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.

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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) >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 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 >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 >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.
2.5. Statistical analysis

Because the Shapiro–Wilk test indicated that the variables had similar normal distribution, we used unpaired t-test to compare (1) disease parameters between ABPE and BECTS and (2) disease parameters and rates of spikes between EEGs with (HFO-positive group) and without HFOs (HFO-negative group) before methylprednisolone treatment in ABPE patients. Fisher’s exact test was applied to investigate the proportion of HFOs in ABPE and BECTS. Before methylprednisolone treatment, seizure frequencies and time lapsed from the last focal motor seizure to the EEG recording between HFO-positive and HFO-negative groups of ABPE patients were compared by the Mann–Whitney U test.

For the association between spikes and HFOs in the pre-methylprednisolone EEG data, the relationship between the highest amplitudes of HFOs and that of these spikes was analyzed by calculating the correlation coefficient. In this comparison, the highest amplitudes of spikes and HFOs were converted into a logarithmic function to obtain a more Gaussian distribution.

Furthermore, we statistically compared the rates of spikes and HFOs in the pre- and post-methylprednisolone EEG data. Statistical analysis included paired samples t test and Wilcoxon for comparison of Gaussian and non-Gaussian data.

Fig. 1. Representative EEG traces and corresponding time–frequency spectra. (A) Raw EEG with the pattern of electrical status epilepticus in sleep during stage II non-rapid eye movement period. (B) Green section in A was expanded in time (1 s/page) and sensitivity (5 μV/cm) with a low-frequency filter of 80 Hz and a high-frequency filter of 200 Hz. (C) The representative time–frequency analysis for the channel P4 in B (red arrow) showed a clear isolated spectra spot in the 120–160 Hz range. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Statistical analysis was performed using SPSS 18. A p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical profiles

Clinical data obtained from 14 patients with ABPE (Table 1) and comparable patients with BECTS (Supplementary Table S1) were analyzed. In ABPE, seizure started as focal motor seizures in 13 patients (92.8%) and as atypical absences in 1 patient (7.1%). All patients except one had multiple seizure types during their epileptic histories. Besides focal motor seizures occurring in all patients, ENM occurred in 10/14 patients (71.4%) and atypical absences in 5/14 patients (35.7%). Other occasional seizure types included myoclonus, epileptic status, and secondarily generalized tonic–clonic seizures. Abnormal head magnetic resonance imaging findings because of perinatal injuries was found in patient 12#.

Thirteen children developed neuropsychological impairments during the course of the disease, such as deficits in attention, visuomotor skills, and a variety of specific language skills. All children were administered multiple AEDs ranging from 2 to 6 medications (mean 3.4) before methylprednisolone treatment. In BECTS, all the children had only focal motor seizures, and 0–3 medications (mean 0.8) were administered before the selected EEG recordings. There was no difference in disease parameters between patients with ABPE and BECTS.

3.2. HFO presence in patients with ABPE and BECTS

In the pre-methylprednisolone EEG data, HFOs were found in 10 of 14 ABPE patients (Table 1), with a mean value of 85.79 per 60 s per patient (range = 0–239). HFOs in the EEG data of BECTS patients were scarce (2/14) (Supplementary Table S1), with a mean value of 1.86 per 60 s per patient (range = 0–13). The proportion of HFOs was significantly higher in the pre-methylprednisolone EEG data of ABPE patients than in the control data (p = 0.006).

Before the methylprednisolone treatment of ABPE patients, disease parameters, spike rates, seizure frequencies, and time lapsed from the last focal motor seizure to the EEG recording were compared between HFO-positive and HFO-negative groups (Table 2). ENM/atypical absences in the HFO-positive group tended to be more often than those in the HFO-negative group (p = 0.011), while no significant difference was found in frequencies of focal motor seizures (p = 0.68), the time from the last focal motor seizure (p = 0.24), and other variables.

3.3. HFO characteristics in the pre-methylprednisolone EEG data

A total of 1201 HFOs and 11,133 spikes were found in the pre-methylprednisolone EEG data of ABPE patients. Of all the HFOs, 683 (56.9%) were associated with spikes, and the remaining 43.1% were isolated from spikes. Of all the spikes, 6.1% were associated with HFOs.

With respect to the 683 spikes and HFOs that were associated with each other, the correlation between the highest amplitudes of HFOs and that of spikes was analyzed (Fig. 2). Statistically, the highest amplitudes of HFOs were significantly positively correlated with those of spikes (R² = 0.077, p < 0.001).

3.4. Effects of methylprednisolone on electro-clinical aspects

Rates of spikes and HFOs in the pre- and post-methylprednisolone EEG data are shown in Fig. 3. Reduction in the rates was 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.

After three courses of methylprednisolone treatment, 11 ABPE patients did not suffer from any type of seizures for at least 3 months (excellent seizure outcome group); the other three had a relapse within 1 month after the treatment (not-excellent seizure outcome group). Because of the low number of patients in the not-excellent seizure outcome group, a statistical correlation between the changes in spikes/HFOs and the post-methylprednisolone seizure outcome was not possible. Instead, we analyzed the percent spike and HFO changes in each group. A difference in the percentage of spike changes was noted between the excellent seizure outcome and not-excellent seizure outcome groups (51.4% decrease in the excellent seizure outcome group vs. 8.6% increase in the not-excellent seizure outcome group). Similarly, a difference was found for the HFO changes (20.3% decrease in the excellent seizure outcome group vs. 7.7% decrease in the not-excellent seizure outcome group).

4. Discussion

In the current study, we detected interictal HFOs in the scalp EEG data of ABPE patients treated with methylprednisolone. Our main finding was that HFOs were prevalent in ABPE patients and were more sensitive to methylprednisolone treatment.

4.1. HFO prevalence in the pre-methylprednisolone EEG data of ABPE

Studies showed that the rates of HFOs were significantly higher in EEG data containing ESES than that containing focal spikes (Kobayashi et al., 2010) and parallel to frequencies of interictal epileptic discharges (Melani et al., 2013). Moreover, HFO rates might be related to the epileptic disease activity and varied largely across patients (Akiyama et al., 2011; Jacobs et al., 2008; Kerber et al., 2013). In the present study, a high rate of HFOs was observed in the scalp EEG data showing ESES before the methylprednisolone treatment, and the rates varied largely from 0 to 239 per 60 s. Both proportion and rates of HFOs were significantly higher in patients with ABPE than in the control patients with BECTS, indicating that the prevalence of HFOs reflected at least some aspect of epileptic severity of ABPE.

It is illustrated that the patient's age might play a role in HFO generation (Matsumoto et al., 2013) and the time from last seizure to EEG recording was shorter in EEGs with HFOs than in those without (Kobayashi et al., 2011). However, in our study, neither age nor time from the last focal motor seizure to the EEG recording should be the primary factor responsible for the presence of HFOs between HFO-positive and HFO-negative groups, as well as spike rates, given that there is no difference in these variables. This discrepancy might be related to our limited number of patients and the focus on time from the last focal motor seizure instead of frequent ENM/atypical absences. In the present study, ABPE patients with HFOs tended to have more frequent ENM/atypical absences than those without. This could be demonstrated in animal studies that HFOs were clearly linked to spontaneous seizures (Bragin et al., 2004). The close relationship between the occurrence of HFOs and seizure frequency indicated that HFOs might provide us more information about seizure propensity than spikes.

4.2. Relationship between HFOs and spikes

Spoke-associated HFOs accounted for 56.9% in all HFOs and 6.1% in all spikes in our study. This was in accordance with previous studies that interictal ripples were often (40–70% of all ripples)
<table>
<thead>
<tr>
<th>Pt No./#</th>
<th>Gender</th>
<th>Age at onset</th>
<th>Age at EEG recording before methylprednisolone treatment</th>
<th>Seizure types in seizure histories</th>
<th>Most common seizure Types</th>
<th>Personal history</th>
<th>Family history</th>
<th>Neuroimaging</th>
<th>Mental status change after onset</th>
<th>Medications used on treatment</th>
<th>HFO</th>
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<tbody>
<tr>
<td>1/M</td>
<td>3y4m</td>
<td>6y4m</td>
<td>FMS, ENM</td>
<td>0/6m ENM/AA</td>
<td>ENM</td>
<td>N</td>
<td>N</td>
<td>Normal</td>
<td>Neuropsychological regression</td>
<td>TPM/VPA/ZNS/LEV</td>
<td>+</td>
</tr>
<tr>
<td>2/M</td>
<td>7y7m</td>
<td>11y2m</td>
<td>FMS, Myoclonus, AA</td>
<td>2/4.5m AA</td>
<td>AA</td>
<td>N</td>
<td>N</td>
<td>Normal</td>
<td>Decline in remembering and computing</td>
<td>VPA/LEV</td>
<td>+</td>
</tr>
<tr>
<td>3/M</td>
<td>6y6m</td>
<td>9y</td>
<td>FMS, AA, ENM</td>
<td>1/1m ENM/AA</td>
<td>ENM/AA</td>
<td>N</td>
<td>N</td>
<td>N/A</td>
<td>Deficits in expressive grammar and verbal fluency</td>
<td>VPA/LEV</td>
<td>+</td>
</tr>
<tr>
<td>4/F</td>
<td>5y9m</td>
<td>8y2m</td>
<td>FMS, ENM</td>
<td>2/1m ENM/AA</td>
<td>ENM/AA</td>
<td>N</td>
<td>Y</td>
<td>N/A</td>
<td>Poor school performance and attention deficit</td>
<td>VPA/LEV</td>
<td>+</td>
</tr>
<tr>
<td>5/F</td>
<td>3y6m</td>
<td>10y6m</td>
<td>FMS, AA, ENM</td>
<td>0/&gt;6m ENM/AA</td>
<td>ENM/AA</td>
<td>N</td>
<td>N</td>
<td>Normal</td>
<td>Deficits in visuomotor skills; poor school performance</td>
<td>VPA/LEV</td>
<td>+</td>
</tr>
<tr>
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<td>8y8m</td>
<td>FMS, AA, ENM</td>
<td>15/23d ENM/AA</td>
<td>ENM/AA</td>
<td>FS</td>
<td>FS</td>
<td>Normal</td>
<td>Decline in school performance</td>
<td>LTG/LEV</td>
<td>+</td>
</tr>
<tr>
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<td>7y3m</td>
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<td>6–10/15d ENM</td>
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<td>N</td>
<td>N</td>
<td>Normal</td>
<td>Deficits in reading comprehension</td>
<td>LEV/LEV</td>
<td>+</td>
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<tr>
<td>8/F</td>
<td>3y</td>
<td>4y6m</td>
<td>FMS, ENM, Epileptic Status</td>
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<td>ENM/AA</td>
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<td>N</td>
<td>Normal</td>
<td>Deficits in remembering</td>
<td>LEV/VPA/LEV</td>
<td>+</td>
</tr>
<tr>
<td>9/M</td>
<td>6y3m</td>
<td>9y</td>
<td>FMS, Secondary generalized seizures, ENM</td>
<td>0/&gt;6m ENM</td>
<td>ENM</td>
<td>N</td>
<td>Y</td>
<td>Normal</td>
<td>Normal</td>
<td>LEV/VPA/LEV/LEV</td>
<td>+</td>
</tr>
<tr>
<td>10/F</td>
<td>8y</td>
<td>10y</td>
<td>FMS, ENM</td>
<td>&gt;15d ENM</td>
<td>Normal</td>
<td>N</td>
<td>Y</td>
<td>Normal</td>
<td>Decline in school performance; reduced speech fluency</td>
<td>LTG/OXC</td>
<td>+</td>
</tr>
<tr>
<td>11/F</td>
<td>3y4m</td>
<td>4y6m</td>
<td>FMS, Secondary generalized seizures, ENM</td>
<td>2/2m ENM</td>
<td>N</td>
<td>N</td>
<td>Normal (CT)</td>
<td>Normal</td>
<td>Poor school performance</td>
<td>LEV/TPM/VPA/LEV</td>
<td>–</td>
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<tr>
<td>12/M</td>
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<td>9y7m</td>
<td>FMS</td>
<td>2–3/4d</td>
<td>–</td>
<td>Perinatal injuries</td>
<td>N</td>
<td>FCD</td>
<td>Attention deficit and anxiety disorder</td>
<td>LEV/LEV</td>
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<tr>
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<td>6y</td>
<td>9y2m</td>
<td>FMS, Secondary generalized seizures, AA</td>
<td>9/&lt;15d AA</td>
<td>FS</td>
<td>Y</td>
<td>Normal</td>
<td>Decline in school performance</td>
<td>VPA/LEV</td>
<td>–</td>
<td></td>
</tr>
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<td>7y1m</td>
<td>FMS, ENM</td>
<td>2/2m ENM</td>
<td>N</td>
<td>N</td>
<td>Normal</td>
<td>Reduced speech fluency and reflecting</td>
<td>VPA/LEV</td>
<td>–</td>
<td></td>
</tr>
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</table>

M, Male; F, Female; y, year; m, month; d, days; FMS, focal motor seizures; ENM, epileptic negative myoclonus; AA, atypical absence; FS, febrile seizures; Y, yes; N, no; FCD, focal cortical dysplasia; N/A, not available; TPM, topiramate; VPA, sodium valproate; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; CZP, clonazepam; NZP, Nitrazepam; PBN, Phenobarbital nitrazepam; a: time lapsed from the last FMS to the EEG recording of pretreatment; b: Occasionally; 9# 2 drop attacks within one month; 11# drop attacks occurred in recent 5 days; 14# once in several days; c: MRI if not mentioned; +, present; –, absent.
Interestingly, we also noted that a comparable number of HFOs (2015) reported that 93.2% of fast oscillations (40–150 Hz) were et al., 2013). However, similar to scalp EEGs, Kobayashi et al. EEGs (Andrade-Valenca et al., 2011; Kobayashi et al., 2015; Melani “riding” on spikes, and less than 10% spikes carried ripples on scalp EEGs (Andrade-Valenca et al., 2011; Kobayashi et al., 2015; Melani et al., 2013). However, similar to scalp EEGs, Kobayashi et al. (2015) reported that 93.2% of fast oscillations (40–150 Hz) were associated with spikes in infants with West Syndrome. This difference could be owed to at least two factors. First, skull resistivity in infants with West Syndrome was lower than that in our patients with ABPE. Second, gamma (40–80 Hz) was included in the analysis of West Syndrome, which was easier to identify than ripples (80–200 Hz) through scalp EEGs (Andrade-Valenca et al., 2011). Interestingly, we also noted that a comparable number of HFOs associated with spikes was detected by invasive EEG evaluation, but more than 40% of spikes carried ripples (Jacobs et al., 2008; Wang et al., 2013). This might be related to the methods used to record and detect events. For example, HFOs are spatially under-sampled with standard scalp electrodes, and bias in event marking is usually inevitable as small spikes are easily missed.

It is illustrated that spikes and HFOs have both connections and differences. On the one hand, HFOs and spikes were closely related in at least several physical properties. A large degree of spike-associated HFOs was reported in previous studies and ours. Studies also reported that the electrode of the highest HFO power was identical or adjacent to that of the spike focus (Kobayashi et al., 2011), and the duration of spike-associated HFOs was generally longer than the isolated HFOs (Jacobs et al., 2008). Moreover, in our study, we found the highest amplitudes of HFOs correlated with that of spikes. The co-occurrence between HFOs and spikes might jointly indicate the severity of the disease. On the other hand, HFOs and spikes were suggested to be possibly two independent entities. From the perspective of cellular mechanisms, spikes reflected excitatory postsynaptic potentials (de Curtis and Avanzini, 2001) while HFOs likely reflected synchronized co-firing of small clusters of principal cells (Bragin et al., 2002). HFOs were believed to be generated by much smaller brain regions than spikes (Chrobak and Buzsáki, 1996; Zemlin et al., 2014). In addition to different cellular mechanisms and generator size, they behaved differently after seizures and medication reduction (Zijlman et al., 2009). Furthermore, a certain number of isolated HFOs were observed in our and previous studies. Further study is required to explore the complex relationship between spikes and HFOs.

### 4.3. HFOs are more sensitive to methylprednisolone than spikes

Both animal and human studies offered new insights into the relationship between HFOs and medications. Earlier, Ito et al. (1977) reported that carbamazepine and phenytoin reduced the ictal high-frequency component in cats. Lately, levetiracetam-treated animals showed significantly lower rates of HFOs and interictal spikes than the control group (Lèvesque et al., 2015). In humans, HFOs clearly increased after medication reduction while spikes were relatively stable (Zijlman et al., 2009). Recently, Katsumi reported that during the course of adrenocorticotropic hormone treatment, the number of fast oscillations was significantly decreased accompanied by the suppression of hypersynchrony (Kobayashi et al., 2015). For the therapy of ABPE, benzodiazepines, ethosuximide (Capovilla et al., 1999), and levetiracetam (Chen et al., 2014b; von Stülpnagel et al., 2010) were recommended. When these AEDs were ineffective, steroids seemed to have the best efficacy (Rating, 2000). Thus, we observed HFOs in ABPE patients with methylprednisolone treatment. Our results showed significant reduction in both HFOs and spikes after methylprednisolone treatment, and the percentage of HFO reduction was more prominent than that of spikes. On the basis of these findings, we speculated that HFOs were more sensitive to methylprednisolone.

### 4.4. HFOs and seizure outcome

The effects of methylprednisolone on electro-clinical improvement have been discussed previously (Chen et al., 2014a). In the present study, the main aim was to investigate whether the change in rates of spikes/HFOs in general was higher in patients with an excellent seizure outcome than in others. Jacobs et al. (2010) showed that removing HFO-generating regions, but not spike-generating regions, resulted in a favorable surgical outcome. Similar results were reported in various forms of epilepsy (Akiyama et al., 2011; Cho et al., 2014; Okanishi et al., 2014; Wu et al., 2010). In our study, a good correlation was found between HFO reduction and seizure outcome. However, as spikes showed the same capability, it could be hardly concluded that HFO reduction

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HFO positive</th>
<th>HFO negative</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age at seizure onset (y)</td>
<td>5.4 ± 1.8</td>
<td>5.1 ± 1.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Age at EEG recording before MPL treatment (y)</td>
<td>8.5 ± 2.0</td>
<td>7.6 ± 2.3</td>
<td>0.50</td>
</tr>
<tr>
<td>Spikes before MPL treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of FMS (seizures within 6m)</td>
<td>0.61</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>~6</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Time laps to last FMS to EEG recording before MPL(m)</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>~6</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Frequency of ENM/AA (seizures within 1 month before MPL)</td>
<td>0.011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Occasionally</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Frequently</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

HFO, high-frequency oscillation; EEG, electroencephalography; MPL, methylprednisolone; FMS, focal motor seizures; ENM, epileptic negative myoclonus; AA, atypical absence; y, year; m, month.
solely represented a preferable seizure outcome. Furthermore, no HFOs were detected in both pre- and post-methylprednisolone EEGs in two patients with not-excellent seizure outcome. In addition, the number of patients was relatively small to draw any absolute conclusion with respect to the relationship. In the future, we will recruit more patients to clarify this question.

4.5. Methodological issues and limitations

Among multiple techniques available to analyze HFOs, visual inspection is the most time- and labor-consuming approach. Moreover, potential bias introduced by reviewers is inevitable. However, HFO analysis is considered relatively reliable in our study. This is because (1) artifacts from muscle activity and epileptic spike filtering (Benar et al., 2010) could be more precisely excluded and (2) small spikes and co-occurrence between events could be calculated. Therefore, our data were mainly derived from manual analysis; time–frequency analysis assisted in confirming visually inspected HFOs.

There were several limitations in our study. First, only 60 s of sleep data were analyzed. Though the short duration could represent major information, more stability would be achieved with a longer period. Second, some of the selected EEG segments were sampled before or after seizures, a condition that might influence the rates of spikes and HFOs. Third, accurate seizure frequencies and objective neurophysiological evaluation could not be obtained. A well-designed prospective study is needed to clarify the effects of methylprednisolone treatment on HFOs and the relationship between HFO changes and clinical aspects.

Acknowledgments

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Conflict of interest: None of these authors have any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2016.07.013.

References


