Juvenile Myoclonic Epilepsy with Frontal Executive Dysfunction is Associated with Reduced Gray Matter Volume by Voxel-based Morphometry

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Abstract

Objective: Frontal executive dysfunction (FED) and abnormalities in volumetric magnetic resonance imaging (MRI) have been described in juvenile myoclonic epilepsy (JME). We aimed to compare JME patients with and without FED by group analysis of voxel-based morphometric (VBM) estimates of brain volume in MRI. **Subjects and Methods:** We studied frontal executive functions in patients with JME and analyzed the possible association of FED with their demographic, clinical, and electrographic characteristics. We aimed to do group analysis of the VBM MRI brain data to compare the gray matter (GM) volumes of JME patients with and without FED. **Results:** We recruited 34 patients (20 women) with JME (mean age 23.7 ± 4.58 years) from the epilepsy outpatient services. FED was detected in twenty patients (58.8%). Group analysis of VBM MRI brain showed significant ($P < 0.001$) reduction in GM volume in dorsolateral prefrontal cortex (left Brodmann area [BA] 10, 46, 9, Z-score 3.36, 2.91, 2.03, respectively, and right BA 10 and BA 45, Z-score 2.98 and 3.36, respectively), left insula (BA 13, Z-score 2.14), temporal lobe (BA 38, Z-score 2.76), in the subgroup of JME with FED. **Inference:** JME with FED has an anatomical correlate in the form of reduced GM volume in dorsolateral prefrontal cortex.

Keywords: Cognitive deficit, functional magnetic resonance imaging, neuropsychology

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is one of the most common age-related genetic generalized epilepsies in neurology practice. It is characterized by normal intelligence and a benign course with excellent response to pharmacotherapy in most patients. Recently, frontal executive dysfunction (FED) and other cognitive impairments have been recognized in some of these patients.[1-4] However, certain other studies have failed to demonstrate such an association.[5] Frontally dominant interictal discharges (IED) in the electroencephalograms (EEG) and adverse cognitive effects of antiepileptic drugs (AEDs) are some of the factors that have been associated with FED in JME. Routine brain magnetic resonance imaging (MRI) images are essentially normal in JME. The published results of the quantitative MRI studies in JME show considerable variation. The frontal gray matter (GM) volume was reported to be increased in one study[6] while another study had shown decreased volume with abnormalities in corpus callosum and hippocampi.[7] The other changes described are smaller thalami,[8] increased frontal cerebrospinal fluid (CSF) volume[8] and abnormal fractional anisotropy in the thalamocortical white matter (WM), and increased fractional anisotropy of putamen.[9] Reduced volume of the anterior thalamocortical bundle with abnormal functional connectivity with frontal lobe was demonstrated for JME patients with reduced phonemic fluency in comparison to healthy individuals.[10]

It is possible that JME may represent a heterogeneous group regarding clinical course and neuropsychological outcome. The majority of them have a benign course with few seizures and normal neuropsychological profile while a minority have poorer

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seizure control or significant neuropsychological dysfunction.[11] There is little information regarding the brain volume changes in JME according to their neuropsychological functional status. We aimed to compare the voxel-based morphometric (VBM) MRI brain data of the two subgroups of JME patients (those with and without FED) by means of group analysis.

METHODS

This hospital-based observational cross-sectional study was conducted in the comprehensive epilepsy care program in Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram, India. Consecutive patients with the diagnosis of JME according to the International League Against Epilepsy classification scheme were screened to identify patients with age between 18 and 35 years and a minimum of 12 years of formal education. We chose to have patients with at least 12 years of formal education to avoid any bias due to variation in education on the neuropsychological tests. We excluded patients with any other neurological, psychiatric, or chronic somatic disorders and those receiving more than two AEDs or any other drugs that may influence cognitive function. Patients were taken for neuropsychology testing at least 24 h after the last generalized tonic–clonic seizures (GTCS) as transient cognitive dysfunction after a GTCS may affect their performance in these tests. This study had the approval of the Institutional Ethics Committee, and informed consent was obtained from the patients. Patients fulfilling these criteria and giving informed consent were recruited for the study. Out of the 49 patients with JME found eligible on screening, 34 had given consent and participated in this study, and all of them underwent neuropsychology evaluation. Eleven patients failed to undergo MRI as the scheduled appointment did not suit them (nine patients) or were claustrophobic (two patients). A structured proforma was used to obtain the demographic details, epilepsy characteristics, and details of AED treatment. Details of EEG were obtained from the clinical records. A standard scalp EEG consisting of at least 20 min of awake recording, activation procedures of hyperventilation, and photic stimulation was performed in all patients. Sleep record was obtained by medication if patients did not sleep naturally. EEG was repeated once if the first EEG was normal.

Neuropsychology evaluation

Neuropsychological evaluation for executive function was done in all patients by qualified neuropsychologists, who were blinded to the patient details. Three tests consisting of Phonemic fluency, Trail B test, and Wisconsin card sorting tests were performed. The results were categorized as normal or impaired according to the normative data of standardization of these tests for the regional population.[12] Accordingly, those with scores less than the 15th centile in any of the three tests were classified as having FED.

Voxel-based morphometry

MRI protocol consisted of image acquisition by gradient echo (magnetization-prepared rapid acquisition gradient echo)

sequence with repetition time 2400, echo time 3.72, inversion time 1000, flip angle 8°, matrix size of 256 × 256, and slice thickness 1 × 1 × 1. Time taken for MRI acquisition was 10 min. For image analysis, cortical gray matter (GM) changes across the entire brain were assessed using VBM8 toolbox in Statistical Parametric Mapping (SPM8-Wellcome Department of Imaging Neuroscience, London) implemented in MATLAB version 7.1 IBM SPSS Statistics for Windows version 21 (Armonk, NY, USA). [13] In the first step of analysis, the three-dimensional images were spatially normalized into Montreal Neurological Institute space using VBM8 DARTEL procedure with custom settings. Then, the images were segmented into GM, WM, and CSF. In the default settings, each tissue classes were normalized in comparison with the template using "nonlinear only option" which corrected for individual brain size differences. After segmentation, the images were checked using visual impression by options of "Display one slice for all images" and "Check sample homogeneity using covariance." This was followed by measuring the volume of a particular tissue (GM, WM, and CSF) and total intracranial volume. Finally, the images were smoothed with an isotropic Gaussian kernel of 8 mm full width half maximum.

Group analysis of the cerebral GM morphometric differences was carried out between the two groups (JME patients with and without FED) using voxel-wise statistical comparison. The statistical comparison of GM volume between the subject groups with and without FED was performed by two sample *t*-tests within the SPM8 general linear model. The regions of significant voxels were obtained with an uncorrected threshold of *P* < 0.001 and an extended threshold of 0 voxels. Finally, the significant atrophic regions were overlaid on T1-weighted standard brain images for better visualization.

Statistics

Chi-square test was used to compare the proportions. Group means were compared by Student's *t*-test. *P* ≤ 0.05 was taken for statistical significance. Data analysis was done using the statistical software SPSS IBM SPSS Statistics for Windows version 21 (Armonk, NY, USA), with the help of a medical statistics specialist. Group analysis of the MRI VBM data was carried out between the two groups: JME patients with versus without FED. The group comparison of MRI VBM was performed by two sample *t*-tests within the SPM8 general linear model. Comparisons were tested with a corrected threshold of *P* < 0.001.

RESULTS

There were 34 patients who were recruited for the study. They belonged to the age groups: 18–23 years, *n* = 18 (10 females), 24–29 years, *n* = 13 (7 females), and 30–35 years, *n* = 3 (3 females). 21 patients (61.8%) had university education while others had formal schooling for at least 12 years.

Age of onset of epilepsy ranged from 10 to 20 years (mean 15.18 ± 2.74 years). Mean duration of epilepsy was 8.53 ± 4.75 years (range 2–18 years). The GTCS frequency in the past 1 year was nil for 18 patients (52.9%) and 1–4 for

the rest. EEG showed generalized IEDs in 18 patients, and 15 of them had frontally dominant IEDs. All patients were on AED treatment (one on dual-drug therapy and others on monotherapy). The AEDs used were valproate 24 (70.5%), levetiracetam 7 (20.5%), and lamotrigine 2 (5.9%) and topiramate 1 (2.9%). The single patient on dual therapy was on valproate and topiramate. The mean daily dose of AEDs was valproate 627 mg (range 300–1000 mg), levetiracetam 1536 mg (range 1000–2000 mg), lamotrigine 300 mg (range 150–450 mg), and topiramate 50 mg. The mean duration of exposure to AEDs was 6.36 ± 4.38 years (range 0.5–15 years).

Neuropsychological tests were impaired on phonemic fluency in 3 (8.8%), Trail B test in 17 (50%), and Wisconsin card sorting test in 6 (17.6). There were twenty patients who were classified as having FED based on impairment in at least one of the three tests. The demographic and clinical characteristics of the JME without FED compared to the JME with FED (in brackets) were as follows: females 9,[11] mean age 22.3 ± 4.4 (24.7 ± 4.6) years, age of onset of epilepsy 14.4 ± 2.7 (15.8 ± 2.7) years, mean number of GTCS in the preceding 12 months 0.86 ± 1.2 (0.8 ± 1.1), and duration of AED therapy in years 6.3 ± 4.4 (6.4 ± 4.4). There was no statistically significant difference between the two groups with regard to the clinical or demographic characteristics.

Eleven patients did not undergo MRI brain. However, on comparing the demographic, clinical, EEG, and neuropsychological profile, there was no statistically significant difference between those who underwent MRI and those who did not. Among the 23 patients who underwent MRI, 15 patients (73.9%) had FED. Group comparison of the VBM data revealed that the subgroup with FED had a significant ($P < 0.001$) reduction in GM volume of the inferior frontal opercular gyrus (Brodmann area [BA] 45), superior frontal gyrus (BA 10), insular cortex (BA 47), fusiform gyrus (BA 20), middle temporal pole (BA 21), superior temporal gyrus (BA 22), and supramarginal gyrus (BA 40) on the right side and precentral gyrus (BA 9), middle frontal gyrus (BA 10), and gyrus rectus (BA 11) on the left side. There was a trend toward lower volume (not statistically significant) for anterior cingulate (BA 24), middle frontal gyrus (BA 46), middle orbitofrontal gyrus (BA 10), and inferior orbitofrontal gyrus (BA 47) on the left side and bilateral caudate nuclei [Figure 1]. The differences with respect to each of the above regions are given in Table 1.

Discussion

This study attempted to characterize the executive function in a cohort of JME patients from South India and ascertain any association between FED and brain volumes by VBM. Our patients fulfilled the ILEA definition of JME and had typical clinical characteristics and AED therapy. More than half of the patients in this cohort had FED on one of the three tests. Previous studies have also reported mild to moderate FED in JME patients.[1,2] We adopted the group analysis of the VBM

data to compare the brain volumes of those with and without FED. There was a significant difference ($P < 0.001$) in the GM volume in BA 45 (inferior frontal opercular gyrus), BA 47 (inferior frontal gyrus), BA 10 (superior frontal gyrus) on the right hemisphere and BA 9 (precentral gyrus), BA 10 (middle frontal gyrus) on the left hemisphere. In addition, a significant but lesser degree of GM volume loss was seen in BA 46 (middle frontal gyrus), BA 47 (inferior orbital frontal gyrus), and BA 10 (middle orbital frontal gyrus) on the left side. These BAs (BA 45, BA 47, BA 9, BA 10) correspond to the dorsolateral prefrontal cortex in humans which is linked to executive functions as evidenced by the postmortem study of 17 individuals by Rajkowska and Goldman-Rakic.[14,15] There are reports of various cognitive dysfunctions in JME patients predominantly affecting frontal lobe functions including executive dysfunction.[1-4] Previous studies that had examined the structural correlate for the cognitive dysfunction by quantitative or functional MRI had targeted the thalamofrontal circuitry including mesial frontal lobe,[6,16] thalamus,[8,17,18] and thalamocortical WM connections.[10] More recent studies have demonstrated abnormalities outside frontal circuitry with the involvement of temporoparietal regions.[19] Unlike most of the previous studies where JME patients were compared with normal controls or patients with other seizure disorders, we had compared VBM profile of JME patients according to the presence or absence of FED. Our observation that patients with JME and FED had different VBM profiles than those without FED point to a structural basis for the FED in JME. The clinical heterogeneity in JME as suggested in long-term follow-up studies[11] can be extended to the neuropsychological profile, and more importantly, it has an anatomical correlate in terms of significant difference in GM volume as seen in our study.
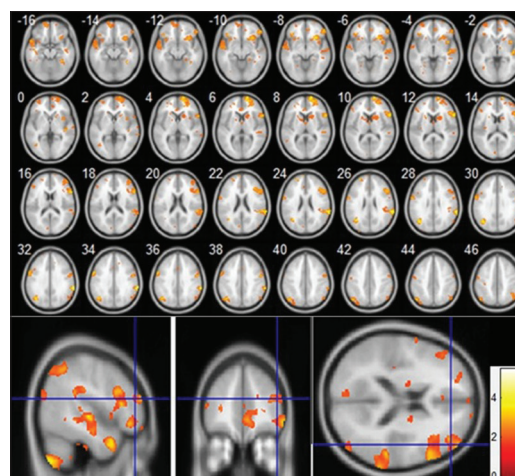

Figure 1: Group analysis of the voxel-based morphometric data superimposed on axial T1 image showing significant thinning of the cortical gray matter in the group with frontal executive dysfunction ($P < 0.001$, uncorrected). Bottom panel: Magnified view of statistical parametric mapping T-Map showing significant activation clusters in the Brodmann area 46 (intersecting lines) of the group with frontal executive dysfunction in sagittal, coronal, and axial view (*Color code showing increasing gray matter volume reduction toward the yellow)

Table 1: Regions showing significant gray matter reduction in the group with frontal executive dysfunction compared to the group without frontal executive dysfunction

Anatomical localization	BA	Side	MNI coordinate areas			Cluster size (mm³)	Z-score
			X	Y	Z		
Middle frontal gyrus	BA 10	Left	−25.5	52.5	25.5	530	3.36
	BA 46	Left	−46.5	36	18	368	2.91
Superior frontal gyrus	BA 9	Left	−18	57	31.5	289	2.03
	BA 10	Right	28.5	57	9	1055	2.98
Inferior frontal gyrus	BA 47	Left	−39	30	−10.5	468	3.25
	BA 45	Right	55.5	19.5	12	732	3.36
Insula	BA 13	Left	−28.5	18	−19	111	2.14
	BA 47	Right	30	22.5	−9	712	3.28
Gyrus rectus	BA 11	Left	−4.5	57	−21	319	2.31
Middle temporal pole	BA 21	Right	48	10.5	−30	756	3.34
Superior temporal pole	BA 38	Left	−55.5	12	−16.5	677	2.76
Fusiform gyrus	BA 20	Right	36	−40.5	−21	66	3.30
Caudate/caudate body	-	Left	−9	6	7.5	267	2.01
	-	Right	16.5	13.5	7.5	225	2.25
Superior temporal gyrus	BA 22	Right	46.5	−19.5	−3	1837	3.21

BA = Brodmann area, MNI = Montreal Neurological Institute

A major limitation of this study was that all patients did not undergo MRI. However, we believe that this has not affected the MRI results as there were no statistically significant differences between the groups who underwent MRI and those who did not.

CONCLUSION

Careful neuropsychological testing can reveal FED in a substantial proportion of subjects with JME. The significant reduction in grey matter volume in the dorsolateral prefrontal cortex in this study point towards an anatomical basis for the FED in JME.

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Conflicts of interest

There are no conflicts of interest.

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