Epilepsy & Behavior 25 (2012) 682–686

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Juvenile myoclonic epilepsy: The impact of clinical variables and psychiatric disorders on executive profile assessed with a comprehensive neuropsychological battery

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ARTICLE INFO

Article history:
Received 5 August 2012
Revised 1 October 2012
Accepted 4 October 2012
Available online 11 November 2012

Keywords:
Attentional functions
Executive functions
Neuropsychology
Juvenile myoclonic epilepsy

ABSTRACT

Executive dysfunction is reported in juvenile myoclonic epilepsy (JME). However, batteries employed in previous studies included no more than three tests of executive function. In this study, we aimed to assess executive and attentional functions in JME using a comprehensive battery of eight tests (encompassing fifteen subtests). We also evaluated neuropsychological profiles using a clinical criterion of severity and correlated these findings with epilepsy clinical variables and the presence of psychiatric disorders. We prospectively evaluated 42 patients with JME and a matched control group with Digit Span tests (forward and backward), Stroop Color-Word Test, Trail Making Test, Wisconsin Card-Sorting Test, Matching Familiar Figures Test and Word Fluency Test. We estimated IQ with the Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Intelligence Scale. The patients with JME showed specific deficits in working memory, inhibitory control, concept formation, goal maintenance, mental flexibility, and verbal fluency. We observed attentional deficits in processes such as alertness and attention span and those requiring sustained and divided attention. We found that 83.33% of the patients had moderate or severe executive dysfunction. In addition, attentional and executive impairment was correlated with higher frequency of seizures and the presence of psychiatric disorders. Furthermore, executive dysfunction correlated with a longer duration of epilepsy. Our findings indicate the need for comprehensive neuropsychological batteries in patients with JME, in order to provide a more extensive evaluation of attentional and executive functions and to show that some relevant deficits have been overlooked.

1. Introduction

According to the International League Against Epilepsy [1], juvenile myoclonic epilepsy (JME) is an idiopathic form of generalized epilepsy. The long-held belief that idiopathic epilepsies do not present with cognitive deficits has been contradicted by evidence that patients with JME have specific cognitive dysfunctions, mainly in functions related to the frontal lobes [2–9].

Using a working memory paradigm, Swartz et al. [10] showed that patients with JME had impairments very similar to those found in patients with frontal lobe epilepsy (FLE). Devinsky et al. [11] studied cognitive frontal lobe function in 16 patients with JME and 15 patients with FLE. The authors observed a significant difference between the two groups in terms of their performance on tests requiring psychomotor speed, planning, verbal fluency, abstract reasoning, and concept formation; the patients with JME performing more poorly. Sonmez et al. [12] and Pascalicchio et al. [13] reported similar results, suggesting that there is specific impairment of executive function processes in JME. In addition, Piazzini et al. [14] investigated frontal cognitive dysfunction in patients with JME, comparing them with patients with FLE, patients with temporal lobe epilepsy (TLE), and control subjects. Those authors found that patients with JME had cognitive impairment, as evidenced by their performance on the Word Fluency Test and Wisconsin Card-Sorting Test (WCST), which was similar to that of the patients with FLE.

To date, all of the evidence of executive dysfunction in patients with JME has been based on the results of studies using test batteries that included no more than three tests. However, executive and attentional functions encompass various functions associated with frontal lobe functioning, such as mental fluency, mental flexibility, working memory, planning, concept formation, inhibitory control, and the attentional processes themselves. Therefore, executive and attentional functions cannot be adequately measured with a limited battery of tests. When interpreting the findings of frontal lobe dysfunction in patients with JME, one must bear in mind the importance of all aspects of executive and attentional functions, the evaluation of which requires the use of a more extensive neuropsychological

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1525-5050
http://dx.doi.org/10.1016/j.yebeh.2012.10.002

battery. In this study, we aimed to assess executive and attentional dysfunction in patients with JME using a comprehensive battery of eight tests (encompassing fifteen subtests) evaluating attention span, working memory, sustained and divided attention, mental fluency and flexibility, concept formation, maintenance of goals, inhibitory control and verbal fluency. In addition, we attempted to identify neuropsychological profiles using a clinical criterion of severity and correlate these findings with epilepsy clinical variables and the presence of psychiatric disorders. To our knowledge, it is the first study of its kind.

2. Methods

2.1. Study population

2.1.1. Patients

We prospectively evaluated 42 consecutive adolescent and adult patients with an unequivocal diagnosis of JME, according to the International League Against Epilepsy [1] proposal for syndrome classification, followed in the Ambulatory Clinic of Epilepsy in the Hospital das Clinicas of the University of São Paulo, Brazil, from 2007 to 2009.

Twenty patients (47.6%) were male with mean age of 26.57 (SD: 8.38; ranging from 16 to 48 years), 10.10 (SD: 1.83) years of education and estimated IQ of 91.5 (SD: 9.94).

2.1.2. Controls

A control group of 42 healthy volunteers was matched to the patients as to gender ($p = 0.827$), age ($p = 0.959$), years of education ($p = 0.653$) and socioeconomic status. The controls were evaluated by a psychiatrist and a neurologists to rule out psychiatric and neurological disorders.

The exclusion criteria for patients and controls included the following: at least 16 years of age, an estimated IQ below 80, clinical signs of drug intoxication or any other condition leading to cognitive impairment, diagnosis of a psychiatric disorder, alcohol or drug abuse, and any brain-related surgical intervention.

2.2. Measures

2.2.1. Neuropsychological evaluation

Patients with JME and control subjects were evaluated with a comprehensive battery of neuropsychological tests, all of which were administered, in a standard sequence, by a trained neuropsychologist. All patients should have had at least 48 h of seizure-free status before neuropsychological evaluation.

Our battery of neuropsychological tests comprised tests evaluating executive and attentional functions in their broadest aspects. The tests were selected from among those included in collections of neuropsychological tests [15,16], from studies of generalized epilepsies and JME [17] and from studies correlating neuropsychological test results with frontal lobe functions [18].

The following tests were used for the measurement of executive and attentional functions:

- the Digit Span Forward and Digit Span Backward tests [19] which evaluate attention span, working memory, and mental control with auditory–verbal stimuli;
- the Stroop Color-Word Test [20] which evaluates the ability to inhibit responses to visual–verbal stimuli;
- the Trail Making Test [16] which evaluates self-monitoring, visuospatial orientation for simple and alternating sequences, sustained attention, and divided attention;
- the WCST [21] which evaluates concept building, mental flexibility, and goal maintenance;
- the Matching Familiar Figures Test [22] which evaluates the ability to inhibit responses to visual stimuli; and
- the Word Fluency Test [16] which evaluates verbal fluency.

The IQ of each subject was estimated with the Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Intelligence Scale [19]. All participating patients gave their written informed consent to participate in this study, which was approved by the Research Ethics Committee of the *Hospital das Clínicas*.

2.2.2. Clinical criteria of severity

We established clinical criteria for the evaluation of the degree of executive dysfunction in patients with JME which were based on the model used by Rzezak et al. [23]. Accordingly, patients whose gross score on a given test was at least one standard deviation below the mean result for at least two paradigms of the same test in control subjects were categorized as having executive dysfunction in relation to the function(s) evaluated by that test. Executive dysfunction was classified as mild if identified in the results of two tests, moderate if identified in those of three or four tests, and severe if identified in those of five or more tests.

2.2.3. Clinical variables

For the patients with JME, we evaluated the age of onset, duration of epilepsy, frequency of myoclonic seizures, frequency of generalized tonic-clonic (GTC) seizures, frequency of absence seizures, VPA doses and family history of epilepsy. Interictal and ictal eletroencephalographic findings were also evaluated.

We also assessed family history of psychiatric disorders and personal history of psychiatric disorders. The patients were interviewed and followed by a clinical psychiatrist and diagnosed according to the criteria of DSM-IV.

2.3. Statistical analysis

The descriptive statistics included means and standard deviations calculated for each variable. Demographic variables (sex, age, and level of education) were compared using the chi-square test in order to verify that the two groups were matched. The differences between the two groups in terms of the estimated IQ were analyzed using independent *t*-tests for continuous variables. We compared performance on the neuropsychological tests using analysis of covariance in which the estimated IQ was the covariate. The level of significance was set at $p \leq 0.05$.

The correlation between the clinical variables and the scores of patients with JME on the Beck Depression Inventory, State-Trait Anxiety Inventory, and neuropsychological tests was compared using Pearson's and Spearman's correlation coefficients. The level of significance was set at $p \leq 0.05$. For the statistical analysis, we used the Statistical Package for the Social Sciences, version 11.0.

3. Results

3.1. Neuropsychological findings

There was a significant difference between the two groups in terms of the estimated IQ ($p = 0.042$). Therefore, as previously mentioned, we used analysis of covariance with the estimated IQ as a covariate.

As can be seen in Table 1, the patients with JME performed more poorly than did the control subjects on the following: Digit Span Forward ($p = 0.001$); Digit Span Backward ($p = 0.001$); time to completion of Stroop Color-Word Test 1 ($p = 0.001$), Stroop Color-Word Test 2 ($p = 0.001$), and Stroop Color-Word Test 3 ($p = 0.001$); number of errors on Stroop Color-Word Test 3 ($p = 0.030$); time to completion on the Trail Making Test, part A ($p = 0.001$) and part B ($p = 0.001$); number of errors on the Trail Making Test, part B ($p = 0.006$);

Table 1
Analysis of covariance, with estimated IQ as the covariate, comparing patients with juvenile myoclonic epilepsy and control subjects on neuropsychological tests.

Test	JME (n = 42)	Controls (n = 42)	p (ANCOVA)
DSF	5.09 ± 1.73	7.02 ± 1.90	0.001
DSB	3.61 ± 1.56	5.35 ± 1.84	0.001
SCWT-1 time	21.78 ± 5.71	14.21 ± 2.78	0.001
SCWT-1 errors	0.03 ± 0.15	0.02 ± 0.11	0.993
SCWT-2 time	26.61 ± 8.0	17.68 ± 4.22	0.001
SCWT-2 errors	0.16 ± 0.0	0.43 ± 0.00	0.030
SCWT-3 time	36.73 ± 10.72	23.80 ± 5.71	0.001
SCWT-3 errors	1.90 ± 0.23	1.87 ± 0.57	0.001
TMT-A time	39.59 ± 10.96	29.21 ± 9.75	0.001
TMT-A errors	0.09 ± 0.29	0.04 ± 0.21	0.541
TMT-B time	73.71 ± 27.32	57.76 ± 24.75	0.006
TMT-B errors	0.80 ± 1.04	0.14 ± 0.41	0.001
WFT(letter F)	9.19 ± 2.22	13.97 ± 3.97	0.001
WFT(letter A)	8.52 ± 2.22	12.35 ± 3.53	0.001
WFT(letter S)	7.97 ± 2.53	12.33 ± 3.72	0.001
WFT total	25.69 ± 5.00	38.66 ± 9.72	0.001
WCST (categories)	2.30 ± 1.17	3.76 ± 1.16	0.001
WCST (TM)	21.02 ± 9.75	8.11 ± 4.24	0.001
WCST (PE)	11.28 ± 5.37	6.07 ± 3.67	0.001
WCST (PR)	13.48 ± 6.82	9.76 ± 4.63	0.009
WCST (SL)	1.43 ± 0.97	0.33 ± 0.61	0.001
MFFT errors	9.64 ± 3.71	6.78 ± 4.08	0.002
MFFT time	372.28 ± 89.34	343.92 ± 105.57	0.165

JME, juvenile myoclonic epilepsy; ANCOVA, analysis of covariance; DF, Digit Span Forward; DB, Digit Span Backward; SCWT, Stroop Color-Word Test; time, time to completion; TMT, Trail Making Test; WFT, Word Fluency Test; WCST, Wisconsin Card-Sorting Test; TM, total number of mistakes; PE, total number of incorrect perseverative responses; PR, total number of correct perseverative responses; SL, set loss; MFFT, Matching Familiar Figures Test.

the Word Fluency Test, specifically for the letters F ($p = 0.001$), A ($p = 0.001$), and S ($p = 0.001$), as well as in terms of the total score ($p = 0.001$); the WCST, in terms of the total number of correct answers ($p = 0.002$), total number of categories completed ($p = 0.002$), total number of mistakes ($p = 0.002$), total number of incorrect perseverative responses ($p = 0.011$), total number of correct perseverative responses ($p = 0.004$), and set loss ($p = 0.001$); and the Matching Familiar Figures Test, in terms of the number of errors ($p = 0.001$) and time to completion ($p = 0.001$). There were no significant differences between the two groups in terms of the number of mistakes on Stroop Color-Word Test 2 ($p = 0.384$) and the number of mistakes on Trail Making Test, part A ($p = 0.981$).

3.2. Severity of attentional and executive dysfunction

In our evaluation of attentional and executive dysfunction in patients with JME, by comparing the outcome of tests of patients with mean scores of the control subjects, we found that two patients (4.76%) showed no dysfunction, five (11.9%) met the clinical criteria for mild dysfunction, eight (19.04%) met the clinical criteria for moderate dysfunction, and 27 (64.28%) met the clinical criteria for severe dysfunction. Therefore, 95.23% of the patients presented attentional/executive dysfunction, which was moderate or severe in 83.3% (35 of the 42 patients).

We also performed an individualized analysis, evaluating in which tests patients with JME performed most poorly. The worst performances were in the time to complete Stroop Color-Word Test 3 in 36 patients (85.71%); in the time to complete Stroop Color-Word Test 1 in 35 (83.33%); in the time to complete Stroop Color-Word Test 2 in 33 (78.57%); on the Digit Span Backward test in 27 (64.28%); on the Digit Span Forward test in 24 (57.14%); and on the Trail Making Test, part B, in terms of the number of correct responses in 21 patients (50.00%) and in the time to completion in 20 (47.61%).

3.3. Correlation with clinical variables

Nineteen patients (45.23%) were seizure-free and 15 (35.71%) had myoclonic seizures. Eight (19.04%) patients had sporadic GTC seizures. Mean age of onset was 14 years (SD: 4.35). The epilepsy duration considering epilepsy onset and treatment was 17.82 years. All patients received sodium valprotate/divalproate. The mean dose was 1.21 g (SD: ± 0.67 g).

As to routine EEGs, performed in the same period of the neuropsychological evaluation, no patients had electrographic or electroclinical seizures; 35% had interictal epileptiform activity and 65% had a normal EEG.

There was a significant correlation between longer duration of epilepsy and a longer time to complete Stroop Color-Word Test 1 ($p = 0.005$), Stroop Color-Word Test 2 ($p = 0.007$) and Stroop Color-Word Test 3 ($p = 0.039$). We also found that a higher frequency of myoclonic seizures was correlated with a longer time to complete Trail Making Test, part A ($p = 0.047$). In addition, a higher frequency of GTC seizures was correlated with a poorer performance on the Digit Span Forward test ($p = 0.048$), the Digit Span Backward test ($p = 0.032$), and Trail Making Test, part A ($p = 0.045$), as well as with a longer time to complete Trail Making Test, part B ($p = 0.048$). Higher doses of VPA were associated with a longer time to complete Trail Making Test, part A ($p = 0.046$) and part B ($p = 0.021$); with worse performance on the Word Fluency Test — total score ($p = 0.047$); the WCST, in terms of the total number of correct answers ($p = 0.047$), total number of categories completed ($p = 0.006$), total number of mistakes ($p = 0.001$) and set loss ($p = 0.037$).

History of psychiatric disorders was correlated with a longer time to complete Trail Making Test, part A ($p = 0.001$), as well as with poorer performance on Word Fluency Test ($p = 0.046$) (Table 2).

Presence of interictal EEG findings was not associated with worse performance on any of the neuropsychological tests.

4. Discussion

The 42 patients with JME evaluated in the present study performed more poorly on tests of executive and attentional functions than did the control subjects, even when IQ was included as a covariate.

Our results, obtained with an extensive battery of tests, not only corroborate those of previous studies identifying executive dysfunction in patients with JME [10–14] but also describe which aspects of executive functions, and especially of attentional functions, are affected. In the present study, we demonstrated that patients with JME perform poorly on tests of executive functions, showing specific deficits in working memory, inhibitory control, concept building, goal maintenance, mental flexibility, and verbal fluency. We also observed attentional deficits ranging from the most basic, such as alertness and attention span, to the most complex, such as those requiring sustained and divided attention.

Although executive and attentional dysfunction was present in most of the patients evaluated in the present study, there were different levels of impairment. The severity of executive and attentional dysfunction had not previously been measured in patients with JME. Therefore, as previously mentioned, we employed the clinical criteria proposed by Rzezak et al. [23] and determined that 83.3% of the patients presented either moderate or severe executive and attentional dysfunction.

It should be borne in mind that there are quantitative differences among patients with JME in terms of cognitive impairment. Although most patients have executive dysfunction, it can manifest differently and to varying degrees from patient to patient. Therefore, the impact of such dysfunction varies.

We observed that distinct clinical variables had a significant impact on executive and attentional dysfunction. Longer duration of

Table 2
Pearson's correlation of clinical variables, and performance of patients with JME on neuropsychological tests.

	Age of onset	Duration of epilepsy	Frequency of myoclonic seizures	Frequency of GTC seizures	Psychiatric disorders	FH of epilepsy	FH of psychiatric disorders
DSF	0.238[a]	0.743[a]	0.452[a]	**0.048**[a]	0.514[a]	0.673[a]	0.332[a]
DSB	0.198[a]	0.916[a]	0.204[a]	**0.032**[a]	0.466[a]	0.762[a]	0.740[a]
SCWT-1 time	0.189[a]	**0.005**[a]	0.266[a]	0.117[a]	0.151[a]	0.951[a]	0.840[a]
SCWT-1 errors	0.285[a]	0.192[a]	0.327[a]	0.325[a]	0.331[a]	0.326[a]	0.324[a]
SCWT-2 time	0.080[a]	**0.007**[a]	0.208[a]	0.435[a]	0.089[a]	0.692[a]	0.988[a]
SCWT-2 errors	0.993[a]	0.944[a]	0.358[a]	0.368[a]	0.578[a]	0.619[a]	0.641[a]
SCWT-3 time	0.161[a]	**0.039**[a]	0.351[a]	0.918[a]	0.274[a]	0.938[a]	0.950[a]
SCWT-3 errors	0.301[a]	0.029[a]	0.148[a]	0.894[a]	0.766[a]	0.697[a]	0.308[a]
TMT-A time	0.531[a]	0.196[a]	**0.047**[a]	**0.045**[a]	**0.001**[a]	0.147[a]	0.435[a]
TMT-A errors	0.538[a]	0.762[a]	0.535[a]	0.790[a]	0.847[a]	0.154[a]	0.715[a]
TMT-B time	0.318[a]	0.270[a]	0.608[a]	**0.048**[a]	0.045[a]	0.946[a]	0.661[a]
TMT-B errors	0.535[a]	0.407[a]	0.051[a]	0.463[a]	0.181[a]	0.851[a]	0.439[a]
WFT total	0.732[a]	0.203[a]	0.076[a]	0.107[a]	**0.046**[a]	0.868[a]	0.109[a]
WCST(categories)	0.286[a]	0.265[a]	0.412[a]	0.670[a]	0.322[a]	0.919[a]	0.532[a]
WCST (TM)	0.535[a]	0.386[a]	0.097[a]	0.286[a]	0.058[a]	0.706[a]	0.493[a]
WCST (PE)	0.918[a]	0.944[a]	0.640[a]	0.734[a]	0.630[a]	0.721[a]	0.422[a]
WCST (PR)	0.811[a]	0.764[a]	0.463[a]	0.733[a]	0.591[a]	0.733[a]	0.312[a]
WCST (SL)	0.365[a]	0.343[a]	0.167[a]	0.586[a]	0.529[a]	0.782[a]	0483[a]
MFFT errors	0.264[a]	0.603[a]	0.163[a]	0.454[a]	0.202[a]	0.936[a]	0.957[a]
MFFT time	0.424[a]	0.082[a]	0.203[a]	0.393[a]	0.256[a]	0.975[a]	0.335[a]

DF, Digit Span Forward; DB, Digit Span Backward; FH, Family History; MFFT, Matching Familiar Figures Test; PE, total number of incorrect perseverative responses; PR, total number of correct perseverative responses; SL, set loss; SCWT, Stroop Color-Word Test; time, time to completion; TM, total number of mistakes; TMT, Trail Making Test; WFT, Word Fluency Test; WCST, Wisconsin Card-Sorting Test.
[a] Pearson's correlation (p).

epilepsy without proper treatment, higher frequency of myoclonic or GTC seizures and the presence of psychiatric disorders were relevant clinical variables. Our findings partially corroborate those of previous studies in which the duration of epilepsy was identified as an important factor for cognitive function in JME [6]. However, unlike other authors, we did not find the cognitive performance of patients with JME to correlate with a family history of epilepsy [13], an earlier age of onset, or absence seizures [13,14]. We also found that attentional processes, such as attention span, sustained attention, and divided attention, more often correlated with clinical variables than did executive function. Mental flexibility, concept formation, and planning were unaffected by clinical variables.

The association between AED dose and poorer performance must be seen with caution. Some AEDs are known for their impact on cognitive function, such as topiramate [24] and phenobarbital [25]. However, the relevance of VPA for cognitive functions is controversial [26]. It is important to remember that patients using higher doses of VPA were those with higher seizure frequency. Therefore, there is an overlap between the drug itself and more severe epilepsy. In this series, patients in need of higher doses of VPA had worse performance on and required a longer time to complete the Trail Making Test, part A and part B, with worse performance on the Word Fluency Test; and with worse performance on the WCST, in terms of the total number of correct answers and total number of categories completed.

Subclinical epileptiform discharges may affect the neuropsychological performance as demonstrated by Sieblink et al. [27]. In our study, there was no correlation between EEG findings and neuropsychological tests. Although, our neuropsychological evaluation was done without concomitant video-EEG, we must take into account that for this study, the patients had gone at least 48 h without seizures, including myoclonic seizures. In addition, all the patients were under treatment with AEDs, in this case VPA, and most had normal EEGs without interictal epileptiform activity at the moment of the evaluation. None of them had ictal epileptiform discharges.

Although the comprehensive battery indicated executive and attentional impairment, some domains were more affected than others, when the number of patients with worse performance in each group was analyzed. Most patients in this study exhibited worst performance on the WCST (mental flexibility), TMT (sustained and alternate attention), Stroop Color-Word Test (inhibitory control) and Digit Span (working memory). Most testing sessions are currently time limited, and a determination of the relative efficacy of the tests may be helpful in establishing a set of tests for clinical practice.

In the majority of the patients with JME, we observed that the paradigms used to evaluate attentional functioning, from the simple (attention span) to the complex (sustained and divided attention), are those in which the patients with JME perform most poorly.

Attentional processes play a pivotal role in executive functioning and must be considered as an integral part of this functional system. Our findings indicate the need for comprehensive neuropsychological batteries in order to provide a more extensive evaluation of attentional and executive functions in patients with JME, as well as showing that certain relevant deficits have been neglected.

Funding statement

Dr. Valente was supported by CNPq 307262/2011-1 and FAPESP 05/56464-9. Dr. Sylvie Moschetta was supported by 07/52110-3.

Contributorship statement

Dr. Moschetta has given substantial contributions to the acquisition, analysis and interpretation of the data and to the drafting of the article.

Dr. Valente has participated in the conception and design of the article, revision of the article critically for important intellectual content and final approval of the version to be published.

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