Juvenile Myoclonic Epilepsy (JME): Neuropsychological Profile and Related Factors with Cognitive Dysfunction

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Objective: The aim of present study was to verify possible cognitive dysfunction in the patients with Juvenile Myoclonic Epilepsy (JME) and its correlation to factors related to epilepsy and patients demographic variables .
Material and Methods: Thirty two consecutive patients with JME and 32 healthy controls were evaluated in neuropsychological domains including orientation, mental control, logical memory, forward and backward digit spans, visual memory, associative learning, and memory quotient (using Persian version of Wechsler Memory Scale (WMS)-Revised), preservative errors (using Wisconsin Card Sorting Test (WCST)), Stroop Test (color and word), IQ score (using Raven's Progressive Matrices test), and depression (using the Persian version of Beck Depression Inventory (BDI)). SPSS 11.0 (SPSS Inc., Chicago, Illinois, USA) software was used for statistical analysis. Student's t-test and the Mann–Whitney U-test were used for independent normally and non-normally distributed continuous variables, respectively.
Results: Our study showed significant differences between patients with JME and control group with respect to scores of mental control (p=0.015), forward digit span (p=0.004), total digit span (p=0.008) and IQ (p=0.003). In addition, age, education level, duration of epilepsy and medication showed an impact on several cognitive functions in the patients with JME .
Conclusion: It is indicated that JME is associated with impairment in specific cognitive domains, despite any evidence in favor of depression.

Keywords: *Juvenile Myoclonic Epilepsy (JME); cognitive dysfunction; neuropsychological asessement, seizure*

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Epilepsy is often associated with reduced general intellectual functioning and specific cognitive impairments, such as general mental slowness, memory impairment and attention deficits (1, 2). Even though understanding of neuropsychological impairment in epilepsy has implications for the treatment and rehabilitation of this common disorder (3, 4), most of the earlier studies have carried out on determining the localization and lateralization of the epileptogenic abnormality in adult patients with focal epilepsy (5) and researchers have recently concentrated on the neuropsychological deficits in non-lesional, so-called idiopathic epilepsies (3). This aspect may provide clues concerning the underlying pathogenic process and the potential compensatory mechanisms that come into play (3). While the cognitive function of patients with Idiopathic Generalized Epilepsy (IGE) is usually within the normal
range, they tend to be somewhat lower than in the general population (6-8). However we should always consider the negative impact of antiepileptic drugs on cognitive function of these patients who receive medications.

Juvenile Myoclonic Epilepsy (JME) is the most common form of IGE (9). Previous studies have shown neuropsychological deficits in patients with JME, affecting mainly frontal lobe functions, such as visual working memory, mental flexibility, concept formation, cognitive speed, executive functions mainly planning, perseveration, task switching, verbal fluency, and response inhibition (10-15). However, the presence of cognitive impairments and related factors in JME patients has not yet been thoroughly investigated despite the extensive literature on cognition in other types of epilepsy. Moreover, most studies on patients with epilepsy have not considered confounding factors such as depression in the neuropsychological evaluation.

The aim of this study was 1) to compare cognitive function in JME patients with sex, age and education-matched healthy controls using several neuropsychological tests and 2) to evaluate changes in cognitive function due to epilepsy and mentioned

demographic variables in a sample of patients with JME in Iran.

Material and Methods

Thirty two consecutive patients with JME admitted at the epilepsy clinic of Sina Hospital, and 32 healthy controls in Tehran, Iran were enrolled in the study. JME was diagnosed using International League Against Epilepsy (ILAE) classification (6). Entry criteria for patients included normal brain MRI, age between 16-60 years, completion of primary school as the minimum level of education, juvenile onset of myoclonic jerks with or without generalized tonic-clonic seizure, generalized discharges of an irregular mixture of 3–6 Hz spike/polyspikes-slow waves on Electroencephalography (EEG). The exclusion criteria were the presence of an illness other than JME that may affect cognitive functions including neurological or psychiatric disorders, occurrence of a generalized seizure within the previous month or myoclonic jerks or absence seizures within the previous 24 hours, mental retardation (IQ score below 85 based on Raven's Progressive Matrices test), progressive psychiatric and neurological disorders, alcohol or drug abuse, ongoing use of any medications affecting central nervous system. Age-, sex- and education-matched healthy control subjects collected from patient's accompanies or other healthy subjects who were admitted to Sina hospital and had no medical, neurological or psychiatric illnesses , neither had family history of seizures and history of medication use which may affect cognitive function. Subjects in both groups signed their written informed consents prior to being included in this study.

JME diagnosis and EEG recording were done by an expert neurologist in the field of Epilepsy. Subjects completed a questionnaire including clinical and socio-demographic information as gender, age, level of education, duration of epilepsy, type and frequency of seizures, and drug treatment. Neuropsychological tests were administered in a sound-attenuated, temperature-controlled room by a single trained neurologist. General information, orientation, mental control, logical memory, forward and backward digit spans, visual memory, associative learning, and Memory Quotient (MQ) from the Persian version of Wechsler Memory Scale (WMS)-Revised were evaluated (17).The Wisconsin Card Sorting Test (WCST) perseverative errors was selected for evaluating executive function (18). Attention and control of inhibition evaluated using the Stroop Test (color and word) (19). IQ scores were obtained from Raven's Progressive Matrices test (20) and depression was evaluated using the Persian version of Beck Depression Inventory (BDI-II) (Cronbach's alpha = 0.87 and r = 0.73) (21).

Cognitive functions and depression between the JME and control groups were compared. In the JME group, we evaluated correlation between cognitive performance and age, sex, level of education, history of febrile convulsion, familial history of epilepsy, disease and medication history.

SPSS 11.0 (SPSS Inc, Chicago, Illinois, USA) software was used for statistical analysis. Student's t-test and the Mann–Whitney U-test were used for independent normally and non-normally distributed continuous variables, respectively. Nominal variables were analyzed by means of Chi square test. Correlation between neuropsychological scores, patient characteristics, and epilepsy variables was evaluated by Pearson's correlation analysis. Significance was defined at the level of $p<0.05$.

Result

The characteristics of 32 patients with JME and 32 controls has been compared in Table 1. There were no significant differences in age, gender, and level of education between the JME and control groups. Twenty one patients (65.6%) had a family history of epilepsy and six patients (18.8%) had experienced febrile convulsion. The duration of epilepsy and medication were 11.8±11.4 and 8.6±8.9 years, respectively. The proportions of patients who received valproate or topiramate were 21 (65.6%) and 1 (3.1%), respectively, and other patients received polytherapy (different combinations of valproate, topiramate, carbamazepine, phenytoein, phenobarbital, lamotrigine, and sodium valproate).

As shown in Table 2, patients with JME exhibit worse performances in more domains of cognitive functions compared to controls. However, significant differences were observed between JME and control groups with respect to scores of mental control (7.2±1.5 vs. 8.1±1.2, p=0.015), forward digit span (5.7±0.7 vs. 6.2±0.7, p=0.004), total digit span (9.8±1.1 vs. 10.6±1.2, p=0.008), and IQ (106.7±11.8 vs. 115.8±11.8, p=0.003). Also, difference in Memory Quotient (MQ) value was significant between two groups in $p<0.06$.

The patients with JME who graduated from the university had higher values of logical memory (11.0±3.4 vs. 8.5±4.3, p=0.015), visual memory (11.1±3.5 vs. 9.2±3.0, p=0.048), forward digit span (6.0±0.7 vs. 5.3±0.5, p=0.013), MQ (110.3±14.3 vs. 102.8±14.1, p=0.044), IQ (113.6±12.5 vs. 106.4±12.8, p=0.036), and lower value of Stroop color (1.8±1.8 vs. 3.8±2.1, $p<0.001$) compared to other patients. However, there were not significant association between the scores of cognitive function tests and sex, history of febrile convulsion and familial history in the patients with JME.

There were significant correlation between age of patients with JME and scores of associative learning (r=-0.663, $p<0.001$), perseverative errors (r=0.394, p=0.028), Stroop color (r=0.616, $p<0.001$), and IQ (r=-0.530, p=0.002).

Table1. Characteristics patients with Juvenile Myoclonic Epilepsy (JME) and control cases; mean (SD) or n (%)

	JME (n = 32)	Controls	*P* values
Age, years	28.7 (11.4)	33.7 (12.3)	0.100
Sex, male	13 (40.6)	17 (53.1)	0.316
Education			
Graduated from school	13 (40.6)	19 (59.4)	0.875
Graduated from university	11 (34.4)	21 (65.6)	
Family history	21 (65.6)		
Febrile convulsion	6 (18.8)		
Duration of epilepsy, years	11.8 (11.4)		
Duration of medication, years	8.6 (8.9)		

Table 2: Cognitive performances of patients with Juvenile Myoclonic Epilepsy (JME) and control cases; mean (SD)

	JME (n = 32)	Controls	*P* values
WMS			
General information	5.9 (0.3)	5.9 (0.3)	0.924
Orientation	5.0 (0.0)	5.0 (0.3)	0.557
Mental control	7.2 (1.5)	8.1 (1.2)	0.015
Logical memory	9.4 (4.2)	10.4 (3.5)	0.344
Digit span, forward	5.7 (0.7)	6.2 (0.7)	0.004
Digit span, backward	4.1 (0.6)	4.4 (0.7)	0.082
Digit span, total	9.8 (1.1)	10.6 (1.2)	0.008
Visual memory	9.8 (3.3)	11.1 (3.4)	0.159
Associative learning	17.5 (2.9)	18.0 (4.2)	0.622
Memory quotient	103.6 (13.3)	110.6 (15.8)	0.059
WCST			
Perseverative errors	8.2 (9.4)	7.5 (10.4)	0.783
Stroop			
Word	0.3 (0.7)	0.2 (0.5)	0.716
Color	2.8 (2.2)	2.3 (2.1)	0.388
IQ score	106.7 (11.8)	115.8 (11.8)	0.003
BDI	11.4 (8.2)	8.5 (6.8)	0.126

WMS, Wechsler Memory Scale; WCST, Wisconsin Card Sorting Test; BDI, Beck Depression Inventory

Duration of treatment and epilepsy had significant correlation with values of mental control (r=-0.574, p=0.001; r=-0.373, p=0.035), backward digit span (r=-0.475, p=0.006; r=-0.370, p=0.037), total digit span (r=-0.517, p=0.002; r=-0.359, p=0.044), associative learning (r=-0.395, p=0.025; r=-0.532, p=0.002), perseverative errors (r=0.446, p=0.012; r=0.437, p=0.014), Stroop color (r=0.782, p<0.001; r=0.608, p<0.001), and IQ (r=-0.603, p<0.001; r=-0.535, p=0.002). Moreover, duration of treatment was correlated with scores of logical memory (r=-0.373, p=0.043) and forward digit span (r=-0.424, p=0.016). However, the poor performances in cognitive function tests in the JME group were not correlated with dose of antiepileptic medications.

Discussion

This study showed the presence of cognitive impairment in the patients with JME. The negative impact of JME is reflected in several cognitive domains including IQ, mental control, forward and total digit span, compared to the healthy controls, whereas mood and education level were similar in two groups. Moreover, age, level of education, duration of epilepsy and medication had an impact on several cognitive functions in the patients with JME.

Executive Functions: Neuropsychological studies have shown that the deficits in the area of behavior, social adjustment and executive functions, which are observed in JME, point to frontal lobe involvement in this disorder (3). Dysfunction of these regions, especially the prefrontal cortex, results in disturbances in the organization and self-regulation of behavior. These functions involve in the elaboration of cognitive and behavioral responses and strategies for the attainment of immediate or future goals (3, 22). In addition, significant executive dysfunction in children with JME has been associated with significantly smaller thalamus and increased frontal cerebrospinal fluid (14). Thus, frontal and thalamic volumes appear to mediate the relationship between executive functioning and brain structure in patients with JME (4). The present study confirmed previous evidences for frontal lobe dysfunction in JME (10, 11, 23-27).

Intelligence Quotient (IQ): Some investigations have shown a decline in the intellectual function of IGE patients (6-8, 28, 29). In agreement with our results, Pascalicchio et al (3) found significantly lower IQ score in the patients with JME compared to controls, whereas some previous studies reported no significant differences in IQ score between these patients and control groups (11, 23, 30). Lower IQ scores were observed in the patients with a younger age at onset, more frequent seizures, more frequent episodes of Status Epilepticus, longer duration of seizure attacks, structural abnormalities in the brain and atypical absence seizures (6, 22 and 31). However, our results showed that the IQ scores of patients with JME had positive correlation with educational level and had negative correlation with age, disease duration and medication.

Level of Education: In agreement with several studies such as Pascalicchio et al (12), we could find a positive relationship between the level of education and higher scores in several cognitive domains in the patients with JME. The neuropsychological assessment of the patients with higher level of education (more than 16 years) showed significant preference in the scores of logical memory, visual memory, forward digit span, MQ and IQ compared to patients with lower level of education. However we could not find similar pattern in Stroop color test.

The implication of this difference might be an important finding for modification of cognitive deficits and its negative consequences on their quality of life. This can be done by encouraging the patients in schooling to promote educational achievement.

Considering the side effects of antiepileptic drugs on cognitive function, the basic neuropathology of seizure disorders including JME, it may not be possible to prevent cognitive deficits in all of the patients, therefore education could be a modifiable variable for more resistance against cognitive deficits in these patients.

Digit Span: This test evaluates attention, short-term memory and working memory capacity. We found significant differences between patients with JME and controls in respect to forward and total digit span score which was in consistent with two previous studies (7, 30). However, Sonmez et al (23) reported no significant difference in the digit span test between patients with JME and control groups. They found the digit span scores of patients with a familial history of seizures were lower than patients without this. Our results showed that this test could be influenced by the level of education, disease duration and medication. One of the justifications of our results may be explained by the known side effects of antiepileptic medications on concentration and memory.

Visual Memory and Visuospatial Function: Sonmez et al. (23) found impaired visual memory and visuospatial function in the patient with JME, which were in contrast to our results and Kim study (30). Also, they reported a significant difference between two groups on Stroop test. These differences might be attributable to the lack of assessment of depression in the study of Sonmez et al; hence their study does not exclude the effect of depressed mood on global cognitive performance. On the other hand, we found deficit in mental control in the patients with JME which was not reported in the previous studies.

Disease Duration: Duration of the epilepsy was correlated with cognitive performance, which confirmed in two previous studies (7, 30). Evidence suggests that prolonged exposure to abnormal neural activity during a critical period of cerebral maturation may disrupt the structural and functional changes in the brain that contribute to the establishment of the neural substrate for language development, learning and lateralization of functions (3). However, the results of our study are not compatible with Somnez et al (23) which did not find such correlation in their series of JME patients. In addition, there was significant correlation between duration of medication use and cognitive function or alternatively, it may be due to duration of disease. Most antiepileptic drugs (AEDs), such as topiramate, have the potential to exert detrimental effects on cognitive function. However, the small percentage of our patients (3.1%) has been on topiramate and 21 patients (65.6%) received valproate that has little detrimental impact on cognitive function (32, 33). Therefore, we did not find significant correlation between dose of medication and cognitive performance .

Depression and Anxiety: Although depression and anxiety were reported as common psychiatric disorders in the patients with epilepsy (34), the results of BDI scores did not differ between the case and controls, which was in consistent with Kim et al study (30). Also, the BDI score was not correlated with cognitive performance.

Limitations

One of the limitations of this study was the lack of functional MRI data of patients which hindered our ability to demonstrate any relationship between localization of epilepsy and cognitive functions. Moreover, it is preferable to investigate patients with epilepsy who are not receiving AED medications, because of adverse effects of AEDs which potentially contribute to cognitive impairment. Finally and in practice, it was not possible to consider a blind examiner for cognitive assessments.

Conclusion

In conclusion, this study indicates that JME is associated with impairment in specific cognitive domains and more specifically in the frontal, prefrontal and memory domains. In addition age, education level, duration of disease and medication had an impact on cognitive performance. However more investigation should be performed in the patients with JME to understand the depth and extension of neuropsychological deficits to provide a better clinical care and neuropsychological rehabilitation in the management of this group of patients .

Another important finding of this study is the presence of a relationship between the level of education and the scores of cognitive tests in the patients with JME. It may be claimed that higher level of education may play a role - as a reserve- against cognitive deficits which seemed to be an inevitable consequence in the patients who have to struggle with both epilepsy and the negative impacts of antiepileptic medications on their cognitive functions.

References

1. Aldenkamp AP. Effect of seizures and epileptiform discharges on cognitive functions. Epilepsia 1997; 38: 52–58.
2. Prevey ML, Delaney RC, Cramer JA and Mattson RH. Complex Partial and Secondarily Generalized Seizure Patients: Cognitive Functioning Prior to Treatment with Antiepileptic Medication. Va Epilepsy Cooperative Study 264 Group. Epilepsy Res 1998; 30: 1-9.
3. Hommet C, Sauerwein HC, De Toffol B, Lassonde M. Idiopathic epileptic syndromes and cognition. Neurosci Biobehav Rev 2006; 30: 85-96.
4. You SJ. Cognitive function of idiopathic childhood epilepsy. Korean J Pediatr 2012; 55: 159-63.
5. Jones-Gotman M, Smith M, Zatorre R. Neuropsychological testing for localizing and lateralizing the epileptogenic region in surgical treatment of the epilepsy. In: Engel J, editor. Epileptic seizures and syndromes. New York: Raven Press; 1993.
6. Farwell JR, Dodrill CB, Batzel LW. Neuropsychological abilities of children with epilepsy. Epilepsia 1985; 26: 395–400.
7. Mandelbaum DE, Burack GD. The effect of seizure type and medication on cognitive and behavioral functioning in children with idiopathic epilepsy. Dev Med Child Neurol 1997; 39: 731–7355.
8. Cutting S, Lauchheimer A, Barr W, Devinsky O. Adult-onset idiopathic generalized epilepsy: clinical and behavioral features. Epilepsia 2001; 42: 1395–1398.
9. Janz, D, Durner M. Juvenile myoclonic epilepsy. In: Egel J, Pedley T, Eds. Epilepsy: A Comprehensive Text Book. Philadelphia: Lippivicott Raven; 1997.
10. Swartz BE, Simpkins F, Halgren E, Mandelkern M, Brown C, Krisdakumtorn T, et al. Visual Working Memory in Primary Generalized Epilepsy: An 18fdg-Pet Study. Neurology 1996; 47: 1203-1212.
11. Devinsky O, Gershengorn J, Brown E, Perrine K, Vazquez B, Luciano D. Frontal Functions in Juvenile Myoclonic Epilepsy. Neuropsychiatry Neuropsychol Behav Neurol 1997; 10: 243-246.
12. Pascalicchio TF, de Araujo Filho GM, da Silva Noffs MH, Lin K, Caboclo LO, Vidal-Dourado M, et al. Neuropsychological Profile of Patients with Juvenile Myoclonic Epilepsy: A Controlled Study of 50 Patients. Epilepsy Behav 2007; 10: 263-267.
13. Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. Frontal Cognitive Dysfunction in Juvenile Myoclonic Epilepsy. Epilepsia 2008; 49: 657-662.
14. Pulsipher DT, Seidenberg M, Guidotti L, Tuchscherer VN, Morton J, Sheth RD, et al. Thalamofrontal Circuitry and Executive Dysfunction in Recent-Onset Juvenile Myoclonic Epilepsy. Epilepsia 2009; 50: 1210-1219.
15. Iqbal N, Caswell HL, Hare DJ, Pilkington O, Mercer S and Duncan S. Neuropsychological Profiles of Patients with Juvenile Myoclonic Epilepsy and Their Siblings: A Preliminary Controlled Experimental Video-Eeg Case Series. Epilepsy Behav 2009; 14: 516-521.
16. Meencke HJ, Janz D. Neuropathological Findings in Primary Generalized Epilepsy: A Study of Eight Cases. Epilepsia 1984; 25: 8-21.
17. Barahani, MN, Nasirian S, Yazdi, B. [Wechsler Memory Scale (A form)-Persian]. Tehran Psychiatric Institute, published report; 1981.
18. Lucy JV, Burness CE, Costa DC. Wisconsin Card Sorting Task (WCST) errors and cerebral blood flow in obsessive-compulsive disorder (OCD). British Journal of Medical Psychology 1997; 70: 403-411.
19. Pujol J, Vendrell P, Deus J, Junque C, Bello J, Marti-Vilalta JL, et al. The Effect of Medial Frontal and Posterior Parietal Demyelinating Lesions on Stroop Interference. NeuroImage 2001; 13: 68-75.
20. Barahani MN. The study of psychometric properties of Raven Advanced Progressive Matrices-Persian. Journal of Psychological Association 1962.
21. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Ebrahimkhani N. Psychometric properties of a Persian-Language version of the Beck Depression Inventory-Second Edition: BDI-II-Persian. Depression and Anxiety 2005; 21: 185-192.
22. Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The Return of Phineas Gage: Clues About the Brain from the Skull of a Famous Patient. Science (New York, N.Y.) 1994; 264: 1102-1105.
23. Sonmez F, Atakli D, Sari H, Atay T, Arpaci B. Cognitive function in juvenile myoclonic epilepsy. Epilepsy Behav 2004; 5: 329-336.
24. Woerman FG, Free SL, Koepp MJ, Sisodiya SM, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI. Brain 1999; 122: 2101-2108.
25. Tae WS, Lee EK, Joo EY, Hong SB. Volume changes of frontal lobe and hippocampus in juvenile myoclonic epilepsy. J Korean Neurol Assoc 2003; 21: 54-61.
26. Tae WS, Joo EY, Hong SB. Distribution of cerebral gray and white matters in juvenile myoclonic epilepsy: voxel based morphometry. J Korean Neurol Assoc 2003; 21: 62-69.
27. Savic I, Lekvall A, Greitz D, Helms G. MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy. Epilepsia 2000; 41: 290-296.
28. Mirsky A, Duncan C, Levav M. Neuropsychology studies in idiopathic generalized epilepsies. In: Jambaque I, Lassonde M, Dulac O. Neuropsychology of Childhood Epilepsy. New York: Springer; 2001.
29. Pavone P, Bianchini R, Trifiletti RR, Incorpora G, Pavone A, Parano E. Neuropsychological

Assessment in Children with Absence Epilepsy. Neurology 2001; 56: 1047-1051.
30. Kim SY, Hwang YH, Lee HW, Suh CK, Kwon SH, Park SP. Cognitive impairment in juvenile myoclonic epilepsy. J Clin Neurol 2007; 3: 86-92.
31. Bourgeois BF, Prensky AL, Palkes HS, Talent BK, Busch SG. Intelligence in epilepsy: a prospective study in children. Ann Neurol 1983; 14: 438-444.
32. Sun W, Wang Y, Wang W, Wu X. Attention changes in epilepsy patients following 3-month topiramate or valproate treatment revealed by event-related potential. Int J Psychophysiol 2008; 68: 235-241.
33. Donati F, Gobbi G, Campistol J, Rapatz G, Daehler M, Sturm Y, et al. The Cognitive Effects of Oxcarbazepine Versus Carbamazepine or Valproate in Newly Diagnosed Children with Partial Seizures. Seizure 2007; 16: 670-679.
34. Jackson MJ, Turkington D. Depression and anxiety in epilepsy. J Neurol Neurosurg Psychiatry 2005; 76: 45-47.