytosis), 0.26 g/L protein, and 3.6 mmol/L glucose (blood glucose 5.7 mmol/L). Laboratory results, including routine blood tests, liver, renal, and thyroid function tests, anti-nuclear antibody, and C-reactive protein, were all unremarkable. Bacterial cultivation from CSF was negative. Although herpes simplex virus immunoglobulin M and G antibodies were negative, intravenous acyclovir was empirically administered under the suspicion of herpes simplex encephalitis (HSE). From hospital day 3 (d3), the patient experienced recurrent episodes of seizure, so levetiracetam (1000 mg/d) and valproate sodium (1200 mg/d) were added. On hospital d8, the patient was intubated because of respiratory failure and assisted by a mechanical ventilator.

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After 20 days' treatment with acyclovir and anticonvulsants, the patient's neurologic state was worse. Seizures were not controlled, and were accompanied by frequent facial and limb dyskinesias. The HSE diagnosis was re-evaluated. On d20, a 30-min recording from a bed-side 8-channel EEG showed EDB with beta bursts riding on the peaks and troughs of delta waves (Fig. 1A), suggesting anti-NMDAR encephalitis. The indirect immunofluorescence technique (IIFT) revealed NMDAR antibody titers of 1:10(+++) in CSF and 1:10(++) in blood, confirming the diagnosis. Treatment with a five-day course of immunoglobulin (400 mg/kg·d, d20–24) and methylprednisolone (500 mg/d, d20–24) was ineffective. An ultrasound demonstrated a cystic mass in the left ovary. On d40, the patient underwent left adnexectomy and cystic teratoma of the ovary was confirmed by pathology. Treatment with a second five-day course of immunoglobulin (400 mg/kg·d, d41–45) and methylprednisolone (500 mg/d, d41–45) was introduced, followed by aggressive immunotherapy with rituximab (375 mg/m^2 once weekly, d75, d82, d89, d96) and cyclophosphamide (750 mg/m^2 once monthly, d76, d106, d136, d166, d196, d226). Five months later, the patient was seizure-free on anticonvulsants. A second 30-min bed-side EEG recording obtained on hospital d185 showed resolution of EDB (Fig, 1B). She was extubated on d201. Seven months later, the patient was still unconscious and could not obey orders such as to opening eyes or moving limbs, but she could respond to external stimuli.

2.2. Case 2

A 45-year-old male presented with delusions, abnormal behavior, and a history of seizure. Six months prior to admission, the patient experienced an episode of tonic–clonic seizure. Three months prior to admission, he experienced another episode of tonic–clonic seizure. Thereafter, he had hallucinations and delusions and was easily irritated, although he did not complain of headache, nausea, or fever. He was brought to a psychiatric unit where he was diagnosed with psychosis and secondary epilepsy. CT scanning of the head was normal. After treatment with quetiapine (600 mg/d), oxcarbazepine (1200 mg/d), and valproate sodium (1000 mg/d) for 20 days, he fell into a state of akinetic mutism and stayed in that hospital for another 2 months. To check for possible etiologies, he was transferred to our hospital.

On admission, he was still in a state of akinetic mutism and could not answer questions or follow verbal commands. T1-weighted, T2-weighted, DWI and FLAIR brain MRI scans were normal. Lumbar puncture showed CSF pressure of 90 mm H_2O. Examination of CSF revealed 0/μL white blood cells, 0.25 g/L protein, and 3.4 mmol/L glucose (blood glucose 5.1 mmol/L). Tests for multiple viral pathogens including herpes simplex virus were negative. On hospital d5, video-EEG with 24 hour recording showed EDB with beta bursting mostly on the troughs of the delta waves (Fig. 2), suggesting anti-NMDAR encephalitis. NMDA receptor antibody titers were 1:10(++) in CSF and 1:10(+) in blood as measured by IIFT. Tests for anti-Hu, anti-Yo, anti-Ri, anti-Ma, anti-amphiphysin, and anti-voltage gated potassium channel antibodies were all negative. Testicle ultrasound and whole-body PET were normal. Treatment with a five-day course of immunoglobulin (400 mg/kg·d, d11–15) and methylprednisolone (500 mg/d, d11–15) was administered under the diagnosis of anti-NMDAR encephalitis, and the patient came out of the akinetic mutism state and was able to interact in a simple way. On d36, aggressive immunotherapy with cyclophosphamide (750 mg/m^2) was introduced, and then the patient was discharged home. Oxcarbazepine was continued, while quetiapine and valproate sodium were tapered off. One month after discharge, the patient could perform activities of daily living and refused another course of immunotherapy with cyclophosphamide. At 6 month follow-up by phone, the patient stated he was working as a cook.

3. Discussion

Anti-NMDAR encephalitis is a severe but treatable autoimmune disorder that depends on sensitive and specific NMDAR antibody testing for definitive diagnosis [8,9]. In many regions, such tests may not be readily available. Moreover, brain MRI is unremarkable or shows only non-specific signal changes, while routine CSF testing may reveal mild lymphocytic pleocytosis and normal or mildly increased protein concentration [1]. Thus, MRI and routine CSF tests cannot provide specific results for preliminary diagnosis of anti-NMDAR encephalitis. In 2012, Schmitt et al. [3] identified a novel EEG pattern in 7 of 23 patients with anti-NMDAR encephalitis termed EDB because of its resemblance to the neonatal EEG pattern known as delta brush. From the small number of patients studied, the sensitivity was 30.4% (7/23).

We report two cases of anti-NMDAR encephalitis with distinct presentation and clinical course. Case 1 exhibited the more typical clinical symptoms, including fever, headache, psychosis, intractable seizures, central hypoventilation, dysautonomia, facial and limb dyskinesias, and comorbidity with ovarian teratoma. CSF testing showed mild lymphocytic pleocytosis, while brain MRI was normal. Case 2 exhibited a less common pattern of current psychosis and history of seizure, but no central hypoventilation or facial dyskinesia. Routine CSF and brain MRI results were both unremarkable. The two patients were first misdiagnosed as having HSE and psychosis, respectively. Once EDB was recognized on EEG, anti-NMDAR encephalitis was suspected and later confirmed by the presence of NMDAR antibodies in CSF and blood.

Extreme delta brush is characterized by rhythmic delta activity at 1–3 Hz with superimposed bursts of rhythmic 20–30 Hz beta activity "riding" on each delta wave [3], so the filter band pass must be 1–70 Hz to capture EDB. Benzodiazepine and barbiturate were not used in our patients, so benzodiazepine- or barbiturate-induced beta activity could be ruled out. Otherwise, only an 8-channel EEG was needed as it is suitable for severe patients on mechanical ventilation.

It is significant that two patients with markedly different clinical presentations both showed EDB. Alteration of NMDAR-mediated currents by antibodies could alter rhythmic neuronal activity, manifesting as

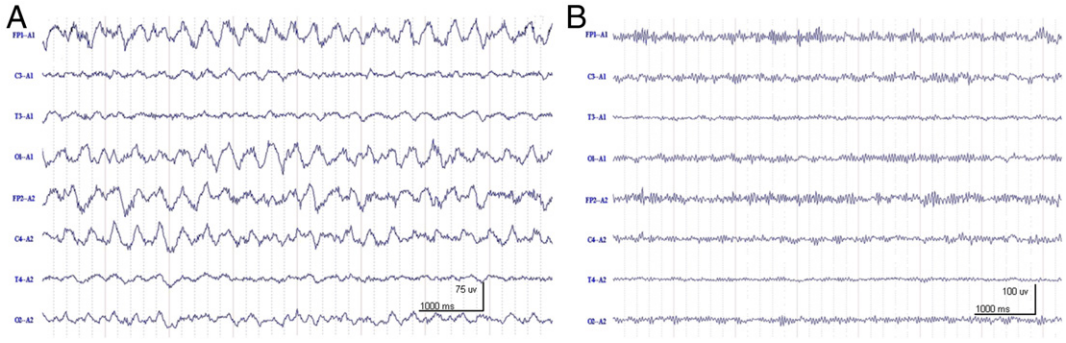

Fig. 1. Electroencephalographic recordings from case 1. A: EEG records obtained with a bed-side 8-channel EEG showing bilateral whole brain fast activity at 20–25 Hz (β bursts) riding on the generalized rhythmic delta activity, a pattern termed the extreme delta brush (EDB). B: EEG showing resolution of EDB. High-pass filter 1 Hz; low-pass filter 70 Hz; notch filter off.

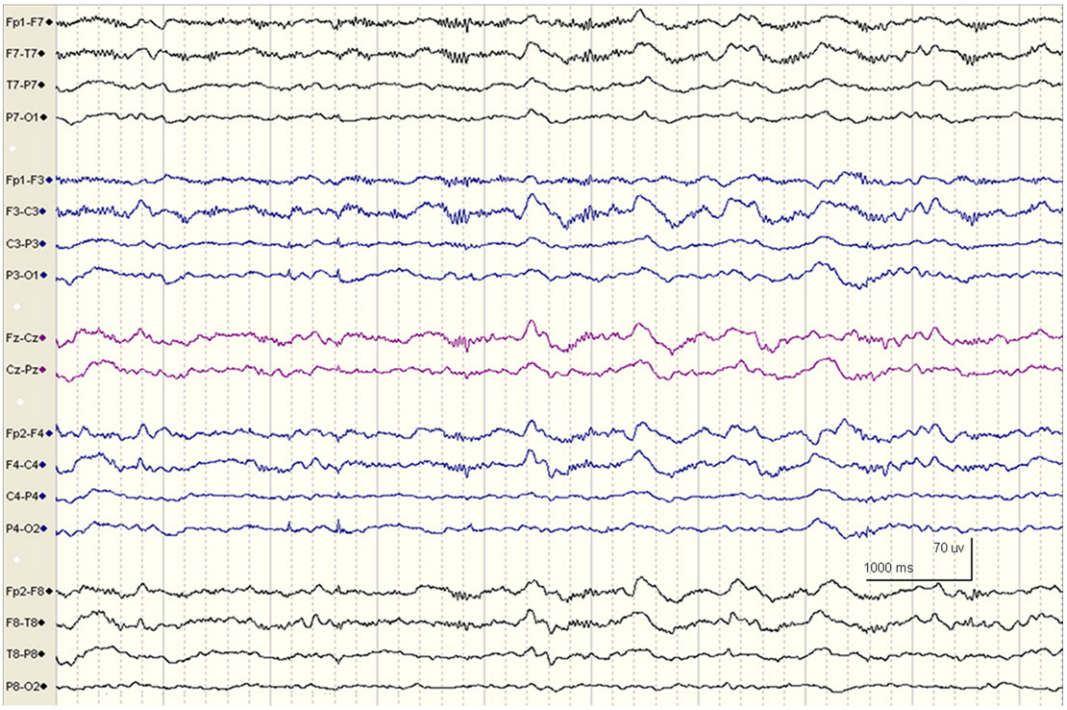

Fig. 2. Electroencephalographic recordings from case 2. EEG shows bilateral frontal-predominant fast activity at 20–25 Hz riding on the generalized rhythmic delta activity, an EDB pattern with beta bursting mostly on the troughs of delta waves. High-pass filter 1 Hz; low-pass filter 70 Hz; notch filter off.

EDB [3,10]. Thus, EDB may represent NMDAR dysfunction and so provide additional information for the diagnosis of anti-NMDAR encephalitis, especially for patients with uncommon presentation such as our case 2 and another recently reported patient [4]. Moreover, the fine characteristics of the EDB may predict outcome. Previous reports have found beta bursting mainly riding on the peaks or/and mainly on the troughs of the delta waves [3–7]. Our case 1 showed beta bursting riding on both peaks and troughs of the delta waves and the patient exhibited poor outcome, while our case 2 showed EDB mainly on the troughs of the delta waves and exhibited good outcome. Future studies are needed to determine whether the delta-wave phase of beta bursting correlates with clinical severity, clinical course, and/or prognosis.

This was a retrospective study, and EEG was not used for seizure monitoring. Intractable seizure was a prominent clinical feature of case 1 and was then controlled with treatment, while seizure EEG was not recorded by the attending physicians for case 2. EEG monitoring is recommended for suspected anti-NMDAR encephalitis as a previous case exhibited prolonged nonconvulsive status epilepticus (SE) [11]. Although we cannot completely exclude nonconvulsive SE in case 1, the second EEG test (Fig. 1B) under anticonvulsant therapy showed no such activity. Similarly, the EEG for case 2 during akinetic mutism (Fig. 2) precluded nonconvulsive SE. Moreover, due to the lack of serial EEG records, we had no information on dynamic EEG changes with treatment. Whether serial EEG findings can be used as a measure of treatment response requires further clarification [7].

The prognosis of anti-NMDAR encephalitis is correlated with antibody titers in CSF and serum [8,9]. Case 1 had higher antibody titers in CSF and serum than case 2 and much poorer outcome, so EBD and antibody titers may be complementary prognostic indicators, a question that also warrants further study.

In conclusion, EBD is a unique EEG pattern in anti-NMDAR encephalitis. As this phenomenon has only been reported in a small number of patients, the diagnostic sensitivity and specificity of EBD warrant further investigation. EDB accompanied by other clinical signs of anti-NMDAR encephalitis could be indicators for prompt immunotherapy prior to antibody testing.

Conflict of interest

The authors have no conflicts of interest to disclose.

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