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Scalp EEG high frequency oscillations as a biomarker of treatment response in epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)

Dezhi Cao[a,b,c], Yan Chen[b], Jianxiang Liao[b], Hiroki Nariai[d], Lin Li[e], Yanwei Zhu[b], Xia Zhao[b], Yan Hu[b], Feiqiu Wen[b], Qiongxiang Zhai[a,c,*]

[a] Second Clinical Medical College, Southern Medical University, Guangzhou, Guangdong, China
[b] Neurology Department, Shenzhen Children's Hospital, Guangdong, China
[c] Guangdong Academy of Medical Sciences, Guangdong General Hospital, Guangzhou, China
[d] Division of Pediatric Neurology, UCLA Mattel Children's Hospital, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
[e] Department of Neurology, University of California Los Angeles, Los Angeles, CA, USA

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ABSTRACT

Purpose: We investigated whether the presence of interictal scalp EEG high frequency oscillations (HFOs) in children with epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) can predict seizure and cognitive outcome after steroid therapy.

Methods: Twenty-two children with CSWS were prospectively enrolled and received methylprednisolone therapy. Interictal scalp HFOs, spike wave index (SWI) and intelligence quotient (IQ) were assessed before and after the treatment. The children were divided into two groups based on the early seizure reduction ratio at 2 weeks (≥50%, "response group"; otherwise "non-response group"). The "response group" was further divided into two subgroups ("relapse" and "non-relapse" subgroups) according to the late seizure outcome (after 3 months).

Results: Interictal HFOs and electrical status epilepticus in sleep (ESES) (defined as SWI ≥ 85%) were detected in all children at the baseline. In the response with relapse group (n = 11), the detection ratio of HFOs was significantly higher than that of ESES at 2 weeks (81.2 vs. 27.3%), 3 months (90.9 vs. 36.4%), and 6 months (100 vs. 54.5%) post-therapy. In the non-response group (n = 4), both HFOs and ESES persisted in all children. The average IQ improved significantly only in the response with non-relapse group. The persistence of HFOs negatively correlated with both the average IQ, yet the persistence of ESES did not.

Conclusion: Interictal scalp HFOs may be a favorable non-invasive biomarker of predicting seizure and cognitive outcome in CSWS.

1. Introduction

The EEG phenomenon of ESES was first described in 1971 in a case series of 6 children with epilepsy who were found to have continuous spike-wave discharges in non–rapid eye movement sleep, with resolution upon awakening. [1] CSWS is a specific clinical syndrome, defined in 1989 as an epileptic encephalopathy during childhood that shows continuous EEG abnormalities during non-REM sleep (often shows ESES), in association with a variety of seizure types, including nocturnal convulsions, atypical absence seizures, and epileptic negative myoclonus. [2,3] Classically, ESES is defined as a SWI that exceeds 85% of non-REM sleep [3], yet other studies have used different cut-off rates. [4–7] Anti-seizure medications including valproate, levetiracetam, benzodiazepines, and steroids have been used to treat epileptic encephalopathy with ESES and other related syndrome including Landau Kleffner syndrome, but the current evidence supports the use of steroids as the most effective therapy [8–11]. SWI has been used to evaluate the efficacy of treatment, yet it does not always reflect seizure and cognitive outcome [4,7,12]. Thus, finding a better biomarker to evaluate the efficacy of treatment and predict the clinical prognosis in CSWS is of critical importance.

Based on prior data, HFOs appears to be a potential biomarker of epilepsy. HFOs was reported in the seizure-onset zones in limbic/hippocampal epilepsy [13–15] and neocortical epilepsy [16–21] using

* Corresponding author at: Guangdong Academy of Medical Sciences, Guangdong General Hospital, Guangzhou, China.
E-mail address: zhaiqiongxiang@sina.com (Q. Zhai).

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Table 1
Patient characteristics of the 3 subgroups.

	Response group (n = 18)		Non-response group (n = 4)
	Non-relapse(n = 7)	Relapse (n = 11)	
Sex			
Male	4	6	2
Female	3	5	2
Etiology			
Unknown	7	8	3
Known	0	3	1
Age of seizure onset	6.1	6.3	7.1
CSWS period pre-therapy (years)	1.7	2.5	3.3
Number of anti-seizure medications	2	2.9	2
Seizure frequency at the baseline (per week)	13.7	17.7	13.7

The differences of each item among the 3 subgroups are not significant statistically.

invasive monitoring. A good surgical outcome was associated with complete resection of cortical sites showing interictal HFOs of 80–500 Hz, especially the fast ripple range of 250–500 Hz [22–28]. Recent studies utilizing non-invasive, scalp EEG also demonstrated that HFOs was detectable in adults [29–31] and children [32–35]. Scalp EEG HFOs seemed to reflect the activity of seizures in children with rolandic spikes [36,37] and treatment response of hormonal therapy in West syndrome [34].

In this study, we hypothesized that HFOs can predict seizure and cognitive outcome after steroid therapy in CSWS..

2. Methods

2.1. Subjects

We prospectively enrolled 22 children (12 male, 10 female), all of whom were diagnosed with CSWS at Shenzhen Children's Hospital between January 2012 and December 2014 (Table 1). Patients' age ranged from 6 years 9 months to 11 years 2 months at the time of enrollment (median 8 years 8 months). The inclusion criteria of the study consisted of: (1) the presence of ESES pattern on EEG (interictal epileptiform activity occupying at least 85% of non-REM sleep, SWI ≥ 85%); (2) cognitive and/or behavioral deterioration that occurred in temporal relation with the ESES pattern; (3) at least weekly epileptic seizures. (Seizure frequency was mainly based on parental seizure diary. The parents were trained to recognize the seizure before this study, especially myoclonic or atypical absences seizure. Sleep was recorded by domestic video monitors to find nocturnal seizure. In addition, the seizures were identified by 24 -h EEG monitoring regularly.); and (4) parental consent for treatment with methylprednisolone pulse therapy for CSWS. Patients' etiologies were considered known (symptomatic) if MRI showed a lesion and unknown (cryptogenic) if MRI was normal. The exclusion criteria consisted of: (1) Landau Kleffner syndrome (due to difficulty in evaluating seizure frequency); (2) any contraindication to steroid therapy; (3) consideration for surgical therapy; (4) children who could not be tested for Chinese Wechsler Intelligence Scale.

2.2. Methylprednisolone pulse (mPSL-P) therapy

All study subjects were admitted and treated with methylprednisolone pulse (mPSL-P) therapy. The protocol included three consecutive courses of mPSL-P treatment, and each course included methylprednisolone intravenous infusion at a dose of 15 mg/kg/d for 3 days, followed immediately by oral administration of prednisolone at a dose of 2 mg/kg/d for 4 days. After three such consecutive courses, oral prednisolone (1–2 mg/kg/d) was started and eventually tapered off for a total combined steroid treatment of 6 months. The dosages of all anti-seizure medications were kept the same and no new anti-seizure medication was added on in the first three months post mPSL-P therapy.

2.3. EEG recording

EEG was recorded using the standard international 10–20 system, with 19 electrodes at a sampling frequency of 1000 Hz (Nicolet/Natus, Wisconsin, USA). A 4 -h video-EEG monitoring included at least one intact spontaneous sleep cycle. The EEG data was analyzed with a bipolar montage. Scalp EEG recording was performed at baseline, then 2 weeks, 3, 6 and 12 months post mPSL-P therapy.

2.4. Spike-wave index and HFOs identification

Two board-certified pediatric epileptologists (DC and YC) (with ≥ 10 years of pediatric neurology experience in China) prospectively analyzed the EEG data independently and blinded to clinical data. The EEGs were analyzed in a bipolar montage. The conventional traces were initially reviewed to mark spikes (10 s/page, 15 μV/mm, low frequency filter of 0.53 Hz, and high frequency filter of 70 Hz). Spike-wave index (SWI) was calculated by measuring the percentage of 1-second epochs containing spikes during the first 5 min of slow wave sleep. [4,7] Subsequently, the spike markings were made invisible, and the same EEG segment was re-reviewed at a sensitivity of 3–5 μV/mm and paper speed of 1–2 s/page, with a low frequency filter of 80 Hz and a high frequency filter of 500 Hz to identify HFOs. HFOs was defined as oscillatory events of ≥4 cycles with a frequency of ≥80 Hz which stand out from the baseline [16,21]. We selected the first three minutes artifact-free EEG segment in slow wave sleep for analysis of HFOs. After the independent scoring, a consensus was made between two raters to determine the presence of ESES (defined as SWI ≥ 85%) and HFOs respectively. In addition, after the mPSL therapy, the reduction ratio of SWI ≥ 50% was defined as "ESES response". The detection ratio of HFOs and ESES (positive cases divided by all cases within each group) were calculated in different time points.

The EEG segments containing visually identified HFOs were further subjected to time-frequency analysis using Morlet wave decomposition on Matlab 6.9 (The Mathworks Inc., Natick, MA, U.S.A.). On the time–frequency map of each identified HFOs, only a primary isolated peak in the frequency range of 80–500 Hz was defined as real HFOs (see examples in Fig. 1).

2.5. Evaluation of seizure outcome and Intelligence quotient (IQ) test

The seizure reduction ratio was calculated by comparing the seizure frequency at each time-point to the baseline period (28 days before the therapy). First, all study subjects were divided into two groups (response and non-response group) according to the therapeutic response at 2 weeks post-therapy. "Post-therapy" was defined as after three courses of mPSL-P treatment, not including the subsequent period of oral prednisolone treatment. Subjects with a seizure reduction ratio ≥50% were classified as response group. Subjects with a seizure reduction ratio < 50% were classified as non-response group. The response group was further divided into two subgroups (relapse and non-relapse subgroups) according to the therapeutic efficacy at 12 months post-therapy. Subjects with a seizure reduction ratio ≥50% at 12 months post-therapy were classified as non-relapse group, and remaining subjects were classified as relapse group. The detectability of HFOs and SWI were analyzed and compared among the different groups and subgroups (see a flow-chart in Fig. 2). Intelligence quotient (IQ) test using Chinese Wechsler Intelligence Scale for children, including verbal and performance IQ, was performed at baseline, then 6 and 12

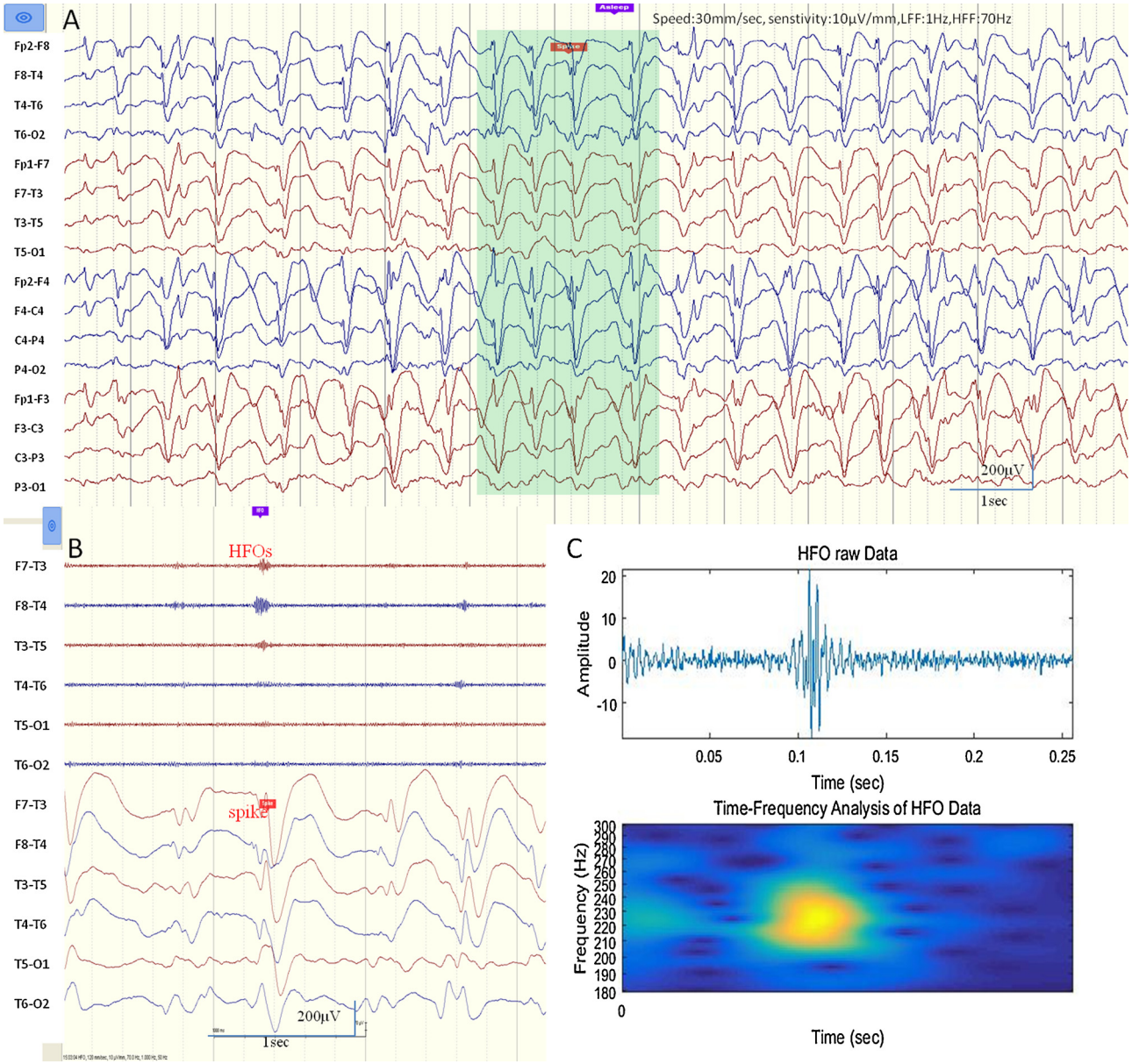

Fig. 1. Representative EEG traces and corresponding time–frequency spectra. (A) Raw EEG trace with the pattern of ESES. (B) Temporally expanded EEG trace (120 mm/s). The upper six channels were set with a low-frequency filter of 80 Hz, a high-frequency filter of 500 Hz and sensitivity at 1μV/mm. HFOs was visually seen on the upper three channels. The lower six channels were set with a low-frequency filter of 0.5 Hz, a high-frequency filter of 70 Hz and sensitivity at 10μV/mm. High-amplitude spike-wave discharges were seen on the lower six channels synchronously. (C) The representative time–frequency analysis for the second channel (F8-T4) in panel B demonstrated a clear isolated spectra spot representing HFOs in the 200–250 Hz range.

months post mPSL-P therapy. IQ tests were performed next day after the EEG recordings in each time point.

2.6. Statistical analysis

Analysis of variance was used to compare the clinical characteristics including age at epilepsy onset, number of anti-seizure medications, CSWS period and seizure frequency before mPSL-P therapy in different subgroups. Multi-way ANOVA analysis was used to compare IQ results among different response subgroups and different time points. T-tests were used to compare IQ results between $HFOs^{+}$ /$HFOs^{-}$ and $ESES^{+}$/ ESES- groups at each time point. Using Pearson Chi-square, we compared the detectability of HFOs and ESES among the different subgroups. The interrator reliability of identification of HFOs and ESES was also calculated and compared using Kappa test. Using Fisher's exact test, the detection ratio of HFOs and ESES were compared in relapse group at each post-therapy time point. Statistical analysis was performed using SPSS 20 (IBM, NY, USA). A p-value less than 0.05 was considered statistically significant. Bonferroni corrections were used when we compared detectability of HFOs/ESES and IQ among multiple groups, so a p-value less than 0.016 was considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics of the different groups are summarized in Table 1. Eighteen subjects were classified as unknown etiology (cryptogenic). The known etiologies (symptomatic) included neonatal hypoxic-ischemic encephalopathy (n = 2), focal cortical dysplasia (n = 1), and post-encephalitis (n = 1). All subjects had epileptic

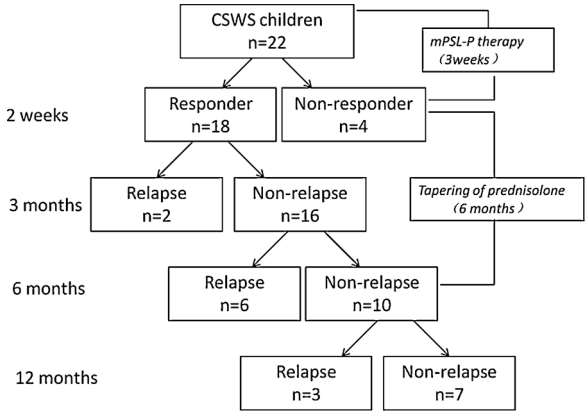

Fig. 2. Treatment profile outcome of the 22 patients in the study.

seizures weekly. The seizure types included focal clonic, tonic, atonic, and atypical absence seizures. Twenty subjects had more than two seizure types. Fifteen subjects had atypical absence status epilepticus at some point. Five subjects were on two anti-seizure medications, two were on four, and the other 15 were on three. Valproate was administered for 19 subjects, lamotrigine for 8, levetiracetam for 12, topiramate for 10, clonazepam for 8, and nitrazepam for 6. No other medication was used on these children. The three subgroups had no statistically significant difference in age at epilepsy onset, number of anti-seizure medications, CSWS period, and seizure frequency at baseline. There was no significant difference between the unknown (cryptogenic) and known (symptomatic) groups regarding the clinical characteristics.

3.2. Efficacy and adverse events of mPSL-P therapy

Eighteen out of 22 (81.2%) subjects were responders (the seizure reduction ratio ≥50%) at 2 weeks post-therapy. The response to the therapy had no significant difference among different types of seizure on the same patients. Seizures were completely controlled in 6 out of 22 (27.3%) subjects at 2 weeks post-therapy. However, only 7 out of 22 (31.8%) subjects were responders without relapse and 4 out of 22 (18.2%) subjects had complete seizure control at the end of one year follow-up. There were 11 patients who had relapse during the follow-up period (from 2 week to 1 year), and most relapse occurred after 3 months post-therapy (82%) (see Fig. 2). The seizure control was related to the etiology. The unknown etiology (cryptogenic) group had higher non-relapse ratio compared to that of known etiology (symptomatic) group ($p < 0.05$) (Table 1).

The adverse events of mPSL-P therapy included vomiting (n = 2), hyperglycemia (n = 4), hypertension (n = 2), hyperactive (n = 5), electrolyte disturbances (n = 4) and acute upper respiratory infections (n = 2). Cushingoid face appeared in 18 subjects, which resolved after 1 month post-therapy in all of them. No patients dropped off due to the adverse events during the study period.

3.3. Intelligence quotient (IQ) results and seizure outcomes

IQ test (Chinese Wechsler Intelligence Scale for children) results included verbal IQ (VIQ) and performance IQ (PIQ). The baseline IQ showed no statistically significant difference between response and non-response group. Both VIQ and PIQ were significantly improved at 6 months ($p = 0.001$ and 0.002, respectively) and 12 months ($p = 0.001$ and 0.001, respectively) post-therapy in the response with non-relapse group, but not in the response with relapse group or the non-response group (Fig. 3). There was no difference in the baseline IQ between known (symptomatic) and unknown (cryptogenic) etiology (mean baseline VIQ and PIQ: 78.8 and 79.7 vs. 80.6 and 81.4, respectively, $p = 0.185$ and 0.196).

3.4. Intelligence quotient (IQ) results and HFOs/ESES

We compared the IQ results based on the presence or absence of HFOs/ESES at 6 and 12 months post-therapy (Fig. 4). Both VIQ and PIQ were significantly lower in the HFOs-positive group compared to the HFOs-negative group ($p < 0.001$), at both the 6 and 12 month post-therapy time points. However, there was no difference in VIQ or PIQ between ESES positive and negative groups ($p = 0.206$, 0.220, 0.191, 0.288 respectively) at the same 2 time points. The mean difference of VIQ and PIQ were 9.29 and 10.00 respectively at 6-month post-therapy, and 10.14 and 11.00 respectively at 12-month post-therapy between HFOs positive and negative groups.

In addition, we also compared the IQ results based on the "ESES response" (defined as the reduction ratio of SWI ≥ 50% after the treatment) at 6 and 12 months post-therapy. There was no difference in VIQ or PIQ between "ESES response" positive and negative groups ($p = 0.156$, 0.189, 0.191, 0.288 respectively) at the same 2 time points.

3.5. Detectability of HFOs and ESES among different groups

HFOs and ESES were detected in all subjects before therapy (at the baseline). Based on the time-frequency analysis, the mean peak frequency of HFOs was 220 Hz (95%CI: 190–250 Hz). Most HFOs (86%) were seen co-occurrence with spikes. At 2 weeks post mPSL-P therapy, HFOs were detected in 11 subjects in the relapse and non-response groups. On the other hand, the presence of ESES was markedly variable among the groups. No HFOs was detected on non-relapse group at 2 weeks post therapy. HFOs were detected on 1 child out of 7 children (14.3%) at 3 months post therapy and 2 children out of 7 children (28.6%) at 6 and 12 months post therapy on non-relapse group. The detection ratio of HFOs showed significant difference among the different subgroups (especially between non-relapse and relapse groups) at all the time points post-therapy ($p < 0.016$). On the other hand, the detection ratio of ESES showed no significant difference among the different subgroups at all the time points post-therapy ($p > 0.05$) (details in Table 2). In relapse group, the detectability of HFOs was much higher than that of ESES at 2 weeks, 3 months and 6 months post therapy ($p = 0.030$, 0.024, 0.035 respectively) (details in Table 3).

Regarding "ESES response", (defined as the reduction ratio of SWI ≥ 50% after the treatment), there was no significant difference among the different subgroups at all time points post-therapy ($p > 0.05$) (details in **Supplementary table**).

We also compared the interrator reliability of identification of HFOs and ESES. The Kappa values of interrator agreement were favorable overall (kappa > 0.8), except that of HFOs at 6 months post therapy (kappa = 0.65). (details in Table 4**)**.

4. Discussion

The current study demonstrated the presence of interictal scalp EEG HFOs around 80–250 Hz (ripple band) in children with CSWS. All subjects showed HFOs at baseline, and HFOs resolved after successful treatment with steroids. Subjects who did not respond or relapsed after methylprednisolone therapy showed persistent HFOs. Importantly, both the presence of ESES (SWI ≥ 85%) and ESES response (defined as the reduction of SWI by ≥ 50%) after the steroid therapy did not show such a clear-cut response after methylprednisolone therapy. Also, persistent HFOs correlated with lower intelligence quotient (IQ), and such correlation was not seen in ESES vs. IQ. Thus, we concluded that persistence of HFOs is a negative predictor of seizure recurrence and worse cognitive outcome in CSWS, and conversely resolution of HFOs predicts better seizure control and improved cognitive outcome in CSWS. In short, HFOs seems to be a favorable biomarker of predicting seizure and cognitive outcome in CSWS.

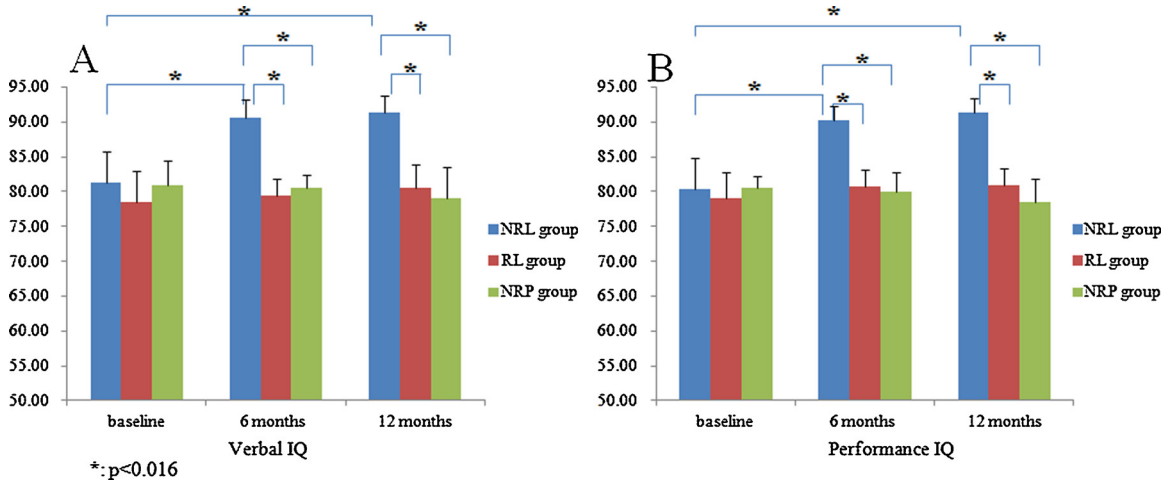

Fig. 3. The Intelligence Quotient test results and seizure outcomes. (A) Verbal IQ (VIQ) at different time points in different subgroups. The differences of VIQ between non-relapse group and relapse group are significant at 6, 12 months post therapy ($p < 0.05$). The differences of VIQ between non-relapse group and non-response group are also significant at 6, 12 months post therapy ($p < 0.05$). The differences of VIQ between baseline and 6,12 months post therapy in non-relapse group were statistically significant ($p < 0.05$), but not in other groups. (B) Performance IQ (PIQ) at different time points in different subgroups. The results were quite similar to that of VIQ.

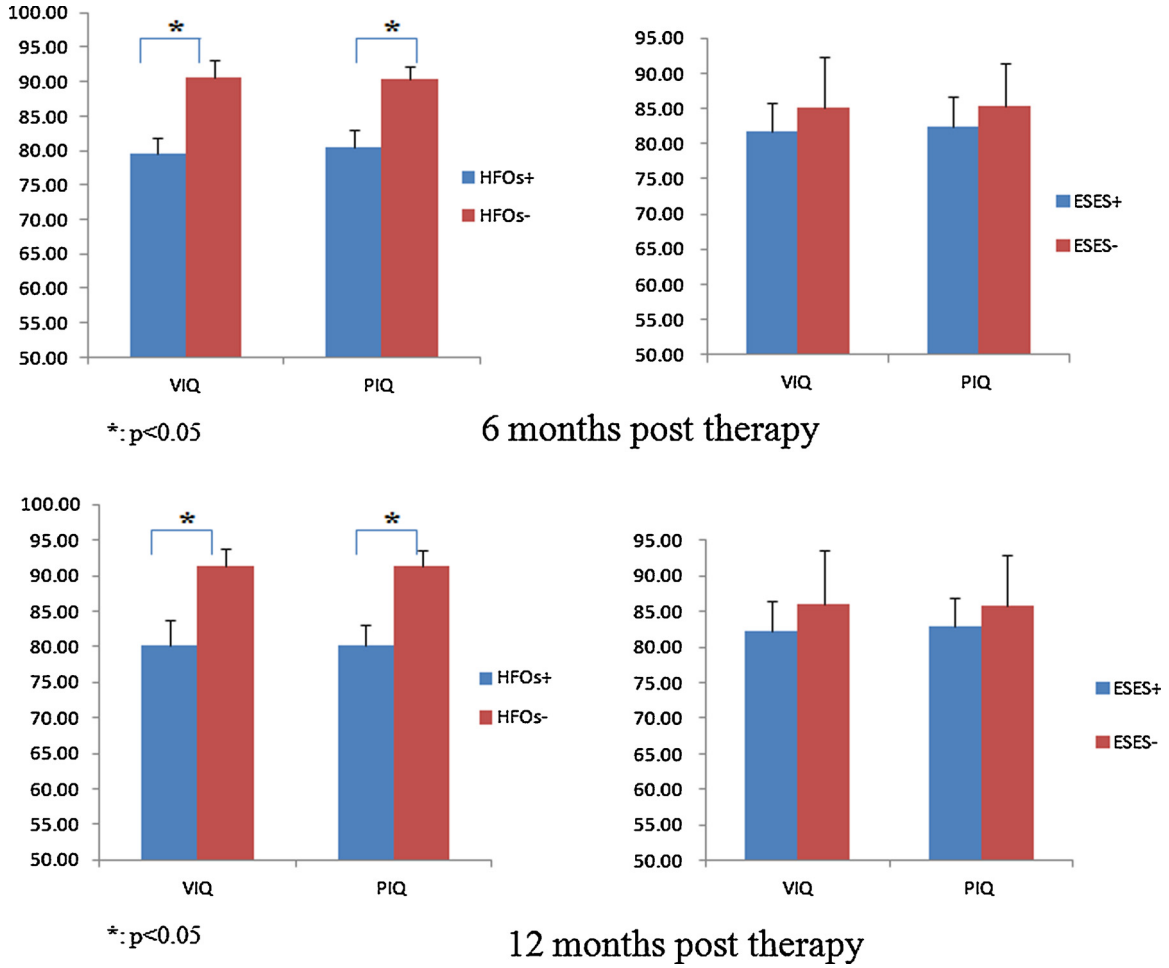

Fig. 4. The Intelligence Quotient test results and HFOs/ESES. In 6 months post therapy, the differences of VIQ/PIQ between HFOs positive and HFOs negative groups were statistically significant ($p < 0.05$). Conversely, the differences of VIQ/PIQ between ESES positive and ESES negative groups were not statistically significant ($p > 0.05$). The similar results were seen at 12 months post-therapy.

Table 2
Detectability of HFOs and ESES on the different groups.

	HFOs				ESES			
	Non-relapse(n = 7)	Relapse (n = 11)	Non-response (n = 4)	p value	Non-relapse(n = 7)	Relapse (n = 11)	Non-response (n = 4)	p value
Baseline	7(100%)	11(100%)	4(100%)	–	7(100%)	11(100%)	4(100%)	–
2 weeks post therapy[#]	0_a(0.0%)	8_b(72.7%)	3_b(75.0%)	**p = 0.006***	4_a(57.1%)	3_a(27.3%)	3_a(75.0%)	p = 0.196
3 months post therapy[#]	1_a(14.3%)	10_b(90.9%)	$3_{a,b}$(75.0%)	**p = 0.004***	4_a(57.1%)	4_a(36.4%)	4_a(100%)	p = 0.090
6 months post therapy[#]	2_a(28.6%)	11_b(100%)	$4_{a,b}$(100%)	**p = 0.001***	3_a(42.9%)	6_a(54.5%)	4_a(100%)	p = 0.163
12 months post therapy[#]	2_a(28.6%)	11_b(100%)	$4_{a,b}$(100%)	**p = 0.001***	2_a(28.6%)	7_a(63.6%)	4_a(100%)	p = 0.062

#The different periods post therapy mean the periods from the end of methylprednisolone pulse therapy (which didn't include the period of oral prednisolone) to the observation time points.* indicates the differences of the detective ratio of HFOs and ESES on different group are significant statistically after Bonferroni correction (p value < 0.016, Exact sig. 2-sided). $_a$ or $_b$ indicates whether the value between two groups have significant difference statistically.

Table 3
Detectability of HFOs and ESES on the relapse group (n = 11).

Baseline	HFOs 11(100%)	ESES 11(100%)	p value p = 1.000
2 weeks post therapy	9(81.8%)	3(27.3%)	**p = 0.030***
3 months post therapy	10(90.9%)	4(36.4%)	**p = 0.024***
6 months post therapy	11(100%)	6(54.5%)	**p = 0.035***
12 months post therapy	11(100%)	7(63.6%)	p = 0.090

* indicates the differences of the detective ratio between HFOs and ESES are significant statistically (p value < 0.05,Exact sig. 2-sided).

Our results are consistent with previous studies which demonstrated scalp EEG HFOs predicts seizure burden in patients with focal epilepsy with rolandic spikes [37], and scalp EEG HFOs resolves after successful treatment with ACTH in patients with West syndrome [34] and after steroid treatment in patients with atypical benign partial epilepsy [38].

The neuropsychological impairment in CSWS includes global or selective regression of cognitive functions, motor impairment, autistic-like or psychotic behaviors, auditory agnosia and language deficits. [3,12,39] In this study, intelligence quotient (IQ) tests were performed pre-therapy and at 6, 12 months post-therapy respectively. Not surprisingly, the average IQ post-therapy was higher than that of pre-therapy. The IQ improved significantly at 6 and 12 months post-therapy in the non-relapse group, which is consistent with the notion that seizure freedom plays a critical role in neurocognitive outcome. To our knowledge, this is the first study to demonstrate that resolution of HFOs after treatment is linked to less seizure relapse and better cognitive outcome in children with epilepsy.

Important limitations of our study include a relatively small cohort of children included, with a specific diagnosis of CSWS, with a specific treatment. Whether these results are generalizable to larger epilepsy groups, with other types of epilepsy, and other treatment types is not known. More specifically whether conventional anti-seizure medications will have similar effects as steroids on the persistence or resolution of HFOs is not known. Previous studies demonstrated that spike-wave index (SWI) value itself is not necessarily associated with clinical (seizure or cognitive) outcome, thus we did not evaluate SWI as continuous value to correlate with seizure and cognitive outcome (we defined ESES as SWI ≥ 85%). Also we defined the "ESES response" after the steroid treatment as reduction of SWI by ≥50%.

Although we were able to determine the presence of absence of HFOs in each case at each time point, we had difficulty determining exact HFOs counts/min. Due to low signal-to-noise ratio, some of the events were difficult to be differentiated from artifacts and deemed "undetermined". This seems an inherent limitation of scalp HFOs analysis [40].

In this study, the response without relapse group only had unknown etiology (cryptogenic) cases, which indicates CSWS with unknown etiology have better clinical outcome. However, based on limited sample size, clinical outcome depending on particular etiology was difficult to tease out. We also investigated children with CSWS with frequent seizures (more than weekly) and with ESES on EEG. Steroid therapy is easily justified for those patients, and we intended to investigate the utility of scalp HFOs as a potential biomarker during improvement of both EEG and cognition in this cohort. Further study is needed to investigate the utility of scalp HFOs in patients with CSWS with infrequent seizures or without ESES pattern.

Hormonal therapy including ACTH or steroid is considered as disease-modifying agent in epileptic encephalopathy [9], and hormonal therapies may exert different effects on HFOs than conventional anti-seizure medications. Also, fast ripples (> 250 Hz) may be a more specific biomarker of epileptogenesis than ripple (80–250 Hz), [22–28], and interictal fast ripples can be detected with scalp EEG in children [35]. However, our study is limited by a sampling frequency of 1000 Hz, thus we are unable to comment on the detectability of fast ripples in CSWS.

Detecting scalp EEG HFOs is challenging, especially due to significant artifacts and low signal-to-noise ratio. Filtering sharp events may result in ringing artifact that can be confused with real HFOs. We took a careful approach to combine both visual analysis to confirm HFOs in unfiltered tracing [41], and computer analysis utilizing time-frequency analysis to confirm the presence of HFOs not explained by artifacts or harmonics [21,32,42]. Visual analysis of HFOs can be

Table 4
Interrater reliability of Identification of HFOs and ESES.

	HFOs				ESES			
	Doctor DC	Doctor YC	Results*	Kappa value	Doctor DC	Doctor YC	Results*	Kappa value
Baseline	22	22	22	–	22	22	22	–
2 weeks post therapy	11	12	11	0.909	11	10	11	0.909
3 months post therapy	14	12	14	0.814	12	13	12	0.908
6 months post therapy	18	15	17	0.645	13	14	13	0.904
12 months post therapy	16	17	17	0.879	12	13	13	0.908

Results* show the last results of reconfirmations after discussion when the two doctors have different results.

challenging and jeopardize its interrater reliability if raters have variable experience [43]. Our interrater reliability of visual HFOs analysis was generally favorable (our lowest kappa value was 0.65) and compatible to previous results from experienced HFOs readers [40].

The existence of physiologic HFOs has also been described and differentiating physiologic from pathologic HFOs can be challenging in intracranial recording [44,45]. The presence of physiological HFOs on scalp EEG is still debated, and we do not have any normal control in our study cohort. Further studies will be needed to investigate the presence or prevalence of physiological HFOs on scalp EEG.

In summary, the current study has demonstrated that interictal scalp HFOs in CSWS seemed to predict seizure and cognitive outcome. Further studies with larger number of patients with various etiology of epilepsy are needed to establish the utility of scalp EEG HFOs as a potential biomarker of predicting treatment response.

Disclosures of conflicts of interest

The authors have no conflict of interests to disclose.

Acknowledgements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

[1] Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases. Arch Neurol 1971;24:242–52.
[2] Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389–99.
[3] Tassinari CA, Rubboli G, Volpi L, et al. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 2000;111(Suppl 2):S94–102.
[4] Van Hirtum-Das M, Licht EA, Koh S, et al. Children with ESES: variability in the syndrome. Epilepsy Res 2006;70(Suppl. 1):S248–58.
[5] Buzatu M, Bulteau C, Altuzarra C, et al. Corticosteroids as treatment of epileptic syndromes with continuous spike-waves during slow-wave sleep. Epilepsia 2009;50(Suppl. 7):68–72.
[6] Scheltens-de Boer M. Guidelines for EEG in encephalopathy related to ESES/CSWS in children. Epilepsia 2009;50(Suppl. 7):13–7.
[7] Fernandez IS, Peters JM, Hadjiloizou S, et al. Clinical staging and electroencephalographic evolution of continuous spikes and waves during sleep. Epilepsia 2012;53:1185–95.
[8] van den Munckhof B, van Dee V, Sagi L, et al. Treatment of electrical status epilepticus in sleep: a pooled analysis of 575 cases. Epilepsia 2015;56:1738–46.
[9] Nariai H, Duberstein S, Shinnar S. Treatment of epileptic encephalopathies: current state of the art. J Child Neurol 2018;33:41–54.
[10] Hirsch E, Marescaux C, Maquet P, et al. Landau-Kleffner syndrome: a clinical and EEG study of five cases. Epilepsia 1990;31:756–67.
[11] Marescaux C1, Hirsch E, Finck S, et al. Landau-Kleffner syndrome: a pharmacologic study of five cases. Epilepsia 1990;31:768–77.
[12] Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. Pediatrics 1997;99:560–6.
[13] Bragin A, Engel Jr J, Wilson CL, et al. Hippocampal and entorhinal cortex high-frequency oscillations (100–500 Hz) in human epileptic brain and in kainic acid–treated rats with chronic seizures. Epilepsia 1999;40:127–37.
[14] Bragin A, Engel Jr J, Wilson CL, et al. Electrophysiologic analysis of a chronic seizure model after unilateral hippocampal KA injection. Epilepsia 1999;40:1210–21.
[15] Staba RJ, Wilson CL, Bragin A, et al. High-frequency oscillations recorded in human medial temporal lobe during sleep. Ann Neurol 2004;56:108–15.
[16] Worrell GA, Parish L, Cranstoun SD, et al. High-frequency oscillations and seizure generation in neocortical epilepsy. Brain 2004;127:1496–506.
[17] Urrestarazu E, Chander R, Dubeau F, et al. Interictal high-frequency oscillations (100-500 Hz) in the intracerebral EEG of epileptic patients. Brain 2007;130:2354–66.
[18] Jacobs J, Levan P, Chatillon CE, et al. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. Brain 2009;132:1022–37.
[19] Crepon B, Navarro V, Hasboun D, et al. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. Brain 2010;133:33–45.
[20] Schevon CA, Trevelyan AJ, Schroeder CE, et al. Spatial characterization of interictal high frequency oscillations in epileptic neocortex. Brain 2009;132:3047–59.
[21] Nariai H, Nagasawa T, Juhasz C, et al. Statistical mapping of ictal high-frequency oscillations in epileptic spasms. Epilepsia 2011;52:63–74.
[22] Jacobs J, Zijlmans M, Zelmann R, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol 2010;67:209–20.
[23] Wu JY, Sankar R, Lerner JT, Matsumoto JH, et al. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. Neurology 2010;75:1686–94.
[24] Akiyama T, McCoy B, Go CY, et al. Focal resection of fast ripples on extraoperative intracranial EEG improves seizure outcome in pediatric epilepsy. Epilepsia 2011;52:1802–11.
[25] van' t Klooster MA, van Klink NE, Leijten FS, et al. Residual fast ripples in the intraoperative corticogram predict epilepsy surgery outcome. Neurology 2015;85:120–8.
[26] van' t Klooster MA, van Klink NEC, Zweiphenning W, et al. Tailoring epilepsy surgery with fast ripples in the intraoperative electrocorticogram. Ann Neurol 2017;81:664–76.
[27] Hussain SA, Mathern GW, Hung P, et al. Intraoperative fast ripples independently predict postsurgical epilepsy outcome: comparison with other electrocorticographic phenomena. Epilepsy Res 2017;135:79–86.
[28] Hussain SA, Mathern GW, Sankar R, et al. Prospective and "live" fast ripple detection and localization in the operating room: impact on epilepsy surgery outcomes in children. Epilepsy Res 2016;127:344–51.
[29] Pizzo F, Frauscher B, Ferrari-Marinho T, et al. Detectability of fast ripples (&250 hz) on the scalp EEG: a proof-of-Principle study with subdermal electrodes. Brain Topogr 2016;29:358–67.
[30] Andrade-Valenca LP, Dubeau F, Mari F, et al. Interictal scalp fast oscillations as a marker of the seizure onset zone. Neurology 2011;77:524–31.
[31] Zelmann R, Lina JM, Schulze-Bonhage A, et al. Scalp EEG is not a blur: it can see high frequency oscillations although their generators are small. Brain Topogr 2014;27:683–704.
[32] Nariai H, Beal J, Galanopoulou AS, et al. Scalp EEG Ictal gamma and beta activity during infantile spasms: evidence of focality. Epilepsia 2017;58:882–92.
[33] Kobayashi K, Oka M, Akiyama T, et al. Very fast rhythmic activity on scalp EEG associated with epileptic spasms. Epilepsia 2004;45:488–96.
[34] Kobayashi K, Akiyama T, Oka M, et al. A storm of fast (40-150Hz) oscillations during hypsarrhythmia in West syndrome. Ann Neurol 2015;77:58–67.
[35] Bernardo D, Nariai H, Hussain SA, et al. Visual and semi-automatic non-invasive detection of interictal fast ripples: a potential biomarker of epilepsy in children with tuberous sclerosis complex. Clin Neurophysiol 2018;4:30264–5.
[36] Kobayashi K, Yoshinaga H, Toda Y, Inoue T, Oka M, Ohtsuka Y, et al. High- frequency oscillations in idiopathic partial epilepsy of childhood. Epilepsia 2011;52:1812–9.
[37] van Klink NE, van' t Klooster MA, Leijten FS, et al. Ripples on rolandic spikes: a marker of epilepsy severity. Epilepsia 2016;57:1179–89.
[38] Qian P, Li H, Xue J, Yang Z. Scalp-recorded high-frequency oscillations in atypical benign partial epilepsy. Clin Neurophysiol 2016;127:3306–13.
[39] Galanopoulou AS, Bojko A, Lado F, et al. The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep. Brain Dev 2000;22:279–95.
[40] Nariai H, Wu JY, Bernardo D. Interrater reliability in visual identification of interictal high-frequency oscillations on electrocorticography and scalp EEG. Epilepsia Open 2018;3(Suppl Suppl 2):127–32.
[41] Benar CG, Chauviere L, Bartolomei F, et al. Pitfalls of high-pass filtering for detecting epileptic oscillations: a technical note on "false" ripples. Clin Neurophysiol 2010;121:301–10.
[42] Amiri M, Lina JM, Pizzo F, et al. High Frequency Oscillations and spikes: separating real HFOs from false oscillations. Clin Neurophysiol 2016;127:187–96.
[43] Spring AM, Pittman DJ, Aghakhani Y, et al. Interrater reliability of visually evaluated high frequency oscillations. Clin Neurophysiol 2017;128(3):433–41.
[44] Mooij AH, Frauscher B, Goemans SAM, et al. Ripples in scalp EEGs of children: co-occurrence with sleep-specific transients and occurrence across sleep stages. Sleep 2018;1(41):1–9.
[45] Melani F, Zelmann R, Mari F, et al. Continuous High Frequency Activity: a peculiar SEEG pattern related to specific brain regions. Clin Neurophysiol 2013;124:1507–16.