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Subcortical grey matter changes in juvenile myoclonic epilepsy

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ABSTRACT

Recent neuroimaging studies have provided converging evidence of structural and functional abnormalities of the thalamus in patients with juvenile myoclonic epilepsy (JME). There has also been limited evidence indicating involvement of the subcortical grey matter structures other than thalamus in JME, but with inconsistent findings across the studies. In the present study, we combined volumetric MRI and diffusion tensor imaging analyses to investigate macrostructural and microstructural alterations of the subcortical grey matter in 64 JME patients compared to 58 matched control subjects. Raw volume, fractional anisotropy (FA), and mean diffusivity (MD) of 6 subcortical grey matter structures (amygdala, hippocampus, caudate, pallidum, putamen, thalamus) were measured in both hemispheres. Between-group (controls versus patients) comparisons of normalized volume, FA, and MD, as well as within-group (patients) correlation analyses between structural changes and clinical variables were carried out. Compared to controls, JME patients exhibited significant volume reductions in left pallidum and bilateral putamen and thalamus. Duration of epilepsy negatively correlated with bilateral putamen volumes. Patients and controls did not differ in FA values of all structures. Compared to controls, JME patients showed significant MD increases in left pallidum and bilateral hippocampus, putamen, and thalamus. Significant positive correlations were found between duration of epilepsy and MD values of bilateral hippocampus and thalamus. We have provided evidence that macrostructural and microstructural abnormalities may not only be confined to the thalamus but also affect basal ganglia and hippocampus in JME. Our findings could further support the pathophysiological hypothesis of striato-thalamo-frontal network abnormality underlying JME, and may implicate disease progression.

1. Introduction

Juvenile myoclonic epilepsy (JME) represents a common subsyndrome of idiopathic generalized epilepsy (IGE) with a strong genetic basis, accounting for approximately 4%–10% of all epilepsies (Camfield et al., 2013). It usually begins in the age at puberty and is clinically characterized by myoclonic jerks of the upper extremities preferentially occurring early in the morning, generalized tonic-clonic seizures (GTCS), and, less frequently, absence seizures (Janz, 1985). Typical interictal electroencephalography (EEG) features of JME consist of 3–6 Hz generalized spike-wave or polyspike-wave discharges on a normal background, dominantly with frontocentral accentuation.

The fundamental pathogenesis of JME remains elusive; however, cumulative evidence over the decades has suggested that the thalamus along with aberrant thalamocortical circuit plays a pivotal role in the generation of generalized spike-wave discharges (Blumenfeld, 2005). In support of this finding from experimental studies, a number of neuroimaging studies have provided converging evidence of both structural and functional abnormalities of the thalamus in patients with JME (Anderson and Hamandi, 2011; Seneviratne et al., 2014). These abnormalities included thalamic volume reduction (Kim et al., 2013; Kim et al., 2007; Mory et al., 2011; Pulsipher et al., 2009), metabolic dysfunction (Bernasconi et al., 2003; Hattingen et al., 2014; Helms et al., 2006; Lin et al., 2009a), altered microstructural integrity of the thalamocortical network (Deppe et al., 2008; Keller et al., 2011; Kim et al., 2012; von Podewils et al., 2015), increased thalamic blood oxygenation level-dependent activity in relation to generalized spike-wave discharges (Gotman et al., 2005; Pugnaghi et al., 2014; Tyvaert et al., 2009), and thalamocortical functional dysconnectivity (Ji et al., 2015; Kim et al., 2014; McGill et al., 2014; O'Muircheartaigh et al., 2012).

The other subcortical grey matter (GM) structures have currently received less attention than thalamus due to a robust finding of thalamic involvement in JME. A few MRI studies showed a reduction in volumes of putamen (Ciumas et al., 2008; Keller et al., 2011; Seeck et al., 2005) and hippocampus (Kim et al., 2015; Lin et al., 2013) in JME patients in comparison with healthy controls. However, the

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majority of above-mentioned studies used relatively a small number of subjects, and the main findings were inconsistent across the studies and not replicated in others (Goldberg et al., 2014; Saini et al., 2013). To our knowledge, there is no currently available study that comprehensively examined microstructural integrity of the subcortical GM structures using diffusion tensor imaging (DTI) in JME. DTI is an advanced and noninvasive MRI technique that can detect the magnitude and directionality of water diffusion in vivo. The most widely used parameters derived from DTI are fractional anisotropy (FA) and mean diffusivity (MD), both of which can provide complementary information on microstructural integrity of the white matter tracts. Although DTI has been primarily developed to evaluate white matter integrity, it is now increasingly used to investigate microstructural changes of GM, particularly the subcortical GM (Cherubini et al., 2010; Luo et al., 2011). In the present study, we combined volumetry and DTI analysis to investigate macrostructural and microstructural alterations of the subcortical GM in a large cohort of JME patients compared with matched healthy controls. We predicted that structural alterations may not only be restricted to the thalamus but also affect other subcortical GM in patients with JME. These in turn would be reflected in the disease status of the patients, as predicted by their clinical variables (i.e., disease duration, seizure frequency).

2. Methods

2.1. Participants

We prospectively recruited 67 patients with JME who were followed up in the outpatient epilepsy clinic of Korea University Guro Hospital. Thirty-three patients were identified from our previous studies (Kim et al., 2012; Kim et al., 2013; Kim et al., 2014). The diagnosis of JME was based on electroclinical criteria according to the ILAE (International League Against Epilepsy) classification. Inclusion criteria we used were as follows: (1) myoclonic seizure preferentially occurring early in the morning, with or without GTCS or absence seizure; (2) seizure beginning from the teens or early twenties; (3) normal neurological examination; (4) normal cognitive functions as briefly assessed by a Mini-Mental State Examination score of 28 or higher (Crum et al., 1993); (5) at least one EEG disclosing typical 3–6 Hz generalized spike-wave discharges on a normal background; and (6) neither abnormal nor unusual findings on clinical MR images. Patients with co-morbid neurological, psychiatric, or chronic systemic disorders were excluded. Demographic data and clinical information such as seizure semiology, age of seizure onset, duration of epilepsy, total number of GTCS, and current antiepileptic drugs were obtained through interviews with the patients and their parents and reviews of medical records.

For group comparison, 60 healthy volunteers matched for age, gender, and education years were prospectively recruited to serve as controls. All control subjects underwent neurological examination and a detailed interview to ensure that they had (1) no neurological abnormality and global cognitive impairment (Mini-Mental State Examination score ≥ 28/30) (Crum et al., 1993); (2) no history of neurological, psychiatric, or systemic disorders; (3) no family history of epilepsy; and (4) no history of alcohol or drug abuse. Control subjects with abnormal MRI findings were also excluded. The local ethics committee approved the study protocol, and all participants gave written informed consent prior to study inclusion.

2.2. MRI data acquisition

All participants were scanned on a Siemens Trio 3T scanner (Erlangen, Germany) with a 12-channel phased array head coil. For identification of structural abnormalities, the following clinical MR images were acquired: axial T2-weighted and fluid-attenuated inversion recovery images (4 mm thickness), and oblique coronal T2-weighted and fluid-attenuated inversion recovery images perpendicular to the long axis of hippocampus (3 mm thickness). The MR images were reviewed by a board-certified neuroradiologist (S.I.S.) for any structural abnormalities and reported as normal in all participants.

For volumetric analysis, a high-resolution 3D magnetization-prepared rapid gradient-echo sequence was acquired using the following parameters: TR = 1780 ms, TE = 2.34 ms, matrix = 256 × 256, FOV = 256 × 256 mm, voxel size = 1 mm^3. For DTI analysis, a single-shot spin-echo echoplanar imaging sequence was acquired with the following parameters: 30 noncollinear diffusion directions (b-value = 1000 s/mm^2) with two nondiffusion gradient (b-value = 0 s/mm^2), TR = 6500 ms, TE = 89 ms, matrix = 128 × 128, FOV = 230 × 230 mm, voxel size = 1.8 × 1.8 × 3 mm^3. The acquisitions were repeated two times to improve the signal-to-noise ratio and to reproduce more diffusion directionalities. Particular attention was taken to center the subject in the head coil and to restrain head movements with cushions and adhesive medical tape. Resting-state functional MRI data were acquired simultaneously but not included in the current analysis. All patients reported no seizure during the scanning.

2.3. Volumetric analysis

Image preprocessing and volumetric measurement were performed using FMRIB's Software Library (FSL 5.0.9, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Automated segmentation of the subcortical GM was carried out using FIRST (FMRIB's Integrated Registration and Segmentation) that uses Bayesian probabilistic approach, as described in detail elsewhere (Patenaude et al., 2011). Briefly, registration in FIRST comprises an affine transformation (12 degrees of freedom) of the raw, volumetric T1-weighted images to MNI 152 standard space. After subcortical registration, subcortical masks were applied in order to locate the different subcortical structures, followed by segmentation based on shape models and voxel intensities. All segmentations were visually inspected for accuracy prior to inclusion in the analysis. Absolute volumes of bilateral amygdala, hippocampus, caudate, pallidum, putamen, and thalamus were measured in cubic millimeters. To reduce the effects of inter-individual variability in head size, volumetric scaling factor was obtained for each subject by using SIENAX tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) from the corresponding volumetric T1-weighted image. Thus, normalized volume for each GM was obtained by multiplying the measured volume from FIRST by the volumetric scaling factor from SIENAX.

Data were first tested for normality of distribution and homogeneity of variance assumption using Kolmogorov-Smirnov test and Levene test, respectively. Differences in normalized volumes of 12 GM structures between patients and controls were assessed by analysis of covariance with age, gender, and education years as nuisance covariates. Given the number of multiple comparisons, all p values were adjusted for multiple significance testing using the false discovery rate (FDR) adjustment by Benjamini and Hochberg (Benjamini and Hochberg, 1995). This adjustment avoids the inflated rate of false negatives arising from Bonferroni adjustments while still controlling for false positives, and has been recommended for use in health studies (Glickman et al., 2014). Statistical significance was thresholded at FDR-corrected $p < 0.05$ in all between-group comparisons. Possible relationships were explored between normalized volumes of significant between-group differences and duration of epilepsy and total number of GTCS using Pearson or Spearman correlation analysis, where appropriate. In addition, partial correlation coefficients were computed between volumes and duration of epilepsy while controlling for the effect of age at seizure onset. Correlations between volumes and duration of epilepsy could not be corrected for age due to the multicollinearity between age and duration of epilepsy (Pearson correlation coefficient, $r = 0.901$, $p < 0.000001$, variance inflation factor = 5.300). All p values for correlations were further corrected for multiple comparisons using FDR (corrected $p < 0.05$). Statistical analyses were performed with the Statistical