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Scalp-recorded high-frequency oscillations in atypical benign partial epilepsy

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HIGHLIGHTS

- Before methylprednisolone treatment, HFOs in ABPE patients were more prevalent than in BECTS.
- ABPE patients with HFOs tended to have more frequent epileptic negative myoclonus/atypical absences than those without HFOs.
- Methylprednisolone treatment in ABPE patients significantly reduced both spikes and HFOs.

ABSTRACT

Objective: To investigate how high-frequency oscillations (HFOs) were affected by methylprednisolone treatment and the clinical significance of HFOs in patients with atypical benign partial epilepsy (ABPE).
Methods: In 14 ABPE patients with methylprednisolone treatment, we measured interictal HFOs and spikes during sleep in pre- and post-methylprednisolone scalp electroencephalography (EEG). Patients with benign childhood epilepsy with centrotemporal spikes (BECTS) were taken as control.
Results: Before methylprednisolone treatment, 10/14 ABPE patients had HFOs, with a mean value of 85.79 per 60 s per patient, while 2/14 BECTS patients had HFOs with a mean value of 1.86 per 60 s per patient ($p = 0.006$). The 10 ABPE patients with HFOs tended to have more frequent epileptic negative myoclonus/atypical absences than the other 4 ABPE patients without HFOs. Rates reduced by methylprednisolone treatment were statistically significant for both spikes ($p = 0.027$) and HFOs ($p = 0.005$). The percentage of reduction was 41.8% (4653/11,133) and 95% (1141/1202) for spikes and HFOs, respectively.
Conclusion: Proportion and rates of HFOs in ABPE were more prevalent than in BECTS. HFO rates reduced by methylprednisolone treatment might be more significant than spike rates.
Significance: Prevalence of HFOs reflected at least some aspect of epileptic severity of ABPE. HFOs were more sensitive to methylprednisolone treatment than spikes.

1. Introduction

High-frequency oscillations (HFOs, ripples: 80–250 Hz, fast ripples: 250–500 Hz) in electroencephalography (EEG) have been associated with epileptogenesis (Melani et al., 2013) and ictogenesis (Staba et al., 2007; Urrestarazu et al., 2007). It has been established that HFOs are more specific in identifying the seizure onset zone than traditional spikes (Jacobs et al., 2008), and the removal of HFO-generating tissue correlates with a favorable post-surgical seizure outcome (Haegelen et al., 2013; Jacobs et al., 2008; Staba et al., 2002; Urrestarazu et al., 2007). Moreover, HFOs might increase after medication reduction (Zijlmans et al., 2009). Although HFOs were mostly identified with invasive recordings, scalp EEG was proved to be not a blur to record HFOs by using simultaneous scalp and intracranial recordings (Zelmann et al., 2014). Scalp-recorded HFOs were reported not only ictally, at the onset of epileptic spasms (Kobayashi et al., 2004) and in absence

Abbreviations: ABPE, atypical benign partial epilepsy; AED, antiepileptic drug; BECTS, benign childhood epilepsy with centrotemporal spikes; EEG, electroencephalography; EMG, electromyogram; ENM, epileptic negative myoclonus; ESES, electrical status epilepticus in sleep; HFO, high-frequency oscillation; NREM, non-rapid eye movement; SWI, spike-wave index.

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seizures (Chaitanya et al., 2015), but also interictally in idiopathic partial epilepsy (Kobayashi et al., 2011) and epilepsy with electrical status epilepticus in sleep (ESES), which included atypical benign partial epilepsy (ABPE) (Kobayashi et al., 2010).

ABPE has been considered to be an atypical variant of benign childhood epilepsy with centrotemporal spikes (BECTS). Such atypical electro-clinical evolutions could be seen in seizure characteristics (i.e., epileptic negative myoclonus (ENM), atypical absences, generalized tonic–clonic seizures) or EEG features (i.e., unusual location, atypical spike morphology, activation of epileptic discharges during sleep as ESES) (Fejerman, 2009). Some patients with ABPE develop mild-to-moderate cognitive problems (Hahn et al., 2001) and are resistant to antiepileptic drugs (AEDs). We previously reported the effectiveness of methylprednisolone in ABPE patients (Chen et al., 2014a). In the present study, we aimed to retrospectively investigate the presence of interictal HFOs in scalp EEGs in ABPE patients and evaluate whether HFOs were sensitive to methylprednisolone treatment.

2. Methods

2.1. Patients

A total of 97 patients were diagnosed to have ABPE in the Pediatric Department of Peking University First Hospital from January 2013 to December 2014. Fourteen consecutive patients were included in the study. The inclusion criteria were as follows: (1) Diagnosis of ABPE: (a) Clinical manifestations resembled BECTS during early course, but exhibited more severe seizures including ENM, atypical absences, and myoclonus; (b) EEG findings showed central and middle temporal spikes and sleep activation of spikes that evolved into ESES. ESES was defined as a condition in which the focal or diffuse spikes and waves became continuous with the spike–wave index (SWI) $\geqslant$50% during non-rapid eye movement (NREM) sleep; (c) variable degree of cognitive or behavioral disturbance occurred during the clinical course. (2) Three courses of methylprednisolone treatment: each course included methylprednisolone intravenous infusion at a dose of 15–20 mg/kg/d for 3 days, followed by oral administration at a dose of 1–2 mg/kg/d for 4 days. After three courses, prednisolone (1–2 mg/kg/d) was tapered off in 6 months. (3) Available EEG data in 1 month before and after methylprednisolone treatment. (4) SWI $\geqslant$ 85% during sleep in the pre-methylprednisolone EEGs. A complete description of the methods can be found in Supplementary Fig. S1.

From clinical records, we reviewed disease parameters, seizure types, antiepileptic medications, seizure frequencies, and the time lapsed from the last focal motor seizure to the EEG recording before methylprednisolone treatment and so on. Disease parameters included age at seizure onset and age at EEG recording before methylprednisolone treatment. As frequencies of ENM and atypical absences were hardly precisely determined using retrospective data, they were classified into frequently (occurring almost every day), occasionally, and none within 1 month before methylprednisolone treatment. We also classified frequencies of focal motor seizures within 6 months: <3 times, ~6 times and >6 times. Time lapsed from the last focal motor seizure to EEG recording before methylprednisolone treatment was classified into <3 months, ~6 months, and >6 months.

With regard to the seizure outcome after methylprednisolone treatment, we mainly focused on the control of ENM/atypical absences for at least 3 months, except that one child had focal motor seizures only during his seizure history and seizures recurred several days after the treatment. Therefore, 14 ABPE patients were classified into an excellent seizure outcome group (not suffering from any type of seizures for at least 3 months) and a not-excellent seizure outcome group (having a relapse within 3 months).

Control EEG data were obtained from 14 patients with BECTS. Diagnosis of BECTS was described by Loiseau and Beaussart (1973). These patients were subjected to at least two EEG recordings, and no SWI $\geqslant$25% in any of these recordings was noted. Disease parameters included the age at seizure onset and age at the selected EEG recording. Seizure types and antiepileptic medications before the selected EEG recording were also reviewed.

This study was approved by the Ethical Committee of Peking University First Hospital, and written informed consents were obtained from the legal guardians (parents) of the subjects.

2.2. EEG recording

EEG was recorded using the standard international 10–20 system, with a sampling frequency of 500 Hz (Neurofax; Nihon-Kohden, Tokyo, Japan). A low-cut filter at 0.016 Hz was used before digital sampling. A 4-h video-EEG monitoring with electromyogram (EMG) recorded from the bilateral deltoid muscles was performed. All children were tested with intermittent photic stimulation, hyperventilation, and the test of holding the arms outstretched to determine ENM. The sleep status for 30–60 min was recorded in all subjects and all recordings in this study.

2.3. Event identification

In each EEG record, continuous EEG segments with spindle waves and low EMG power of above 5 min were visually reviewed in a referential montage and selected as stage Ⅱ NREM sleep data. We then randomly selected artifact-free NREM sleep data with duration of 60 s. Two well-trained epileptologists analyzed the EEG data jointly, and they were blinded to clinical data. A consensus meeting of all investigators was held to define the markings as spikes and HFOs. The EEGs were analyzed in a referential montage of A1 and A2 earlobe electrodes. The conventional traces were initially reviewed to mark spikes (10 s/page, 15–30 μV/mm, LF: 0.53 Hz and HF: 70 Hz). Subsequently, the spike markers were made invisible, and we modified the sensitivity (3–5 μV/mm) and paper speed (1–2 s/page) with a low frequency of 80 Hz and a high frequency of 200 Hz to identify HFOs. A HFO was defined as one event containing at least 4 consecutive and regular oscillations with an amplitude distinctly higher than its surrounding background (Andrade-Valenca et al., 2011). After marking all events, one of the epileptologists reviewed the EEG segments for a second time for confirmation. HFOs had to be recurrent and with a frequency of more than 2 per 5 min to mark similar events in the selected 60-s EEG epoch.

The EEG segments containing visually inspected HFOs were further subjected to time frequency analysis using Morlet wave decomposition (Fig. 1). The analysis was performed using Matlab 6.9 (The Mathworks Inc., Natick, MA, U.S.A.) (Wang et al., 2013). On the time–frequency map of each inspected HFO, only a primary isolated peak in the frequency range of 80–200 Hz was defined as a true HFO.

2.4. Quantitative analysis

In the pre- and post-methylprednisolone EEGs of ABPE patients, we calculated the rates (events/60 s) of HFOs (if present), spikes, and their co-occurrence for each channel. If a HFO occurred with a spike, their highest amplitudes were also calculated. Further, in the selected EEGs of BECTS patients, the rates of HFOs (if present) were calculated as well.