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Extrafrontal structural changes in juvenile myoclonic epilepsy: A topographic analysis of combined structural and microstructural brain imaging

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ABSTRACT

Purpose: An increasing amount of evidence has demonstrated that juvenile myoclonic epilepsy (JME) is associated with structural abnormalities in not only the thalamofrontal system but its adjacent regions such as temporal or parieto-occipital areas. The goal of this study was to systematically characterize morphological changes and the subsequent pathophysiological implications in JME patients using the combined structural and diffusion tensor MRI analysis.
Methods: Comparisons of white matter (WM) water diffusivity and gray matter (GM) cortical thickness were analyzed with tract-based spatial statistics (TBSS) and a Constrained Laplacian-based Anatomic Segmentation with Proximity (CLASP) algorithm, respectively. Additionally, volumes of the bilateral thalami and hippocampi were obtained using manual volumetry (MV).
Results: Compared with 22 normal controls, 18 patients with JME exhibited WM alterations in the antero-superior corona radiata, corpus callosum, both centro-parietal regions, and the left temporal lobe. JME patients also had reduced GM thickness (right paracentral lobule, precuneus, dorsolateral parietal and inferior temporal cortex; left dorsolateral frontal and anterior temporal areas). Furthermore, MV analyses revealed a significant volume reduction in the bilateral thalami and hippocampi.
Conclusions: In addition to structural changes in the thalamofrontal system, there was a conspicuous alteration of WM diffusivity in widespread extra-frontal areas and an associated decreased GM thickness in temporoparietal regions, including a significant reduction of hippocampal volume. These findings suggest that the pathophysiology of JME may be not confined to the thalamofrontal circuit but may also involve extensive areas of the extra-frontal network which encompasses temporo-parietal regions.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalized epilepsy (IGE) that comprises approximately 8–10% of all epilepsies and is characterized by an age-specific onset of myoclonic jerks, generalized tonic–clonic seizures (GTCs), and absence seizures [1]. Seizures generally occur in the early morning or after awakening, and typical electroencephalography (EEG) findings show a 4–6 Hz rapid generalized spike-wave discharge (GSWD) pattern or a polyspike-wave discharge (SWD) pattern [2].

In general, JME patients do not appear to have structural abnormalities following conventional neuroimaging. Recently, however, several studies investigating JME patients have revealed microstructural and functional changes when using state-of-the-art imaging techniques. For example, studies using voxel-based analyses found topographical abnormalities in frontal cortical gray matter (GM) concentration and volume [3–5]. Moreover, studies using diffusion tensor imaging (DTI) or magnetic resonance spectroscopy (MRS) analyses observed changes in white matter (WM) and GM connectivity that indicated abnormal function within the thalamofrontal network in JME patients [6,7]. An emphasis on abnormal function in the frontal lobe of JME patients

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was reinforced by findings from neuropsychological testing [8] and EEG analyses [9], but several recent studies have also identified extra-frontal, focal cortical, and regional abnormalities [4,10]. Several volumetry and MRS studies revealed the hippocampal structural changes in JME, that suggest the hippocampus has important role in JME patient [11,12].

Therefore, the purpose of this study is to investigate the structural changes beyond the thalamofrontal network in JME patients. We use combined structural and microstructural neuroimaging analysis techniques to clarify the microstructural characteristics of cortical GM (surface analysis) and WM (DTI analysis) and their related subcortical structures (thalamus and hippocampus manual volumetry).

2. Methods

2.1. Subjects

This study included 18 right-handed JME patients who were followed for at least 1 year in the outpatient epilepsy clinic at Yeouido St. Mary's Hospital. All JME patients were diagnosed using the International League Against Epilepsy (ILAE) criteria for epilepsy and epileptic syndromes. The neurological exams of all patients were normal, and none of them demonstrated evidence of developmental delays or cognitive impairments on the mini-mental state examination (MMSE; score $\geq$ 28/30).

Additionally, 20 right-handed subjects with no familial or personal history of neurological, medical, or psychiatric disorders were recruited as normal controls. Control subjects were selected to exclude those without a history of seizure-like episode, syncope, head trauma or family history of epilepsy. All control subjects underwent conventional magnetic resonance imaging (MRI) and neurological examinations and did not show neurological abnormalities or have a history of drug or alcohol abuse. A board certificated radiologist and neurologist reviewed all control's brain MRI and data of neurological examination. If abnormal or unusual findings were seen on the conventional MRI or neurological exam, they were excluded. This study was approved by the local ethics committee, and all subjects provided informed consent.

2.2. MRI acquisition

Conventional MRI, DTI, and high resolution T1-weighted spoiled gradient echo (SPGR) MRI scans were obtained using a 1.5-Tesla MRI scanner (Signa Excite 11.0; GE Medical Systems; Milwaukee, WI, USA). DTI scans were acquired using a diffusion sensitizing gradient (b value = 1000 s/mm^2) along 25 directions in conjunction with axial images without diffusion weighting (b value = 0). All scans had the following characteristics: repetition time (TR) = 10,000 ms, echo time (TE) = 83.3 ms, matrix size = 128 mm $\times$ 128 mm, field of view (FOV) = 260 mm $\times$ 260 mm, number of excitations (NEX) = 1, 33 axial slices, and slice thickness = 4 mm with no inter-slice gap. For the SPGR analyses, approximately 128 adjacent axial slices parallel to the anterior–posterior commissure (AC-PC) line were obtained. All scans had the following characteristics: TR = 22 ms, TE = 6.0 ms, flip angle = 10, FOV = 256 mm $\times$ 256 mm, matrix size = 256 $\times$ 256, NEX = 1, voxel size = 0.94 mm $\times$ 0.94 mm, and slice thickness = 1.4 mm. A standard correction for field inhomogeneities was applied.

2.3. DTI processing and analysis

The raw DTI data (DICOM files) were converted to a single multivolume NIfTi file using dcm2nii software (http://www.cabiatl.com/mricro/mricron/dcm2nii.html). These DTI files were preprocessed using FMRIB's Diffusion Toolbox (FDT), a part of FSL 4.1 (http://www.fmrib.ox.ac.uk/fsl). All DTI files underwent eddy current correction for head motion correction, and the brain extraction tool (BET), a part of the FSL program, was utilized to remove non-brain structures by applying a threshold of 0.3. Subsequently, fractional anisotropy (FA) and mean diffusivity (MD) maps were generated using DTI-FIT.

A tract-based spatial statics (TBSS) algorithm, which contains the image registration and a creation of the skeleton image, was applied to analyze the data. Each skeletonized FA and MD image was then used for the voxel-wise analyses using a nonparametric test with 5000 random permutations in the "Randomise" program (http://www.fmrib.ox.ac.uk/fsl/randomise/index.html). A two sample t-test was employed for between-group comparisons with intracranial volume (ICV), age and sex treated as covariates of no interest. Statistical significance was thresholded at $p < 0.05$ and was corrected for multiple comparisons with a threshold-free cluster enhancement (TFCE).

2.4. Cortical thickness analysis

Data from one JME patient and two control subjects were excluded due to the poor quality of the SPGR images. Thus, the final sample utilized for this study was comprised of 17 JME patients and 18 normal control subjects. The MR images were first processed using the CIVET MRI analysis pipeline (version 1.1.9) that was developed at the Montreal Neurological Institute (MNI) to automatically extract and co-register the cortical surfaces for each subject. The main pipeline processing steps included the following: (1) the native three-dimensional structural MRI scan of each subject corrected for non-uniformity using the N3 algorithm, (2) brain volume classified into GM, WM, cerebrospinal fluid, and background using the INSECT algorithm, (3) the Constrained Laplacian-based Anatomic Segmentation with Proximity (CLASP) algorithm applied to generate a model of the cortical surface, which was composed of 40,962 vertices and 81,920 triangular meshes for each hemisphere, and (4) cortical thickness measured using the t-link metric, which computes the Euclidean distance between the linked vertices, respectively, of the inner and outer cortical surfaces [13]. To compare the thickness of corresponding regions between subjects, thickness values were spatially normalized using a surface-based two-dimensional registration with a sphere-to-sphere warping algorithm in which the vertices of each subject were nonlinearly registered to an average template on the sphere by matching the crowns of gyri between subjects with a crown-distance transformation. Diffusion smoothing with a full-width half-maximum (FWHM) of 20 mm was used to blur each map of cortical thickness, which increased the signal-to-noise ratio as well as the statistical power [14]. In order to analyze localized differences and the statistical map of cortical thickness on the surface model, an analysis of covariance (ANCOVA) was performed on a vertex-by-vertex basis and was corrected for multiple comparisons. Additionally, a statistical map of differences in cortical thickness between the groups was constructed using a surface model with ICV, age and gender as a covariate.

2.5. Volume measurements of the hippocampus and thalamus

The regions of interest (ROIs), which encompassed the hippocampus and thalamus, were manually outlined for segmentation using sequential oblique coronal T1-weighted MRI. The SPGR T1 sequence images were converted into cubic voxel dimensions of 0.89 mm^3 and reoriented to the hippocampal axis. The horizontal axis was parallel to a line extending from the rostral pole to the caudal pole of the hippocampus. A single expert (JH Cho) blinded to all identities and characteristics of the subjects