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Letter to the Editor

High frequency oscillations (HFOs) as a unique pattern of EEG in a patient with anti-NMDA receptor encephalitis

1. Introduction

Anti-NMDA receptor (NMDAR) encephalitis is an autoimmune paraneoplastic disorder caused by antibodies targeting the extracellular epitopes of GluN1 (NR1) subunit resulting in alteration of synaptic function. Initially described in an adult female with ovarian teratoma it typically presents with psychiatric symptoms, dyskinesias, dysautonomia, and seizures (Dalmau et al., 2011).

Considering its high mortality (25%) and association with malignancy while being responsive to treatment, an early diagnosis is crucial. Therefore, a set of diagnostic criteria for definite and probable disease has been proposed (Graus et al., 2016). Accordingly, a definitive diagnosis requires one clinical symptom plus positive serum or CSF antibodies to the NMDAR. However, since antibody levels cannot be available at the presentation, a probable diagnosis would require the presence of four major clinical symptoms plus either an abnormal electroencephalography (EEG), or cerebrospinal fluid (CSF) pleocytosis, or oligoclonal bands (Dalmau et al., 2011).

Among the supportive tests, EEG can often be obtained rapidly which would facilitate a probable diagnosis while awaiting the antibody results. Therefore, establishing specific EEG markers in these patients can be of significant diagnostic value by differentiating suspected cases of anti-NMDAR encephalitis from primary psychiatric diseases. Several nonspecific EEG patterns including focal or diffuse slowing, disorganized activity, and epileptiform discharges have been reported in these patients. Schmitt et al., have reported a more specific pattern, i.e., extreme delta brush (EDB) in patients with anti-NMDAR encephalitis (Schmitt et al., 2012).

High frequency oscillations (HFO) constituting frequencies above 80 Hz are considered a biomarker of epileptogenic zones (Jiruska et al., 2017). Animal studies indicate an association between HFOs and increased synaptic activity, acquired channelopathies, and neuronal loss (Jones et al., 2015). Here we present a case of HFOs as a unique EEG pattern in a patient with anti-NMDAR encephalitis.

A previously healthy 27-year old woman was admitted to an outside hospital for new onset episodes of confusion, slurred speech, and convulsions lasting 30 min. Three days later, she had a witnessed convulsive seizure, lasting 1–2 min. She had two more similar convulsions in the emergency room. She had normal brain MRI, MR venography, and routine EEG. Serum was negative for HIV, syphilis, and Lyme disease. CSF showed mild pleocytosis, 8 white blood cells (WBC), normal red cell count, normal glucose and protein, negative human herpes simplex virus 1 and 2. Bacterial culture was negative. She was started on levetiracetam and was discharged home. Two days later she developed more frequent episodes of confusion and strange behavior, using profanity and inappropriate remarks, new stereotyped episodes in sleep consisting of screaming and stiffening of her entire body followed by hand posturing ("claw like position"), smiling and laughing, and whole body shaking. She was admitted to our hospital. Her neurological exam was intact between these episodes, except for a score of 17/30 on the Montreal cognitive assessment (MoCA). A second brain MRI with contrast was normal. A second lumbar puncture showed worsening pleocytosis (24 WBC; 89% lymphocytes, 0% neutrophils). CSF paraneoplastic panel and extensive viral and bacterial studies were sent. Long-term video-EEG recorded six events of slurred speech, eye fluttering, emotional lability, and subtle shaking that were not associated with any ictal discharges. However, interictally, there were occasional bursts and brief runs of sharp discharges in the left fronto-central head regions (Fig. 1A) with overlapping HFOs. Over the course of a 4-day EEG recording this pattern evolved into frequent bursts and runs of semi-rhythmic delta activity with more pronounced overlapping HFOs in the left frontal leads, at times propagating to the right, with occasional monophasic sharp discharges in the fronto-temporal leads more pronounced on the left (Fig. 1B and C). These discharges were not associated with abnormal clinical activity although she had a convulsive seizure while being off EEG monitoring. Given her clinical presentation and CSF pleocytosis, a diagnosis of probable autoimmune encephalitis was made, and she was started on intravenous methylprednisolone 1000 mg daily for five days and levetiracetam was replaced with oxcarbazepine with no further seizures and significant improvement in her behavior.

On day 19 since the initial clinical presentation the CSF anti-NMDAR antibody came back positive (titer 1:40). The remaining paraneoplastic, autoimmune, and infectious CSF studies were all negative. This finding confirmed a definite anti-NMDAR encephalitis. Whole body imaging and transvaginal ultrasound ruled out neoplasm or adnexal mass.

Her symptoms continued to improve with no further seizures or confusion. She was transitioned to prednisone and rituximab. In follow-up she showed progressive cognitive improvement with no seizures. Positron emission tomography (PET) scan on day 34 showed two small abutting foci of FDG accumulation in the left frontal lobe of unclear etiology and with no MRI correlate at the respective site (Fig. 1D). A repeat EEG 5 month after discharge was normal.

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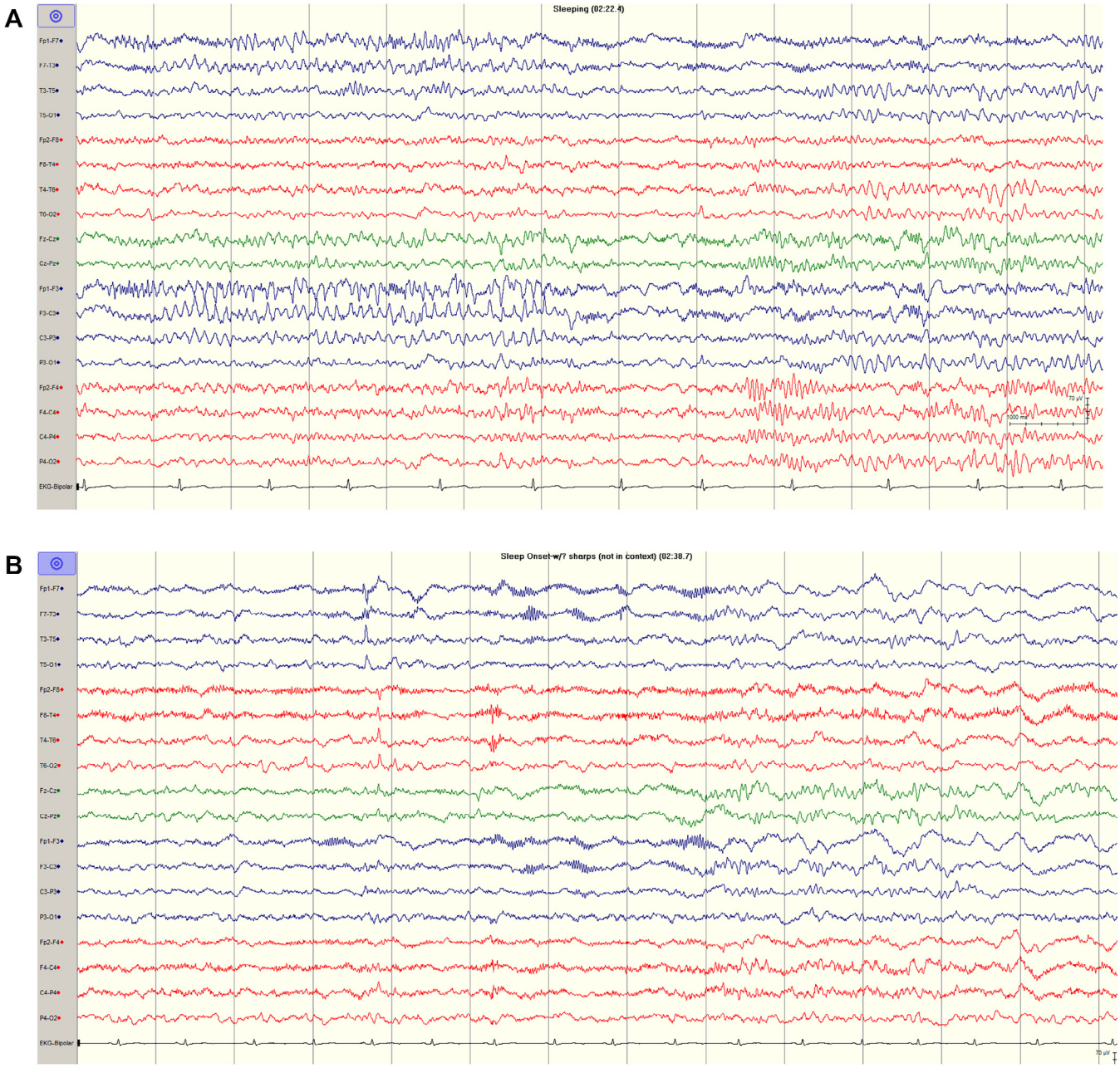

Fig. 1. Standard 30 mm/s EEG traces recorded using 10–20 electrode system; longitudinal montage, 1–100 Hz, sampling rate 512 Hz. (A) A single mono-phasic sharp discharge in the fronto-temporal head regions, more pronounced on the left, precedes delta slow activity and high frequency oscillations (HFOs). (B) A brief run of left fronto-central sharp discharges (max F3 electrode) with overlapping HFOs. (C) Runs of delta slow activity maximally present in the left frontal head regions with overlapping HFOs in the left frontal leads (electrodes FP1, F7). (D) Positron emission tomography; two small abutting focus of FDG accumulation in the left frontal lobe (arrow).

Schmitt et al. have demonstrated that 7 of 23 patients (30.4%) with positive anti-NMDAR antibody had a characteristic generalized rhythmic and semi-rhythmic 1 Hz delta activity with superimposed, frontally predominant bursts of rhythmic beta discharges (Schmitt et al., 2012). This pattern was seen in more severe disease and was associated with prolonged hospital stay and worse outcome. A recent nationwide cohort study showed that abnormal EEG has a high sensitivity in anti-NMDA encephalitis (96%), however EDBs were only present in severe cases. Other non-specific EEG patterns such as ictal sharp and slow waves, unilateral rhythmic delta activity, and generalized rhythmic patterns have been reported in anti-NMDAR encephalitis, but most of these patients had non-convulsive status epilepticus.

This case may offer new insight into the diagnostic and prognostic values of EEG in anti-NMDA encephalitis. This patient's EEG showed progression from a nonspecific pattern of rhythmic sharp discharges to more pronounced HFOs and delta activity, most pronounced in the left frontal regions correlating with her PET scan finding (either a comorbidity or a consequence of HFO discharges). In our patient, no electrographic or clinical seizures arose from the HFOs, which are distinct from patients with EDB pattern where the seizures usually arise from the overriding fast discharges

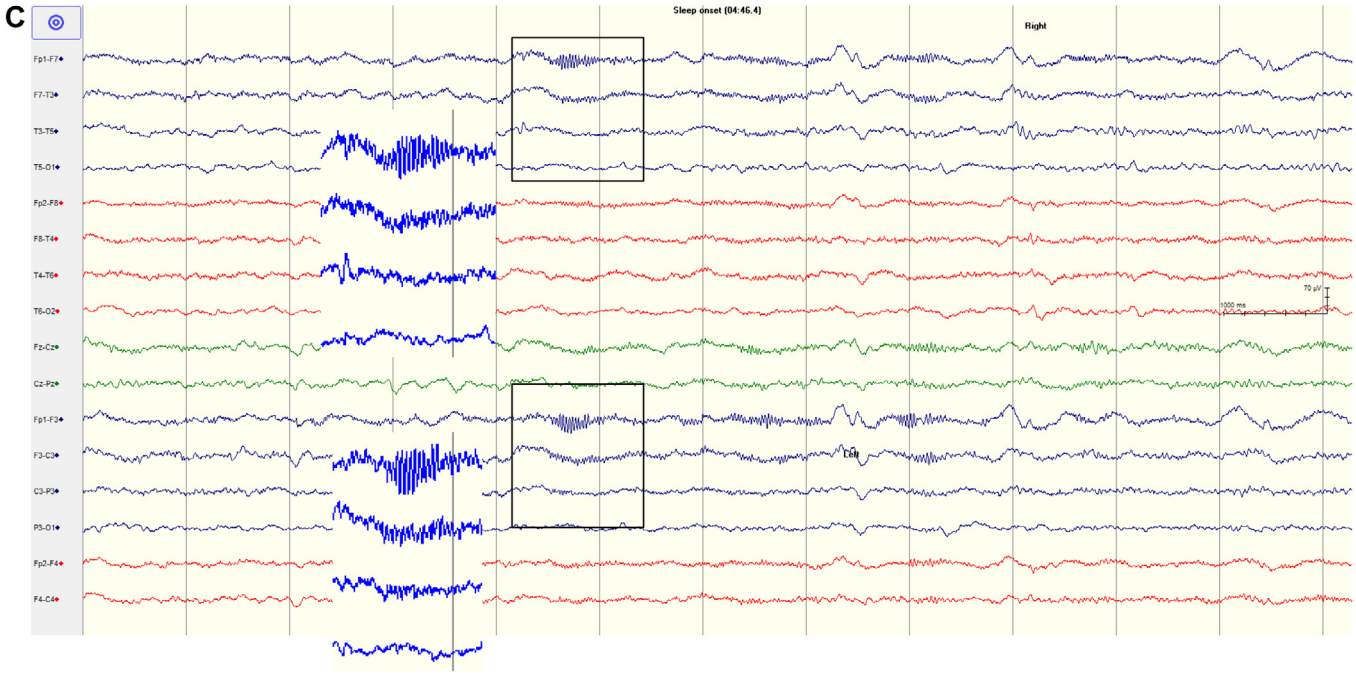

Fig. 1 (*continued*)

(Schmitt et al., 2012). This may suggest HFOs as a marker for favorable outcome.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to disclose.

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