



Case Report

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

Takefumi Hitomi^{a,b,c,*}, Morito Inouchi^{b,d}, Hirofumi Takeyama^{b,d}, Katsuya Kobayashi^b, Shamima Sultana^b, Takeshi Inoue^b, Yuko Nakayama^c, Akihiro Shimotake^{b,e}, Masao Matsushashi^f, Riki Matsumoto^{b,e}, Kazuo Chin^d, Ryosuke Takahashi^b, Akio Ikeda^e

^a Department of Clinical Laboratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

^b Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan

^c Department of Clinical Laboratory, Kyoto University Hospital, Kyoto, Japan

^d Department of Respiratory Care and Sleep Control Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

^e Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, Kyoto, Japan

^f Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan

ARTICLE INFO

Article history:

Received 7 June 2018

Received in revised form 20 September 2018

Accepted 27 September 2018

Available online 16 October 2018

Keywords:

Benign adult familial myoclonus epilepsy (BAFME)

Epileptiform discharges

Effects of sleep modification on cortical irritability

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 ($1.3 \pm 1.2/\text{min}$) than those during light sleep stages ($0.02 \pm 0.04/\text{min}$) ($P < 0.05$). 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.

© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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.

Abbreviations: ADCME, autosomal dominant cortical tremor, myoclonus, and epilepsy; BAFME, benign adult familial myoclonus epilepsy; EEG, electroencephalography; EMG, electromyography; FCMTE, familial cortical myoclonic tremor with epilepsy; nCPAP, nasal continuous positive airway pressure; PSG, polysomnography; REM, rapid eye movement; ULD, Unverricht-Lundborg disease.

* Corresponding author at: Department of Neurology, Kyoto University Graduate School of Medicine, Department of Clinical Laboratory Medicine, Kyoto University School of Medicine, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan.

E-mail address: hitomi46@kuhp.kyoto-u.ac.jp (T. Hitomi).

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 TTCA and TTTA 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

Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine is an endowment department supported with grants by GlaxoSmithKline K.K., NIHON KOHDEN CORPORATION, Otsuka Pharmaceutical Co., and UCB Japan Co., Ltd.

Acknowledgements

This study was supported by the Kyoto University Research Fund for Senior Scientists and by a Grant-in-Aid for Scientific Research on

Innovative Areas (Non-linear Neuro-oscillology: Towards Integrative Understanding of Human Nature) KAKENHI Grant Number 15H05874, a Grant-in-Aid for Scientific Research (C), KAKENHI Grant Number 17K09798) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

- [1] Ikeda A, Kakigi R, Funai N, Neshige R, Kuroda Y, Shibasaki H. Cortical tremor: a variant of cortical reflex myoclonus. *Neurology* 1990;40:1561–5.
- [2] Yasuda T. Benign Adult Familial myoclonic epilepsy (BAFME). *Kawasaki Med J* 1991;17:1–13.
- [3] van Rootselaar AF, van Schaik IN, van den Maagdenberg AM, Koelman JH, Callenbach PM, Tijssen MA. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. *Mov Disord* 2005;20:665–73.
- [4] Guerrini R, Bonanni P, Patrignani A, Brown P, Parmeggiani L, Grosse P, et al. Autosomal dominant cortical myoclonus and epilepsy (ADCME) with complex partial and generalized seizures: a newly recognized epilepsy syndrome with linkage to chromosome 2p11.1-q12.2. *Brain* 2001;124:2459–75.
- [5] De Fusco M, Vago R, Striano P, Di Bonaventura C, Zara F, Mei D, et al. The alpha2B-adrenergic receptor is mutant in cortical myoclonus and epilepsy. *Ann Neurol* 2014;75:77–87.
- [6] van Rootselaar AF, Groffen AJ, de Vries B, Callenbach PMC, Santen GWE, Koelewijn S, et al. δ -Catenin (*CTNND2*) missense mutation in familial cortical myoclonic tremor and epilepsy. *Neurology* 2017;89:2341–50.
- [7] Ishiura H, D.K., Mitsui J, Yoshimura J, Matsukawa MK, Fujiyama A, et al. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nat Genet* 2018.
- [8] Hitomi T, Kobayashi K, Sakurai T, Ueda S, Jingami N, Kanazawa K, et al. Benign adult familial myoclonus epilepsy is a progressive disorder: no longer idiopathic generalized epilepsy. *Epileptic Disord* 2016;18:67–72.
- [9] Derry CP, Duncan S. Sleep and epilepsy. *Epilepsy Behav* 2013;26:394–404.
- [10] Hitomi T, Ikeda A, Kondo T, Imamura H, Inouchi M, Matsumoto R, et al. Increased cortical hyperexcitability and exaggerated myoclonus with aging in benign adult familial myoclonus epilepsy. *Mov Disord* 2011;26:1509–14.
- [11] Hitomi T, Kobayashi K, Jingami N, Nakagawa T, Imamura H, Matsumoto R, et al. Increased clinical anticipation with maternal transmission in benign adult familial myoclonus epilepsy in Japan. *Epileptic Disord* 2013;15:428–32.
- [12] Hitomi T, Kondo T, Kobayashi K, Matsumoto R, Takahashi R, Ikeda A. Clinical anticipation in Japanese families of benign adult familial myoclonus epilepsy. *Epilepsia* 2012;53:e33–6.
- [13] Rechtschaffen A, K.A.. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute; 1968.
- [14] Oliveira AJ, Zamagni M, Dolso P, Bassetti MA, Gigli GL. Respiratory disorders during sleep in patients with epilepsy: effect of ventilatory therapy on EEG interictal epileptiform discharges. *Clin Neurophysiol* 2000;111(Suppl. 2):S141–5.
- [15] Ferlazzo E, Magaudo A, Striano P, Vi-Hong N, Serra S, Genton P. Long-term evolution of EEG in Unverricht-Lundborg disease. *Epilepsy Res* 2006;219–27.
- [16] Kyllerman M, Sommerfelt K, Hedstrom A, Wennergren G, Holmgren D. Clinical and neurophysiological development of Unverricht-Lundborg disease in four Swedish siblings. *Epilepsia* 1991;32:900–9.
- [17] Usami K, Matsumoto R, Kobayashi K, Hitomi T, Shimotake A, Kikuchi T, et al. Sleep modulates cortical connectivity and excitability in humans: direct evidence from neural activity induced by single-pulse electrical stimulation. *Hum Brain Mapp* 2015;36:4714.
- [18] Kaleyias J, Loddenkemper T, Vendrame M, Das R, Syed TU, Alexopoulos AV, et al. Sleep-wake patterns of seizures in children with lesional epilepsy. *Pediatr Neurol* 2011;45:109–13.