Seizure 22 (2013) 230–235

Contents lists available at SciVerse ScienceDirect

Seizure

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

# Subcortical structural abnormalities in juvenile myoclonic epilepsy (JME): MR volumetry and vertex based analysis

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ARTICLE INFO

*Article history:*
Received 31 March 2012
Received in revised form 29 December 2012
Accepted 1 January 2013

*Keywords:*
Juvenile myoclonic epilepsy
JME
MRI
Thalamus
Shape analysis
VBM
Volumetry

ABSTRACT

*Purpose:* Imaging studies in juvenile myoclonic epilepsy (JME) have shown abnormalities of the thalamus and frontal cortex. The purpose of this study was to systematically investigate the morphological changes in the deep gray matter (GM) structures using techniques of voxel based morphometry (VBM), MR volumetry and shape analysis.
*Methodology:* The study included 40 patients with JME (M:F = 21:19; age 22.8 ± 5.3 years) and 19 matched controls (M:F = 13:6; age 24.5 ± 4.2 years). All subjects underwent MRI using standard protocol that included T1-3D TFE (Turbo Field Echo) images with 1 mm thickness. VBM analysis and MR volumetry were performed. The volumes of deep subcortical GM structures were extracted and vertex-wise shape analysis was performed using FSL-FIRST (FSL-Integrated Registration and Segmentation Toolbox) software.
*Results:* VBM analysis with a thalamic mask revealed focal thalamic alterations in the anteromedial aspect of the thalamus ($p < 0.05$, false discovery rate (FDR) corrected) which remained significant after adjusting for age, gender and intracranial volume (ICV). Significant volume loss was noted in both the thalami. Vertex-wise shape analysis showed significant focal surface reductions in the thalami bilaterally in patients that were predominantly seen in the medial as well as lateral aspects of the thalamus ($p < 0.05$, FDR corrected). The disease duration correlated with left hippocampus volume while age of onset correlated with right hippocampus volume.
*Conclusions:* This study confirms the presence of thalamic alterations in patients with JME. Shape analysis technique provided complementary information and disclosed the presence of focal atrophic changes in patients' thalami. The striatum and hippocampus did not show any significant alterations.


## 1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common and well-defined idiopathic generalized epilepsy (IGE), established as an epileptic syndrome in 1989. The disorder may be inherited and has equal gender distribution. Patients manifest with myoclonic jerks starting often at puberty, sometimes associated with generalized tonic–clonic seizures (GTCS) and infrequently absences. Myoclonic jerks are bilateral, single or repetitive, arrhythmic, predominantly in the arms, not associated with disturbance in consciousness, occurring shortly after awakening and often precipitated by sleep deprivation.[1–3] Patients respond to sodium valproate but some anti-epileptic drugs (AEDs) like carbamazepine and phenytoin might worsen the myoclonic jerks and absence seizures. Standard Electroencephalography (EEG) in JME typically shows 3–6 Hz generalized spike wave or polyspike-wave activity, with fronto-central predominance. EEG plays an important role in the diagnosis.[3–5] In a study by Holmes et al., all 10 patients had epileptiform discharges, which localized to sources that included orbitofrontal/medial frontopolar cortex, while basal-medial temporal lobe sources were observed in 50% of patients.[6] Recent neuroimaging studies have contributed immensely to the understanding of JME by revealing focal brain abnormalities.

Routine magnetic resonance imaging (MRI) in patients with JME is often normal on visual inspection. Multiple MRI studies using advanced image processing methods and newer MR contrasts have revealed abnormalities of the thalamus, frontal cortex and thalamo-frontal connections in these patients.[7–14] Among the subcortical structures, thalamus is most studied area and has been investigated in detail using multiple analysis and imaging techniques like voxel based morphometry (VBM), volumetry, shape analysis and MR spectroscopy (MRS).[11,13,15–19]

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http://dx.doi.org/10.1016/j.seizure.2013.01.001

However, there is growing evidence to suggest abnormalities of basal ganglia structures and hippocampus in JME.[13,15,20–22] The results of these studies support the presence of structural and biochemical changes in basal ganglia. Hippocampus does not appear to be directly involved in generalized seizure disorder. In contrast, hippocampus involvement in JME has been supported by the presence of metabolic abnormalities on MRS and CBF changes on SPECT studies.[13,23]

Most of the previous imaging studies that have used whole brain voxel wise approach to analyze structural MRI have failed to identify abnormalities in basal ganglia and hippocampus.

In view of lack of consistency of previous results, in the present study we investigated the morphological changes in the deep gray matter structures and hippocampus by using multiple analysis methods (which includes VBM, volumetry and shape analysis to the structural MRI data).

## 2. Materials and methods

### 2.1. Subjects

Forty JME patients (M:F = 21:19; age at evaluation = 22.8 ± 5.3 years) and 19 age-matched controls (M:F = 13:6; age at evaluation: = 24.5 ± 4.2 years) were enrolled for the study. All patients were examined by a specialist in epilepsy (SS) and the diagnosis of JME was based on the ILAE criteria for JME.[24,25] Patients were primarily recruited for another study on 'sleep in JME' and were also simultaneously evaluated for the present study. Patients with other medical illnesses or on any medications (other than sodium valproate) known to affect sleep, and those with substance abuse were excluded. Nineteen normal healthy age-matched volunteers without family history of seizures or any other neurodegenerative disease were enrolled as controls. All patients underwent a structured evaluation that included recording of detailed clinical, family and treatment history, neurological examination, 16-channel digital EEG using the international 10–20 system of electrode placement, MRI and other investigations (when indicated).

All the controls were clinically examined by a neurologist. Subjects with any other neurological or significant psychiatric illnesses and those who were claustrophobic or had contra-indications for MRI were excluded. The present study was approved by the Institute's Ethics Committee. A written informed consent was obtained from all subjects (patients and healthy volunteers) before the initiation of study.

### 2.2. MRI

MR imaging of all the subjects was performed on an Achieva 3T MR imaging scanner (Achieva, Philips Healthcare, Best, Netherland) with an 8-channel head coil. The study included conventional MR imaging techniques including standard T2-weighted and T1-weighted, as well as Fluid Attenuation and Inversion Recovery (FLAIR), T2 gradient echo (GRE) and Diffusion weighted imaging (DWI) as per standard protocol to exclude presence of other structural lesions. MR imaging for structural analysis was performed with following parameters, slice thickness 1.0 mm, no gap, 160 sections, scanning time ~7 min 41 s, TR/TE 10/4.3 ms, number of signal-intensity averages 1, matrix 256 × 256, flip angle 8. The final voxel size was 1 mm ($x$) × 1 mm ($y$) × 1 mm ($z$).

### 2.3. Image processing

#### 2.3.1. Voxel based morphometry

The image processing was performed on Statistical Parametric Mapping 5 software (SPM5) using VBM tools 5.1 toolbox (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm).[26] VBM5 uses a unified segmentation approach that integrates image registration, MRI inhomogeneity bias correction, and tissue classification. The VBM tools 5.1 segmentation algorithm in SPM5 additionally warps the prior images to the data and tries to minimize the impact of the template and the prior images.[27] It also applies Hidden Markov Field model to the segmented images and removes the uncorrected voxels that were unlikely to represent determined tissue. The image pre-processing as integrated in VBM tools 5.1 involves a number of defined stages:

*Normalization of gray/white matter images*. The original T1 images were spatially normalized to MNI template image given in the SPM5 package, to generate optimally normalized whole brain template. Thus the images are in a uniform space so that a specific location in one subject's brain scan corresponds to the same location in another subject.

*Segmentation and extraction of normalized whole brain images*. The optimally normalized whole brain structural images, were then segmented into gray and white matter images.

*Modulation*. As a result of nonlinear spatial normalization, the volumes of certain brain regions may grow, whereas others may shrink. In order to preserve the volume of a particular tissue (gray or white matter or CSF) within a voxel, modulation and smoothening were required. This involved multiplying (or modulating) voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step.

*Smoothing*. The modulated gray matter images were then smoothed with a Gaussian filter to make the data less noisy. The previous modulation step itself involves some smoothening in its process.[27] We used Gaussian filter of 8 mm Full width half maximum (FWHM) for smoothening. The process of smoothing conditioned the residuals to conform more closely to the Gaussian random field model underlying the statistical process used for adjusting '$p$' values.[28]

This normalized, segmented, modulated, and smoothed gray matter images with a voxel size of 1 $mm^3$ were used for further statistical analysis. On VBM statistical analysis, initially comparison was performed between the whole brain GM followed by the region of interest (ROI) based the comparison using the standard thalamic mask from Oxford thalamic connectivity atlas.[30] The group comparisons between patients and controls were performed using Analysis of Covariance (ANCOVA), within the framework of general linear model in SPM5. Multiple regression model in SPM5 was used to evaluate the GM areas correlating with disease duration and age of onset as the main regressor. For all these SPM tests we used age, sex, and ICV as nuisance regressor in the design matrix (confounding covariates) and a priori decided significance level of false discovery rate (FDR) corrected $P < 0.05$. The coordinates of the significant voxels were converted into talairach space.

#### 2.3.2. FSL-FIRST

FSL-integrated registration and segmentation toolbox (FSL-FIRST) software, version (1.2) (http://www.fmrib.ox.ac.uk/fsl/first/index.html) was used for both evaluation of deep sub cortical structures.[29] FSL-FIRST is a model based automated registration/segmentation tool. The subcortical structures, viz. bilateral hippocampus, amygdala, caudate, putamen and thalamus were segmented from the T1-weighted MR images using FSL-FIRST. The deformable surfaces of deep GM structures were used to automatically parameterize the volumetric labels in terms of meshes. The normalized intensities along the surface of meshes were sampled and modeled. The shape and appearance model was based on multivariate Gaussian assumptions. Shape was then expressed as a mean with modes of variation (principal components).[29] After the automated segmentation by the software

the segmentations were manually checked and confirmed for the proper segmentation of all the subcortical structures. Following the vertex-wise shape analysis along with the surface of the segmented subcortical structures was performed using age, sex and total brain volume as covariate of no interest in the statistical design at $p < 0.05$ FDR corrected.[29] The volumes of thalamus, hippocampus, amygdala, caudate and putamen were extracted and statistical comparison was performed using SPSS 15 software.

*2.3.3. Statistics*

For all the non-SPM/FSL analysis, the data was tested for normal distribution before implementing parametric tests. Comparison between groups was done by independent sample t test and analysis after adjusting for covariates (age, sex and ICV) was carried out by general linear model (GLM) with categorical variables as fixed effect and continuous variables as covariates. Analysis of relationship between volumes of the structures with disease duration and age of onset of seizures was done using partial correlations after adjusting age and ICV correlation coefficient ($r$). For all the non-SPM/FSL analysis a priori decided significance level of $p < 0.05$ was considered statistically significant with Bonferroni correction applied for multiple testing.

## 3. Results

### 3.1. Clinical characteristics

The demographic and clinical characteristics of the patients are given in Table 1.

### 3.2. MRI characteristics

*3.2.1. Voxel based morphometry*

The VBM analysis comparing the subjects and controls did not reveal any areas with significant GM difference ($p < 0.05$, FDR corrected). The VBM analysis with thalamic mask, revealed that the patients with JME had significant GM differences in the medial aspect of the bilateral thalami (Fig. 1).

*3.2.2. Volumetry*

Comparison of volumes of thalamus, hippocampus, caudate nucleus, putamen, amygdala, total WM and total GM between the patients and healthy controls is summarized in Table 2. The thalamic volumes were significantly decreased in the patients relative to the healthy controls ($p < 0.05$). Rest of the subcortical structure volumes did not show any significant volume differences.

**Table 1**
The demographic and clinical characteristics of patients with JME.

| Features | JME ($n = 40$) |
|---|---|
| M:F | 21:19 |
| Age at evaluation (years) | 22.8 ± 5.3 |
| Age at onset (years) | 15.4 ± 5.01 |
| Onset of illness <15 years | 16 |
| Duration of illness (years) | 7.2 ± 5.17 |
| Age at first evaluation (years) | 16.5 ± 5.5 |
| Age at diagnosis (years) | 20.5 ± 4.5 |
| Delay in diagnosis (years) | 5.05 ± 4.08 |
| Delay in diagnosis >5 years | 24 |
| GTC seizure | 37 |
| Myoclonus | 40 |
| Absence seizure | 3 |
| Worsening on awakening | 37 |
| EEG showing spike/polyspike | 27 |

*3.2.3. Volume correlation with clinical parameters*

The disease duration showed significant correlation with the total GM volume ($r = -.354$, $p = 0.032$), left hippocampus ($r = -0.339$, $p = 0.040$), right amygdala ($r = -.384$, $p = 0.035$), right caudate nucleus ($r = -.384$, $p = 0.019$) and right hippocampus volumes ($r = -.353$, $p = 0.032$). After applying corrections for age, sex and ICV, the left hippocampus volume showed significant correlation with the duration of JME ($r = -.382$, $p = 0.024$), while the right hippocampus volume showed significant correlation with the age at onset of illness ($r = .388$, $p = 0.021$).

*3.2.4. Vertex based shape analysis*

The shape analysis (FDR corrected, $p < 0.05$) revealed regional areas of significant shape difference in the bilateral thalami as compared to the healthy controls (Fig. 2). Analysis showed presence of regional shape abnormality in medial as well as lateral aspects of the bilateral thalami. No areas of regional expansion were noted when compared to the healthy controls. Other structures did not show any morphological changes on shape analysis. Shape analysis did not show any correlation with the disease duration and age at onset of symptoms.

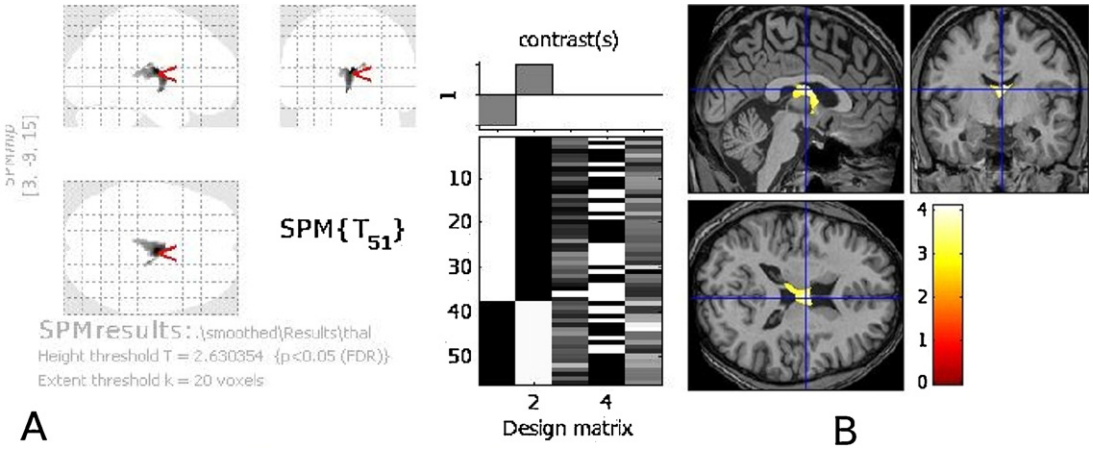


**Fig. 1.** Statistical parametric map (SPM) result of comparison between the patients with JME and controls with the region of interest analysis using the thalamic mask at statistical significance level of $p < 0.05$ (FDR corrected) and adjusted for age, gender and ICV. Statistical design matrix isalso displayed. (A) shows the results in glass brain (B) shows the areas of significant result on the T1W MRI image. Significant alterations noted in the superomedial aspect of bilateral thalami. ICV: intracranial volume; FDR: false discovery rate.

**Table 2**
Summary of subcortical volumes in patients with JME and controls.

| Subcortical areas of brain | JME | | Controls | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *p* |
| Left amygdala ($mm^3$) | 1118.6 | 223.3 | 1182.2 | 238.1 | NS |
| Right amygdala ($mm^3$) | 1156.9 | 325.4 | 1214.8 | 226.6 | NS |
| Left caudate ($mm^3$) | 3238.7 | 409.5 | 3540.0 | 428.0 | NS |
| Right caudate ($mm^3$) | 3389.0 | 417.5 | 3664.7 | 566.7 | NS |
| Left putamen ($mm^3$) | 4476.0 | 555.0 | 4807.3 | 422.7 | NS |
| Right putamen ($mm^3$) | 4656.9 | 540.3 | 4983.3 | 531.7 | NS |
| Left thalamus ($mm^3$) | 6826.7 | 644.7 | 7826.2 | 639.9 | <0.001 |
| Right thalamus ($mm^3$) | 6560.9 | 622.4 | 7550.4 | 669.4 | <0.001 |
| Left hippocampus ($mm^3$) | 3474.2 | 584.3 | 3693.8 | 631.5 | NS |
| Right hippocampus ($mm^3$) | 3601.5 | 555.5 | 4032.8 | 443.0 | NS |
| Total GM ($cm^3$) | 590.6 | 101.8 | 693.1 | 123.8 | NS |
| Total WM ($cm^3$) | 323.6 | 57.8 | 399.7 | 84.5 | NS |
| TBV ($cm^3$) | 914.2 | 156.5 | 1092.7 | 206.2 | NS |
| ICV ($cm^3$) | 1329.8 | 123.2 | 1432.8 | 157.9 | NS |

TBV: total brain volume; ICV: intracranial volume; GM: gray matter; WM: white matter; NS: not significant.

## 4. Discussion

The current study evaluated patients with JME using structural MRI techniques, namely VBM, volumetry and shape analysis, for identifying abnormalities of deep gray matter structures and hippocampus. Using multiple techniques, we could demonstrate thalamic morphological changes in JME. Shape analysis results revealed regional shape differences in the thalamus of these patients. Further, significant correlation was noted between the hippocampal volumes and disease duration suggesting hippocampal structural alterations with prolonged illness in patients with JME.

Previous results of VBM in JME have been inconsistent. Some authors have reported increased GM concentration in the basifrontal region[9] while others have observed decreased GM concentration in the prefrontal region.[12,20] Tae et al. reported decreased cortical thickness in the frontal lobe.[14] Previous VBM studies have also reported increased GM concentration in the mesial frontal region.[7,10] Roebling et al. attributed these differences in the results of previous imaging studies to the differences in study population, small sample size, methodological differences and underlying genetic heterogeneity.[32] Another major reason for differences in earlier report was the use of different statistical thresholds selected for reporting of results. In the study of Liu et al., the corrected VBM analysis showed no differences between patient and control groups, the spatial extent cluster corrected VBM analysis suggested a trend of gray matter volume reduction in frontal and central regions.[33] Similarly, in the study by Roebling et al., no differences were found and they used fully corrected VBM analysis.[32]

The current study applied standard technique with similar stringent statistical significance levels as used in earlier studies.[32,33] We also applied corrections for age, sex and ICV, as these factors might also significantly influence the results. However, on using mask to observe for local changes in VBM analysis, focal thalamic abnormality was observed. This was supported by shape analysis which revealed multiple areas of focal shape abnormalities in the thalamus. Our results indicate presence of regional thalamic abnormalities in JME which could not be detected on using whole brain analysis method. However with regards to the thalamic structural changes also, variables findings have been reported with some studies refuting presence of any alterations of thalamus,[9,22,34] while others reporting focal thalamic alterations.[10,20] MRS studies have shown neuronal loss in the form of decreased NAA/Cr in the thalamus.[16,31] Functional imaging study using SPECT has also revealed perfusion disturbance in the thalamus.[13]

In our study, we observed structural changes in the thalamus using multiple methods of evaluation and large areas of focal shape differences were seen in the anteromedial as well as lateral aspect of the thalamus. Neuropsychological assessment of JME subjects has shown presence of executive dysfunction which also correlated with the thalamic and frontal atrophy in JME patients.[11] These findings suggest that the thalamus might be a structural correlate of the clinical dysfunction observed in these patients. Though speculative, absence of structural changes in the thalamus in whole brain VBM might be due to low prevalence of absence seizures in our study cohort.

Previous VBM results[10] and SPECT study[13] found focal atrophy and hypoperfusion of the ventrolateral thalami respectively, while Mory et al.[18] reported focal differences in the anterior and inferior aspects of the thalamus. Focal abnormalities in the thalamus are supported by involvement of specific thalamic nuclei noted during spike wave discharges. Anterior, centromedian and parafascicular nuclei activity has been recorded during the EEG-fMRI recordings in idiopathic generalized epilepsy.[35] Executive dysfunction observed in the patients with JME also supports the involvement of the anterior thalamic nucleus which in turn projects to the frontal lobe. In future, improved MR resolution may allow us to identify abnormalities of individual thalamic nuclei with greater confidence however results of the present study may be secondary to abnormalities of the anterior and centromedian nuclei.

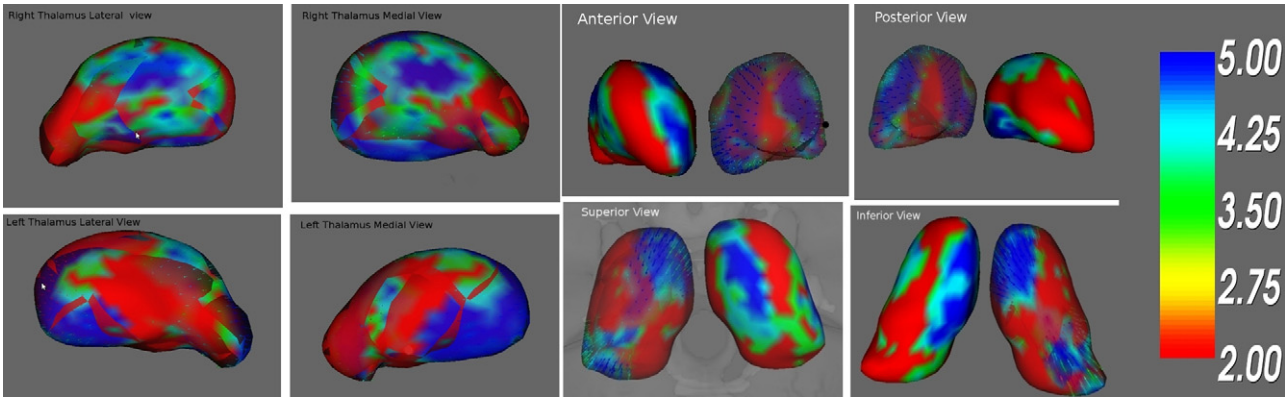


**Fig. 2.** Comparison of the patients with JME and controls using vertex wise shape analysis of thalamus. The results are viewed from all the directions, with the color bar indicating the *Z* score map; an increase from red to blue is going from a lower to higher statistical significance. Results are statistically significant at $p < 0.05$ (FDR corrected) and adjusted for age, sex and TBV. Anteromedial as well as lateral aspects of bilateral thalami showing significant regional volume changes. TBV: total brain volume; FDR: false discovery rate. (For interpretation of the references to color in the artwork, the reader is referred to the web version of the article.)

The basal ganglia structures are possibly not directly involved in the genesis of seizures but have been found to affect the cortical excitability as well as modulating the seizure activity.[36,37] In an animal model with mutation affecting the BRD2 gene, it was shown that animal with mutated gene had increased susceptibility to GTCS and pathological analysis showed loss of GABAnergic neurons in the neocortex, striatum, substantia nigra and ventral medial thalamic nucleus.[21] The BRD2 gene has been linked with the presence of JME in humans.[21] The putaminal abnormalities have been found using 18F-Fallypride ([18F]FP) positron emission tomography (PET), which demonstrated reduced dopamine binding on the D2/D3 receptor of the posterior putamen in patients with JME.[38] Keller et al. have shown increased fractional anisotropy and decreased volume of putamen in patients with JME.[19]

One previous MRI study had evaluated basal ganglia for the presence of structural changes using the technique of volumetry and authors found decreased volume of putamen and caudate nucleus in JME patients.[22] In another investigation where subjects of IGE with only GTCS were studied, volumetry revealed significantly decreased volumes of putamen and caudate nucleus.[20] In our study structural abnormality in striatal regions in the subjects were not detected. This variable result might be due to differences in the study population, underlying genetic factors and methodological differences. In our study, the majority of patients was on treatment for variable duration as well as had all the seizure types known to occur in JME. These factors might also contribute toward variable results. JME is a genetically heterogeneous disease and has been associated with multiple gene mutations. Further, these mutations have not been universally present in all the ethnic populations.[21] This genetic heterogeneity and study of different population in previous imaging literature may also account for variable results. Another possibility is that basal ganglia may be functionally or biochemically abnormal as revealed by MRS or PET studied but may not necessarily show morphological alterations.

Bernasconi et al. speculated that the abnormalities observed in patients of JME are related to disease duration and they increase with passage of time.[19] However, Pulsipher et al. found significant volumetric abnormalities in patients of JME who were analyzed relatively early in the course of the disease.[11] They reported significant neuropsychological abnormalities in these patients that correlated with the volume loss observed on MRI study. They hypothesized that structural abnormalities are present even before the onset of first seizure and they are possibly developmental in origin.[11] In the current study, lack of correlation between seizure duration and volumetry of thalamus supports the observations of Pulsipher et al.[11]

The other important finding in our study was significant correlation between hippocampus volumes and disease timeline variables like disease duration and age at onset of disease. However, no significant hippocampal changes were noted in JME subjects in both volumetric and shape analysis. Previous morphological studies have not been able to show structural abnormalities of the hippocampus; however temporal lobe volume loss was reported by Tae et al.[12,14] In one of the SPECT study decreased rCBF was noted in the left hippocampus.[13] One recent MRS study has also reported abnormal metabolite ratios in the both hippocampi.[23] Serotonin 1A receptor binding potential measured with PET has revealed reduced binding potential in the hippocampus of patients of JME.[39] Although hippocampus is not directly involved in the pathophysiology of JME, hippocampal abnormalities have been documented in previous studies. Correlation has been observed between the disease duration and age at onset of disease in our study indicates presence of progressive hippocampal damage. For definite conclusion we need to do serial evaluation to look for progressive changes. Correlation with seizure frequency and number of seizures may also be useful. These changes might be related to seizure spread leading to secondary hippocampal damage reflected in structural and functional impairment revealed by MRS and SPECT.

This study does not allow us to conclude cause-effect relations for the JME and only makes an attempt to identify structural changes in the subcortical structures. Important limitations of our study are modest sample size and lack of longitudinal evaluation to confirm these findings. Longitudinal study may give answers to many important questions like whether the structural changes are progressive in nature or remain unchanged. It may also allow studying the effects of medication and seizure control on brain morphology. Another limitation was the possible effect of seizure subtypes on structural abnormalities which may be one of the important reasons for variations in the results of previous neuroimaging studies. Selecting more homogenous seizure types in future studies may provide better understanding about the morphological changes in JME. However, this could not be carried out in our study as there were only three patients with absence seizures while majority had GTCS and myoclonic jerks. Another factor that was not taken into account was the use of AEDs which may also influence the brain morphology.[40] Therefore these results needs to be interpreted with caution and larger studies are required to verify these findings.

In conclusion, the present study demonstrated structural alterations in specific thalamic regions in patients with JME; however it did not find any significant volume loss or shape abnormality of striatum, amygdala and hippocampus. Shape analysis is a useful adjunct to other structural analysis methods as it may reveal complementary information.

## Acknowledgment

This study was supported by partial funding from the Department of Science and Technology, Govt. of India, New Delhi (SR/SO/HS/108/2007). We appreciate the sincere efforts of Dr. P.R. Naidu, MD; Medical advisor, Biocon Ltd. for copy/editing the manuscript.

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