Case Report

Sleep is associated with reduction of epileptiform discharges in benign adult familial myoclonus epilepsy

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ABSTRACT

To clarify the effects of sleep on cortical irritability in benign adult familial myoclonus epilepsy (BAFME), we retrospectively compared epileptiform discharges of electroencephalographies (EEGs) between awake and sleep periods in 5 patients (mean age: 49.6 ± 20.3 years). We also analyzed polysomnography (PSG) of 1 patient. Epileptiform discharges were significantly more frequent during the awake period (1.3 ± 1.2/min) than those during light sleep stages (0.02 ± 0.04/min) (P < 0.05). Regarding PSG analysis, epileptiform discharges were also reduced during all sleep stages compared to those during awake periods. Our study suggests a relative reduction in cortical irritability during sleep in BAFME.

1. Introduction

Benign adult familial myoclonus epilepsy (BAFME) shows as a clear autosomal dominant trait with high penetration and its major two symptoms are cortical tremor mimicking essential tremor and infrequent generalized seizures. BAFME has been reported under various designations in Japan from early 1990s [1,2], whereas familial cortical myoclonic tremor with epilepsy (FCMTE) [3] and autosomal dominant cortical tremor, myoclonus, and epilepsy (ADCME) [4] came from Europe after the new millennium. Despite different terminologies, Japanese BAFME and European ADCME and FCMTE share the features of core clinical symptoms and electrophysiologically proven cortical reflex myoclonus [3]. As for a recent genetic study, a novel in-frame insertion/deletion in the 2-adrenergic receptor subtype B was found to be associated with ADCME [5] and δ-catenin was proposed as the causal gene in FCMTE [6]. Furthermore, abnormal expansions of TTTCA and TTTTA repeats were reported in Japanese BAFME [7].

Previous electroencephalography (EEG) studies in Japanese BAFME showed generalized- spike and- wave complexes with photosensitivity [2]. Additionally, we recently showed that the frequency of the posterior dominant rhythm of BAFME was significantly slower than the age-matched control subjects regardless of anti-seizure drug usage, which suggests that Japanese patients with BAFME have mild diffuse brain dysfunction [8]. These EEG findings mainly focused on the awake period, but did not investigate the sleep period. Epileptiform discharges and epileptic seizures usually increase during sleep [9], and thus sleep is generally considered a precipitating factor of cortical irritability in epilepsy. However, no studies have been conducted to address the change in cortical irritability during sleep in BAFME. The present study analyzed epileptiform discharges in BAFME to determine whether cortical irritability as indicated by epileptiform discharges was modified by sleep.

Table 1
Patient profiles.

	Age	Cortical tremor onset age	Generalized seizure onset age	Anti-seizure drugs
Pt 1	73	50	62	Clonazepam
Pt 2	40	20	28	Clonazepam
Pt 3	30	19	24	Piracetam
Pt 4	35	27	35	None
Pt 5	70	48	48	Clonazepam, Levetiracetam

2. Material and methods

2.1. Conventional EEG analysis

We retrospectively analyzed 31 EEGs of 12 patients with a clinical diagnosis of BAFME in whom EEG was taken from 2008 to 2015 in our institute. Some of the patients were reported elsewhere for completely different purposes [8,10–12]. The electroclinical diagnostic criteria of BAFME are the same as in our recent studies [8,10–12], and the details are described elsewhere [10]. In addition, 10 out of 12 patients showed genetic abnormality [7], but remaining 2 patients did not undergo genetic testing. As for medications, 2 patients had clonazepam, 1 patient had piracetam, 1 patient had clonazepam and levetiracetam, and remaining 1 patient had none (Table 1).

Routine EEG with scalp electrodes was conventionally recorded according to the International 10–20 system. Routine EEG was recorded at least 30 min during daytime. Electrooculogram, electrocardiogram and electromyogram (EMG) from wrist extensor muscle were also recorded. The bandpass filter was set to 0.53–120 Hz for visual inspection. We checked 3 recording conditions and excluded the conventional EEGs from further analysis if they were not suitable for this study. First, we excluded 6 EEGs because they showed less than 5 epileptiform discharges throughout the EEG recording. Second, we excluded 18 EEGs because they showed an awake or sleep EEG of less than 10% of the total EEG recording. Third, we excluded 1 EEG with abundant artifacts. We finally analyzed 6 EEGs in 5 BAFME patients (5 women, age 49.6 ± 20.3 years) (Table 1), and 4 out of 5 patients showed genetic abnormality [7], but remaining 1 patient (Patient 5) did not undergo gene analysis.

Each sleep stage [awake: W, Stage I and II (light sleep); III and IV (slow-wave sleep); and REM (rapid eye movement)] was defined by a board-certified electroencephalographer (T.H) every 30 s based on the standard sleep staging criteria established by Rechtschaffen and Kales [13], although surface EMG was recorded using the wrist extensor muscle instead of the chin muscle. After sleep staging, we counted the epileptiform discharges for each sleep stage and compared the number and frequency of epileptiform discharges for each sleep stage using the Wilcoxon signed ranks test because only awake (31.3 ± 9.1 min) and Stage I and II (light sleep) (19.2 ± 14.9 min) were observed. $P < 0.05$ was considered statistically significant.

2.2. Polysomnography (PSG) analysis

One BAFME patient (59-year-old female) was incidentally suspected as having obstructive sleep apnea and underwent PSG before and after nasal continuous positive airway pressure (nCPAP) therapy. The patient also showed genetic abnormality [7]. Each sleep stage was also defined based on standard sleep staging criteria [13]. We counted the epileptiform discharges during each awake and sleep stage and then compared the number and frequency of epileptiform discharges during the awake and sleep stages.

3. Results

3.1. Conventional EEG analysis

Five BAFME patients showed generalized spikes maximal in the posterior hemisphere during the awake period (42.6 ± 37.9/record) (Fig. 1A, Table 2), however, these epileptiform discharges nearly disappeared during light sleep (0.6 ± 1.3/record; p < 0.05) (Fig. 1B, Table 2). With respect to the frequency recorded as number of events/min, epileptiform discharges also significantly decreased during light sleep (0.02 ± 0.05) compared to the awake stages (1.3 ± 1.3; p < 0.05) (Table 2).

3.2. PSG analysis

PSG before nCPAP therapy showed severe obstructive sleep apnea (apnea hypopnea index: 39.2). Sleep stages were classified into Awake (105 min), Stage I and II (147 min), III and IV (0 min), and
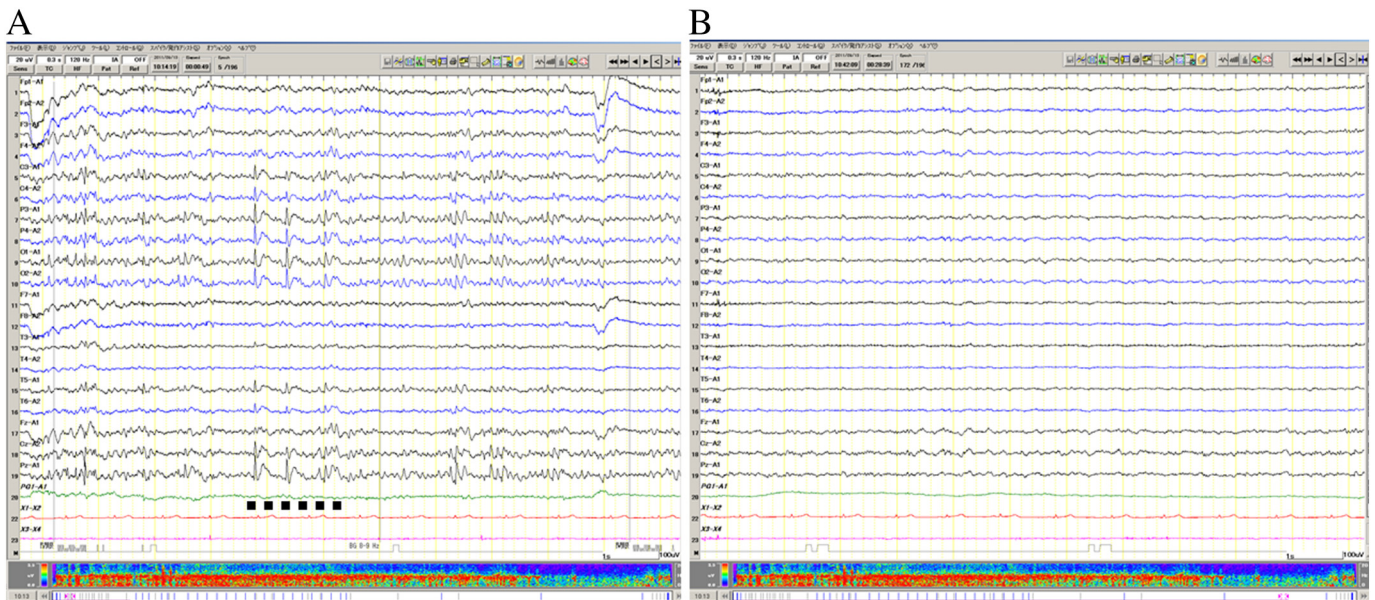

Fig. 1. EEG in a patient with BAFME (patient 4). Spikes were maximized in the posterior hemisphere during the awake period (A); these spikes disappeared during the light sleep period (B).

Table 2
Summary of the electroencephalography analysis.

	Sleep staging (min)		Number of epileptiform discharges		Frequency of epileptiform discharges (number/min)	
	Awake	SI and II	Awake	SI and II	Awake	SI and II
Pt 1	40	19	81	0	2.03	0.00
Pt 2	22	39	8	0	0.36	0.00
Pt 3	42	28	33	3	0.78	0.11
Pt 4	27	6	84	0	3.16	0.00
Pt 5	26	4	7	0	0.27	0.00
Mean	**31.3**	**19.2**	**42.6**	**0.6**	**1.3**	**0.02**
SD	**9.1**	**14.9**	**37.9**	**1.3**	**1.3**	**0.05**

SI and II: sleep stage I and II.
* P <0.05 (Wilcoxon signed rank test).

REM (27.5 min). There were frequent epileptiform discharges during the awake period (106), however, the number of epileptiform discharges clearly decreased during Stages I and II (5) and the REM stage (2) (Table 3). The frequency of epileptiform discharges also showed the same tendency: awake period: 1.01, Stage I and II: 0.03, and stage REM: 0.07 (Table 3). PSG after nCPAP therapy showed a normalized apnea hypopnea index (4.0). The sleep stages were classified into Awake (88 min), Stage I and II (228 min), Stage III and IV (14 min), and stage REM (0 min). Some epileptiform discharges occurred during the awake period (7), likely due to a reduction in cortical irritability through nCPAP therapy [14], and no epileptiform discharges were observed during Stage I, II, III, or IV (Table 3). The frequency of epileptiform discharges (number/min) also showed the same tendency: awake period: 0.08, Stage I and II: 0, and stage III and IV: 0 (Table 3).

4. Discussion

Our study showed a clear reduction in epileptiform discharges during sleep regardless of sleep stage in patients with BAFME. This result contrasted with our expectations because epileptiform discharges, as known from a previous study, usually increase during the sleep period in most focal and generalized epilepsies [9]. Notably, Unverricht-Lundborg disease (ULD), which is a type of progressive myoclonus epilepsy, showed a reduction in paroxysmal abnormalities during non-REM and REM sleep [15]. Additionally, ULD showed generalized spikes with predominance in the posterior region [16], which is consistent with the distribution of generalized spikes in BAFME as shown in Fig. 1A. Taken all together, ULD and BAFME showed a similar pathological mechanism of cortical irritability in terms of spatial distribution and the response to state changes.

There is a hypothesis regarding the reduction of epileptiform discharges during the sleep period in BAFME. First, generalized epilepsy usually showed diffuse epileptiform discharges with frontal predominance. Additionally, frontal lobe epilepsy also showed focal epileptiform discharges in the frontal region, which often produces epileptic seizures while asleep [9]. These findings were supported by emphasized high gamma activity and neuronal synchrony during sleep in the frontal lobe compared to other lobes [17]. In contrast, occipital lobe epilepsy tended to occur while awake [18]. In addition, BAFME and ULD show diffuse epileptiform discharges but its predominance was sometimes in the occipital area, and both also could show fragmented occipital spikes as well. Thus, BAFME and ULD may share the similar tendency to occipital lobe epilepsy at least partly for the effects of sleep on the cortical irritability of the brain.

BAFME was considered to have a benign clinical course, unlike progressive myoclonus epilepsy. However, we recently demonstrated an increase in the amplitude of somatosensory evoked potential with age [10], clinical anticipation [12] and its exaggeration by maternal transmission [11], and a mild slowing of the posterior dominant rhythm of EEG [8] in BAFME. Based on our recent observations, we now believe that BAFME is not completely benign but has a slow progressive pathophysiology that occurs with age. Therefore, the findings in this study were consistent with our recent hypothesis because BAFME showed a similar degree of cortical irritability in its spatial distribution and its response to state change in ULD, which is one of the milder forms of progressive myoclonus epilepsy. The functional change during sleep periods may provide novel insights into the pathophysiology of BAFME. However, the pathogenesis of BAFME remains unknown, although it was shown that abnormal expansion of TTTCA and TTTTA repeats in BAFME [7] and abnormal expansion of dodecamer repeats in ULD.

Table 3
Summary of the polysomnography analysis.

	Number of epileptiform discharges during awake and sleep period				Frequency of epileptiform discharges during awake and sleep period (number/min)			
	Awake	SI and II	SIII and IV	REM	Awake	SI and II	SIII and IV	REM
PSG (pre nCPAP) AHI: 39.2	106	5	–	2	1.01	0.03	–	0.07
PSG (post nCPAP) AHI: 4.0	7	0	0	–	0.08	0	0	–

SI and II: stage I and II (light sleep), SIII and IV: sleep stage III and IV (slow wave sleep), REM: sleep stage REM (rapid eye movement).
PSG: Polysomnography, nCPAP: nasal continuous positive airway pressure therapy, AHI: apnea hypopnea index.

This study has a number of limitations. First, the number of studied patients in conventional EEG analysis was relatively small. More than half of the EEG data were eliminated because of the strict criteria of this study. However, we showed statistically significant differences in epileptiform discharges in this study. Second, only 1 patient underwent a PSG study, and thus we could not show statistically significant differences between the slow wave sleep and REM periods, notably, epileptiform discharge consistently decreased during slow wave and REM sleep as well as the light sleep periods. Third, sleep staging was performed based on the information with conventional EEG recordings; however, sleep staging in this study appears to be accurate because only the awake and Stage I and II (light sleep) periods were observed. This likely occurred because the routine EEG was recorded only during daytime.

5. Conclusion

Our retrospective EEG and PSG analysis showed a clear reduction of the epileptiform discharges during sleep in BAFME, which suggests a reduction in cortical irritability during sleep in BAFME. Since ULD, a type of progressive myoclonus epilepsy, also demonstrates a similar degree of cortical irritability represented by epileptiform discharges, BAFME and ULD may share a similar phenomenological mechanism.

Author's contributions

All authors gave substantial contribution to the submitted manuscript. Takefumi Hitomi: conception, data collection, statistical analysis, manuscript draft and revision. Morito Inouchi, Katsuya Kobayashi: data collection and technical advice, Shamima Sultana, Takeshi Inoue, Yuko Nakayama, Akihiro Shimotake, Masao Matsuhashi, Riki Matsumoto: data collection, Kazuo Chin, Ryosuke Takahashi: data collection and technical advice, Akio Ikeda: data analysis and manuscript revision.

Ethical publication statement

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.

Disclosure of conflicts of interest

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