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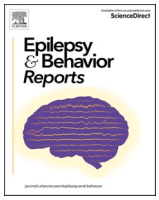

Case Report

Seizure control with treatment of delayed sleep-wake phase disorder in juvenile myoclonic epilepsy: A case report

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ABSTRACT

Juvenile Myoclonic Epilepsy (JME) is an idiopathic generalized epilepsy associated with a characteristic sleep/wake rhythm, with the tendency to go to bed later at night, to get up later in the morning. In the pediatric population, we have previously observed specific circadian and sleep/wake patterns of generalized seizures (6 am-12 pm) and myoclonic seizures (in wakefulness, 6 am to noon). Delayed Sleep-Wake Phase Disorder (DSWPD) is characterized by sleep initiation insomnia when attempting sleep at conventional times and difficulty waking at the required time. Here we present the case of a 20-year-old man with JME, diagnosed DSWPD (sleep schedule 3 am to 11 am), presenting with nocturnal seizures out of sleep, always between 5 and 6am. Improvements in seizure control (seizure frequency from 8 per month to 0 per month) were achieved with timed evening melatonin, combined with behavioral sleep-wake scheduling (sleep schedule 10 pm to 6 am) and morning light therapy. Recognition and characterization of DSWPD in JME, together with assessment of circadian and diurnal seizure patterns, may offer therapeutic consideration for better control of seizures.

Introduction

Juvenile Myoclonic Epilepsy (JME) is an idiopathic generalized epilepsy, characterized by myoclonic seizure and generalized tonic-clonic seizures occurring upon awakening, often triggered by sleep deprivation [1]. JME patients have a distinct circadian chronotype, with the tendency to go to bed later at night and to get up later in the morning [2]. Sleep disorders are common in JME patients, including insomnia, obstructive sleep apnea syndrome, narcolepsy, and parasomnias [3]. Delayed Sleep-Wake Phase Disorder (DSWPD) is a circadian rhythm sleep-wake disorder, characterized by sleep initiation insomnia when attempting sleep at conventional times and difficulty waking at the required time [4]. Seizures in JME have been observed to follow specific circadian patterns, with occurrence predominantly in the morning [1]. Although there is an overlap in demographics between these two disease populations, we have yet to identify a report on JME with comorbid DSWPD. Here we report a case of JME with DSWPD whose nocturnal seizures were successfully treated by correcting his sleep schedule, using a combination of pharmacologic and behavioral interventions. We aim to raise awareness to the role of sleep disorders in seizure management, for it may be a significant contributor to pseudoresistence [5] in patients with idiopathic generalized epilepsy.

Case presentation

A 20-year-old man with JME was referred to our neurology clinic. He had history of seizures since age 17, when he presented with an unprovoked generalized tonic-clonic seizure in the morning. At that time, he reported also frequent myoclonic jerks, in the form of sudden brief movements of his legs and occasionally his arms, mostly when sitting in school. A second unprovoked generalized tonic-clonic seizure was reported after 2 weeks. His electroencephalogram (EEG) showed diffuse bilateral bursts of 4 Hz spike-and-wave complexes confirming the diagnosis of JME. Patient had no history of perinatal or developmental problems and no family history of epilepsy. He was started on an initial dose of lamotrigine 25 mg/day, which was later increased to 200 mg/day. The myoclonic jerks disappeared, and no recurrence of generalized tonic-clonic seizure was observed until age 19. At that time, he reported about 12 seizures per month. He was switched to levetiracetam at the dose of 2000 mg/day in two divided AM and PM doses, which lead to a reduction in seizure frequency to about 8 times per month. At this point patient moved out of state and his care was transferred to our clinic.

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A careful examination of his seizure history revealed that current seizures occurred only in early morning, always between 5 and 6 a.m. He reported always being in bed at that time. He could not recall his seizure onset and did not recall being awake before the seizures. His events were always noted by family members and described and tonic-clonic seizures. When asked about his sleep habits, he reported going to sleep late at night and waking up later in the morning daily. He was currently out of school for about a year and in transition to college. He reported an at least 6 months history of extreme difficulty waking up in the morning preventing him from pursuing regular academic work. He did not report snoring and reported waking up rested when allowed to wake up later in the morning. His BMI was 23 Kg/m^2 and his Epworth Sleepiness Scale 10. His 2-week sleep diary showed a sleep schedule ranging from 3 to 5am bedtime and 10am-1 pm wake up time, consistent with Delayed Sleep-Wake Phase Disorder (DSWPD) (Fig. 1). Polysomnography was not performed, as the clinical picture was consistent with DSWPD and there was no indication of other sleep disorders. Together with the close cooperation of his parents, we implemented an aggressive pharmacological and behavioral plan. Timed evening melatonin (10 mg taken at 9 pm), combined with a gradual shift in sleep-wake scheduling and morning light therapy (470 nm wavelength for 1 to 2 h in the morning after waking up) were administered over 5 months. Sleep diaries data showed a progressive shift in sleep schedule ranging from 11 pm to 12am bedtime and 7am-9am wake up time (Fig. 2). Therapy with levetiracetam at the dose of 2000/day in two divided AM and PM doses (9am and 9 pm) was continued. A concomitant improvement in seizure control was also noted, with seizure frequency from 1.75 to 2/per week to 0/per week after 5 months. At his 3-month follow up patient reported continuing rigorous sleep schedule with melatonin and light therapy, and one seizure in the context of missing one dose of levetiracetam.

Discussion

JME is one of the most common type of primary generalized epilepsy syndromes. It is characterized by frequent myoclonic jerks, occurring typically in the morning upon awakening, followed by generalized tonic-clonic seizures, and less often, absence seizures. JME is known to have a unique circadian pattern and a distinct susceptibility to sleep deprivation [2].

Janz and Christian first described the characteristic sleep chronotype of JME patients in their 1957 article “Impulsiv-Petit mal”. Notably, JME patients have a tendency to go to bed later at night, to get up later in the morning, and are also more active during night [6]. This distinct sleep-wake pattern was re-demonstrated by Pung and Schmitz in 2006 utilizing the standardized “Morningness-Eveningness Questionnaire” (MEQ). The study recruited 20 JME and 20 temporal lobe epilepsy (TLE) patients, and showed that JME patients were significantly more likely to be “evening type” than those with TLE [7]. A study in 2015 noted 36% of patients with generalized epilepsy were evening types, in comparison to 11% of patients with focal epilepsy [8]. JME patients were also found to be “evening types” compared to healthy controls [9]. Employing a combination of subjective (MEQ) and objective measure evaluating dim light melatonin onset and melatonin secretion pattern, patients with primary generalized epilepsies have been found to have a slight evening orientation and a slower melatonin surge pattern, similar to patients with DSPS [10–11].

Several sleep disorders have been described in JME patients, including insomnia, obstructive sleep apnea syndrome, narcolepsy, parasomnias, periodic limb movements of sleep [3]. Despite the high incidence of sleep disorders in JME, and the “evening” chronotype shared within this patient group, the literature lacks studies about circadian rhythm sleep-wake disorders in this population.

DSWPD is the most common type of circadian rhythm sleep-wake disorder. It is due to a failure of synchronization between individual’s intrinsic circadian rhythm and the 24-hour day cycle. Patients with DSWPD have a significant delay in sleep-wake cycle compared to the desired timing or to what is considered socially acceptable. However, sleep quality is often reported as normal when the indivual sleeps at the desired times [4]. DSWPD prevalence is approximately 1.51% among adults [12], and 3.3%–8.4% among adolescents and young adults [13,14]. A comprehensive review of an individual’s sleep history, including the utilization of sleep diaries, is essential for an accurate

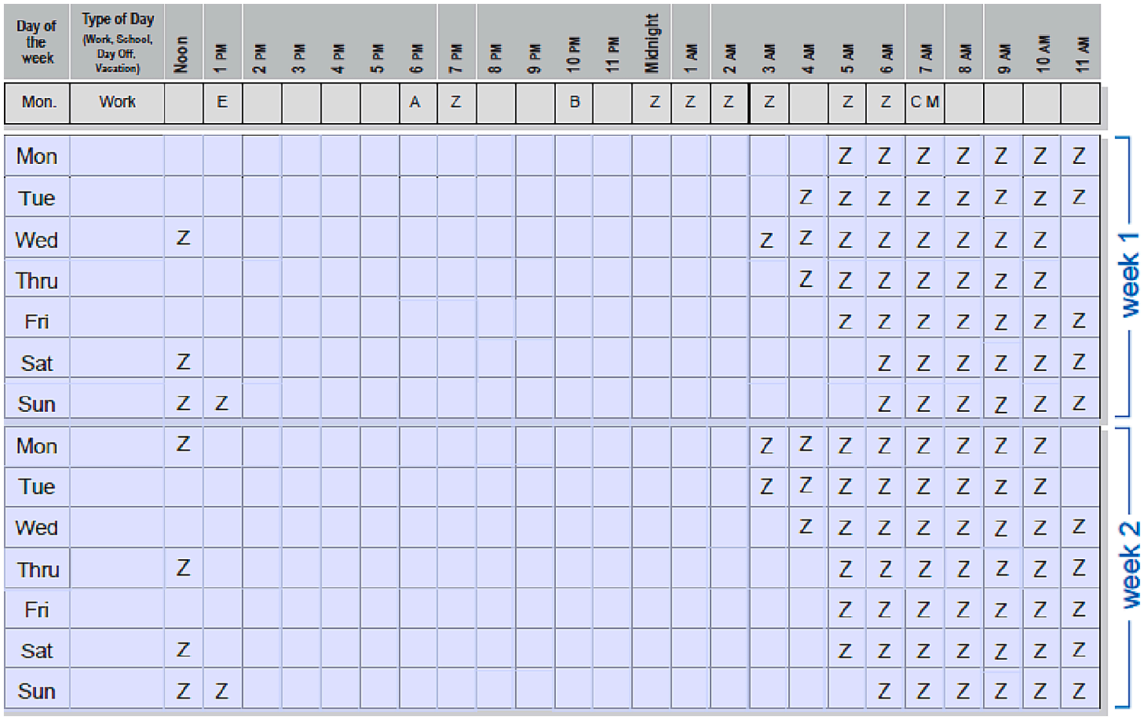
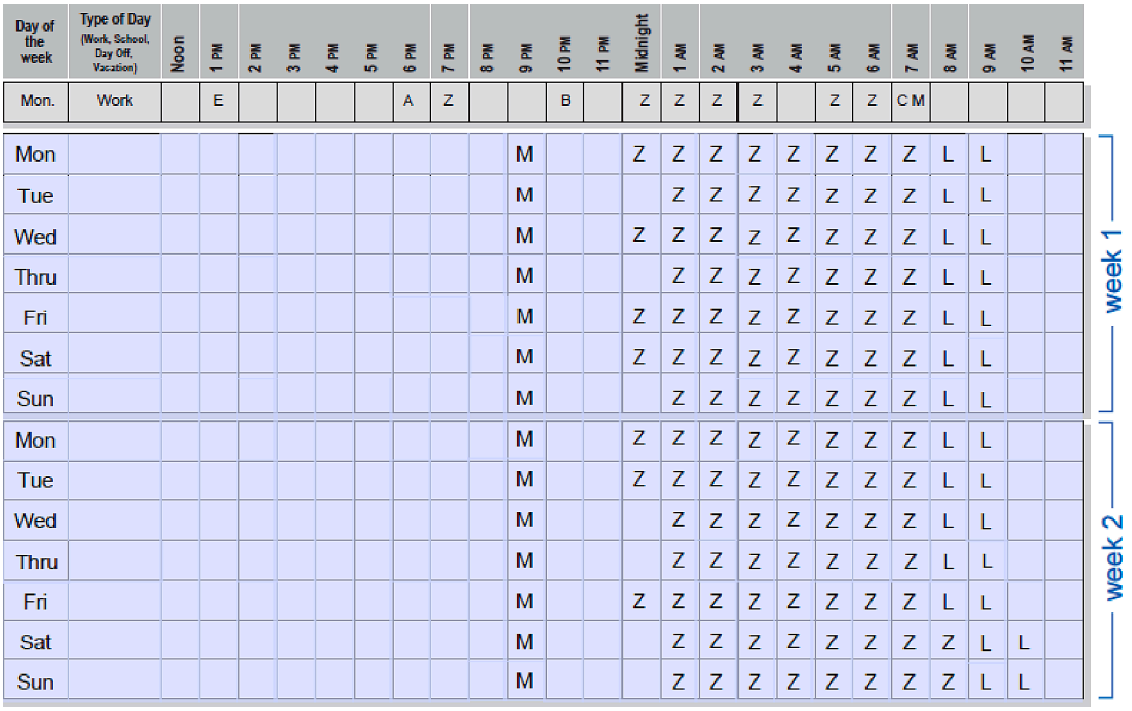


Fig. 1. Initial sleep diary recording showed a sleep schedule ranging from 3 to 5am bedtime and 10am-1 pm wake up time, consistent with Delayed Sleep-Wake Phase Disorder (DSWPD). Z – sleep.



Day of the week	Type of Day (Work, School, Day Off, Vacation)	Noon	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	Midnight	1 AM	2 AM	3 AM	4 AM	5 AM	6 AM	7 AM	8 AM	9 AM	10 AM	11 AM	
Mon.	Work		E					A	Z			B		Z	Z	Z	Z		Z	Z	C M					
Mon											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			week 1
Tue											M				Z	Z	Z	Z	Z	Z	Z	L	L			
Wed											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			
Thru											M				Z	Z	Z	Z	Z	Z	Z	L	L			
Fri											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			
Sat											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			
Sun											M				Z	Z	Z	Z	Z	Z	Z	L	L			
Mon											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			week 2
Tue											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			
Wed											M				Z	Z	Z	Z	Z	Z	Z	L	L			
Thru											M				Z	Z	Z	Z	Z	Z	Z	L	L			
Fri											M			Z	Z	Z	Z	Z	Z	Z	Z	L	L			
Sat											M				Z	Z	Z	Z	Z	Z	Z	Z	L	L		
Sun											M				Z	Z	Z	Z	Z	Z	Z	Z	L	L		

Fig. 2. Post-intervention sleep diary recording showing a shift in sleep schedule ranging from 12am bedtime and 7am-8am wake up time. M – melatonin, 1 mg dosed at 9 pm; L – light therapy, administered for 1 to 2 h in the morning after waking up; Z – sleep.

DSWPD diagnosis [4].

Our patient's sleep pattern initially suggested an "evening" chronotype, but a thorough examination of the sleep diary revealed a DSWPD diagnosis. Although we did not gather actigraphy data, the patient's family was able to provide a reliable collection of sleep/wake scheduling to support the DSWPD diagnosis. Treatment of DSWPD includes strategically timed melatonin, phase-advancing intervention with morning light exposure, behavioral sleep-wake schedulings, and chronotherapy in selected patients who do not respond to the first line intervention [15].

It has been observed that seizures can present with distinct circadian patterns depending on their localization onset and semiology [16]. In a pediatric population, Zarowski et al noted generalized tonic-clonic seizures occurring more frequently during sleep, with a peak occurrence between 6 and 9 a.m., while other generalized seizure types (including clonic, absence, atonic, myoclonic seizures and epileptic spams) were seen more often during wakefulness [16].

In the present case, our patient experienced tonic-clonic seizures exclusively during the early morning hours, consistently between 5 and 6 a.m., it is not clear whether his seizures were out of sleep or out of wakefulness. The fact that he did not recall the onset of the events and he could not report an aura may suggest that his seizures were out of sleep. The major limitation of this report lies in the missing nocturnal electroencephalogram (EEG) data that would have allowed for the determination of the patient's sleep stage during seizures. These observations may be in line with the findings of the aforementioned studies. Several factors could contribute to the observed circadian pattern of seizures. First, electrographical studies in JME patients have shown increased cortical excitability in the early morning compared to the evening [17], as well as following sleep deprivation [18]. Gamma-aminobutyric acid (GABA) ergic pathways exhibit circadian rhythmicity [17], which is regulated by the primary circadian pacemaker, suprachiasmatic nucleus. In JME patients, there is a notable reduction in GABAergic inhibitory activity, contributing to the thalamocortical hyperexcitability [19]. The complex interplay between these two elements – the circadian rhythmicity and the diminished inhibitory function – is likely responsible for the observed phenomenon.

Second, there is a marked reduction in rapid eye movement (REM) sleep and an increase in non-REM (NREM) sleep in JME patients [20]. Because of the marked neuronal synchronization of NREM sleep, epileptic seizures predominantly occur during these lighter stages [21]. It is plausible that lighter stages of NREM sleep persists in the early morning sleep, in contrast to the typical predominance of REM sleep, therefore predisposing these patients to early morning seizures [20].

A third factor is related to the exacerbated decline in sleep quality and alteration of sleep architecture experienced by DSWPD patients [22,23] and JME patients [20]. It may result in higher cortical excitability and in turn a decrease in seizure threshold, explaining the higher predisposition of seizures during sleep.

In the present case, successful seizure control was achieved by addressing DSWPD with a combination of timed evening melatonin, and gradual shifts in sleep schedule and morning light therapy without antiseizure medication (ASM) adjustment. The improvement in seizure outcome may be due to improvement of overall sleep quality by aligning the internal circadian rhythm to the 24-hour day and modifications in sleep stages resulting from the advancement of the sleep cycle, which subsequently reduced the influence of cortical excitability during morning hours [17]. In a double-blind randomized clinical trial investigating the efficacy of melatonin treatment combined with behavioral sleep-wake scheduling in well-characterized DSWPD patients, melatonin treatment improved sleep disturbances, insomnia severity, and functional disability, with a greater proportion of patients showing clinician-rated improvement compared to those on placebo [24]. Out patient's family was also very diligent with strict timed light therapy. Light therapy has been shown to be a powerful tool to correct circadian dysallignements [25]. The successful management of seizure without ASM adjustment also suggests the presence of pseudoresistance. Pseudoresistance, a phenomenon characterized by recurrent seizures resembling resistance to ASM, is often observed in the context of nonadherence to ASM regimens, or taking the wrong ASM due to misclassified epilepsy [5]. It can also be seen in patients who fail to follow behavioral recommendations, such as avoidance of alcohol use or sleep

deprivation. Our case suggests sleep disorders, as a primary cause of sleep deprivation, could significantly contribute to pseudoresistance in IGE.

Conclusion

Our case underscores the potential benefit of recognizing DSWPD in individuals with JME. We suspect DSWPD is under-recognized in this population, this could be due to JME patients' sleep patterns, if not carefully examined, could be misattributed to the "evening" chronotype commonly observed in this cohort. Treatment of sleep disorders has significant therapeutic implication for sleep-sensitive epilepsies like JME. Therefore, it is imperative for physicians to be aware of pseudoresistence and its contributing factors, and incoporate sleep screening strategies in their daily practice. Synchronizing the circadian rhythm to a 24-hour day can potentially improve sleep quality, together with assessment of circadian seizure patterns, may offer new strategies for improving seizure outcome.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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