



Delineating behavioral and cognitive phenotypes in juvenile myoclonic epilepsy: Are we missing the forest for the trees?

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ARTICLE INFO

Article history:

Received 19 June 2015

Revised 15 September 2015

Accepted 22 October 2015

Available online xxxx

Keywords:

Epilepsy

Juvenile myoclonic epilepsy

Executive function

Impulsive behavior

Neuropsychological tests

ABSTRACT

Introduction: Patients with juvenile myoclonic epilepsy (JME) have executive dysfunction and impulsive traits. There are lines of evidence that JME is a heterogeneous epilepsy syndrome considering outcome. In this study, we aimed to analyze this heterogeneity beyond seizure control. The objective was to identify whether the pattern of cognitive dysfunction and impulse control is also heterogeneous, in an attempt to establish possible differences in patients with easy- and hard-to-control epilepsies.

Methods: Essentially, 57 patients with JME were compared with 44 controls. Patients and controls were assessed with a neuropsychological battery for executive, attention, and memory functions. The expression of impulsive traits was evaluated with the Temperament and Character Inventory – novelty seeking domain. Then, patients were categorized according to seizure control as having easy- and hard-to-control JME.

Results: Patients with hard-to-control JME showed worse performance in 12 out of 25 neuropsychological tests than those with easy-to-control JME. Patients with hard-to-control JME also demonstrated significantly higher scores in novelty seeking – subfactor impulsiveness ($p = 0.002$).

Significance: Our study demonstrated the existence of distinct or more severe cognitive and psychiatric profiles in a subset of patients with JME. Patients with treatment-refractory seizures seem to present a broader impairment related to both cognitive deficits and impulsive traits. These findings suggest that patients with JME are not equally compromised by executive and memory deficits or dysfunction, neither by their impulsive traits. Thus, there is a need for a better characterization of patients with JME to include diverse phenotypes since our results suggest a possible existence of distinct groups of patients with JME.

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1. Introduction

Juvenile myoclonic epilepsy (JME) is classified as genetically determined generalized epilepsy (IGE), being the most common form of IGE in adults. This electroclinical syndrome is characterized by myoclonic seizures in all cases and generalized tonic-clonic (GTC) seizures in approximately 90%. The onset occurs during adolescence with a slight female predominance [1–3]. Classical precipitant factors are sleep deprivation, stress, menstruation, fatigue, and alcohol consumption [2,3]. Other triggering factors are complex cognitive functions [4] and praxis induction [5].

Few studies have focused on the long-term prognosis of JME, but nonetheless they have provided discrepant results considering the outcome and its clinical predictors [2,6–9]. Psychiatric disorders have been reported as a predictor of worse outcome [8]. Although JME is defined as a “benign” form of epilepsy, personality disorders, especially related to Cluster B [10,11], and personality traits [12] related to impulse control and difficulty in accomplishing goals have been reported. Besides, neuropsychological studies suggest that these patients have impaired performance in multiple subtests that evaluate cognitive functions, especially those associated with frontal lobe functioning [13–17]. Finally, some epilepsy variables, especially higher seizure frequency and longer duration of epilepsy, seem to be associated with the prevalence of psychiatric disorders [11,18] and impaired cognitive performance [13,15,17].

One fact that emerges from these data is that JME is a heterogeneous epilepsy syndrome. Based on that and on our clinical observation, the authors postulate that a more detailed analysis of patients with JME

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may demonstrate the presence of subgroups of patients with distinctive profiles, not only related to seizure control. Therefore, it would be reasonable to attempt to distinguish these groups by providing an assessment that goes beyond identifying the presence or absence of changes in personality and cognition, to include a measure of the severity of these deficits.

In this study with patients with JME, we aimed to verify the performance on executive/attentional tests and the expression of personality traits related to a worse seizure control. In this context, we aimed to identify whether the pattern of cognitive dysfunction and impulse control reported in patients with JME is also heterogeneous, in an attempt to establish possible differences related to seizure control.

2. Methods

2.1. Characterization of studied population

All patients were followed up in the outpatient clinic of two tertiary centers (University of Sao Paulo and University of Campinas).

Patients' medical histories and EEG studies were the basis for the diagnosis. If necessary, medical history provided by parents, siblings, spouses, and other relatives was considered. The EEG studies at the time of diagnosis and during the course of the disease were performed in all patients using the international 10–20 system of electrode placement.

Inclusion criteria were (1) the diagnosis of classic JME according to the International League Against Epilepsy [19], (2) use of valproate in monotherapy, (3) normal neurologic examination, (4) absence of major psychiatric disorder, (5) age range from 18 to 35 years, and (6) IQ range from 80 to 110. Diagnostic criteria of JME included the history of myoclonic seizures with or without additional GTC and/or absence seizures. Although not necessary for the diagnosis, neuroimaging studies were performed in all patients included in this study.

A neurologist and psychiatrist evaluated patients and controls, thereby excluding persons as controls who had psychiatric disorders, according to DSM-IV, and those with previous or current history of neurological disorders. We excluded patients with (1) a history of brain trauma, (2) previous neurosurgery, (3) less than eight years of formal education, (4) major psychiatric disorders such as psychosis that could compromise neuropsychological evaluation, (5) signs of intoxication, and (6) previous and current epilepsy syndromes other than JME.

Electroclinical subtypes of JME such as patients with childhood absence epilepsy persisting and evolving into JME, JME with adolescent-onset pyknoleptic absence, and JME with astatic seizures were excluded [6]. We also excluded patients using AEDs other than valproate.

We also excluded controls with the following: (1) an estimated IQ below 80 and over 110, (2) clinical signs of drug intoxication or any other condition leading to cognitive impairment, (3) diagnosis of a psychiatric disorder, (4) alcohol or drug abuse, and (5) any brain-related surgical intervention. Controls included were matched by age, years of schooling, gender, and socioeconomic level.

The study was performed in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all participants before inclusion in the study, which was approved by the local ethics committee of the University of Sao Paulo.

2.2. Measures

2.2.1. Neuropsychological assessment

A trained neuropsychologist (S.P.M.) administered the tests in a standard sequence. The tests used for the measurement of executive and attentional functions were published elsewhere [14] and comprised the following: Digit Forward (DF) and Digit Backward (DB), Stroop Color Test (SCT), Trail Making Test (TMT), Wisconsin Card Sorting Test (WCST), and Verbal Fluency (Control Oral Word Association). Memory

was assessed with WMS-IV using the subtests Logical Memory and Visual Reproduction.

2.2.2. Temperament and Character Inventory (TCI)

Impulsivity was assessed using the Temperament and Character Inventory–TCI [20,21]. The TCI is suitable for measuring both normal and abnormal behavioral patterns. It is composed of four factors of the temperament dimension and three factors of the character dimension. We used the factor of temperament novelty seeking to evaluate impulsivity [12].

Depressive symptoms were assessed using the Brazilian version of the Beck Depression Inventory (BDI) [22]. The current level of anxiety was assessed using the Brazilian version of the State-Trait-Anxiety Inventory (STAI) [23]. Depression and anxiety may have had an impact on the performance of these patients on the TCI, and for this reason, they were considered in this analysis.

2.2.3. Correlation with clinical subgroups

Estimation of the frequency of seizures was based on the review of seizure calendars and specific questioning of the patient and family members. We evaluated seizure control according to Prasad et al. [24] as follows: GTC seizures – good (<1 seizure per year), moderate (1–4 seizures per year), or poor (>4 seizures per year); myoclonic seizures – good (<5 single seizures or clusters per month, rare seizures, or occasional seizures), moderate (5–14 single seizures or clusters per month, several seizures, or frequent seizures), or poor (>15 single seizures or clusters per month or daily seizures); and absence seizures – good (<5 seizures per month, rare seizures, or occasional seizures), moderate (5–14 seizures per month, several seizures, or frequent seizures), or poor (>15 seizures per month, frequent seizures, or daily seizures).

Then, patients were classified as having “pharmacoresistant” seizures if they experienced moderate or poor seizure control despite prior or current exposure to a dosage of at least 1000 mg/day of sodium valproate (VPA).

Patients were classified into two groups – Group I: easy-to-control JME, characterized by seizure freedom, or good seizure control for all seizure types in the last five years with lower doses (<1.0 g/day) of VPA ($n = 40$) and Group II: moderate or poor seizure control with higher doses (≥ 1.0 g/day) of VPA ($n = 17$).

2.2.4. Statistical analysis

Descriptive analysis consisted of mean and standard deviations of each variable. Demographic variables of patients and controls were compared by using the Pearson chi-square test for gender and by using the t-test or Wilcoxon–Mann–Whitney test for numerical variables.

We compared the three groups and covaried for BECK, STAI, and QI in all analyses using ANCOVA for all variables and regression of Poisson for errors. Further, 2-way comparisons were corrected by Bonferroni–Holm correction for multiple comparisons. The Bonferroni–Holm correction for multiple comparisons is a sequentially rejective version of the simple Bonferroni correction for multiple comparisons and strongly controls the family-wise error rate at an alpha level. The Bonferroni–Holm correction also decreases the number of type II errors observed when simple Bonferroni is used.

3. Results

Fifty-seven patients composed this group; 30 (52.6%) were female with a mean age of 27.42 years ($SD \pm 8.22$) and 10.2 years ($SD \pm 1.8$) of formal education. Forty-four healthy individuals [24 (54.5%) were female with a mean age of 28.09 years ($SD \pm 8.99$) and 10.75 years ($SD \pm 2.51$) of formal education] composed our control group. Controls were matched by gender ($p = 0.848$), age ($p = 0.698$), and years of education ($p = 0.653$).

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