

ARE THERE ANY CLINICAL AND EEG FEATURES ASSOCIATED WITH THE OCCURRENCE OF EXECUTIVE DYSFUNCTIONS IN PATIENTS WITH JME?

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Abstract: The aim of the study was to determine the possible relationship between different clinical and EEG features and executive functions in patients with juvenile myoclonic epilepsy (JME), i.e. to determine if sex, age, duration, absences, clinical asymmetric seizures, asymmetry or focality in epileptiform activity in EEG, EEG slow activity and familiar occurrences are associated with frontal dysfunction in JME patients. 28 patients (17 females, 11 males), mean age – 22 y. were enrolled in the study. Executive functions were evaluated with the Wisconsin Card Sorting Test (WCST). Crosstabulation of certain characteristics have been used.

The mean age at the beginning of epilepsy for the whole group was 13.5y. and duration 8.5 y. All patients had myoclonic jerks, 28.6% of patients described unilateral predominance. Absences were registered in 42.9% patients. Bilateral spike or polyspikes/wave complexes were registered in 89.2% of patients, asymmetry of generalized discharges or focality in at least one EEG in 53.6% of patients, with anterior slow activity in 25% of them. Familiar occurrence was found in 42.9%. Of 28 patients, 14 had normal findings on WCST, while the other half of the patients did very poorly, achieving only 1–3 categories. Statistical analysis showed that only the female sex had p-value of 0.05, while other clinical and EEG features were not significantly associated with the occurrence of frontal impairment.

Aside from female sex, no other clinical or EEG parameters were associated with the occurrence of executive dysfunction. But considering the relatively small sample

size, our study may have been underpowered to detect subtle association and in our opinion, the current results must be replicated with a larger group of subjects to confirm the findings.

Key words: juvenile myoclonic epilepsy, executive functions, EEG.

Introduction

Juvenile myoclonic epilepsy (JME) is an idiopathic generalized epileptic syndrome (IGE) characterized by myoclonic jerks and generalized tonic-clonic seizures and generalized 4–6 Hz spike and polyspike discharges on electroencephalography (EEG) [1]. Although by definition IGE is not associated with structural lesions on routine neuroimaging and neurological exam is normal, there is rising neurophysiological, neuropsychological and anatomical evidence of frontal lobe dysfunctions in patients with JME. A number of structural neuroimaging studies showed: great volumetric and density abnormalities in anterior and medial nuclei of the thalami [2, 3, 4], an increase in mesial frontal grey matter thickness [5], and reduced prefrontal concentrations of N-acetyl aspartate suggestive of a prefrontal neuronal lesion [6, 7].

EEG studies found focal abnormalities in 30.3% [8] and in 36.7% of EEGs in patients with JME [9]. Dipole modeling and brain-distributed source analysis showed pre-frontal medial current sources corresponding to spikes and diffuse sources in cortical regions corresponding to wave components of PSWC in patients with JME [10].

Neuropsychological investigations provided evidence of executive dysfunction in JME. Executive functions encompass skills necessary for purposeful, goal-directed activity that enable an individual to synthesize information, plan an appropriate strategy, and execute that strategy. Specifically, impairments in concept formation, abstract reasoning, mental flexibility, cognitive speed and planning have been reported in patients with JME [11, 12, 13, 14, 15]. Converging evidence from neuroimaging and neuropsychological studies provide a strong basis to hypothesize that frontal lobe and thalamic dysfunction underlie executive impairments in JME [11, 16]. Specific frontothalamic brain volume abnormality has important cognitive implications in recent-onset JME [17], although there are some studies that could not detect an fMRI correlate of previously reported differences in working memory in JME [18].

Although there is substantial neuropsychological evidence of frontal brain dysfunction, the proportion of JME patients affected is also important (a few patients affected to a large degree or many patients affected to a moderate degree) [19]. Indeed, in our recent study the mean number of categories in the Wisconsin Card Sorting Test (WCST) was insignificantly lower than normative

and the mean number of perseverative responses exceeded the upper normal limit, but the proportion of patients that showed frontal involvement was about half. As a matter of fact there were two distinct groups of patients: the first one which performed excellently (achieving 5–6 categories on WCST) and the second which, on the contrary, performed very poorly, achieving only 1–3 categories [20].

Considering all the previous investigations and results, in order to provide more detailed information, we aimed to analyse some possible factors that may be associated with frontal dysfunction in patients with JME. In fact, no study has been carried out thus far that has compared the clinical and EEG features of two distinct groups of JME patients: with and without frontal dysfunction (FD). The aim of the current study was to determine the possible relationship between different clinical findings and executive function in patients with JME, i.e. to determine if sex, age, duration, absences, clinical asymmetric seizures and familiar occurrence are associated with frontal dysfunction in JME patients. Also, we investigated the possible relationship between the occurrence of frontal cognitive dysfunctions and findings of asymmetry in amplitude of generalized discharges, focal (frontal) beginning of generalized discharges and anterior slow activity (which are found in some percentage of EEGs of patients with JME).

Methods

Patients

Study participants were recruited from the Neurology Clinic in Skopje (from January 2008 to September 2009). 28 patients (17 females, 11 males), predominantly aged between 14 and 24, were enrolled in the study according to the following criteria: diagnosis of JME according to the International League Against Epilepsy (ILAE) classification scheme (1) and education level equal to or higher than elementary school. More specifically, the diagnosis of JME was determined by history, clinical features, EEG data and MRI. We excluded patients with a psychiatric background. Also we did not include those receiving medication other than antiepileptic drugs (AEDs), in order to avoid activating or depressing effects of some drugs on vigilance, attention and cognition or EEG and to evaluate cognitive functions per se.

Considering the contribution of medication to cognitive functioning and the activating effects of AEDs, all JME subjects in this study were on monotherapy (mostly valproate, exceptionally lamotrigine). Valproate (the primary AED in the JME group) has been shown to have the fewest cognitive side-effects compared to other conventional AEDs [21]. In one study it was shown that LTG improves cognitive activation on simple reaction-time measurements, i.e. has an activating effect demonstrated by the cognitive tests [22], but only 2 patients in our study received LTG, a number too small to make a correlation.

The following neurophysiological examinations were carried out: standard awake EEG, with activation procedures: hyperventilation and photostimulation, as well as awake and sleep EEG after partial sleep deprivation in patients in whom routine EEG did not show specific abnormalities. EEG recordings were made in the neurophysiological laboratory at the Neurology Clinic, using a Medelec digital EEG recorder. 16 electrodes were used, placed according to the 10–20 international system. The type and distribution of epileptiform as well as other abnormal activities were evaluated.

Neuropsychological evaluation

One of the most current tests for assessment of frontal executive functions (quantitative measurement of mental flexibility, formation of concepts and perseverance) – the Wisconsin Card Sorting Test (WCST) – was administered to patients with JME. Patients were requested to sort at maximum two sets of 64 cards according to colour, shape, and number. The number of trials achieved out of six was documented, along with the number of perseverative responses.

The upper normal limit for perseverative responses was 19, categories 5 or more were considered normal.

Statistical analyses

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 15.0. The following tests were used: percent of structure for sex, absence, EEG changes, coefficient of the structure and other tests for analysis of attributive characteristics, and for numerical data, such as age and duration, mean and standard deviation, as well as median and modus. Cross-tabulation of certain characteristics was used in order to test the hypothesis of association between certain risk factors and the occurrence of frontal cognitive dysfunction. Fisher's and Pearson's tests were used and the statistical significance was set at < 0.05

Results

There were 17 females and 11 males in our patient group, whose mean age was 22 (SD 6, 5). The mean age of the onset of epilepsy was 13.5 (SD 3, 6), and duration 8.5. All patients had myoclonic jerks on awakening, dominantly bilateral and 28.6% of the patients described unilateral predominance. Generalized tonic-clonic seizures also occurred in all of them. Absences were registered in 42.9% of patients. Bilateral spike/wave or polyspikes/wave complexes were registered in 89.2% of patients, amplitude asymmetry or focal (frontal) beginning of generalized discharges were registered in at least one EEG in 53.6% of

patients, with anterior slow activity in 25% of them. There was familiar occurrence in 42.9 %. Of 28 patients, 14 had normal findings on WCST (excellent achieving 5 or 6 categories on WCST and less than 19 perseverative responses) while the other half of the patients did very poorly, achieving only 1–3 categories and more than 19 perseverative responses.

The results of cross-tabulation of several clinical and EEG characteristics and achievement on WCST are shown in the following tables.

Table 1 – Табела 1

Association between sex and frontal cognitive dysfunctions
Асоцираності йоме́у по́лої на па́цієнтів
и фронтальний ко́гнітивни дисфункції

	With FCD*	Without FCD	Total	p-value
Sex				0.05
Males	3	8	11	
Females	11	6	17	
Total	14	14	28	

* Frontal cognitive dysfunctions assessed by WCST

* фронтальні когнітивні дисфункції оцінені за ВТСК

Table 2 – Табела 2

Association between age of the patients and frontal cognitive dysfunctions
Асоцираності йоме́у воста́н на па́цієнтів
и фронтальний ко́гнітивни дисфункції

	With FCD	Without FCD	p-value
Age (y.)			0.3
Mean	21.9	22	
SD	6.5	6.7	

Table 3 – Табела 3

Association between duration of epilepsy and frontal cognitive dysfunctions
Асоцираності йоме́у воста́н на па́цієнтів
и фронтальний ко́гнітивни дисфункції

	With FCD	Without FCD	p-value
Duration of epilepsy (y.)			0.3
Mean	9.18	7.18	
SD	5.67	4.96	

Table 4 – Табела 4

Association between clinical asymmetry in seizures and frontal cognitive dysfunctions
Асоцираносќи помеѓу клиничката асиметрија на нападите
и фронталните когнитивни дисфункции

Asymmetry clinical	With FCD	Without FCD	Total	p-value
Yes	2	6	8	0.1
No	12	6	20	
Total	14	14	28	

Table 5 – Табела 5

Association between occurrence of absences and frontal cognitive dysfunctions
Асоцираносќи помеѓу постојењето на абсанси
и фронталните когнитивни дисфункции

Absences	With FCD	Without FCD	Total	p-value
Yes	8	4	12	0.25
No	6	10	16	
Total	14	14	28	

Table 6 – Табела 6

Association between familiar occurrence and frontal cognitive dysfunctions
Асоцираносќи помеѓу фамилијарното јавување
и фронталните когнитивни дисфункции

Familiar occurrence	With FCD	Without FCD	Total	p-value
Yes	6	6	12	1.0
No	8	8	16	
Total	14	14	28	

Table 7 – Табела 7

Association between occurrence of asymmetry of amplitude or focal (frontal) beginning of generalized epileptiform discharges in EEG and frontal cognitive dysfunctions
Асоцираносќи помеѓу постојење на асиметрија во амплитудата
или фокален почеток на епилептиформна активност
на ЕЕГ и фронталните когнитивни дисфункции

EEG epileptiform asymmetry	With FCD	Without FCD	Total	p-value
Yes	9	6	15	0.25
No	5	8	13	
Total	14	14	28	

Table 8 – Табела 8

Association between occurrence of anterior slow activity
in EEG and frontal cognitive dysfunctions*
*Асоцираносћ помеђу постојење на антиериорна бавна активносћ
на ЕЕГ и фронталније когнитивни дисфункции*

EEG slow activity	With FCD	Without FCD	Total	p-value
Males	4	3	7	1.0
Females	10	11	21	
Total	14	14	28	

* although not expected by the definition, the finding of an increased amount of anterior slow activity in EEG is not unusual in patients with JME [23]. It also occurred in a number of our patients.

Results showed that only the female sex had a p-value of 0.05 for association with FCD, while all other clinical (age, duration of epilepsy, asymmetry in seizures, presence of absences, familiar occurrence) and EEG (asymmetry or focality of epileptiform discharges, occurrence of slow activity) factors were not significantly associated with the occurrence of frontal impairment on WCST.

Discussion

Our results also show that executive dysfunction occurred in half of our patients (out of 28 patients, 14 had normal findings on WCST, while the others did very poorly, achieving only 1–3 categories and more than 19 perseverative responses). Apart from more frequent occurrence in females, no other of the variables influenced cognitive impairment. The explanation of female predominance in the group with executive dysfunction may probably be due to the relatively small number of patients investigated. No difference was found in mean age between the two groups, nor did duration of epilepsy seem to influence the occurrence of executive dysfunction. This is in accordance with findings of Pulsiher *et al.* [17], whose results also show that executive dysfunction, as measured by both cognitive and behavioural measures, is seen early in the course of JME. Their findings also suggest that thalamic and frontal lobe abnormalities are not primarily the result of factors associated with chronic duration of seizures.

JME is known to have a strong genetic inheritance, with a family history in our group in 42.9% of cases and in another study as many as 50% of cases [24]. According to Pulsiher *et al.* [17] the possibility that genetic vulnerability may underlie, at least in part, the observed abnormalities in the thalamus and frontal lobes or their related functioning and may be present at the time of, or even prior to, the first recognized seizure cannot be excluded. Although our study did not reveal any association between familiar occurrence and frontal lobe dysfunctions, it will be interesting to see the results of the further examina-

tion of the presence of mutations in certain genes (Myoclonin1/EFHC1) and the occurrence of executive dysfunctions.

Thalamocortical circuitry is known to be a primary pathologic factor in multiple IGE syndromes [25], although the extent to which this circuit is involved or structurally affected may depend upon syndrome and seizure types. The effect of various combinations of seizure types is unknown. This may be an important factor, as myoclonic, absence, and GTCS types are frequently seen in JME [26, 27, 28]. In our group the presence of absence seizures did not influence significantly the executive functions.

The percentage of asymmetry in amplitude of generalized discharges, focal (frontal) beginning of generalized discharges and anterior slow activity in our study did not differ significantly from the literature [29]. As a matter of fact there is a recent study that suggests that epileptiform discharges in patients with JME are not "generalized" in the sense of bilaterally synchronous diffuse onset but rather, discharges have both localized onsets and a restricted cortical network during propagation that includes regions of the frontal and temporal cortex [30].

No association was found between focality in EEG and executive dysfunctions.

Finally, considering the contribution of medication to cognitive functioning, all JME subjects in this study were on monotherapy (mostly valproate, exceptionally lamotrigine). Valproate (the primary AED in the JME group) has been shown to have the fewest cognitive side-effects compared to other conventional AEDs (e.g. phenytoin, carbamazepine), with one study indicating improved memory in children on valproate compared to the other AEDs [22]. Therefore, the literature suggests that the medications used in this study do not adversely affect cognitive functioning

A number of limitations of this study should be noted. Our sample sizes in this study were relatively small; as a result, our study may have been underpowered to detect subtle association between certain clinical and EEG features and frontal cognitive impairment in JME patients. Also, event-related potentials may be used as neurophysiological measure of cognitive functions [31]. In our opinion, the current results must be replicated with a larger group of JME subjects to confirm the findings.

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Резиме

ПОСТОЈАТ ЛИ КЛИНИЧКИ И ЕЕГ КАРАКТЕРИСТИКИ ПОВРЗАНИ СО ПОЈАВА НА ЕГЗЕКУТИВНИ ДИСФУНКЦИИ КАЈ ПАЦИЕНТИ СО ЈМЕ?

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Целта на студијата беше да се детерминира можната врска помеѓу различни клинички и електроенцефалографски (ЕЕГ) наоди и егzekутивни-

те функции кај пациенти со јувенилна миоклонусна епилепсија (ЈМЕ), т.е. да се одреди дали полот, возраста, времетраењето на болеста, присуството на абсансни напади, клинички асиметрични напади, асиметрија во епилептиформната ЕЕГ активност, бавна активност на ЕЕГ и фамилијарно јавување се поврзани со фронтална дисфункција кај пациенти со ЈМЕ. Во студијата беа вклучени 28 пациенти (17 од женски, 11 од машки пол), на средна возраст од 22 г. Егзекутивните функции беа евалуирани со Висконсин тест на сортирање на карти (ВТСК). Средна возраст на започнување на болеста за целата група беше 13,5 години и траење на болеста 8,5 години. Кај сите пациенти беа регистрирани миоклонии, доминантно билатерални, кај 28,6% со унилатерална доминантност. Абсансни напади се регистрираа кај 42,9% од пациентите. Билатерални шилец или полишилец/бран комплекси беа регистрирани во ЕЕГ кај 89,2% од пациентите, додека асиметрија на генерализираните избивања или фокална активност во најмалку еден од ЕЕГ беше регистрирана кај 53,6% од пациентите, а бавна активност кај 25% од нив. Од 28 пациенти, кај 14 наодите на ВТСК беа во граници на нормала, додека кај останатите резултатите беа мошне лоши, постигнаа само 1–3 категории. Статистичката анализа покажа дека само женскиот пол има р-вредност од 0,05, додека останатите клинички и ЕЕГ наоди не беа сигнификантно асоцирани со појава на фронтална егзекутивна дисфункција. Но, имајќи во предвид дека се работи за релативно мала група на пациенти, можно е да не е постигната сигнификантност за суптилни асоцијации, и сметаме дека резултатите треба да се реплицираат во поголеми серии за да се потврдат наодите.

Клучни зборови: јувенилна миоклонусна епилепсија, егзекутивни функции, ЕЕГ.

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