ARTICLE

Circadian rhythm and profile in patients with juvenile myoclonic epilepsy and temporal lobe epilepsy

Ritmo e perfil circadiano em pacientes com epilepsia mioclônica juvenil e epilepsia de lobo temporal

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ABSTRACT

Objective: This study intended to compare the circadian rhythm and circadian profile between patients with juvenile myoclonic epilepsy (JME) and patients with temporal lobe epilepsy (TLE). **Method:** We enrolled 16 patients with JME and 37 patients with TLE from the Outpatient Clinic of UNICAMP. We applied a questionnaire about sleep-wake cycle and circadian profile. **Results:** Fourteen (87%) out of 16 patients with JME, and 22 out of 37 (59%) patients with TLE reported that they would sleep after seizure ($p < 0.05$). Three (19%) patients with JME, and 17 (46%) reported to be in better state before 10:00 AM ($p < 0.05$). **Conclusion:** There is no clear distinct profile and circadian pattern in patients with JME in comparison to TLE patients. However, our data suggest that most JME patients do not feel in better shape early in the day.

Keywords: juvenile myoclonic epilepsy, circadian rhythm, temporal lobe epilepsy, sleep.

RESUMO

Objetivo: Este estudo pretende comparar o ritmo circadiano e o perfil circadiano entre pacientes com epilepsia mioclônica juvenil (EMJ) e epilepsia de lobo temporal (ELT). **Método:** Nós entrevistamos 16 pacientes com EMJ e 37 com ELT do ambulatório da UNICAMP. Nós aplicamos um questionário sobre ciclo sono-vigília e perfil circadiano. **Resultados:** Quatorze (87%) de 16 pacientes com EMJ e 22 de 37 (59%) pacientes com ELT relataram que eles apresentam sonolência pós-crise ($p < 0,05$). Três (19%) pacientes com EMJ e 17 (46%) relataram um melhor estado geral antes das 10h00min ($p < 0,05$). **Conclusão:** Não há uma clara diferença de ritmo e de perfil circadiano entre pacientes com EMJ e ELT. No entanto, nossos dados sugerem que a maioria dos pacientes com EMJ não se sentem em sua melhor forma cedo pela manhã.

Palavras-chave: epilepsia mioclônica juvenil, ritmo circadiano, epilepsia de lobo temporal, sono.

Epilepsy is a chronic neurological disease, comprising different group of causes that have in common seizures that recur in the absence of toxic-metabolic disease or fever. The classification of epilepsies or epileptic syndromes proposed by ILAE[1] attempts to group epilepsy in different subsets based on similarities in seizure type, age of onset, clinical and neurological signs, family history, findings of complementary tests (EEG, imaging) and prognosis.

Juvenile myoclonic epilepsy (JME), focus of this study, is one type of the generalized idiopathic epileptic syndrome. JME has clinical presentation between 12 and 18 years old, with short and sudden muscle contractions called myoclonic seizures. These manifestations may be associated with tonic-clonic and also absence seizures[2]. The treatment of JME is based on the administration of antiepileptic drugs (AEDs) and controlling precipitating factors (sleep deprivation, emotional stress and alcohol use)[3,4,5,6,7]. Although, patients can have seizure controlled with medication, the recurrence rate is high, thus there is a need to continue their medications without interruption[3].

One important factor of worsening in seizure frequency of JME is related to lack of sleep, so as to suggest that there is a causal relationship between these two factors[8]. There is

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Conflict of interest: There is no conflict of interest to declare.

Support: Aya Fukuda was student of a scholarship from the Programa Institucional de Bolsas de Iniciação Científica (PIBIC) which is associated to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Ministério da Ciência e Tecnologia (MCT).

Received 10 June 2014; Received in final form 13 September 2014; Accepted 03 October 2014.

also evidence that sleep deprivation causes seizures in patients with epilepsy, and sleep apnea can intensify these seizures. In addition, NREM (synchronized nonrapid eye movement) sleep stage facilitates the occurrence of seizures, while another stage of sleep known as REM (desynchronized rapid eye movement) hinders their occurrence[8].

Pung and Schmitz[9] studied a group of 20 patients with JME and described their patients with alterations in the circadian rhythm, whereas the patients were considered of "evening types"[9]. Thus, if we assume that there is a specific profile that characterizes patients with JME in relation to the circadian rhythm, this has significance in directing the clinical treatment of patients, given the evidence of close relationship between sleep and epilepsy. However, one could argue that other factors may be in place, as social-cultural background of patients instead of neurobiological factors related to JME. Therefore, our objective is to compare the circadian rhythm and circadian profile between patients with JME and temporal lobe epilepsy (TLE).

METHOD

We invited in this study adult patients (not less than 18 years) with diagnosis of JME and TLE undergoing treatment at the *Ambulatório de Epilepsia do Hospital de Clínica da Universidade Estadual de Campinas* from 14/June/2010 to 30/May/2011. Patients with co-morbidities, especially psychiatric, were excluded.

We used the questionnaire for identifying the characteristics of sleep-wake cycle and circadian profile based on an existing questionnaire[1] by Pung and Schimit. We translated and adapted the questionnaire for Brazilian Portuguese. This questionnaire is composed by six topics which asks about the patient's preferences about doing a task before or after 10:00 AM, about being a nocturnal or diurnal person, about the physical state at the morning and about how awake he or she feels after waking.

In addition, we collected the demographic data about the patients during the interview and complemented with information from patient's file whenever needed.

On the concepts of the analysis, we defined seizure-free as a period of twelve months without seizures. We also defined the sedative antiepileptic drugs, which could affect the sleepiness of the patient as the following drugs: clobazam, clonazepam and phenobarbital.

Ethics

The Research ethics committee (CEP) of *Faculdade de Ciências Médicas* of *Universidade Federal de Campinas*, meeting all the provisions of the resolutions no. 196/96 and complementary, approved without restrictions on May 13, 2010, the research protocol, as well as the Consent term and all other attachments included in the survey. The document proving this approval is the opinion of the CEP no. 169/2010.

The participation of the research subjects is voluntary and participants are aware of the whole process. They have signed terms of informed consent, in which it is informed that the data are collected under guard of scientific and professional secrecy.

RESULTS

We enrolled 53 patients in this study. Sixteen (30%) had JME, mean age 32 (range 21 to 53), with four men (25%). The mean age of onset was 12 (range from 2 to 21). Eight patients (50%) were on monotherapy (valproic acid = 5; lamotrigine = 2; topiramate = 1).

Thirty-seven had TLE (70%), mean age 47 (range 23 to 66), with 14 men (38%). The mean age of onset was 16 (range from 1 to 62). Sixteen patients (43%) were on monotherapy (Carbamazepine = 12; Phenobarbital = 1; topiramate = 1, lamotrigine = 1; clonazepam = 1).

We used Chi-square to assess statistical difference, assuming the corrected p-value < 0.05 as significant. We opted for individual assessment, knowing the caveat of such approach, but having in mind as a way for an exploratory view of the data. The circadian rhythm is shown in Table 1 and the circadian profile is shown in Table 2.

The statistical significant differences were: TLE patients tend to be in better state before 10:00 AM and JME patients use to sleep after seizure.

There are 5 (31%) patients with JME that are in use of sedative antiepileptic drugs, in contrast to 16 (44%) patients with TLE that are in use of these type of with medication (Chi-square=0.80, p=0.16). These numbers show that there

Table 1. Circardian rhythm of patients with JME and TLE.

	JME (n = 16)	TLE (n = 37)	Chi-square	p-value
Sleep easily	13 (81%)	26 (70%)	0.69	0.19
With sleep disruptions	7 (44%)	25 (68%)	2.64	0.06
Seizures during sleep	7 (44%)	19 (51%)	0.25	0.20
With sleep symptoms	2 (13%)	7 (19%)	0.32	0.27
Reported waking up tired	6 (38%)	11 (30%)	0.30	0.21
Use to sleep after seizure	14 (88%)	22 (59%)	4.03	0.03

JME: Juvenile myoclonic epilepsy; TLE: Temporal lobe epilepsy.

Table 2. Circardian profile of patients with JME and TLE.

	JME (16)	TLE (37)	Chi-square	p-value
To be in better state before 10:00 AM	3 (19%)	17 (46%)	3.51	0.04
To prefer doing an exam before 10:00 AM	7 (44%)	21 (57%)	0.75	0.16
To prefer to do two hours of heavy physical exercise before 10:00 AM	8 (50%)	23 (62%)	0.68	0.16
To be a morning type	14 (88%)	30 (81%)	0.32	0.27
To have a good physical form between 7:00 AM and 8:00 AM	11 (69%)	29 (78%)	0.55	0.20
To feel sleepy in the first hour after waking up	9 (56%)	12 (32%)	0.64	0.06

JME: Juvenile myoclonic epilepsy; TLE: Temporal lobe epilepsy; AM: Ante Meridian.

is no significant difference between these 2 groups for the information about number of sedative antiepileptic drugs in use.

Considering that seizure-free is defined by a period of 12 months without seizures, five (33%) patients with JME are not-seizure-free, in contrast to 24 (65%) patients with TLE who are not-seizure-free (Chi-square=4.30, p=0.03). These numbers show that there is significant difference between these 2 groups for the information about seizure-free period.

DISCUSSION

The circadian rhythm between the JME and the TLE patients shows similar pattern between both groups. The only tendency was the fact that patients with JME appear to sleep more after the seizure. This is possibly explained by the seizure type, as mostly, patients with JME had tonic-clonic seizure compared to TLE that has complex partial seizure.

In circadian profile, TLE patients tend to be in better state before 10:00 AM when compared to the JME patients. Comparing these data to data from Pung and Schimtz[9], in both of the studies, we found the same information that the TLE patients tend to feel in better state before 10:00 AM.

On the other hand, in our study there is no definition about the patients on being "evening types" or "morning types", in contrast to the results from the Germany study, in which the JME patients were defined as "evening types"[9] and the TLE patients as "morning types". This can be in part due to the sociocultural differences between the countries from where the patients were taken.

Previous studies report that pattern of seizure occurrence in JME patients tend to be on awakening (diurnal seizures)[10,11,12,13,14], while TLE patients tend to have seizures during sleep (nocturnal seizures)[11,12]. These studies argue against our finding that TLE patients tend to feel in better state before 10:00 AM, who should be more sleepy at the morning if they have had the sleep interruptions secondary to seizures during sleep. Therefore, the controversial data shows that the seizure factor does not contribute to sleepiness on morning on the TLE patients of our study.

According to the property of the anticonvulsant drugs to improve sleep by decreasing seizures but to cause sleep disruptions by mechanisms of independent neuromodulation[15,16,17,18,19,20,21], it is important to discuss the therapy in use by the patients. For example, the excessive daytime sleepiness were reported to be associated to low seizures control and to monotherapy with low antiepileptic drugs serum levels[21]. There is also a link between the number of antiepileptic drugs in use and the increase of the seizure's frequency with the excessive daytime sleepiness[22,23,24]. The type of the antiepileptic drug is also an important factor. For example, there are a few ones that promote stabilization and normalization of the sleep, such as phenytoin[25,26], carbamazepine[20,25,27], phenobarbital[25] and benzodiazepines[28,29]. However, there are some sedative antiepileptic drugs that may increase the sleepiness, such as clobazam, clonazepam and phenobarbital, which we defined as sedative AEDs. There is no difference between the JME and the TLE patients about the information of the number of sedative AEDs in use. Therefore, this information is not significant to this study.

CONCLUSION

In conclusion, there is no clear distinct profile and circadian pattern in patients with JME in comparison to TLE patients. However, our data suggest that most JME patients do not feel in better shape early in the day. It is likely that the sociocultural behavior rather than neurobiological factors influence the circadian pattern of sleep. Reinforcement of proper behavior and sleep hygiene should be encouraged to help control of seizure in JME.

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