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# EEG RECORDING AFTER SLEEP DEPRIVATION IN A SERIES OF PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY

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ABSTRACT - Seizures in Juvenile Myoclonic Epilepsy (JME) are dependent on the sleep-wake cycle and precipitant factors, among which sleep deprivation (SD) is one of the most important. Still an under diagnosed syndrome, misinterpretation of the EEGs contributes to diagnostic delay. Despite this, a quantitative EEG investigation of SD effects has not been performed. We investigated the effect of SD on EEGs in 41 patients, aged 16-50 yr. (mean 25.4), who had not yet had syndromic diagnosis after a mean delay of 8.2 yr. Two EEG recordings separated by a 48-hour interval were taken at 7 a.m. preceded by a period of 6 hours of sleep (routine EEG) and after SD (sleep-deprived EEG). The same protocol was followed and included a rest wakefulness recording, photic stimulation, hyperventilation and a post-hyperventilation period. The EEGs were analyzed as to the effect of SD on the number, duration, morphology, localization and predominance of abnormalities in the different stages. A discharge index (DI) was calculated. Out of the 41 patients, 4 presented both normal EEG recordings. In 37 (90.2%) there were epileptiform discharges (ED). The number of patients with ED ascended from 26 (70.3%) in the routine EEG to 32 (86.5%) in the sleep-deprived exam. The presence of generalized spike-wave and multispike-wave increased from 20 (54.1%) and 13 (35.1%) in the first EEG to 29 (78.4%) and 19 (51.4%) in the second, respectively ($p<0.05$ and $p<0.01$). As to localization, the number of generalized, bilateral and synchronous ED increased from 21 (56.8%) to 30 (81.1%) ($p<0.01$). The DI also increased; while 8 patients (21.6%) presented greater rate in the routine EEG, 25 (67.6%) did so in the sleep-deprived EEG mainly during somnolence and sleep ($p<0.01$). Moreover, the paroxysms were also longer in the sleep-deprived EEG. Sleep-deprived EEG is a powerful tool in JME and can contribute significantly to the syndromic characterization of this syndrome.

KEY WORDS: sleep deprivation, EEG diagnosis, juvenile myoclonic epilepsy.

**Registros eletrencefalográficos após privação de sono em uma série de pacientes com epilepsia mioclônica juvenil**

RESUMO - Na epilepsia mioclônica juvenil (EMJ), uma síndrome epiléptica ainda subdiagnosticada, as crises são dependentes do ciclo vigília-sono e de fatores precipitantes, entre os quais a privação de sono (PS) é um dos mais importantes. A interpretação inadequada dos EEGs contribui para atraso no diagnóstico. Ainda não foi realizada investigação quantitativa sobre os efeitos da PS. Avaliamos o efeito da PS nos EEGs de 41 pacientes entre 16 e 50 anos (média 25,4) com EMJ em dois registros eletrencefalográficos, separados por intervalo de 48 horas. Os exames foram realizados às 7 horas da manhã, precedidos por um período de 6 horas de sono (EEG de rotina) e após PS (EEG com PS). Seguimos o mesmo protocolo que incluiu o registro em vigília em repouso, fotostimulação, hiperventilação e pós hiperventilação. O efeito da PS foi analisado sobre o número, duração, morfologia, localização e predominância das anormalidades nos diferentes estágios. Calculamos o índice de descargas por minuto. Dos 41 pacientes, 4 tiveram ambos os registros normais. Em 37 (90,2%) houve algumas descargas epileptiformes (DE). O número de pacientes com DE ascendeu de 26 (70,3%) no EEG de rotina para 32 (86,5%) no exame em PS. A presença de descargas de espícula-onda generalizadas e multispícula-onda aumentou de 20 (54,1%) e 13 (35,1%) no primeiro EEG para 29 (78,4%) e 19 (51,4%) no segundo, respectivamente ($p<0,05$ e $p<0,01$). Quanto à localização, o número de descargas ascendeu de 21 (56,8%) para 30 (81,1%) ($p<0,01$). O índice de descargas (ID) também aumentou; enquanto 8 pacientes (21,6%) apresentaram ID maior no EEG de rotina, 25 (67,6%) o tiveram no EEG em PS, principalmente durante sonolência e sono ($p<0,01$). Ainda mais, os paroxismos também foram mais longos no EEG em PS. EEG em PS é um instrumento poderoso para o diagnóstico de EMJ podendo contribuir significantemente na caracterização desta síndrome.

PALAVRAS-CHAVE: privação de sono, diagnóstico EEG, epilepsia mioclônica juvenil.

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Juvenile myoclonic epilepsy (JME) is an idiopathic generalized syndrome, clinically and electroencephalographically defined by Janz and Christian[1] that accounts for 2.8-11.9% of all epilepsies[2]. Typically appearing around puberty it is characterized by myoclonic jerks, present in all cases, associated or not to generalized tonic-clonic seizures (GTCS) and infrequent absences[3]. The seizures are dependent on the sleep-wake cycle and precipitant factors, such as sleep deprivation, fatigue, alcohol intake and photic stimulation[1,4,5]. Generalized interictal 4-6/s spike-wave complexes are seen more frequently than the multispike-wave complexes, constituted of 5-20 spikes preceding the slow wave, considered the most typical EEG finding in JME[1,6]. Many recent reports on JME emphasize that it still is an under diagnosed syndrome[7-9]. Among some other clinical factors such as recognition of the typical myoclonic seizures and asymmetry of jerks, misinterpretation of the EEG has been reported to contribute to the diagnostic delay in 21-75% of misdiagnosed cases[9,10]. Failure to recognize JME may result in uncontrolled seizures, status epilepticus, irreversible brain damage, social-educational failure, and even death[7].

The recognition of the activation effect of lack of sleep, led Janz and Christian[1] to use sleep deprivation as a diagnostic tool. This method of activation was used for the precipitation of seizures and EEG abnormalities, by advising their patients not to go to bed earlier than 1 a.m. for 1-2 nights and to drink strong coffee or a bottle of wine before that. The EEGs were then recorded early on the following morning when possible usually soon after awakening. Since then, all authors stressed the importance of repeated EEG recordings whenever the diagnosis is not clear and pointed out that EEG recording after sleep deprivation is the most important and most powerful diagnostic procedure. Despite this, a proper quantitative electroencephalographic investigation of sleep deprivation effects has not been performed[11].

The aim of this study was to investigate the effect of sleep deprivation on EEG in a series of 41 JME patients who had not yet had syndromic diagnosis.

## METHOD

In this study we evaluated the role of sleep deprivation in obtaining EEGs in a series of 41 patients who had not been diagnosed for JME before being attended at the Epilepsy Section of the Escola Paulista de Medicina, Universidade Federal de São Paulo. The diagnosis was finally established after a delay of 8.2 years (15 days to 24 years). Among the possible clinical factors implied in the difficulties of diagnosis were, the lack of identification of myoclonias in 18 patients (43.9%), asymmetry of the myoclonic jerks in 12 (29.3%) and occurrence of GTCS as inaugural type of seizures in 15 (36.6%). Thirty-nine patients had had 1 to 9 EEG recordings (mean 2.5) before being accepted for this study. Electrographical factors possibly implied in the difficulties of diagnosis were identified such as normal tracings in 16 (41%) and presence of focal alterations in 12 (36.4%). Some patients presented a combination of clinical and electrographical factors.

For the electroencephalographic characterization, this protocol included two EEG recordings separated by a 48-hour interval. Advantages and risks for participation were explained and informed consent was taken. All the recordings were obtained with a 32-channel EEG machine, without modifications in the previous chronic medication, which included sodium channel blockers (carbamazepine, phenytoin and lamotrigine) in 10 (24.4%) and broad spectrum drugs (phenobarbital, valproate and benzodiazepines) in 18 (43.9%) in monotherapy. Eleven patients (26.8%) were receiving both types of antiepileptic drugs and two were not taking any medicines.

The two exams were referred to as routine and sleep-deprived EEG.

The first was obtained at 7 a.m., preceded by a period of 6 hours of sleep. The duration of the recording was 20 to 30 minutes and included rest wakefulness, intermittent photic stimulation, hyperventilation for 5 minutes followed by a 2 minutes post-hyperventilation with or without a period of drowsiness and sleep. This recording was called routine EEG.

The second was also recorded at 7 a.m., after sleep deprivation and included intermittent photic stimulati/n (being performed with opening and closing the eyes), two hyperventilation periods of 5 minutes each followed by a 2 minutes post-hyperventilation either with or without a recording of drowsiness and sleep. The second hyperventilation was performed with the patient in sitting position, with eyes closed and counting the respiratory incursions. The minimum duration of this exam was 50 minutes and it was called prolonged, sensitized or sleep-deprived EEG.

Frequency of flickering during photic stimulation was 1-3-6-9-12-15-18-21-24-Hz, for a period of 10 seconds and followed by a 10 seconds interval.

The EEGs were analyzed as to the effect of sleep deprivation in the number, duration, morphology, localization and predominance of epileptiform abnormalities during wakefulness, intermittent photic stimulation, closing of the eyes, hyperventilation, post-hyperventilation period, drowsiness and sleep. The paroxysms were counted in isolation as well as in bursts, independent of their duration. A discharge index per minute in all the different phases was calculated.

For comparison of routine and sleep-deprived EEGs we used the t-test paired off for numerical variables. For the categorical variables the McNemar test was used in order to compare the proportions of epileptiform graphoelements and discharges localization between the two exams. P<0.01 was considered significant.

## RESULTS

Both EEG were recorded in all 41 patients aged 16 to 50 (mean 25.4 years). Epileptiform activity was verified in 37 (90.2%). We report the data obtained in both, routine and sleep-deprived EEGs, as: number of abnormal recordings, presence, distribution and type of epileptiform graphoelements and discharge indexes.

*Routine EEG* – This recording was altered in 26 patients (70.3%) showing in 20 (54.1%) epileptiform activity with generalized, bilateral and synchronous distribution predominating in frontocentral areas; 4 cases showed generalized and bilateral although asymmetric discharges which in 2 cases had posterior predominance. Focal epileptiform discharges were observed in 9 patients being six frontal, two temporal and one multifocal. As for the morphology of the graphoelements, 21/41 (51.2%) presented irregular spike-wave complexes and 2 rhythmic complexes (one 3/s; one less than 3/s). Multispike-wave complexes were seen in 13 (35.1%), including the presence of double and triple spikes. Eight cases (19.5%) had slow sharp waves, six (14.6%) slow spike waves, 3 (7.3%) bursts of slow waves, 2 (4.9%) groups of sharp waves, 2 (4.9%) groups of spikes and 1 (2.4%) rapid rhythm. Two patients presented absences during hyperventilation; one patient presented myoclonic seizures also during hyperventilation and in another photoparoxystic response was seen during photic stimulation.

*Sleep-deprived EEG* – This recording was altered in 32 patients (86.5%). As to the type of graphoelement, 29 patients (78.4%) presented irregular spike-wave complexes (4-6/s) and one had regular spike-wave complexes at 3/s. Nineteen cases (51.4%) showed multispike-wave complexes including double and triple spikes. Single spike wave occurred in 12 (29.3%), single sharp wave in 8 (19.5%), sharp waves in 3 (7.3%), bursts of slow waves in 3 (7.3%) and groups of spikes in two (4.9%). The distribution of the epileptiform activity was generalized, bilateral and synchronous, with frontocentral predominance in 30 patients (81.1%) being asymmetric in 12 and showing posterior predominance in 1. There were focal discharges in 12 (29.3%) being 7 frontal, 3 frontotemporal, 1 temporal and 1 multifocal. One patient presented absence during hyperventilation and in another there were myoclonic seizures during hyperventilation and photic stimulation. Fig 1 compares the epileptiform graphoelements in the routine and sleep deprived EEG.

Fig 2 shows the locatization of the epileptiform activity verified in the routine and in the sleep-deprived EEG.

The comparison between the two groups showed an increase in the number of generalized, bilateral and synchronous discharges with anterior

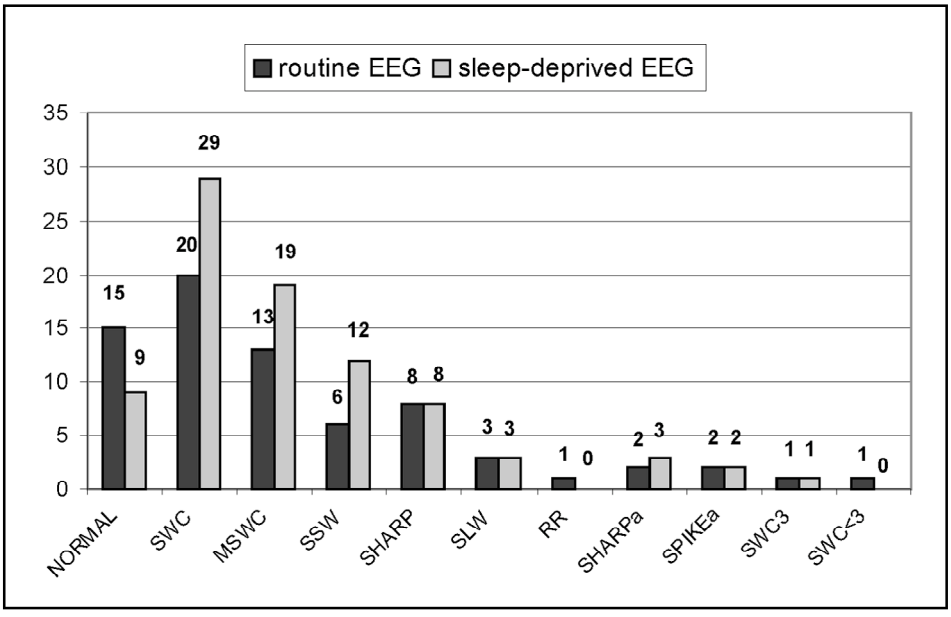


*Fig 1. Characterization of epileptiformgraphoelements encountered on EEG 1 (routine EEG) and 2 (sleep-deprived EEG). SWC, spike-wave complexes; MSWC, multispike-wave complexes; SSW, single spike-wave; sharp, sharp-wave; SLW, slow-wave; RR, rapid rhythm; sharp a, grouped sharp-waves; spike a, grouped spikes; SWC3, 3 cycles spike-wave complexes; SWC<3, less than 3 cycles spike-wave complexes.*

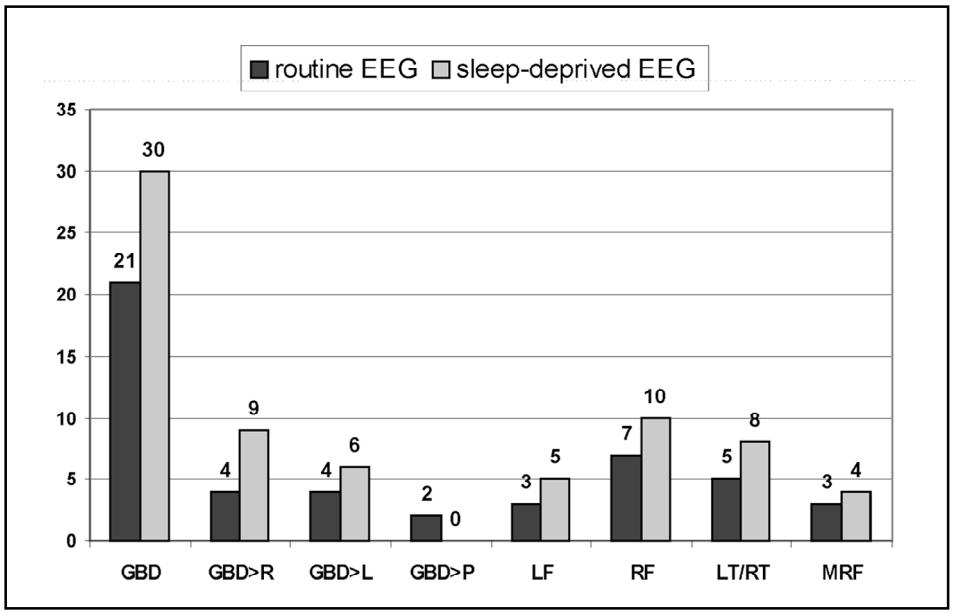


*Fig 2. Localization of epileptiform graphoelements on EEG 1 (routine EEG) and 2 (sleep-deprived EEG). GBD, generalized bilateral discharges; GBD>R, generalized bilateral discharges, predominant to the right; GBD>L, generalized bilateral discharges, predominant to the left; LF, left frontal; RF, right frontal; LT/RT, left/right temporal; MRF, median right frontal.*

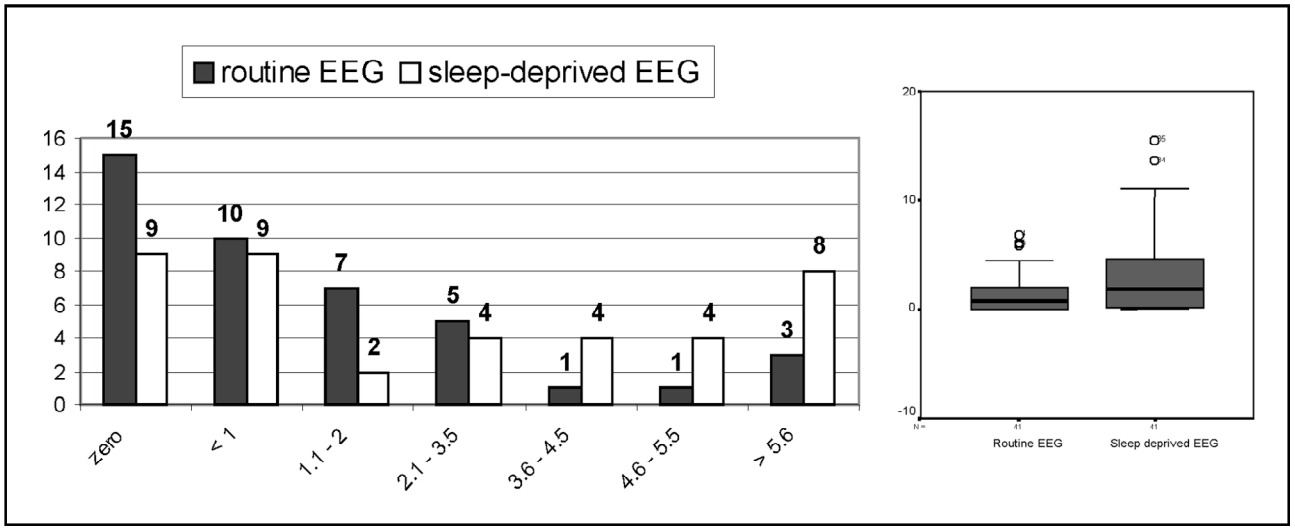


*Fig 3. Discharge indexes in routine and sleep-deprived EEG.*

predominance (21 x 30; p<0.01) and of the irregular spike-wave complex (20 x 29; p<0.05) in the sleep deprived EEG.

*Discharge index per minute* – The global discharge index was calculated and compared between the routine and the sleep deprived EEG. Of the 41 patients, 25/37 (67.6%) had a greater number of discharges in the sleep-deprived EEG, 8 in the routine and 8, had the same amount of discharges in both. The difference of the discharge index between routine and sleep-deprived EEG was statistically significant (t paired off test; p<0. 01).

In Fig 3, the routine and sleep-deprived EEG discharge indexes are shown with Box-plot analysis. We also calculated the discharge index in wakefulness, drowsiness, sleep, hyperventilation and post-hyperventilation period.

The distribution of the discharges in the routine EEG in decreasing order of occurrence was: hyperventilation 11 (26.8%); post-hyperventilation period 8 (19.5%); sleep 5 (12.1%); drowsiness 2 (4.9%) and while resting in 2 (4.9%).

In the sleep-deprived EEG: hyperventilation in 9 (22%); post-hyperventilation in 10 (24.4%); sleep, 8 (19.5%); drowsiness, 4 (9.8%) and while resting in 1 (2.4%).

There were no statistic differences in the fre-

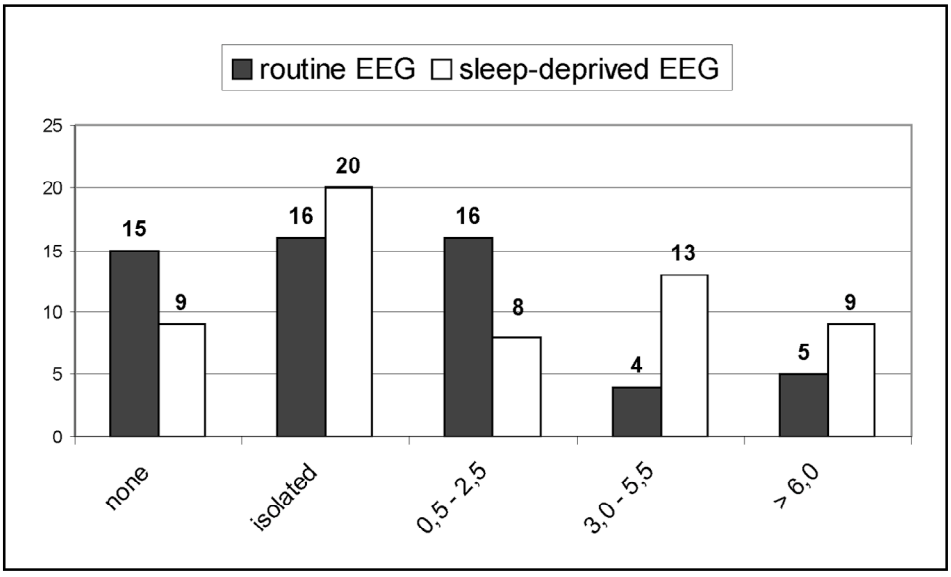


*Fig 4. Duration of discharges in routine and sleep-deprived EEG.*

quency of epileptiform graphoelements in the various phases studied.

In the sleep-deprived EEG, there was no difference between the two periods of hyperventilation in 13 patients (31.7%); it was greater in the first in 10 (24.4%) and in the second in 18 (43.9%).

Finally, the duration of discharges was greater in the sleep-deprived EEG (Fig 4).

None of our patient presented myoclonic status or GTCS before, during or after the EEG recordings.

## DISCUSSION

In a study about the effects of spontaneous and provoked awakening on the frequency of polyspike and wave discharges in bilateral massive epileptic myoclonus in 18 patients, Touchon et al.[12] evaluated the number of epileptiform discharges on awakening after a first habitual night of sleep and after a second night in which the sleep was interrupted by five provoked awakenings. There was more epileptic activity after the spontaneous morning awakening after the second night sleep recording than after the spontaneous awakening of the first night. It is precisely during the second night that the total duration of sleep was shortened and its structure altered by provoked awakenings. These experimental modifications are very similar in fact to those observed in insomniacs and chronic alcoholics. These observations can be likened to well known precipitating factors, such as deprivation of sleep and excessive alcohol consumption.

Our results confirmed the classic statement that JME is a type of epilepsy sensible to sleep deprivation[1], since the sleep-deprived EEG increased the sensitivity of the method in 73.3% (out of 15 patients with normal routine EEG, 11 presented epileptiformdischarges in the second recording). On the other hand, the activating effect of deprivation of sleep was clearly verified in the global index of discharges, seen three times more frequently in the sleep deprived than in routine EEG (25 versus 8 patients, respectively). Halász et al.[13], studying the effect of deprivation of sleep in 10 patients with idiopathic generalized epilepsies of which only one with JME, observed that this activating method caused an increase in the density of spike-waves complexes in all the stages of the sleep-wake cycle, including in the state of wakefulness. Normal EEGs, present in 5-38% of the cases is considered an important factor for misdiagnosis of JME[5,14-16] .

As for the localization of the graphoelements, the majority of the discharges occurred in a generalized, bilateral and synchronous form predominating in the frontocentral areas in both recordings. This is considered the more usual distribution of discharges in JME[1,17]. However, there was an increase in the presence of this type of graphoelement from 21 cases (56.8%) to 30 (81.1%) in the routine and sensitized EEG, respectively.

In the same way, asymmetric generalized discharges present in 4 patients rose to 12. The occurrence of lateralized abnormalities in patients with idiopathic generalized epilepsies, particularly in JME, is amply accepted[5,16,18], even though it represents one of the misdiagnosis factors since it could suggest the presence of focal epilepsy. The results as to the lateralized abnormalities of this series are similar

to those reported by Panayiotopoulos et al.[5] and Montalenti et al.[16]. Lancman et al.[19] reported that the average time of delay for the establishment of diagnosis in patients with asymmetry was greater than in those with symmetric alterations.

The most common pattern of epileptiform discharges, irregular spike-wave complexes (4-6/s), verified in 20 (54.1%) of the routine exams went up to 29 (78.4%) of the sensitized EEG while the percentage of the multispike-wave complexes, considered the most typical electrographical pattern of JME, also ascended from 13 (35.1%) to 19 (51.4%) in the first and second recordings, respectively. Multispike-wave complexes were also more common than irregular spike-wave complexes in the Tsuboi et al.[20] series.

Some authors[5,21] described focal discharges in JME, in this study present in 9 patients in routine EEG compared to 12 in the sleep-deprived EEG. In the series of Aliberti et al.[14], besides the typical generalized abnormalities, focal alterations were seen in at least one EEG in more than half of the patients and asymmetry of generalized discharges in an even a greater proportion.

The co-existence of focal and generalized epileptiform abnormalities in JME could promote diagnostic difficulties, being suggestive of partial epilepsies with secondary generalization[14,21]. Not one patient presented focal discharges as the only type of alteration in both recordings.

Among the activation procedures, the hyperventilation, known as an important factor in promoting the appearance of epileptiform activity, recognized as such also in JME, promoted the greatest discharge index[1,22].

In conclusion, in this series of 41 patients with JME, 33 (80.5%) had not had syndromic diagnosis. The presence of some normal EEG in 30 patients (73.2%) might have contributed to difficulties in diagnosis although tracings persistent normal were seen in only 4 cases (9.8%). Routine EEG did not show a suggestive EEG pattern of JME in 19 cases. Sleep-deprived EEG significantly contributed to the diagnosis in 32 patients. Lack of electroclinical correlation caused a median delay in diagnosis of 8.2 years. An even greater delay (11.6 years) was verified in patients with asymmetry in epileptiform discharges. Greater the delay and the institution of adequate treatment in JME the greater the consequences of uncontrolled epilepsy.

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