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Case report

EEG-Delta brushes in DPPX encephalitis – Welcome to the club

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ABSTRACT

Background: Extreme Delta Brushes are a rare interictal EEG pattern that was first described in NMDA-R encephalitis and has been considered a pathognomonic pattern for this subtype of autoimmune encephalitis. Recently, extreme delta brushes have been described as a rare EEG phenomenon in other forms of encephalitis.

Case report: We describe to our knowledge the first occurrence of EEG Delta brushes in DPPX encephalitis. In this article, we present a comprehensive case report and discuss clinical differential diagnosis with special emphasis on the diagnostic value of the EEG, leading the way to the correct diagnosis. We also present current diagnostic criteria and clinical screening scales for initial evaluation for patients with suspected autoimmune encephalitis.

1. Case report

A 51-year-old male patient was admitted to our center for a variety of symptoms that had started acutely 5 years earlier with fatigue, hypersomnia, concentration deficits and personality changes with mood instability. Walking disturbances and muscle pain predominantly in the upper legs were noticed. Moreover, the patient described involuntary jerky movements of both arms and the head, intermittent task specific tremor of both hands and a feeling of hypersensitivity towards touch. In addition, he experienced dysautonomous symptoms such as urinary hesitancy, obstipation and erectile dysfunction as well as excessive weight loss (−40 kg within 4 months) and hypersomnia. The previous workups had revealed no underlying illness and the patient had been treated for depression at the time of presentation.

On neurologic examination, he presented with pronounced startle response for tactile but also auditory stimuli as well as cerebellar dysfunction with a marionette-like broad-based gait, limb ataxia and saccadic eye movements. Furthermore, hyperreflexia and leg spasticity was observed. Neuropsychological testing revealed moderate memory deficits, slight attention deficits and moderate deficits in executive function. Brain MRI was consistent with microvascular leukoencephalopathy (Fazekas Grade 1). The routine blood examination was normal. FDG-PET showed unspecific enhancement in the colon without any corresponding findings in colonoscopy. CSF analysis showed normal cell count, elevated protein (843 mg/l) and intrathecal IgG synthesis with CSF-specific oligoclonal bands. The EEG on admission displayed normal background activity, but intermittent frontal fast activity superimposed on high amplitude periodic delta waves (Fig. 1). This EEG pattern has recently been included in the current ACNS classification of critical care EEG terminology (Hirsch et al., 2021) as extreme delta brushes (EDB). Of note, the EEG in our case showed blunt periodic delta waves with superimposed fast activity with a stereotyped relationship to the delta wave, fulfilling the ACNS criteria of definite periodic EDB (Hirsch et al., 2021). To confirm this EEG finding, a 20-minute standard EEG in wakefulness was repeated 3 days later, showing the identical frontal EEG pattern (Fig. 2A). Importantly, the recorded beta activity was still time-locked to the delta waves and with bifrontal predominance, ruling out electrode or muscle artifacts as the source of intermittent beta oscillations. Extreme delta brushes are regularly observed in anti-NMDAR and rarely in other forms of autoimmune encephalitis. Therefore, these findings triggered subsequent antibody testing in serum and CSF for autoimmune encephalitis. The diagnostic criteria for possible autoimmune encephalitis according to Graus criteria (Graus et al., 2016) were fulfilled, the APE2 score was 4 points suggesting a high pre-test probability of autoimmune etiology of the encephalitis (Dubey et al., 2019). Serum and CSF were positive for dipeptidyl-peptidase-like protein 6 (DPPX) antibodies and negative for all other tested autoantibodies commonly observed in autoimmune encephalitis (including anti-NMDAR antibodies). The patient was treated with high-dose corticosteroid pulse therapy and plasma exchange, which mildly improved gait ataxia and

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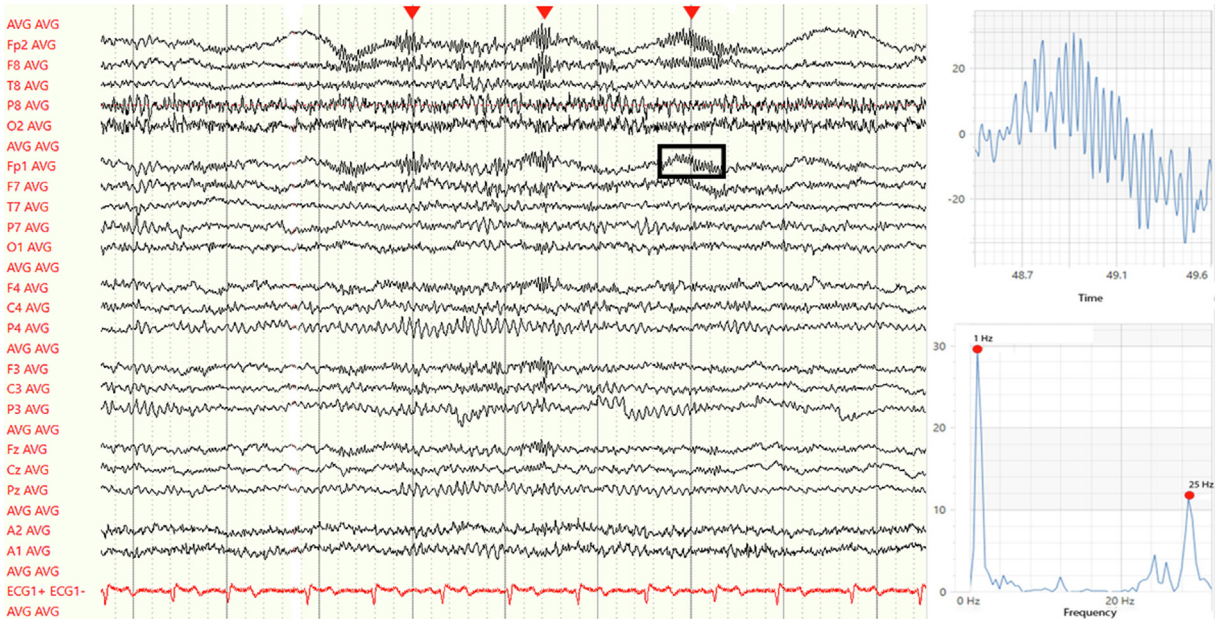

Fig. 1. Electroencephalography upon admission. A: series of extreme delta brushes are visible in the frontopolar EEG channels showing the typical pattern of high-frequency beta activity superimposed on periodic blunt delta waves (marked with red triangles). One "*extreme delta brush*" (black rectangle) is highlighted in the right panels. The upper right panel shows the enlarged detail section of the EEG in an epoch of 1 s (enlarged in the right upper panel). The power spectrum of this epoch (lower right panel) displays the mixed frequency spectrum of beta activity (20–30 Hz) and delta activity (peak at 1 Hz). Importantly, the frontal intermittent fast activity is in stereotyped association with the periodic delta activity and not present in delta down-states. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cognitive deficits. Follow up EEG after 4 weeks showed a complete remission of the encephalopathic EEG pattern, including the EDB (Fig. 2B). Maintenance treatment with 2 cycles of 375 mg/m^2/cycle rituximab 6 months apart led to a slow, but steady and marked improvement of fatigue, coordination deficits and autonomic dysfunction including hypersomnia and bowel dysmotility.

2. Discussion

Extreme delta brushes are a phenomenon observed in 30 to 60% of all patients with anti-NMDAR encephalitis (Hara et al., 2017; Jeannin-Mayer et al., 2019). The pattern was initially considered pathognomonic for anti-NMDAR encephalitis, but has been shown to occur rarely in other encephalitic syndromes as well (Baykan et al., 2018; Farias-Moeller et al., 2017). Here, we report to our best knowledge the first case of anti-DPPX encephalitis-related extreme delta brush-EEG. Of note, the unusual EEG-pattern and the CSF-specific oligoclonal bands, as well as the positive APE score triggered the rapid serological testing for autoimmune encephalitis, which led to the correct diagnosis.

Anti-DPPX encephalitis is a rare type of autoimmune encephalitis, which has first been described by Boronat et al. (2013). About 40 cases have been published so far (Zhou et al., 2020). DPPX is a subunit of the Kv4.2 potassium channel regulating the membrane potential of neurons in the hippocampus, cerebellum and myenteric plexus (Boronat et al., 2013). The widespread distribution of the receptors explains the multifocal disease manifestations. Patients often report diarrhea and significant weight loss before they become neurologically manifest with symptoms of CNS hyperexcitability (hyperekplexia, myoclonus, tremor, muscle rigidity or seizures) and cognitive dysfunction. Additionally, sleep disorders, sensory symptoms, and autonomic dysfunction have been reported, most of which were presenting symptoms in our case. Some cases are associated with B cell neoplasia, suggesting a possible paraneoplastic etiology (Hara et al., 2017). This comprehensive review also revealed a considerable male predominance of published DPPX cases with approximately-two-third of all cases being male (Hara et al., 2017). The prevalence and severity of many autoimmune diseases differ between male and female patients suggesting sex-related differences in autoimmune dysregulation. Sex hormones, sex chromosome-encoded immune factors, sex-related epigenetic dysregulation, or sex-related differences in gut microbiota are discussed as factors influencing sex association in autoimmune disease (Ngo et al., 2014; Selmi and Gershwin 2019). Until now, it is not clear which of these factors are responsible for the male preponderance in DPPX encephalitis. In clinical routine diagnostics, patients with DPPX encephalitis may present with mild CSF pleocytosis, unspecific MRI lesions and diffuse slowing in the EEG. Our case corroborates the diagnostic value of EEG in the assessment of patients with unclear encephalopathy or suspected encephalitis. While extreme delta brushes are not unique to anti-NMDAR encephalitis, its occurrence should trigger testing for autoimmune encephalitis in diagnostically unclear cases.

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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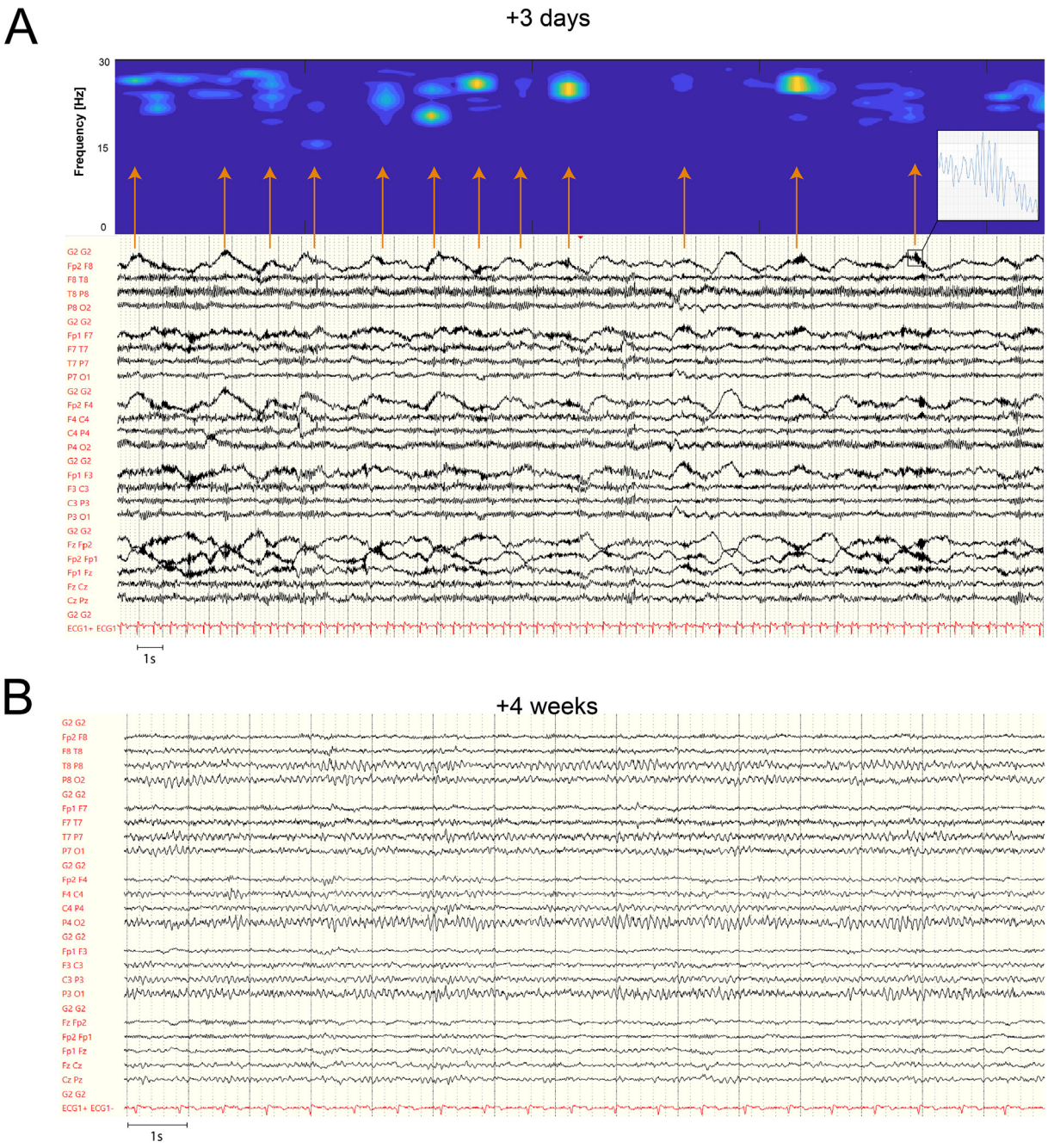

Fig. 2. EEG recording 3 days (A) and 4 weeks (B) after initial presentation. A: 3 days after admission, the EDB pattern persisted. EEG shows unchanged high-frequency beta activity superimposed on periodic blunt delta waves in a 40 s EEG epoch. In this time resolution, the sinusoid beta activity is only visible as short beta bursts in the surface-negative delta up-phase (inlet in panel A shows one enlarged beta burst). Time-frequency spectrum confirms the time-locked co-occurrence of delta and beta waves (arrows). B: EEG after 4 weeks shows complete remission of the pathological EEG pattern and a normalization of background activity.

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