

RESEARCH ARTICLE

A Biomarker for Benign Adult Familial Myoclonus Epilepsy: High-Frequency Activities in Giant Somatosensory Evoked Potentials

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ABSTRACT: Background: Benign adult familial myoclonus epilepsy (BAFME) is one of the diseases that cause cortical myoclonus (CM) with giant somatosensory evoked potentials (SEPs). There are no useful diagnostic biomarkers differentiating BAFME from other CM diseases.

Objective: To establish reliable biomarkers including high-frequency oscillations (HFOs) with giant SEPs for the diagnosis of BAFME.

Methods: This retrospective case study included 49 consecutive CM patients (16 BAFME and 33 other CM patients) who exhibited giant P25 or N35 SEPs. SEPs were processed by a band-pass filter of 400–1000 Hz to analyze HFOs. Clinical and SEP findings were compared between (1) BAFME and other CM groups and (2) patients with presence and absence of P25-HFOs (HFOs superimposed on giant P25). The diagnostic power of each factor for BAFME was calculated.

Results: All 16 BAFME patients showed SEP P25-HFOs with significantly higher occurrence ($P < 0.0001$)

compared with that of other CM groups. The presence of P25-HFOs significantly correlated with a BAFME diagnosis ($P < 0.0001$) and high SEP P25 and N35 amplitudes ($P = 0.01$ and $P < 0.0001$, respectively). BAFME was reliably diagnosed using P25-HFOs with high sensitivity (100%), specificity (87.9%), positive predictive value (80%), and negative predictive value (100%), demonstrating its superiority as a diagnostic factor compared to other factors.

Conclusions: P25-HFOs with giant SEPs is a potential biomarker for BAFME diagnosis. P25-HFOs may reflect cortical hyperexcitability partly due to paroxysmal depolarizing shifts in epileptic neuronal activities and higher degrees of rhythmic tremulousness than those in ordinary CM. © 2021 International Parkinson and Movement Disorder Society

Key Words: cortical myoclonus; myoclonus epilepsy; cortical tremor; giant somatosensory evoked potentials; high-frequency oscillations

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Benign adult familial myoclonus epilepsy (BAFME), also known as familial cortical myoclonic tremor with epilepsy, autosomal dominant cortical myoclonus and epilepsy, or familial adult myoclonic epilepsy,^{1,2} is one of the disorders that cause cortical myoclonus, which is characterized symptomatically by fine rhythmic tremor referred to as cortical tremor.^{1,3} Electrophysiologically, most patients with cortical myoclonus show features such as enlarged P25 or N35 amplitudes in somatosensory evoked potentials (giant SEPs),⁴ suggesting a cortical origin of their myoclonus. As with other cortical myoclonus patients, most BAFME patients, 77.6% reported in Japan,⁵ show giant SEPs.⁵⁻⁷ Although recent genetic studies have demonstrated that abnormal intronic expansions cause BAFME,⁸⁻¹¹ its pathophysiology remains unclear.¹² Furthermore, convenient and useful diagnostic biomarkers accurately differentiating BAFME from other cortical myoclonus diseases remain to be identified.

Wide-band electroencephalogram (EEG) analysis has allowed the detection of high-frequency oscillations (HFOs).¹³⁻¹⁵ As for SEPs, few small notches superimposed on the N20 component have previously been reported¹⁶ – which were later called HFOs – and are mostly regarded as physiological features.¹⁷⁻¹⁹ In contrast, HFOs with P25 may have aspects of pathological features.²⁰⁻²³ The giant SEP P25 component observed in cortical myoclonus patients may correspond to cortical hyperexcitability, which could be partly attributed to paroxysmal depolarizing shifts in epileptic neuronal activities.^{4,24} Thus, not only P25, but also HFOs with P25, particularly observed in patients with myoclonic epilepsy,^{21,22} may reflect the degree of cortical hyperexcitability and behave differently in BAFME and other cortical myoclonus diseases.

In this study, we determined the clinical and electrophysiological features, including ‘P25-HFOs’ (HFOs with P25), as potential candidates of reliable and useful biomarkers for selectively diagnosing patients with BAFME.

Patients and Methods

Participant Selection Criteria and Clinical Profiles

This retrospective study included 49 consecutive patients (98 giant SEPs) who had (1) involuntary movements of myoclonus or tremor and (2) giant SEPs of at least unilateral central scalp area to median nerve stimulation (giant SEP is defined in the section below).³ That is, the subject patients were clinically diagnosed as having cortical myoclonus or cortical tremor. All patients were examined at Kyoto University Hospital from January 2008 to December 2018. Data from some

patients was already reported in other articles for other purposes.^{6,24-26}

Of the 49 patients, 16 were diagnosed with BAFME and 33 with other causes of cortical myoclonus. Patients were diagnosed by two or more certified neurologists (who differed from those who analyzed SEPs and HFOs in this study) based on disease symptoms and course, neurophysiological and pathological examinations, neuroimaging, family history, and genetic studies. BAFME was diagnosed using genetic analysis⁸ or the following clinical and electrophysiological criteria,⁵ which fit with previous reports^{1,2,6,7}: (1) autosomal dominant inheritance, (2) myoclonus or tremor, (3) infrequent epileptic seizures, (4) features of cortical myoclonus demonstrated by electrophysiological studies, (5) lack of evident cognitive decline, cerebellar ataxia, and other neurological symptoms in the early stage of clinical course, and (6) lack of clear progression of cortical tremor which impairs the activities of daily living (ADL) in the early stage of clinical course. “Definite” BAFME was defined when all (1)–(6) points were satisfied. “Probable” BAFME was defined when points (1), (5), (6) and two items out of (2)–(4) were satisfied. Patients with diseases causing other types of cortical myoclonus were listed based on the etiological classification of myoclonus,²⁷ and divided into ‘epileptic syndrome’ and ‘non-epileptic, symptomatic disease’ (Table 1). Within the diseases, the category ‘progressive myoclonus epilepsy (PME) etiology unknown’ refers to patients who had progressive myoclonus, ataxia, and epilepsy, but refused genetic tests. The myoclonus rating score ranges from 0 to 4 degrees of global disability impression due to myoclonus used in previous studies^{24,28}: absence of myoclonus = 0; mild myoclonus without disturbance of daily activity = 1; moderate, some disturbance of daily activity = 2; severe, clear disturbance of daily activity = 3; and marked, causing incapacity = 4.

For data analysis, we performed SEP examinations as part of the clinical evaluation after obtaining informed consent. The Medical Research Ethics Committee of Kyoto University approved the study protocol (R0483/1625).

SEP Recording

Scalp SEPs were recorded using two devices: Viking (Nicolet, Biomedical, Madison, WI) from 2008 to 2018, and Neuropack (Nihon Kohden Corp., Tokyo, Japan) from 2016 to 2018, using previously described recording procedures.^{4,6,29} Briefly, SEPs were recorded bilaterally to median nerve stimulation at the wrists. A constant current stimulation for a duration of 0.2 ms and a frequency of 1.1 Hz was repeated 200–500 times per side. The stimulus intensity was adjusted to 120% of the motor threshold to produce a clear twitch of the

TABLE 1 Clinical profiles and somatosensory evoked potential findings for patients with and without benign adult familial myoclonus epilepsy

Parameter	All (n = 49)	BAFME (n = 16)	Other CM diseases (n = 33)	P value
Underlying disease				
BAFME, n	16 (32.7%)			
Other CM diseases, n	33 (67.3%)			
<i>Epileptic syndrome</i>				
ULD	6 (12.2%)			
Gaucher's disease	1 (2.0%)			
PME etiology unknown	4 (8.1%)			
JME	1 (2.0%)			
Epilepsy etiology unknown	1 (2.0%)			
<i>Non-epileptic, symptomatic disease</i>				
CBS	9 (18.3%)			
FTLD	2 (4.1%)			
SCD	1 (2.0%)			
AD	1 (2.0%)			
CJD	2 (4.1%)			
Post-infectious encephalitis	1 (2.0%)			
Drug-induced syndromes	3 (6.1%)			
Paraneoplastic encephalitis	1 (2.0%)			
Number of SEP examinations, n	98	32	66	
Age, y (mean $\pm$ SD)	55.8 $\pm$ 18.3	55.3 $\pm$ 14.9	55.7 $\pm$ 20.4	0.72
Male, n	14 (28.6%)	2 (12.5%)	12 (36.4%)	0.10
Onset age of myoclonus or cortical tremor, y (mean $\pm$ SD)	41.9 $\pm$ 23.2	30.4 $\pm$ 11.2	47.4 $\pm$ 25.6	0.043^b
Myoclonus rating score (0–4)	2.0 $\pm$ 1.0	1.6 $\pm$ 0.7	1.4 $\pm$ 1.1	0.63
Use of antiepileptic drug, n	31 (63.3%)	15 (93.8%)	16 (48.5%)	0.0035^b
Number of antiepileptic drugs, n	1.2 $\pm$ 1.3	1.4 $\pm$ 0.9	1.1 $\pm$ 1.4	0.11
SEP P25 amplitude, μ V	16.1 $\pm$ 9.5	17.6 $\pm$ 6.6	15.3 $\pm$ 9.7	0.07
SEP N35 amplitude, μ V	21.0 $\pm$ 17.5	31.9 $\pm$ 15.0	15.8 $\pm$ 14.7	0.0001^b
SD value of baseline amplitude in filtered waveform	0.072 $\pm$ 0.034	0.078 $\pm$ 0.036	0.069 $\pm$ 0.027	0.51
Z value of peak amplitude in filtered waveform ^a	8.3 $\pm$ 11.7	17.5 $\pm$ 15.2	3.9 $\pm$ 2.8	<0.0001^b
Presence of P25-HFOs, n	20 (40.8%)	16 (100%)	4 (12.1%)	<0.0001^b

BAFME, benign adult familial myoclonus epilepsy; CM, cortical myoclonus; ULD, Unverricht–Lundborg disease; PME, progressive myoclonus epilepsy; JME, juvenile myoclonic epilepsy; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; SCD, spinocerebellar degeneration; AD, Alzheimer's disease; CJD, Creutzfeldt–Jakob disease; SEP, somatosensory evoked potential; y, year; SD, standard deviation; HFO, high-frequency oscillation.

^aDuring the 20–30 ms latency after stimulation.

^bStatistically significant.

thenar muscle. According to the international 10–20 system, electrodes were placed on C3' and C4' (2 cm posterior to C3 and C4) and referenced to an earlobe electrode placed ipsilateral to the electrical stimulation. The band-pass filter of the amplifier was set to

1–1500 Hz, and the sampling rate was set to 4–20 kHz. For Viking, the analysis window was 50 ms when the sampling rate was over 5 kHz and 200 ms when the sampling rate was within 5 kHz, and 200 ms for Neuropack. If multiple sessions were available during

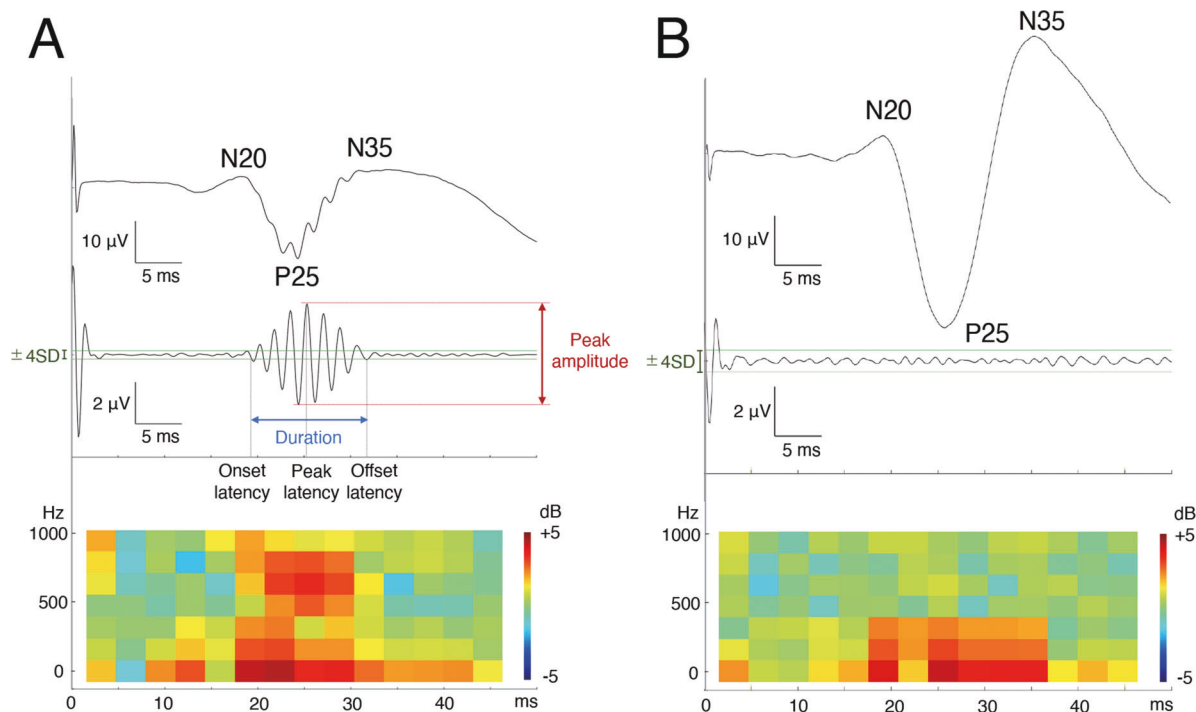


FIG 1. Representative waveforms and time-frequency analysis. (A) A 43-year-old male benign adult familial myoclonus epilepsy patient (Supplementary Table S1, Pt No. 12) with high-frequency oscillations superimposed on P25 of giant somatosensory evoked potentials, namely 'P25-HFOs'. (B) A 15-year-old female patient (Supplementary Table S1, Pt No. 20) without 'P25-HFOs'. [Color figure can be viewed at wileyonlinelibrary.com]

the recording, an overall average was calculated for all trials to obtain a single SEP waveform.

SEP Components and Definition of Giant SEPs

Nomenclature for the N20, P25, and N35 peaks, P25 and N35 amplitude measurements, and giant SEP definition were adopted from our previous reports.^{6,29} If SEP examination was performed more than once in the same patient, the data collected at a younger age with less antiepileptic drug exposure were adopted. The current study included all patients with giant SEPs defined when the P25 amplitude was $>6.3 \mu$ V or the N35 amplitude was $>9.8 \mu$ V on either side.²⁹

P25-HFOs (as HFOs with P25)

To identify HFOs, averaged SEPs were digitally filtered using an eighth-order zero-phase Butterworth band-pass 400–1000 Hz filter according to the previous SEP HFO studies.^{20–23,30–33} The baseline was set at 150–200 ms following stimulation if the analysis window was 200 ms and at 5–15 ms or 35–45 ms following stimulation if the analysis window was 50 ms. These baselines were derived from the data obtained by common SEP recording devices (Viking and Neuropack) in accordance with previous studies^{20,31,33,34} and as independent as possible from the activities around 25 ms which were the subject of this study. As an operational definition, P25-HFOs were

defined as four consecutive peaks (equivalent to two cycles) or more that exceeded ± 4 SD from the baseline in the filtered waveform with an offset latency (HFO end latency) of more than 22 ms to exclude the possibility of HFOs with N20. The reason for selecting a threshold at 4 SDs from the baseline was that clearer oscillations than those observed in previous studies using 2 or 3 SDs^{20,22,30,31} could be detected. In addition, since previous studies have reported that 22 ms is the approximate time point where the appearance and generator source of HFOs change,²³ the boundary between HFOs with N20 and P25-HFOs was also set at appropriately 22 ms. Measured HFO parameters included onset and offset latency, duration, peak-to-peak amplitude, and latency of peak amplitude (Fig. 1). To confirm the presence of a high-frequency activity, a time-frequency analysis was conducted using a short-time Fourier transformation (fast Fourier transform size = 64, time shift = 3.2 ms) of raw SEPs. The SD value of the baseline amplitude and the Z value of the peak amplitude during the 20–30 ms latency in the filtered waveform were calculated. The baseline amplitude may widely vary; hence, the SD value of the baseline amplitude was also calculated. Similarly, to provide a standardized value, since the HFO amplitude could vary, the Z value of the peak amplitude during the 20–30 ms latency in the filtered waveform was calculated. In other words, the average value of the baseline amplitude was subtracted from the peak amplitude

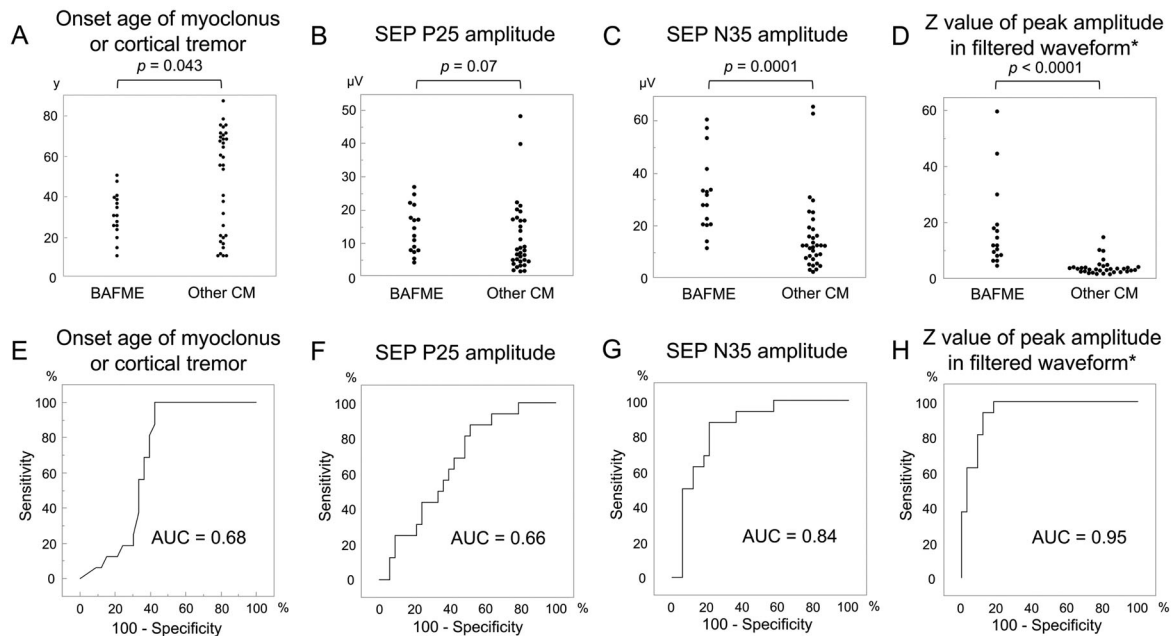


FIG 2. Comparison of factors between benign adult familial myoclonus epilepsy (BAFME) and other cortical myoclonus diseases. **(A–D)** Comparisons of the values of each factor between BAFME and other cortical myoclonus groups. **(E–H)** Receiver operating characteristic (ROC) curves of each factor for BAFME diagnosis. The highest area under the curve (AUC) among these factors was 0.95 for the Z value. *During the 20–30 ms latency after stimulation. SEP, somatosensory evoked potential.

and then divided by the SD value of the baseline amplitude to obtain the Z value.

Statistical Analysis

Clinical profiles, giant SEP amplitudes, the SD and Z values, and the presence of P25-HFOs were univariately analyzed using the Wilcoxon signed-rank test or the Fisher's exact test for comparisons between BAFME and other cortical myoclonus diseases. Since other cortical myoclonus groups included various diseases, to restrict evaluation to epileptic syndromes, the same statistical comparison was also performed in BAFME and other epileptic syndromes with cortical myoclonus. The SEP amplitude and the SD and the Z values were shown as the average of the amplitudes on bilateral sides. To determine the diagnostic usefulness of each factor for diagnosing BAFME, receiver operating characteristic (ROC) curves of the candidate factors obtained by the previous univariate analysis were plotted and their areas under the curves (AUCs) were calculated.

Factors contributing to the presence of P25-HFOs were univariately analyzed using the Wilcoxon signed-rank test and the Fisher's exact test between the two patient groups with and without P25-HFOs. From the results of the presence of P25-HFOs, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of P25-HFOs for the clinical diagnosis of BAFME were calculated. Finally, to determine the most reliable biomarker for BAFME

diagnosis, we compared the sensitivity, specificity, PPV, and NPV of the candidate factors obtained by the previous univariate analysis for the comparisons between BAFME and other cortical myoclonus diseases.

All waveform analyses and statistical analyses were performed using MATLAB (2018, Mathworks, Natick, MA) and JMP Pro software version 14.0.0 (SAS Institute, Cary, NC). Values of $P < 0.05$ were considered statistically significant.

Results

Clinical Profiles

Patients' clinical profiles are shown in Table 1. The mean age $\pm$ standard deviation (SD) of enrolled patients was 55.8 ± 18.3 years. Of the 16 patients with BAFME, 10 were genetically diagnosed and six were diagnosed with definite or probable BAFME according to clinical and electrophysiological criteria.⁵ Details of all individual patient data are included in Supplementary Table S1.

Differences in Clinical and SEP Findings Between BAFME and Other Cortical Myoclonus Diseases

Patients with BAFME had significantly earlier onset of cortical myoclonus/cortical tremor ($P = 0.043$), more patients were prescribed antiepileptic drugs ($P = 0.0035$), had larger N35 amplitudes of SEP ($P = 0.0001$), and higher Z value of the peak amplitude

TABLE 2 Clinical and electrophysiological findings with and without P25- high-frequency oscillations

Parameter	P25-HFOs(+) (n = 20)	P25-HFOs(-) (n = 29)	P value
Number of SEP examinations, n	35	63	
Age, y (mean ± SD)	54.5 ± 16.2	56.3 ± 20.4	0.50
Male, n	4 (20%)	10 (34.4%)	0.34
Underlying disease			
BAFME, n	16 (80%)	0	<0.0001^b
Other CM diseases, n	4 (20%)	29 (100%)	
<i>Epileptic syndrome</i>			
ULD	0	6 (20.7%)	
Gaucher's disease	0	1 (3.4%)	
PME etiology unknown	0	4 (13.8%)	
JME	0	1 (3.4%)	
Epilepsy etiology unknown	1 (5%)	0	
<i>Non-epileptic, symptomatic disease</i>			
CBS	2 (10%)	7 (24.1%)	
FTLD	1 (5%)	1 (3.4%)	
SCD	0	1 (3.4%)	
AD	0	1 (3.4%)	
CJD	0	2 (7.0%)	
Post-infectious encephalitis	0	1 (3.4%)	
Drug-induced syndromes	0	3 (10.3%)	
Paraneoplastic encephalitis	0	1 (3.4%)	
Onset age of myoclonus or cortical tremor, y (mean ± SD)	34.3 ± 15.7	47.1 ± 26.2	0.09
Disease duration of myoclonus or tremor, y (mean ± SD)	20.2 ± 16.1	12.9 ± 9.3	0.0035^b
Myoclonus rating score (0–4)	1.5 ± 0.8	1.4 ± 1.2	0.87
Use of antiepileptic drug, n	15 (75%)	16 (55.1%)	0.23
Number of antiepileptic drugs, n	1.2 ± 1.0	1.2 ± 1.5	0.77
SEP P25 amplitude, μV	17.8 ± 7.5	15.1 ± 10.4	0.01
SEP N35 amplitude, μV	30.1 ± 18.0	16.0 ± 15.2	<0.0001^b
SD value of baseline amplitude in filtered waveform	0.076 ± 0.040	0.070 ± 0.032	0.43
Z value of peak amplitude in filtered waveform ^a	17.7 ± 15.6	3.1 ± 1.3	<0.0001^b
P25-HFO components			
Onset latency, ms	20.0 ± 1.5		
Offset latency, ms	27.0 ± 2.6		
Peak latency, ms	23.4 ± 1.7		
Duration, ms	7.0 ± 2.9		
Peak amplitude, μV	2.4 ± 1.9		

HFO, high-frequency oscillation; SEP, somatosensory evoked potential; y, year; SD, standard deviation; BAFME, benign adult familial myoclonus epilepsy; CM, cortical myoclonus; ULD, Unverricht–Lundborg disease; PME, progressive myoclonus epilepsy; JME, juvenile myoclonic epilepsy; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; SCD, spinocerebellar degeneration; AD, Alzheimer's disease; CJD, Creutzfeldt–Jakob disease; ms, millisecond.

^aDuring the 20–30 ms latency after stimulation.

^bStatistically significant.

TABLE 3 Diagnostic usefulness of benign adult familial myoclonus epilepsy

Parameter	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Onset age of myoclonus or cortical tremor, <50 y	100 (84.0–100)	57.6 (49.8–57.6)	53.3 (44.8–53.3)	100 (86.5–100)
SEP P25 amplitude, >11.39 μ V	87.5 (68.5–96.4)	48.5 (39.3–52.8)	45.2 (35.4–49.7)	88.9 (72.0–96.8)
SEP N35 amplitude, >20.095 μ V	87.5 (68.9–96.3)	78.8 (69.8–83.0)	66.7 (52.5–73.3)	92.9 (82.3–97.9)
Z value of peak amplitude in filtered waveform ^a , >4.4323	100 (84.7–100)	81.8 (74.4–81.8)	72.7 (61.6–72.7)	100 (90.9–100)
Presence of P25-HFOs	100 (85.3–100)	87.9 (80.7–87.9)	80.0 (68.2–80.0)	100 (91.9–100)

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; y, year; SEP, somatosensory evoked potential; HFO, high-frequency oscillation.

^aDuring the latency of 20–30 ms after stimulation.

during the 20–30 ms latency ($P < 0.0001$) than those with other diseases. Furthermore, P25-HFOs occurred much more frequently in patients with BAFME compared to patients with other diseases (100% vs. 12.1%, $P < 0.0001$) (Table 1). The high occurrence rate of P25-HFOs in BAFME patients remained in comparison with other epileptic syndromes with CM (100% vs. 7.7%, $P < 0.0001$). This comparison also showed that patients with BAFME were older, had an older onset age, and lesser antiepileptic drug use than patients with other epileptic syndromes causing cortical myoclonus (Supplementary Table S2). Representative waveforms are shown in Fig. 1 and Supplementary Figure S1.

Based on univariate analysis results, we selected the onset age of myoclonus or cortical tremor, the SEP P25 amplitude, SEP N35 amplitude, and Z value of the peak amplitude in the filtered waveform as factors for BAFME diagnosis and plotted ROC curves for each (Fig. 2). Among these factors, the AUC of the Z value was the highest, at a value of 0.95, with sensitivity, specificity, PPV, and NPV of 100%, 81.8%, 72.7%, and 100%, respectively.

Factors Contributing to the Presence of P25-HFOs

P25-HFOs occurred in 20 patients (40.8%). P25-HFOs started at a latency of 20.0 ms and ended at 27.0 ms. The peak amplitude latency of P25-HFOs was 23.4 ms. BAFME diagnosis was significantly associated with the presence of P25-HFOs ($P < 0.0001$). The disease duration of myoclonus or tremor, SEP P25 amplitude, SEP N35 amplitude, and Z value of the peak amplitude in the filtered waveform with P25-HFOs were also significantly larger than in those without P25-HFOs ($P = 0.0035$, $P = 0.01$, $P < 0.0001$, and $P < 0.0001$, respectively) (Table 2). Myoclonus disease

duration ranged from 1 to 52 years in patients with P25-HFOs and from 0 to 45 years in the patients without.

Regarding the underlying diseases with and without P25-HFOs, all 16 BAFME patients and four patients with other diseases had P25-HFOs (Table 2). One patient with epileptic myoclonus, classified as epilepsy etiology unknown, was a 26-year-old woman who had a single unconscious seizure at 17 years of age and constant postural tremor without cerebellar ataxia. Her EEG showed generalized epileptiform discharges. Conversely, most patients (29/33 patients) with other diseases did not have P25-HFOs.

P25-HFOs as a Diagnostic Factor for BAFME

Based on the results of the underlying diseases with and without P25-HFOs, to predict BAFME diagnosis in patients with cortical myoclonus and giant SEPs, P25-HFOs provided high sensitivity (100%), specificity (87.8%), PPV (80%), and NPV (100%). These values were all superior to the degree of the diagnostic power of other factors (Table 3).

Discussion

This study demonstrated that of the 49 patients with cortical myoclonus, all 16 BAFME patients showed P25-HFOs, that is, HFOs with P25 in giant SEPs according to our criteria, with clear peak latency later than N20. BAFME patients differed significantly from those with other cortical myoclonus diseases in terms of onset age of involuntary movements, antiepileptic drug usage, high SEP amplitudes, and Z value of the peak amplitude during the 20–30 ms latency in the filtered waveform. The presence of P25-HFOs was also significantly correlated with the disease duration of

myoclonus or tremor and high SEP P25 and N35 amplitude; therefore, the possibility that disease duration and high SEP amplitudes caused P25-HFOs should be considered. Of note, the presence of P25-HFOs in giant SEPs predicted BAFME with much higher diagnostic usefulness than other factors. Although the clinical and electrophysiological features of BAFME are similar to those of other cortical myoclonus diseases, particularly PME such as Unverricht–Lundborg disease (ULD), the current results showed that BAFME and the remaining cortical myoclonus were well differentiated by P25-HFOs. ■

Possible Generator Sources for P25-HFOs

Regarding the possible source of P25-HFOs, the first hypothesis is that, in this study, the presence of P25-HFOs was significantly associated with high P25 and N35 amplitudes, which may contribute to the generation of P25-HFOs. This indicates that larger SEPs would lead to more and larger P25-HFOs. However, P25-HFOs were observed specifically in BAFME patients and not in other CM patients, even though both had similar high SEP amplitudes. Taken together, it is less likely that P25-HFOs are associated only with high SEP amplitude. A second hypothesis is that disease duration may also be associated with P25-HFO generation. However, even patients with a short duration (1 year) were represented in the P25-HFO group. Additionally, in subgroup analysis, although disease duration was not significantly different between BAFME and other epileptic syndromes with cortical myoclonus, BAFME patients specifically showed P25-HFOs. These suggest that disease duration is probably not a strong factor contributing to P25-HFO generation.

It is also possible that P25-HFOs could reflect a pathological hyperexcitable activity of the primary somatosensory cortex.^{19,22} HFOs in EEG are sometimes accompanied with spikes and are reported to be closely related to epileptogenicity,^{35,36} especially in faster HFOs.³⁷ Giant SEP P25 has been thought to reflect hyperexcitability and possibly partly paroxysmal depolarizing shifts, which could generate epileptic discharges.^{4,24,38} Hence, as shown in epileptic HFOs of EEG (since EEG is spontaneous activity and SEP waveforms are evoked and averaged activities, we do not believe that HFOs observed in EEG are exactly the same activity as HFOs observed in SEPs) and P25 of giant SEPs, P25-HFOs would also be associated with hyperexcitability and epileptogenicity. To verify this hypothesis, more case studies and basic research are warranted.

P25-HFOs in Previous Studies

This study is not the first to describe the activities of P25-HFOs,¹⁹ although the term ‘P25-HFOs’ has not been used previously, herein, we refer to it as

‘P25-HFOs’ for better clarity. Several SEP studies have shown that the physiological 500–1000 Hz HFOs around N20 can be divided into early and late HFOs in individuals who do not show giant SEPs. Specifically, early HFOs denote the five wavelets before the N20 peak in the original waveform, while the five to six wavelets after the N20 peak are termed as late HFOs.^{20,39} This definition is not based on HFO latency or amplitude. However, several previous reports have indicated that the offset latency of late HFOs in control individuals is approximately 24–26 ms, with some superimposition on the P25 peak.^{21,23} Therefore, we speculate that our observed P25-HFOs most likely correspond to the late N20 HFOs in previously reported patients without giant SEPs,^{20,23,31,32,39} or HFOs at P25.

Accordingly, we next focus on the late N20 HFOs in giant SEPs. Previous studies have reported that late HFOs, possibly corresponding to P25-HFOs, show large amplitudes and delayed latencies in patients with myoclonic epilepsy,²¹ non-progressive myoclonic epilepsy,²² and parkinsonism with myoclonus.²² The current results showed that P25-HFOs were present in patients with BAFME, corticobasal syndrome (CBS), frontotemporal lobar degeneration (FTLD), and epilepsy etiology unknown. Thus, the myoclonic epilepsy and non-progressive myoclonic epilepsy described previously might correspond to European and Japanese BAFME, and parkinsonism with myoclonus might correspond to CBS.^{21,22}

Relevance of P25-HFOs to Clinical Features Especially in BAFME

The present study showed that patients with BAFME had P25-HFOs, whereas most of the patients with other cortical myoclonus did not have P25-HFOs. Moreover, P25-HFO maintains a high specificity even in comparison with other epileptic syndromes with cortical myoclonus. These results suggest that the underlying pathology of giant SEPs may differ between BAFME and other cortical myoclonus diseases.

Cortical tremor may be a key symptom in explaining the specific presence of P25-HFOs in BAFME patients. Cortical tremor consists of fine rhythmic movements, observed specifically in BAFME patients.^{1,2,40} BAFME patients often present with both tremulous and myoclonic movements, and some researchers suggest that cortical tremor should be included in cortical myoclonus due to their presumed common pathophysiology.⁴¹ However, at least phenomenologically, the cortical tremor of BAFME patients differs from the myoclonus of other cortical myoclonus patients.^{3,5,42,43} Moreover, CBS patients, in whom P25-HFOs were observed in this study, were reported to have low-amplitude rhythmic tremor.^{44,45} Electrophysiologically, movement-related

cortical potential studies have shown that a normal cerebellar efferent pathway, particularly in BAFME patients, may be associated with the generation of the characteristic rhythmicity.⁴⁰ Whereas cortical tremor may result from an unstable or hypersynchronous cerebello-thalamic-cortical loop like epilepsy partial continua,¹² or from some cerebellar abnormality based on imaging and pathological findings.⁴⁶⁻⁵⁰ The pathogenesis of cortical tremor and the relationship between the tremor and HFOs remains unclear. However, it would be interesting if P25-HFOs can link cortical tremor and rhythmicity characteristically observed in BAFME or parts of CBS.

Usefulness of P25-HFOs for Diagnosing BAFME

The high sensitivity (100%), specificity (87.8%), PPV (80%), and NPV (100%) of P25-HFOs for predicting BAFME suggest that screening for P25-HFOs is a useful tool in patients with giant SEPs when differentiation from other cortical myoclonus diseases is needed. The significant differences in age at onset of involuntary movements, SEP amplitude, and Z value between BAFME and other diseases are also novel findings in this study. Although these may be available for BAFME diagnosis, the presence of P25-HFOs, as tentatively defined here, had much higher diagnostic power.

The main question to be answered is how accurately we can diagnose BAFME using P25-HFOs. In addition to BAFME patients, two patients with CBS and one with FTLT also demonstrated P25-HFOs in our cohort. However, based on the clinical course and other symptoms, we could easily distinguish BAFME from CBS and FTLT. An additional patient with epilepsy etiology unknown also showed P25-HFOs. In this case, the patient's symptoms were compatible with BAFME, except for absence of family history.⁵ Although patients' diagnosis should always be performed carefully and comprehensively, a confirmation of a clinical course and the detection of P25-HFOs are simple procedures that require no additional equipment or patient load. Thus, P25-HFOs can be a cost-effective tool for diagnosing BAFME with giant SEPs prior to genetic testing.

Limitations

This study has several limitations. First, we tentatively defined the threshold of P25-HFOs using an operational definition. Although the settings used to define this parameter were based on previous reports, there might be better settings than the ones used herein. Therefore, further studies with larger sample sizes are warranted to validate the accuracy of the settings used in this study. Second, this is a retrospective study in which patients varied in age, disease duration, and the status of antiepileptic drug therapy, which might have

affected the appearance of P25-HFOs. To minimize these effects, we adopted the SEP data at the earliest time during the clinical course available for each patient, when patients were youngest and with the least antiepileptic drug exposure. Third, not all patients had been diagnosed by genetic testing; the diagnosis was made carefully, and all patients in which genetic testing could not be performed were judged by two or more certified neurologists using clinical diagnostic criteria.^{1,2,5-7} Nevertheless, this point should be carefully considered in interpreting our results. Fourth, this study did not include normal healthy controls; thus, whether P25-HFOs are also present even in control individuals without giant SEPs remains to be determined. Since HFOs with normal SEPs could not be validated as pathological HFOs, we used a case series design in patients with giant SEPs. Fifth, not all patients with cortical myoclonus have giant SEPs. It remains unclear whether both P25-HFOs and giant SEPs behave in parallel or independently. As a further potential limitation, whether P25-HFOs are true cortical responses remains to be determined. To estimate the source of these high-frequency activities, previously reported methods of HFOs in EEG, such as simultaneous scalp and intracranial recordings⁵¹ and mathematical model simulations,⁵² may be considered in the future. Nevertheless, it is surprising that the electrophysiological behavior is distinctly different in certain types of diseases.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Supplementary materials

Pt No.	Age, y	Sex	Underlying disease	Basis for diagnosis	Myoclonus onset age, y	Myoclonus rating score	Antiepileptic drug	SEP recording machine	Sampling rate, kHz	SEP P25		SEP N35 amplitude, μ V	Baseline, ms	SD value*	Z value*	P25-HFOs	P25-HFO components				
										Side	amplitude, μ V						Onset latency, ms	Offset latency, ms	Peak latency, ms	Duration, ms	Peak amplitude, μ V
1	66	F	BAFME	G	14	1	PHT	NP	10	L	24.03	48.72	150–200	0.040	77.198	+	17.4	29.6	24.5	12.2	6.08
2	78	F	BAFME	C, E (Definite)	30	1	LEV	Viking	19.2	R	30.65	58.85	150–200	0.059	42.513	+	19.5	29.1	23.7	9.6	4.96
										L	27.45	38.09	5–15	0.130	30.011	+	20.6	31.0	24.8	10.5	7.67
3	30	F	BAFME	G	19	1	PB	Viking	10	R	21.47	27.84	5–15	0.261	8.443	+	21.3	27.7	25.4	6.5	4.29
										L	10.41	19.69	5–15	0.072	9.645	+	17.5	22.3	20.2	4.8	1.39
4	40	F	BAFME	G	25	1	CZP	Viking	20	R	12.37	21.07	5–15	0.098	11.028	+	16.6	23.1	20.2	6.5	2.09
										L	11.4	19.5	5–15	0.103	6.042	-					
5	65	F	BAFME	C, E (Probable)	40	3	CZP	Viking	10	R	14.32	25.58	5–15	0.091	9.980	+	22.1	26.6	24.7	4.6	1.77
										L	12.53	18.02	5–15	0.063	2.539	-					
6	44	F	BAFME	C, E (Probable)	34	1	VPA	Viking	10	R	4.48	9.59	5–15	0.045	6.325	+	21.3	24.6	23.4	3.3	0.54
										L	17.71	36.28	5–15	0.131	8.451	+	19.1	24.3	22.4	5.2	2.21
7	42	F	BAFME	G	30	2	CZP	Viking	10	R	14.05	30.58	5–15	0.054	15.003	+	19.2	27.1	22.6	7.9	1.57
										L	8.35	14.38	5–15	0.055	6.844	+	21.8	24.8	23.8	3.0	0.75
8	77	F	BAFME	G	50	2	CZP, VPA, LEV, PB	Viking	10	R	15.5	25.81	5–15	0.088	16.619	+	21.6	29.8	27.0	8.2	2.86
										L	24.48	38.2	5–15	0.065	7.474	+	20.0	24.1	21.7	4.1	0.97
9	67	F	BAFME	G	39	3	CZP, DZP	Viking	5	R	16.2	25.34	5–15	0.070	4.984	-					
										L	27.19	44.18	150–200	0.054	12.476	+	20.6	26.0	22.8	5.4	1.35
10	54	M	BAFME	G	23	1	CZP, VPA	Viking	20	R	22.81	39.48	150–200	0.067	6.280	+	22.4	26.8	25.2	4.4	0.81
										L	10.32	13.93	5–15	0.058	9.589	+	19.5	25.0	22.1	5.5	1.08
11	55	F	BAFME	G	10	2	CZP	Viking	20	R	8.85	8.41	5–15	0.025	24.252	+	20.4	27.5	23.3	7.1	1.21
										L	24.3	46.39	5–15	0.084	21.375	+	19.3	27.4	22.4	8.1	3.42
12	43	M	BAFME	C, E (Definite)	38	1	CZP	NP	10	R	11.71	21.2	5–15	0.112	14.416	+	18.6	26.1	21.1	7.5	3.02
										L	19.7	21.36	150–200	0.050	49.189	+	19.4	31.9	25.3	12.5	4.83
13	59	F	BAFME	G	36	1	VPA	Viking	10	R	20.67	19.45	150–200	0.040	40.211	+	18.9	31.1	26.3	12.2	3.20
										L	9.51	25.62	5–15	0.098	6.109	+	20.7	24.5	23.3	3.8	1.17
14	70	F	BAFME	C, E (Definite)	47	2	CZP, LEV	Viking	4	R	14.23	30.05	5–15	0.082	10.432	+	19.7	27.6	23.1	7.9	1.70
										L	35.32	74.31	150–200	0.063	8.358	+	21.0	24.8	24.3	3.8	1.02
15	35	F	BAFME	G	27	1	-	Viking	10	R	23.46	41.08	150–200	0.065	20.662	+	21.7	29.5	25.5	7.8	2.54
										L	12.61	30.4	5–15	0.062	16.439	+	19.4	30.5	24.1	11.1	2.05
16	60	F	BAFME	C, E (Definite)	25	2	CZP, VPA	Viking	19.2	R	29.13	91.52	5–15	0.085	43.635	+	19.9	30.6	24.1	10.7	7.25
										L	15.38	26.29	5–15	0.051	6.341	+	20.4	24.4	22.2	4.0	0.63
17	34	M	ULD	G	10	2	CZP, VPA, ZNS	Viking	20	R	13.99	29.42	5–15	0.077	6.084	+	19.9	23.2	22.1	3.3	0.93
										L	9.99	15.41	35–45	0.050	2.479	-					
18	32	F	ULD	G	10	3	CZP, VPA, TPM, PER	Viking	19.2	R	5.51	9.1	35–45	0.030	3.766	-					
										L	19.82	26.67	35–45	0.030	1.810	-					
19	42	F	ULD	G	14	2	CZP, VPA, ZNS, PB	Viking	20	R	20.3	23.43	35–45	0.041	1.349	-					
										L	13.33	17.59	5–15	0.107	1.836	-					
20	15	F	ULD	G	11	2	VPA, PRM	NP	10	R	23.54	19.35	5–15	0.054	1.143	-					
										L	46.51	71.67	150–200	0.067	2.955	-					
21	25	F	ULD	G	10	3	CZP, VPA	Viking	20	R	36.01	60.19	150–200	0.076	2.447	-					
										L	6.17	4.57	35–45	0.050	1.735	-					
22	65	M	ULD	G	20	3	CZP, VPA, PB	Viking	10	R	8.25	5.85	35–45	0.049	2.120	-					
										L	5.81	5.49	5–15	0.027	1.896	-					
23	33	M	Gaucher's disease	G	31	2	VPA, LEV	NP	5	R	9.5	10.82	5–15	0.014	2.324	-					
										L	6.85	26.29	150–200	0.047	3.694	-					
24	58	F	PME etiology unknown	C, E	20	4	DZP, VPA, CBZ, CZP, PB	Viking	20	R	11.95	33	150–200	0.054	3.858	-					
										L	21.66	14.01	35–45	0.023	3.681	-					
25	42	F	PME etiology unknown	C, E	19	2	CZP, VPA	Viking	20	R	12.85	10.44	35–45	0.035	2.831	-					
										L	11.01	4.18	5–15	0.064	1.613	-					
										R	14.11	4.66	5–15	0.052	1.108	-					

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Pt No.	Age, y	Sex	Underlying disease	Basis for diagnosis	Myoclonus onset age, y	Myoclonus rating score	Antiepileptic drug	SEP recording machine	Sampling rate, kHz	SEP P25		SEP N35 amplitude, μ V	Baseline, ms	SD value*	Z value*	P25-HFOs	P25-HFO components				
										Side	amplitude, μ V						Onset latency, ms	Offset latency, ms	Peak latency, ms	Duration, ms	Peak amplitude, μ V
26	19	F	PME etiology unknown	C, E	17	1	CZP	Viking	20	L	8.23	4.53	35–45	0.095	2.071	-					
27	64	M	PME etiology unknown	C, E	37	3	PB, TPM	Viking	10	R	10.21	5.21	35–45	0.061	3.663	-					
										L	12.36	9.24	5–15	0.103	1.804	-					
28	27	F	JME	C	25	1	CZP, CBZ	Viking	20	R	7.96	8.37	5–15	0.040	4.291	-					
										L	6.59	12.23	35–45	0.052	6.495	-					
29	18	F	Epilepsy etiology unknown	C, E	16	1	-	Viking	20	R	5.53	12.23	35–45	0.077	3.345	-					
										L	17.07	35.68	35–45	0.066	6.470	-					
30	67	M	CBS	C, I	66	3	-	Viking	10	R	12.73	26.03	35–45	0.073	6.831	+	19.1	25.5	21.3	6.5	0.98
										L	11.51	11.49	5–15	0.080	11.063	+	19.7	25.1	22.3	5.4	1.72
31	54	F	CBS	C	53	1	-	NP	10	R	12.76	11.58	5–15	0.081	18.314	+	18.6	27.6	22.7	9.0	2.90
										L	11.48	16.49	150–200	0.044	17.350	+	17.7	28.8	21.3	11.1	1.38
32	76	F	CBS	C, I	71	0	-	Viking	10	R	9.65	7.83	150–200	0.051	2.848	-					
										L	13.65	12.66	5–15	0.081	1.646	-					
33	79	F	CBS	C, I	78	2	VPA	Viking	10	R	10.03	11.5	5–15	0.060	2.621	-					
										L	9.43	11.85	5–15	0.058	4.152	-					
34	75	F	CBS	C, I	74	0	-	Viking	10	R	6.8	5.04	5–15	0.060	4.487	-					
										L	12.07	8.69	35–45	0.110	2.423	-					
35	68	F	CBS	C	68	1	-	Viking	20	R	5.51	5.14	35–45	0.055	2.411	-					
										L	22.39	15.94	35–45	0.054	2.923	-					
36	74	F	CBS	C, I	71	0	CZP	Viking	10	R	22.83	15.43	35–45	0.064	2.487	-					
										L	3.26	3.44	5–15	0.068	1.782	-					
37	68	M	CBS	C, I	69	2	-	NP	5	R	9.08	2.08	5–15	0.046	1.733	-					
										L	29.57	30.5	150–200	0.106	3.084	-					
38	69	F	CBS	C, I	68	0	-	Viking	10	R	11.25	14.17	150–200	0.043	4.159	-					
										L	11.94	2.19	5–15	0.107	3.010	-					
39	66	M	FTLD	C, I	64	0	-	NP	10	R	5.67	1.81	5–15	0.092	3.796	-					
										L	25.31	15.29	150–200	0.060	6.870	+	24	27.9	25.6	3.9	0.8248
40	66	M	FTLD	C, P	67	0	-	Viking	20	R	23.08	14.9	150–200	0.066	12.648	+	21.2	29.9	25.7	8.7	1.624
										L	11.04	5.07	5–15	0.127	3.037	-					
41	70	M	SCD	C, I	60	0	-	Viking	10	R	10.44	3.5	5–15	0.056	4.389	-					
										L	14.25	11.67	5–15	0.051	3.667	-					
42	75	M	AD	C, I	75	2	-	Viking	10	R	8.08	8.67	5–15	0.035	2.144	-					
										L	11.51	5.1	5–15	0.078	3.983	-					
43	70	F	CJD	G	55	0	-	Viking	20	R	14.26	9.62	5–15	0.084	3.781	-					
										L	10.07	11.06	5–15	0.058	5.154	-					
44	87	F	CJD	G	87	0	-	Viking	20	R	8.35	11.23	5–15	0.126	1.986	-					
										L	18.86	9.48	5–15	0.086	3.434	-					
45	40	M	Post-infectious encephalitis	C, E	40	2	-	Viking	10	R	21.33	17.15	5–15	0.112	3.219	-					
										L	3.5	0.58	35–45	0.033	6.942	-					
46	56	M	Drug-induced syndromes	C, E	55	1	DZP	Viking	10	R	9.22	5.29	35–45	0.063	2.546	-					
										L	20.32	19.6	5–15	0.134	1.771	-					
47	75	F	Drug-induced syndromes	C, E	75	1	-	Viking	10	R	21.49	12.36	5–15	0.123	2.839	-					
										L	28.03	28.11	5–15	0.072	3.881	-					
48	69	F	Drug-induced syndromes	C, E	70	1	-	Viking	10	R	18.3	22.57	5–15	0.061	2.785	-					
										L	57.12	69.31	5–15	0.144	5.409	-					
49	59	F	Paraneoplastic encephalitis	C, E	59	2	CZP	Viking	10	R	40.79	57.16	5–15	0.168	2.524	-					
										L	16.88	13.78	5–15	0.090	1.591	-					
										R	33.38	24.59	5–15	0.068	3.144	-					

Supplementary Table S1. Details of clinical data, SEP settings and findings.

*During the 20–30 ms latency after stimulation

AD = Alzheimer's disease; BAFME = benign adult familial myoclonus epilepsy; C = clinical findings; CBS = corticobasal syndrome; CBZ = carbamazepine; CJD = Creutzfeldt–Jakob disease; CZP = clonazepam; DZP = diazepam; E = electrophysiological findings; FTLN = frontotemporal lobar degeneration; G = genetic test results; HFO = high frequency oscillation; I = neuroimaging findings; JME = juvenile myoclonic epilepsy; L = left; LEV = levetiracetam; No. = number; NP = Neuropack; P = pathological findings; PB = phenobarbital; PER = perampanel; PHT = phenytoin; PME = progressive myoclonus epilepsy; PRM = primidone; Pt = patient; R = right; SCD = spinocerebellar degeneration; SD = standard deviation; SEP = somatosensory evoked potential; TPM = topiramate; ULD = Unverricht-Lundborg disease; VPA = valproic acid; y = year; ZNS = zonisamide.

	BAFME (n=16)	Other cortical myoclonus diseases (Epileptic syndrome) (n=13)	P value
Number of SEP examinations, n	32	26	
Age, y (mean $\pm$ SD)	55.3 $\pm$ 14.9	36.5 $\pm$ 17.0	0.012
Male, n	2 (12.5%)	4 (30.8%)	0.36
Onset age of myoclonus or cortical tremor, y (mean $\pm$ SD)	30.4 $\pm$ 11.2	18.5 $\pm$ 8.4	0.018
Myoclonus disease duration, y (mean $\pm$ SD)	24.9 $\pm$ 14.6	18 $\pm$ 14.8	0.17
Myoclonus rating score (0–4)	1.6 $\pm$ 0.7	2.2 $\pm$ 0.9	0.12
Use of antiepileptic drug, n	15 (93.8%)	13 (100%)	1.0
Number of antiepileptic drugs	1.4 $\pm$ 0.9	2.5 $\pm$ 1.3	0.023
SEP P25 amplitude, μ V	17.6 $\pm$ 6.6	14.0 $\pm$ 9.4	0.11
SEP N35 amplitude, μ V	31.9 $\pm$ 15.0	18.3 $\pm$ 17.0	0.022
SD value of baseline amplitude in filtered waveform	0.078 $\pm$ 0.036	0.055 $\pm$ 0.019	0.16
Z value of peak amplitude in filtered waveform*	17.5 $\pm$ 15.2	3.0 $\pm$ 1.5	<0.0001
Presence of P25-HFOs, n	16 (100%)	1 (7.7%)	<0.0001

Supplementary Table S2. Clinical profiles and SEP findings for patients with BAFME and epileptic syndromes of other cortical myoclonus diseases.

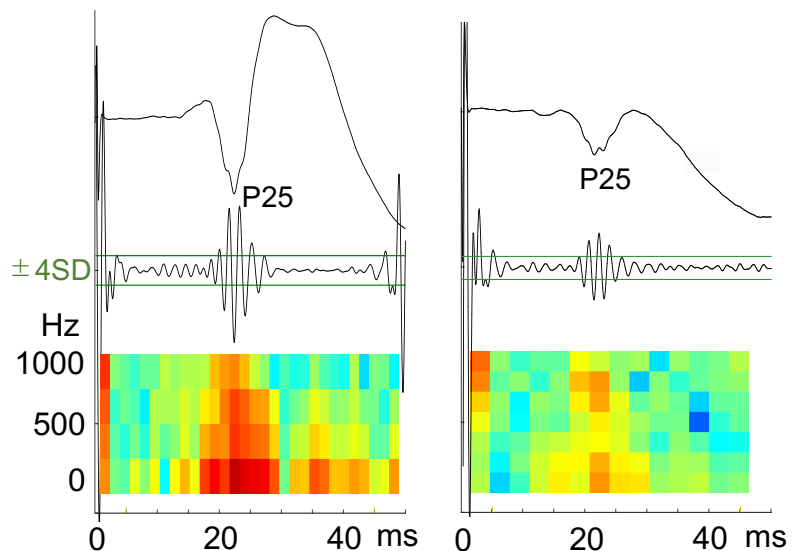
*During the 20–30 ms latency after stimulation

BAFME = benign adult familial myoclonus epilepsy; HFO = high-frequency oscillation; SD = standard deviation; SEP = somatosensory evoked potential; y = year.

P25-HFOs (+)

Pt11 BAFME

Pt30 CBS

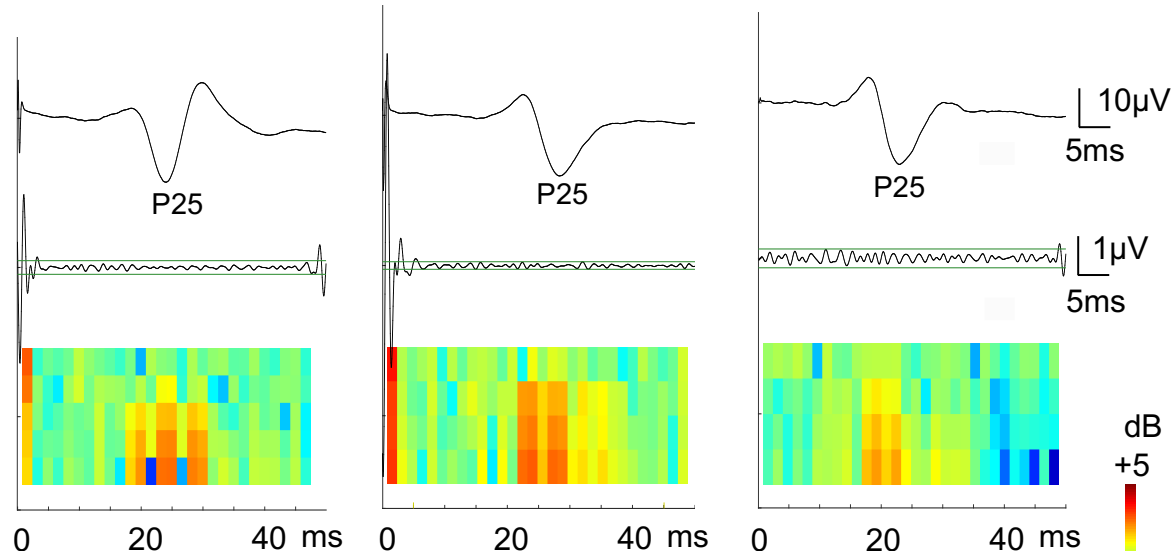


P25-HFOs (-)

Pt18 ULD

Pt24 PME

Pt35 CBS



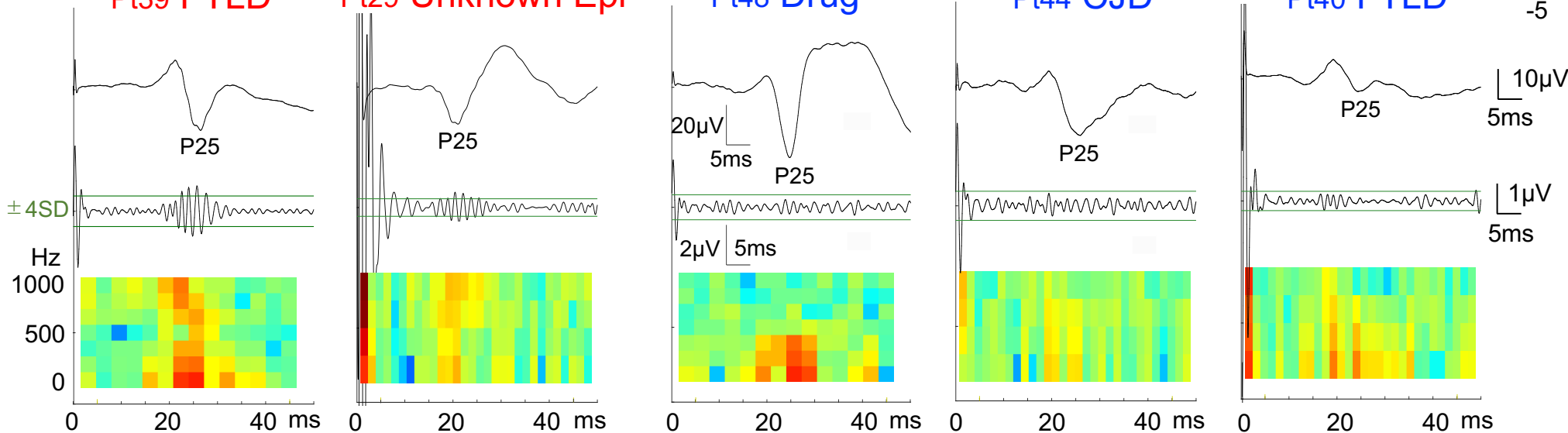
Pt39 FTLD

Pt29 Unknown Epi

Pt48 Drug

Pt44 CJD

Pt40 FTLD



Supplementary Figure S1. Representative waveforms and time–frequency analysis.

The SEP waveforms and time–frequency analysis of the four cases with high-frequency oscillations (HFOs) superimposed on P25 of giant somatosensory evoked potentials (SEPs), namely ‘P25-HFOs’, and the six cases without ‘P25-HFOs’. The number following Pt corresponds to the patient number (Pt No.) in Supplementary Table S1. In each figure, the top plots a raw SEP waveform. The middle depicts a digitally filtered SEP waveform by an eighth-order zero-phase Butterworth band-pass 400–1000 Hz filter. The bottom depicts the time–frequency analysis results (0–1000 Hz) obtained by short-time Fourier transform (fast Fourier transform size = 64, time shift = 3.2 ms) of raw SEPs. Note the clear oscillations in the filtered waveforms in the cases with P25-HFOs, and no similar activity in the cases without P25-HFOs.

BAFME = benign adult familial myoclonus epilepsy; CBS = corticobasal syndrome; CJD = Creutzfeldt–Jakob disease; Drug = drug-induced syndromes; FTLN = frontotemporal lobar degeneration; HFO = high frequency oscillation; PME = progressive myoclonus epilepsy; SD = standard deviation; SEP = somatosensory evoked potential; ULD = Unverricht-Lundborg disease; Unknown Epi = Epilepsy etiology unknown.