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Phenotyping juvenile myoclonic epilepsy. Praxis induction as a biomarker of unfavorable prognosis

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ABSTRACT

Purpose: Juvenile myoclonic epilepsy (JME) is a heterogeneous syndrome with seizures presenting typical fluctuation in diurnal cycle and relation with awakening. Few publications have approached clinical expressions of praxis induction (PI) in the nosology of JME as well as its impact on outcome. The aim of this study is to characterize PI as the only reflex trait in JME and its relation with prognosis.
Method: JME with PI reported on a questionnaire and confirmed by video-EEG testing (Group 1, 20 patients) were compared with JME without any reflex epileptic trait (Group 2, 25 patients) and followed for a mean of 7.82 years (SD = 3.98). Circadian distribution and frequency of seizures were assessed in a diary. Patients also had psychiatric evaluation.
Results: Prevalence of PI was 20/133 (15%) JME patients, and was predominant in males (1.5 male: 1 female; OR 13; $p = 0.042$). Among Group 1 patients, only 2/20 presented seizures exclusively in the morning ($p = 0.013$), and none, exclusively on awakening ($p < 0.001$). PI patients had worse prognosis regarding control of myocloni ($p = 0.02$) and absences ($p = 0.01$); only 7/20 (35.0%) could be treated with VPA in monotherapy ($p = 0.01$). At the last follow-up, 2/20 (10.0%) of Group 1 and 10 (40.0%) of Group 2 patients were free of all three seizure types ($p = 0.02$). Even though relative risk of stress as a precipitant of seizures increased 3.82 times in Group 1, psychiatric comorbidities were not different between groups.
Conclusion: PI reflex trait in JME is related to seizures without preferential circadian occurrence and reduced response to antiepileptic drugs.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common type of idiopathic generalized epilepsy (IGE); comprising 5–10% of all epilepsies [1]. The cardinal symptoms are myoclonic jerks of upper extremities; often precipitated by sleep deprivation [2,3]. Chronosensitivity is necessary for diagnosis. Occurrence of myoclonia exclusively on or after awakening and age of onset between 10 and 25 years are considered Class I diagnostic criteria while Class II comprises myoclonia occurring predominantly on or after awakening; sensitivity to visual stimuli; praxis induction (PI) and a wider 6–25 years range for onset of epilepsy [4]. Generalized tonic-clonic seizures (GTCS) are present in approximately 80–95% of patients and one third has absences [2]. Recently; data regarding long term prognosis of JME have been published [5–10]. Despite the recognition of some prognostic predictors such as presence of all three types of seizures; psychiatric comorbidity and drug resistance [10–13]; clinical diversity of JME is remarkable and the severity of the disorder itself has only rarely been analyzed [14–16].

PI, one of the four reflex epileptic traits that occur in JME, is defined as precipitation of seizures or epileptiform discharges (ED)

Abbreviations: NPP, neuropsychological protocol; ORM, orofacial reflex myocloni; PI, praxis induction.

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by complex, cognition-guided tasks, often involving visuomotor coordination and decision making [17–19]. Language and non-verbal triggers can be understood as mechanistically similar paradigms for seizure induction by verbal and non-verbal cognitive tasks [20,21]. Since in these patients seizures can be triggered by daily activities using their hands, the typical circadian distribution of seizures in JME would be lost [22].

Although Matsuoka et al. [14] in 1992 had recognized PI as a sign of worse prognosis in JME, few studies have approached its impact on JME outcome [16,23,24].

Moreover, there is no published prospective studies comparing JME patients with PI as the only reflex trait and JME patients without any reflex traits.

The aim of this study is to characterize PI as the only reflex trait in JME patients and its relation with prognosis.

2. Methods

2.1. Clinical evaluation

We used a semi-structured interview based on a questionnaire in order to endophenotype 133 JME patients according to their reflex epileptic traits. All had unequivocal diagnosis of JME based on electroclinical characteristics, including normal physical and neurological examinations, routine blood tests and brain imaging (CT/MRI) and generalized 4–6 Hz spike or polyspike-wave complexes, sometimes asymmetric, on a normal background in routine EEGs [25–27]. Inappropriate used AEDs encompassed carbamazepine, oxcarbazepine and phenytoin, as these are generally ineffective and might even aggravate seizures in JME. They were followed in the outpatient clinic of a tertiary center (Epilepsy Section, Department of Neurology and Neurosurgery, Universidade Federal de São Paulo, São Paulo, Brazil).

First, a clinical interview focused on myoclonic seizures occurrence and their circadian distribution (exclusively or predominantly on awakening, and the period of occurrence during the day) and a questionnaire regarding the precipitant factors including three questions were applied [23]: (a) Have you noticed any situations or states which do cause you to have more seizures?; (b) Can you identify some precipitating factor on this list: stress, sleep deprivation, specific thoughts/concentration, flashing lights, performing hand activities and complex finger manipulation, playing games, calculation, speaking in public, alcohol intake, playing musical instruments, listening to music, writing, dancing, drawing, menses, and others?; (c) Can you identify some factors or situations that would stop or inhibit your seizures?

Psychiatric comorbidity was then analyzed through Schedule Clinical Interview for DSM-IV, Axis I (SCID-I), and/or MINI [28] and State-Trait Anxiety Inventory (STAI), aiming to measure state (STAI-S) and trait (STAI-T) anxiety components [29].

2.2. Video-EEG

After obtaining informed consent, all 133 consecutive patients had a 4–6 h video-EEG monitoring, comprehending a research protocol approved by the Ethics Committee of our institution. Video-EEG was recorded on a digital equipment (Biologic 1, software Ceegraph 1) using the 10–20 International Electrode System, in addition to perioral and deltoid electrodes. For patients who had presented GTCS over the last 48 h, the protocol was postponed. Antiepileptic drugs (AEDs) were maintained in all patients. After having slept for at least 4 h, they had 30 min of awake EEG baseline recording, followed by a neuropsychological protocol (NPP), composed by tasks such as reading silently and aloud, talking, writing, performing mental and written calculations, drawing and spatial construction puzzles (for details, see Guaranha et al. [24]). The protocol and its analysis were based on criteria reported by Matsuoka et al. [20] and Mayer and Wolf [19]. PI tasks were performed at least 2 h after awakening. The sequence of tasks was administered randomly in different patients. PI was ascertained if at least one NPP task produced myoclonic seizures or ED activation (defined as ED per minute during NPP task at least the double of that in baseline EEG) [19,20]. Aiming to confirm true activation in case of none ED in the baseline, the task was applied again [24]. ED were classified as generalized or focal, and evaluated with respect to amplitude, using at least two montages. Bilateral anterior or posterior ED were not considered as focal abnormalities.

At the end of NPP, habitual activation methods as eye-closure, hyperventilation, intermittent photic stimulation, were performed.

2.3. Inclusion and exclusion criteria

Forty-five out of 133 JME patients were enrolled. Among them, two groups were selected: Group 1—JME with PI reported on questionnaire and confirmed by video-EEG NPP constituted by 20 (44.4%) patients and Group 2—JME without any reflex epileptic trait, by 25 (55.6%) patients. Three patients out of 20 (15%) included in Group 1 had language-induced orofacial reflex myocloni (ORM) in addition to PI [30]. Activation by other reflex traits, as photosensitivity/eye-closure sensitivity (40/133) or failure to confirm PI in NPP (7/133) were exclusion criteria. Patients who had presented photosensitivity/eye closure sensitivity on routine EEG (18/133) were also excluded as well as those with age less than 16 years (2/133), drugs/alcohol abuse intake and/or noncompliance (6/133), and less than a year of follow-up (15/133).

2.4. Follow-up

Seizure types and precipitant factors, AED therapy and treatment adherence were observed. Patients were oriented to avoid sleep deprivation and alcohol consumption. They received sodium valproate (VPA) as first choice drug, in mono or polytherapy and other AEDs considered reasonably effective in JME treatment, such as topiramate, lamotrigine, phenobarbital and benzodiazepines. Levetiracetam is not commercially available in our country. Doses and AEDs were chosen according to clinical response and adverse effects. Standard seizure calendars monitored seizure frequency. Myoclonia and absences were quantified as seizure days per month at the first clinical interview and currently. GTCS frequency per month was estimated at the first evaluation. GTCS frequency currently was the sum of all seizures occurred over the last year of follow-up. In addition, the total number of GTCS during life was estimated at the last evaluation.

Patients were followed-up for one to 15 years (mean 7.82 years; SD = 3.98).

3. Statistics

Comparisons between Groups 1 and 2 were performed by the nonparametric Mann–Whitney test for quantitative variables, the Fisher's exact test for qualitative variables, and the Student's *t*-test for the averages. The relation between PI reflex trait and the studied variables was estimated by odds ratio (OR). Demographic and clinical variables associated with PI reflex trait were calculated by multivariate logistic regression method. A p-value <0.05 was considered statistically significant.