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Review

Juvenile myoclonic epilepsy and sleep

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ABSTRACT

Juvenile myoclonic epilepsy (JME) is a sleep-related epilepsy syndrome, and only a few studies have addressed the relationship between JME and sleep disorders. In this review, the sleep characteristics of patients with JME were summarized based on the features of circadian rhythm, the possible cause of the early morning seizures, the common subjective and objective sleep disorders, the alterations in sleep architecture, and the effect of sleep deprivation and sodium valproate (VPA). The aims of this study were to summarize the interaction between JME and sleep, to reveal JME sleep characteristics, to encourage clinicians to focus on JME and sleep, to heighten the positive diagnosis rate, to guide the treatment, to improve the prognosis, and to enhance the daily life quality of patients with JME. At the same time, this study aimed to present existing controversies, in order to necessitate further studies.

1. Introduction

Epilepsy and sleep have a complicated and close relationship, and they influence each other. For example, nocturnal seizures and the use of antiepileptic medications can cause sleep fragmentation, change the sleep architecture, and result in a decline in sleep efficiency. Some types of seizures, such as those in frontal lobe epilepsy (FLE), continuous spike–waves during slow sleep (CSWS), benign childhood epilepsy with centrotemporal spikes (BECTS), and West syndrome, usually occur during sleep; whereas those in some other types, such as juvenile myoclonic epilepsy (JME) and juvenile absence epilepsy (JAE), occur during the waking state. Sleep deprivation induces seizures, and sleep disorders may cause poorly controlled epilepsy, thereby severely affecting the patient's quality of life. Thus, improving the diagnosis and treatment of epilepsy, as well as the prognosis of patients with epilepsy, is essential. Hence, understanding the relationship between epilepsy and sleep with respect to sleep disorders in patients with epilepsy is imperative.

Juvenile myoclonic epilepsy is one of the most common idiopathic generalized epilepsy (IGE) syndromes. The first definition of JME by the International League Against Epilepsy (ILAE) in 1985 was as follows: this syndrome appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, and irregular myoclonic jerks, predominantly in the arms. Some patients may suddenly fall from a jerk. No disturbance of consciousness is noticeable. The disorder may be inherited, and sex-based distribution is equal. Generalized tonic–clonic seizures (GTCS) are frequent, and absences are less frequent. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation. Interictal and ictal electroencephalograms (EEGs) have rapid, generalized, often irregular spike–waves, and polyspike waves; no phase correlation between EEG spikes and jerks is established. Frequently, the patients are photosensitive. Response to appropriate drugs is satisfactory [1]. Owing to the different seizure types, the circadian distribution and precipitation by sleep deprivation are different, indicating that JME is a classic epilepsy syndrome that is appropriate for studying the relationship between epilepsy and sleep [2]. Sleep disorders are common in patients with JME; however, only a few studies are currently available. We searched the electronic databases including PubMed, Embase, Web of Science, and the Cochrane Library up to October 2017. No language or date restrictions were applied. The following terms were used as key words: Juvenile myoclonic epilepsy AND sleep disorder. In addition, other references that may have been missed in the electronic databases were manually searched from selected references. Then, the papers related to the topic of this review were selected.

2. Circadian rhythm characteristics in patients with JME

Circadian rhythms regulate the biological function, and the effect of circadian misalignment may severely affect health. According to the characteristics of circadian rhythm, patients with epilepsy can be divided into “morning types” and “evening types”. Persons characterized as “morning types” usually wake up early in the morning, go to bed early in the evening, and have more energy in the morning; whereas, persons described as “evening types” wake up late in the morning and fall asleep late in the evening; they are rather willing to do the

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main work in the afternoon and evening. "Evening types" have one of the risk factors for circadian misalignment, and it influences the therapeutic efficacy in patients with epilepsy. Patients with generalized epilepsy have the potential to become "evening types" as compared with patients with focal epilepsy or healthy controls [3]. Presently, the studies on the circadian rhythm characteristics of patients with JME are not consistent. Previously, Janz and Christian conducted a study on 47 patients with JME and found a typical sleep–wake cycle and typical personality traits: they wake up late and go to bed late, and their main work is prolonged until the afternoon or evening [4]. The recent results of the study by Pung and Schmitz were in agreement with that by Janz and Christian. Pung and Schmitz studied a group of 20 patients with JME in comparison with patients having temporal lobe epilepsy (TLE). The study used the standardized questionnaires about the sleep–wake rhythm—"Morning type–Evening type Questionnaire"—and personality profiles, which confirmed that patients with JME exhibit a characteristic circadian rhythm and personality traits; in the case that their circadian rhythm changes, the patient is considered as "evening types" [5]. Subsequent studies also used questionnaires for comparing the circadian rhythms and their characteristics in 16 patients with JME and 37 patients with TLE; however, they did not conclude that patients with JME were "evening types", and the poor state early in the day may be related to social–cultural background rather than neurobiological factors [6]. In 2010, Hofstra et al.'s findings were contrary to previous findings; they performed a large questionnaire study about chronotypes and subjective sleep parameters in 200 patients with epilepsy (TLE; n = 46, FLE; n = 30, JME; n = 38, and others; n = 86) and 4042 general people using both the Morningness–Eveningness Questionnaire and Munich Chronotype Questionnaire; their results showed that patients with epilepsy were more morning-oriented, while patients with TLE, FLE, and JME have no difference in chronotypes and subjective sleep parameters. The reasons for the discrepancies may be that the average age of the subjects was somewhat older than that in the previous study, and the sample size was also larger [7]. There are few studies on the correlation between JME and chronotype, and the conclusions are inconsistent, so further comprehensive and objective research is needed.

3. Putative mechanism underlying early morning seizures

Juvenile myoclonic epilepsy is related to a sleep–wake cycle, and myoclonic jerks in the early morning are one of the hallmarks; JME frequently occurs in the morning shortly after awakening [8]. Most studies have reported that myoclonic seizures in patients with JME occur between 6 a.m. and noon [9]. In 2009, Badawy et al. studied the differences in cortical excitability between day and night in patients with epilepsy, using the method of transcranial magnetic stimulation (TMS). The study demonstrated that drug-naïve patients with IGE, especially JME, showed an increase in cortical excitability early in the morning as compared with that in the evening that might explain the increased likelihood of seizures in the early morning. The authors also postulated the occurrence of circadian variation in γ-aminobutyrate (GABA)-mediated inhibition by the suprachiasmatic nuclei (the key circadian pacemaker in the mammalian brain) that caused increased cortical excitability in the early morning as compared with that in the afternoon in IGE [10]. Labate et al. performed a routine EEG in patients with JME in the morning and afternoon, respectively, and illustrated that a larger number of generalized epileptiform abnormalities were recorded in the morning than in the afternoon [11]. Therefore, a routine EEG in the morning in patients with JME assisted in improving the diagnostic rate.

4. Common sleep disorders in patients with JME

The incidence of sleep disorders in patients with epilepsy is high. At the present time, several studies are available on sleep disorders in patients with various types of epilepsy (such as FLE and TLE); however, only a few studies related to sleep disorders in patients with JME are available. The common sleep disorders in patients with JME include insomnia, obstructive sleep apnea syndrome, narcolepsy, periodic limb movements, and parasomnias. In 2012 and 2014, Krishnan et al. undertook a clinical assessment and evaluated the sleep questionnaires in patients with JME and healthy control groups, respectively. The study found that patients with JME have significant sleep disorders such as insomnia and excessive daytime somnolence despite receiving adequate medications and having good seizure control; the mean Epworth sleepiness scale (ESS) and Pittsburgh sleep quality index (PSQI) scores were significantly higher in patients with JME than in controls [12,13]. The other studies involving sleep questionnaires on patients with JME also showed a significantly high prevalence of insomnia and excessive daytime somnolence, and the sleep quality was poor [14–16]. Some research results showed that although patients with JME suffered from obstructive sleep apnea syndrome, there was no significant difference as compared with healthy controls [13,15]. The results of the studies on periodic limb movements in patients with JME are controversial; some reports revealed that the incidence of periodic limb movements in patients with JME was significantly higher than that in the healthy individuals [16]. On the other hand, some authors speculated that the frequency of periodic limb movement disorder in the JME groups did not differ from the healthy individuals; however, the patients receiving <600 mg/day valproate (VPA) had a higher prevalence of isolated limb movements as compared with those with >600 mg/day VPA [13]. In 2015, Joshi et al. reported only three cases of the coexistence of JME and narcolepsy and pointed out the shared genetic predisposition. Currently, HLA-DQB1*0602 is known as a susceptibility gene for narcolepsy, located at position 6p21.3, the same as that of JME's. Hence, JME and narcolepsy could potentially coexist. Thus, clinicians should inquire whether a patient with JME has symptoms of narcolepsy, and vice versa [17]. Considering the infrequent coexistence of JME and narcolepsy mentioned in Joshi's research, more evidence should be provided to make categorical statements on the relationship between JME and narcolepsy, and research about this aspect should be strengthened in the future. Parasomnias are a group of sleep disorders defined as undesirable physical events or experiences that occur during the initiation of sleep, during sleep, or during arousal from sleep. It can be divided into three clusters: nonrapid eye movement (NREM)-related parasomnias, rapid eye movement (REM)-related parasomnias, and other parasomnias [18]. The most common parasomnias are nightmare disorders belonging to the REM-related parasomnias, and sleep talking belongs to other parasomnias [12,16]. The current studies about parasomnias in patients with JME are scanty, thereby necessitating further exploration.

5. Sleep architecture is disturbed in JME

Normal sleep can be divided into NREM and REM. The NREM sleep is made up of stages 1, 2, 3, and 4. Stages 1 (N1) and 2 (N2) refer to light sleep, and stages 3 and 4 are combined into stage N3 and considered deep sleep or slow-wave sleep. Sleep macrostructure and microstructure can be monitored by polysomnography (PSG). The commonly used parameters that reflect the sleep macrostructure include total sleep time (TST), sleep efficiency, and sleep onset latency, while the commonly used parameters that reflect the sleep microstructure, include arousal index and cyclic alternating pattern (CAP). The arousal index refers to the number of arousals per hour of sleep; whereas CAP is periodic EEG activity of NREM sleep that reflects the sleep microstructure. A CAP sequence contains several CAP cycles; the CAP cycle is defined as an A phase followed by a B phase. The A phase can be classified into three subtypes: A1, A2, and A3. The main CAP parameters are CAP time, CAP rate, phase A1 index, phase A2 index, and phase A3 index. The CAP rate (percentage ratio of CAP time to total NREM sleep time) is the most widely used clinically, defined as the increase of CAP rate response to the decrease in sleep quality [19]. The effect of JME

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