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Cerebellar white matter changes in patients with newly diagnosed partial epilepsy of unknown etiology

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ABSTRACT

Objective: We hypothesize that pre-existing susceptible structures in the brain may be associated with the development of newly diagnosed partial epilepsy of unknown etiology.
Methods: Twenty-two patients with newly diagnosed partial epilepsy of unknown etiology and 36 healthy controls were enrolled in this study. In addition, we included 24 patients with chronic partial epilepsy of unknown etiology as a disease control group. We analyzed whole-brain T1-weighted MRIs using FreeSurfer 5.1. The volumes of the hippocampus, amygdala, thalamus, caudate, putamen, pallidum, brainstem, cerebellar gray and white matter, as well as cerebral gray and white matter were compared between the groups. We also analyzed the changes in brain volumes associated with the chronicity of epilepsy in the patients with chronic epilepsy compared to newly diagnosed epilepsy.
Results: The volume of cerebellar white matter in patients with newly diagnosed epilepsy was significantly smaller than that which was observed in the healthy controls ($p = 0.0001$). This finding was also observed in patients with chronic epilepsy ($p < 0.0001$). Cerebral white matter volume was negatively correlated with the duration of epilepsy ($r = -0.4$, $p = 0.04$).
Conclusion: These findings support our hypothesis that cerebellar white matter changes may constitute a pre-existing susceptible structure in the brain that is associated with the development of partial epilepsy of unknown etiology. In addition, cerebral white matter was the structure that was the most vulnerable to the progression of epilepsy.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, with partial epilepsy accounting for 70% of all epilepsy cases [1]. Structural lesions that are observed in brain magnetic resonance imaging (MRI) upon visual inspection can be found in approximately half of all epilepsy patients [1]. Moreover, there is growing evidence that the brains of patients with partial epilepsy have structural lesions and anatomic abnormalities beyond the lesions that are visually observable in MRI. Several studies have demonstrated, using voxel-based morphometry (VBM), a significant volume reduction in the hippocampus as well as in the extra-temporal gray matter of patients with mesial temporal lobe epilepsy and hippocampal sclerosis [2–6]. Previously studies have also found alterations in the extra-temporal white matter using diffusion tensor imaging (DTI) [5–7]. Although there are anatomic abnormalities beyond the visual lesions observed in MRI in patients with partial epilepsy with structural lesions, the pathogenesis of epilepsy might still be directly related to these visual lesions.

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However, the mechanism of partial epilepsy of unknown etiology is unclear. Epilepsy of unknown etiology is presumed to be symptomatic in nature and of an unidentified cause. Both genetic and environmental factors likely play a role to varying extents in individual patients. Nevertheless, a recent genome-wide association study with a large cohort did not identify common variants that influence the risk for epilepsy among patients with partial epilepsy of unknown etiology [8]. Meanwhile, there have been reports that there are anatomic abnormalities in patients with partial epilepsy of unknown etiology. Several reports have demonstrated a volume reduction in the thalamus, cerebellum, hippocampus, caudate, and cerebral white matter [6,9–11]; whereas other studies did not find any anatomic abnormalities in patients with partial epilepsy of unknown etiology [12,13]. These discrepancies are most likely due to methodological differences, such as the method of analysis, the correction for multiple comparisons, and the thresholds set for cluster extent. Furthermore, previous studies shared the problem of enrolling heterogeneous patient groups, thereby mixing patients with newly diagnosed epilepsy (NDE) with those who experienced chronic epilepsy (CHE) [2–7,9–13]. Thus, they could not determine whether the anatomic abnormalities existed before the onset of epilepsy or were the cumulative effects of seizure-induced damage. Therefore, studies that only include patients with NDE are needed. From these studies, we may obtain information concerning the role of pre-existing anatomic abnormalities before the onset of epilepsy in the development of epilepsy of unknown etiology. In this present study, we only enrolled patients with NDE to increase homogeneity, and we included patients with CHE as a disease control group.

VBM analysis does a voxel-by-voxel comparison to search for differences in volumes, whereas analysis using FreeSurfer image analysis suite can segment the brain into individual structures and directly measure the volumes of these structures [14–18]. There have been no studies that investigate the anatomic abnormalities in patients with newly diagnosed partial epilepsy of unknown etiology, especially using FreeSurfer image analysis suite. The aim of this study is to clarify whether the anatomic abnormalities existed before the onset of epilepsy in patients with newly diagnosed partial epilepsy of unknown etiology. We hypothesize that pre-existing anatomic abnormalities may be associated with the development of partial epilepsy of unknown etiology.

2. Materials and methods

2.1. Patient subjects

This study was conducted with the approval of the Institutional Review Board of our institution. This study was consecutively performed in a single tertiary hospital. We prospectively enrolled 22 patients with a clinical diagnosis of newly diagnosed partial epilepsy of unknown etiology. The diagnosis of epilepsy was made on the basis of clinical histories and electroencephalographic (EEG) findings. We excluded patients that had already displayed only auras or febrile convulsions before their first episodes of unprovoked epileptic seizures. All patients had normal MRI results upon visual inspection using conventional brain MRI protocols, including T1- and T2 weighted images and fluid attenuated inversion recovery (FLAIR) images. All patients had cryptogenic partial epilepsy using the International League Against Epilepsy (ILAE) classification [19] and had epilepsy of an unknown cause according to the current ILAE classification [20]. In addition, we included 24 patients with chronic partial epilepsy of unknown etiology as a disease control group. The definition for CHE in this study was that the epilepsy persisted for more than 2 years. Patients did not have any history of other neurological or psychiatric diseases due to the potential influence of these conditions on the brain atrophy. We collected demographic data such as age, sex, age of onset, and the duration of epilepsy from these patients at the time of the MRI.

2.2. Normal controls

The control group consisted of 36 age- and sex-matched healthy subjects. All subjects had a normal neurological examination and no history of cardiovascular, neurological or psychiatric disease or of diabetes, hypertension, or dyslipidemia. All healthy controls had a normal MRI upon visual inspection.

2.3. MRI data acquisition

All patients with NDE had an MRI protocol performed at the initial diagnosis, whereas the patients with CHE had an MRI protocol performed at least 2 years after diagnosis. All scans were performed on a 3.0T MRI scanner (AchievaTx, Phillips Healthcare, Best, The Netherlands) that was equipped with an 8-channel head coil. All subjects underwent conventional brain MRI protocols, including axial and coronal 2D T2-weighted images, which were obtained with a turbo spin echo (TSE) sequence (repetition time (TR)/echo time (TE) = 3000/80 ms, slice thickness = 5 mm, echo train length = 14, field of view (FOV) = 210 mm, matrix size = 512 × 512) as well as axial and coronal 2D T1-weighted images, which were obtained with an inversion recovery (IR) sequence (inversion time (TI) = 800 ms, TR/TE = 2000/10 ms, slice thickness = 5 mm, echo train length = 7, FOV = 210 mm, and matrix size = 512 × 512).). In addition, 2D axial-oriented FLAIR images were obtained to evaluate the lesions in these images (TI = 2800 ms, TR/TE = 10,000/120 ms, slice thickness = 5 mm, echo train length = 26, FOV = 210 mm, matrix size = 512 × 512). Sagittal-oriented high-resolution contiguous 3D T1-weighted images were obtained. The 3D T1-weighted images were obtained using a turbo-field echo (TFE) sequence with the following parameters: TI = 1300 ms, TR/TE = 8.6/3.96 ms, Flip angle (FA) = 8°, and 1 mm^3 isotropic voxel size. To speed-up data acquisition, SENSE (SENSitivity Encoding) parallel imaging was applied with an acceleration factor of two.

2.4. MRI data processing and analysis using FreeSurfer

Volumetric analysis was performed based on the 3D T1-weighted images using FreeSurfer image analysis suite (version 5.1; http://surfer.nmr.mgh.harvard.edu/), on a 64-bit Linux CentOS 5. The automated procedures for volumetric measures of the different brain structures are described by Fischl et al. [21,22]. Briefly, we first performed image preprocessing, including linear registration, B1 field correction, and non-linear registration. For linear registration, each volume is rigid registered with a specific atlas, such as the Talairach space. Next, any non-homogenous signal intensity due to the B1 bias field is corrected. Then, high dimensional, non-linear morphing to the atlas is performed. After this image preprocessing, the volume is labeled. To label both the cortical and the subcortical volumes in a segmented fashion, we use three pieces of information to disambiguate the labels: (1) the prior probability of a given tissue class occurring at a specific atlas location, (2) the likelihood of the image intensity given that tissue class, and (3) the probability of the local spatial configuration of labels given the tissue class. The technique has previously been shown to be comparable in accuracy to manual labeling [21]. In addition, all segmentations were visually inspected for accuracy prior to inclusion in the group analysis to correct for a potential error in the automated procedure. All images were visually inspected by two neurologists, in which the extent of spatial overlap was identified between overlaid segmented gray or white matter structures. In addition, we used raw T1-weighted images to ensure that obvious errors in skull stripping and tissue segmentation did not occur. As no cases had errors,