Original article

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Benign adult familial myoclonus epilepsy is a progressive disorder: no longer idiopathic generalized epilepsy

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ABSTRACT – *Background.* Brain dysfunction in Japanese benign adult familial myoclonus epilepsy (BAFME) has not been elucidated.
Aim. To clarify diffuse brain dysfunction as indicated by posterior dominant rhythm (PDR) slowing in patients with BAFME.
Methods. The frequency of PDR on EEG was studied in 19 BAFME patients (50.6±15.7 years) and 38 age-matched control subjects (50.1±14.5 years). We investigated the relationship between age and PDR in both groups.
Results. PDR frequency in the patient group (9.1±0.7 Hz) was significantly slower than that of age-matched control subjects (10.4±1.1 Hz; $p<0.0001$), regardless of the use of anticonvulsants. There was no significant difference in PDR slowing with age between groups.
Conclusions. These findings suggest that Japanese patients with BAFME have mild diffuse brain dysfunction with minimal progression.

Key words: benign adult familial myoclonus epilepsy (BAFME), diffuse brain dysfunction, posterior dominant rhythm

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Benign adult familial myoclonus epilepsy (BAFME) manifests as an autosomal dominant trait and is characterized by cortical tremor resembling essential tremor and generalized tonic-clonic seizures. BAFME is reported as many different syndromes in Japan (Ikeda *et al.*, 1990; Yasuda, 1991), and as familial cortical myoclonic tremor with epilepsy (FCMTE) (van Rootselaar *et al.*, 2005) and autosomal dominant cortical tremor, myoclonus, and epilepsy (ADCME) (de Falco *et al.*, 2003) in Europe. Despite similarities in the phenotypes, linkage

analysis shows that different loci are affected in Japanese BAFME (Plaster *et al.,* 1999) and European FCMTE and ADCME (de Falco *et al.,* 2003). Recently, mutation, a novel in-frame insertion/deletion, in the α2-adrenergic receptor subtype B has been shown to be associated with ADCME (De Fusco *et al.,* 2014). However, the causative gene remains unclear in Japanese BAFME (Kato *et al.,* 2012). Electrophysiological studies revealed that BAFME, ADCME, and FCMTE commonly manifest features of cortical reflex myoclonus (Ikeda *et al.,* 1990; Striano *et al.,* 2009a). Previous EEG studies showed a higher frequency of generalized spike-and-wave complexes in Japanese BAFME than in those with epilepsy only, generalized tonic-clonic seizures, and photosensitivity (Yasuda, 1991; Uyama *et al.,* 2005; Toyota *et al.,* 2014).

BAFME is considered to follow a relatively benign clinical course, unlike progressive myoclonus epilepsy (PME). We recently revealed, however, that enlarged somatosensory evoked potential (SEP) amplitudes increase with age in BAFME, suggesting a progressive increase in cortical excitability in Japanese BAFME (Hitomi *et al.,* 2011). In addition, another recent study reported gradual and progressive slowing of the posterior dominant rhythm (PDR) with age in European patients with ADCME, based on EEG (Coppola *et al.,* 2011). There has been no systematic analysis of PDR in comparison with normative data.

In the present study, we investigated whether diffuse brain dysfunction, as indicated by PDR slowing, was present in BAFME by analysing the frequency of PDR in BAFME patients, as compared with a control group. If diffuse brain dysfunction is present in BAFME, it would be important to clarify whether the degree of PDR slowing with age is similar to that in normal physiological aging, or whether it is consistent with progressive changes in the underlying pathophysiology.

Material and methods

We retrospectively analysed 19 patients (five men and 14 women; mean [SD] age: 50.6±15.7 years old; range: 26-76 years) with a clinical diagnosis of BAFME in whom EEG was performed in our institutes. The diagnostic criteria for BAFME were the same as in our recent studies (Hitomi *et al.,* 2011, 2012, 2013) and the details are described elsewhere (Hitomi *et al.,* 2011).

The clinical data of each patient is shown in *table 1*. Of 19 patients, 16 had already taken anticonvulsants at the time of the first EEG for this analysis, as most of the patients had been treated previously at other hospitals. We also investigated the chronologic EEG changes in nine patients in whom EEG was recorded more than twice. For control data, among consecutively recorded digital EEGs in the central EEG laboratory at Kyoto University Hospital from March 2008 to July 2010, EEGs of 102 adult patients from the Neurology Department, older than 20 (44 men and 58 women; mean [SD] age: 38.2±13.9 years; range: 21-77 years), were judged to be normal by an EEG board-certified author (AI). The control group consisted of 29 patients with idiopathic generalized epilepsy, 33 patients with focal epilepsy, eight patients with syncopal attack, 11 patients with movement disorders, and 21 patients with other various kinds of aetiology (*e.g.* sleep disorders, psychiatric disorders, and so forth). Among them, we further extracted 38 age-matched adults as age-matched control subjects (10 men and 28 women; mean [SD] age: 50.1±14.5 years; range: 26-77 years) whose clinical information was blinded from the investigators. Furthermore, to evaluate the effect of anticonvulsants, the 38 age-matched control subjects were divided into two groups according to the anticonvulsant taken. We then analysed 24 age-matched control subjects under treatment with anticonvulsants (six men and 18 women; mean [SD] age: 45.0±12.7 years; range: 26-68 years) and 14 age-matched control subjects not treated with anticonvulsants (4 men and 10 women; mean [SD] age: 58.7±13.5 years; range: 35-77 years). The number of anticonvulsants taken by the 16 BAFME patients (1.6±0.7) and 24 age-matched control subjects taking anticonvulsants (1.5±0.7) was similar. However, the variation of anticonvulsants used in age-matched control subjects was somewhat diverse, mainly because of heterogeneous clinical background (*table 2*).

Routine EEG with scalp electrodes was recorded conventionally according to the international 10-20 system. The bandpass filter was set to 0.53-120 Hz for visual inspection. The predominant maximum frequency of PDR was determined by visual inspection of patients and control subjects with 0.5 Hz steps. For the control data, a frequency analysis program was also applied to facilitate visual inspection if the values varied.

To analyse PDR frequency, we first compared PDR frequency in 19 BAFME patients and 38 age-matched control subjects using the Mann-Whitney U test. We also compared the PDR frequency between 19 BAFME patients and 24 age-matched control subjects with anticonvulsants, and 14 age-matched control subjects without anticonvulsants using the Mann-Whitney U test. To evaluate the effect of age on PDR frequency, we investigated the relationship between PDR frequency and age at which the EEG was recorded in 19 BAFME patients and 38 age-matched control subjects by Spearman rank coefficients. In addition, we investigated the chronologic changes in PDR frequency in nine BAFME patients in whom EEG recordings were repeated more than twice using the Wilcoxon signed ranks test. A $p<0.05$ was considered statistically significant.

Table 1. Clinical profile of 19 patients with BAFME.

Patient No.	Age	Sex	PDR	Age at seizure onset	Age at onset of cortical tremor	Giant SEP	Medication
1*	58	M	10	–	50	+	–
2*	34	M	9.5	33	24	–	VPA, CZP
3	50	F	9	–	45	+	–
4	26	F	8	17	–	+	VPA
5	35	M	9.5	30	10	+	–
6	45	F	8.5	–	35	+	VPA
7	69	M	8	35	25	+	PHT, CZP, DZP
8	76	F	8	62	59	+	VPA
9	37	F	9.5	23	–	+	VPA
10*	72	F	9	–	40	+	CZP
11*	40	F	9.5	30	35	+	CZP
12	45	M	9	44	25	+	VPA, CZP
13*	30	F	9.5	24	19	+	PB
14*	55	F	8.5	–	10#	+	CZP
15	59	F	9.5	33	36	+	VPA, CZP
16	35	F	10.5	35	27	+	CBZ
17	59	F	9.5	52	58	+	VPA
18	70	F	8.5	48	47	+	VPA, CZP, LEV
19	67	F	8.5	39	39	+	CZP, DZP

*patients from the same pedigree; #patient (Pt 14) could not remember the exact onset age of cortical tremor, but this appeared to start within the second decade of her life. Giant SEP (somatosensory evoked potential): P25 > 10.0 μV or N35 > 8.1 μV for younger group (50 years or less); P25 > 20.0 μV or N35 > 14.8 μV for older group (more than 50 years of age). VPA: valproic acid; CZP: clonazepam; PHT: phenytoin; DZP: diazepam; PB: phenobartibal; CBZ: carbamazepine; LEV: levetiracetam.

Results

The frequency of PDR was significantly lower in the 19 BAFME patients (9.1±0.7 Hz) than in the 38 age-matched control subjects (10.4±1.1 Hz; $p<0.0001$; *figure 1*). This finding was consistent regardless of the anticonvulsants used in the normal EEG group, because PDR frequency was also significantly lower in the 19 BAFME patients than in the age-matched control subjects taking anticonvulsants (24 subjects; 10.6±0.9 Hz; $p<0.0001$) or not taking anticonvulsants (14 subjects; 10.0±1.2 Hz, $p=0.0068$).

There was a non-significant tendency for PDR to slow with age in the 19 BAFME patients ($Y=9.992-0.019\times X$) and in the 38 age-matched control subjects ($Y=11.22-0.016\times X$; *figure 2*). Consistent with this finding, there was no significant chronologic change in the PDR frequency between the first EEG (9.2±0.8 Hz; 48.7±17.1 years) and the last EEG (9.4±1.0 Hz; 54.2±17.0 years) in the nine BAFME patients with a mean interval between measurements of 5.4±2.1 years. Comparison of the gradient of the PDR frequency for age between BAFME and control subjects revealed no significant difference (*figure 2*).

Discussion

PDR was significantly slower in Japanese BAFME patients compared to subjects with normal EEG,

Table 2. Results of usage of anticonvulsants in BAFME patients and age-matched control subjects.

	19 Patients with BAFME	38 age-matched control subjects
Valproic acid	9 (47%)	13 (34%)
Clonazepam	9 (47%)	2 (5%)
Diazepam	2 (10%)	1 (3%)
Phenytoin	1 (5%)	3 (8%)
Phenobarbital	1 (5%)	4 (10%)
Carbamazepine	1 (5%)	4 (10%)
Levetiracetam	1 (5%)	0 (0%)
Clobazam	0 (0%)	2 (5%)
Primidone	0 (0%)	2 (5%)
Zonisamide	0 (0%)	2 (5%)
Gabapentin	0 (0%)	1 (3%)

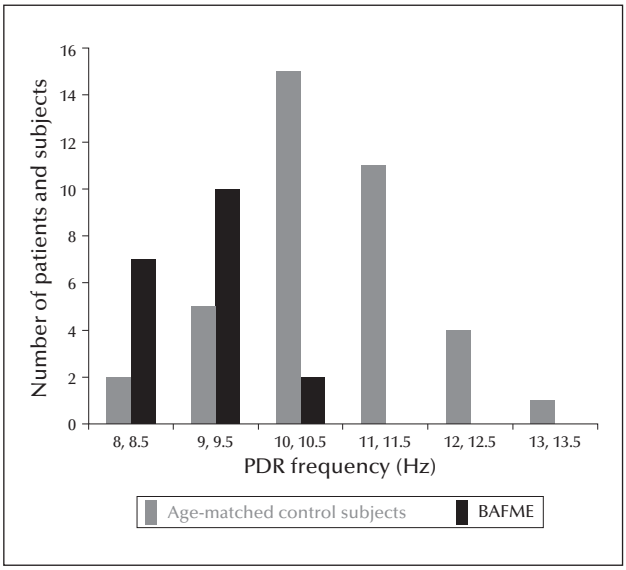

Figure 1. Histogram of the frequency of the posterior dominant rhythm (PDR) in 19 benign adult familial myoclonus epilepsy (BAFME) patients and 38 age-matched control subjects. There was a clear difference between the distribution of PDR frequency in BAFME patients and age-matched control subjects. The PDR frequency was slower in BAFME patients than in age-matched control subjects.

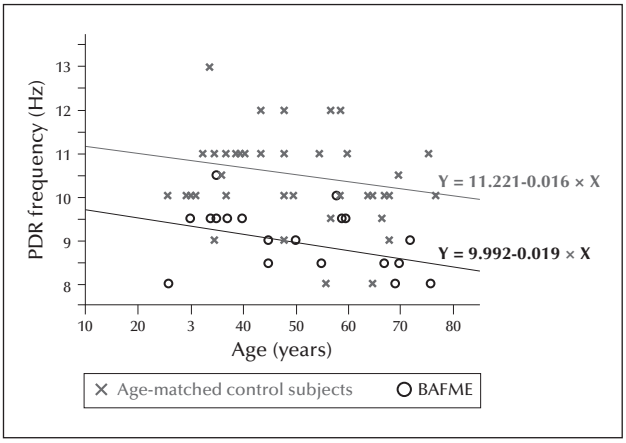

Figure 2. Linear regression between age at the time of EEG recording and frequency of PDR in 19 BAFME patients and 38 age-matched control subjects. A simple regression curve for BAFME patients is represented by the black line, and for age-matched control subjects by the grey dotted line. Open circles indicate BAFME patients and crosses indicate age-matched control subjects. There was a non-significant tendency for a slowing of PDR with age in both BAFME and age-matched control subjects. Comparison of the gradients corresponding to PDR frequency relative to age between the two groups revealed no significant difference. Definitions of PDR and BAFME are shown in the legend for *figure 1*.

regardless of age and use of anticonvulsants. This finding suggests mild, but clearly diffuse, brain dysfunction in BAFME patients.

Gradual and progressive PDR slowing in itself is reported in European ADCME families (Coppola *et al.*, 2011). Coppola *et al.*, however, focused mainly on the chronologic changes within the same patients. Thus, no systematic stastistical analysis compared with the control data was performed, and the effect of anticonvulsants was not investigated. Therefore, the pathological significance of PDR slowing in European ADCME patients may be only partly conclusive. Our findings clarify that Japanse BAFME patients manifest mild, but clear diffuse, brain dysfunction, at least based on the clinical EEG. In addition to the progressive increase in cortical excitability revealed by increased SEP amplitudes (Hitomi *et al.*, 2011), the present findings suggest diffuse brain dysfunction in BAFME. These findings also support the notion that BAFME is not non-progressive or so-called "benign", and could thus be regarded as a very mild form of PME. In other words, this disease entity should be appropriately placed between idiopathic and progressive myoclonus epilepsy (Striano *et al.*, 2010). However, the degree of PDR slowing in BAFME is much less than that of PME because PDR was reported to disappear within a few years in Lafora disease (Kobayashi *et al.*, 1990).

Previous studies of brain function and imaging in BAFME, ADCME, and FCMTE have been performed mainly in European families and are rather controversial. Head MRI revealed no significant abnormalities (Striano *et al.*, 2009b). On the other hand, head MRI showed mild diffuse brain atrophy in some patients

with FCMTE (Suppa *et al.,* 2009), whereas the SEPs and C reflex were within normal limits. Magnetic resonance spectroscopy showed an increase in the Ch/Cr ratio in the cerebellum, but no abnormalities in the cerebrum in ADCME families (Striano *et al.,* 2009b). Neuropsychological studies showed no clear abnormalities in FCMTE (Suppa *et al.,* 2009). On the other hand, a neuropathological study showed cerebellar Purkinje cell degeneration (van Rootselaar *et al.,* 2007). In summary, the abnormalities in BAFME, ADCME, and FCMTE have not been clearly dilineated based on neuroimaging and neuropsychological studies. The genetic heterogeneity of this disease entity (Mikami *et al.,* 1999; Striano *et al.,* 2004) could partly explain these inconsistent results. Despite this controversial situation, our findings suggest that clinical EEG is useful to evaluate brain function in patients with Japanese BAFME.

The degree of PDR slowing with age in BAFME was comparable with that in control subjects, suggesting that the mild diffuse brain dysfunction in BAFME patients does not necessarily have a clear progressive pathology and that aging of BAFME patients has a similar mechanism to that of physiological aging, at least with regards to PDR. The relationship between diffuse brain dysfunction and aging differs from the progressive increase of cortical hyperexcitability with age (Hitomi *et al.,* 2011). Our findings in this study are consistent with clinical observations, that cognitive impairment is essentially not present in elderly BAFME patients, and only cortical tremor becomes exaggerated with age and interferes with the activities of daily living.

Chronologic changes in PDR on EEG were not observed within the relatively shorter follow-up period of five years, suggesting that the diffuse brain dysfunction did not progress rapidly. This finding appears to differ from that of a recent study demonstrating gradual and progressive slowing of PDR in European families with a follow-up of one to several decades (mean [SD]: 14.0±5.8 years) (Coppola *et al.,* 2011). This discrepancy may be accounted for, in part, by the shorter follow-up period in the present study. However, a previous EEG study showed a relatively stable PDR during the long-term follow-up period in Unverricht-Lundborg disease, a relatively mild form of PME (Ferlazzo *et al.,* 2007).

There was, however, a limitation to our study. For EEG control data, EEG was not recorded from normal healthy subjects because it is currently difficult, in practice, to record EEG from healthy subjects at the central EEG laboratory at the University Hospital. However, PDR in our control group was comparable to that of previous studies from the large EEG database (Aurlien *et al.,* 2004).

Conclusions

This EEG analysis showed that PDR was significantly slower in Japanese BAFME patients, but the degree of PDR slowing with age in BAFME was comparable to that in control subjects. These findings suggest mild, but clearly diffuse, brain dysfunction with minimal progression in Japanese BAFME patients.

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com

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TEST YOURSELF

(1) What are the clinical characteristics of benign adult familial myoclonus epilepsy (BAFME)?

(2) What is the significance of a slow frequency of the posterior dominant rhythm (PDR) on EEG in BAFME?

(3) Why is BAFME not idiopathic generalized epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".