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White matter abnormalities in patients with temporal lobe epilepsy and amygdala enlargement: Comparison with hippocampal sclerosis and healthy subjects

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ABSTRACT

Purpose: Cases of temporal lobe epilepsy (TLE) with ipsilateral amygdala enlargement (AE) have increasingly been reported. However, the white matter (WM) abnormalities of TLE patients with AE remain poorly investigated. Here we explored macrostructural and microstructural WM abnormalities in TLE patients with AE compared to normal controls and TLE patients with hippocampal sclerosis (HS).
Material and methods: We selected 17 patients with unilateral TLE with AE (TLE-AE) based on automated amygdala volumetry using FreeSurfer software, and 34 healthy controls and 35 patients with unilateral TLE with HS (TLE-HS) were also recruited. Subsequently, differences in gray matter (GM) and WM volumes and fractional anisotropy (FA) among the three groups were analyzed using SPM8 software.
Results: The volume analysis of GM obtained results that are consistent with the structural characteristics of TLE with AE and with HS (i.e. amygdala increase in the TLE-AE, and mesial temporal atrophy in the TLE-HS). In the volume of WM, only the TLE-HS patients had WM reductions mainly in the ipsilateral temporal lobe. Compared to the controls, the TLE-AE group showed a significant FA decrease in the ipsilateral anterior cingulum and the corpus callosum, whereas an extended FA decrease in the whole cerebrum was observed in the TLE-HS group.
Conclusion: Our findings regarding the WM of TLE patients with AE may reflect characteristic pathophysiology such as the anatomical and functional connection between the amygdala and medial prefrontal cortex, and our results may thus provide insights into TLE with AE.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common epilepsy among adults (Engel, 1996), and in recent years an increasing number of cases of TLE showing ipsilateral amygdala enlargement (AE) have been reported (Bower et al., 2003; Coan et al., 2013; Kim et al., 2012; Kimura et al., 2015; Minami et al., 2015; Mitsueda-Ono et al., 2011; Sone et al., 2015; Takaya et al., 2014). TLE with AE is currently considered a distinct nosological and relatively heterogeneous subtype of TLE (Lv et al., 2014). Regarding the neuroimaging of cases of TLE with AE, previous studies have focused on gray matter (GM) changes (Coan et al., 2013; Kimura et al., 2015; Takaya et al., 2014) or metabolic abnormalities (Sone et al., 2015; Takaya et al., 2014), but white matter (WM) abnormalities in TLE with AE have been poorly investigated.

Abbreviations: TLE, temporal lobe epilepsy; AE, amygdala enlargement; GM, gray matter; WM, white matter; HS, hippocampal sclerosis; DTI, diffusion tensor imaging; VBM, voxel-based morphometry; FA, fractional anisotropy; MPRAGE, magnetization prepared rapid acquisition with gradient echo; LI, laterality index; SPM8, statistical parametric mapping 8 software program; DARTEL, diffeomorphic anatomical registration using the exponentiated lie; FWHM, full-width at half-maximum; TBSS, Tract-Based Spatial Statistics; FSL, FMRIB Software Library; FWE, family wise error.

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There have been many studies about WM changes in TLE—especially in cases with hippocampal sclerosis (HS)—using diffusion tensor imaging (DTI) (Otte et al., 2012) as well as voxel-based morphometry (VBM) (Keller and Roberts, 2008). VBM can be used to statistically analyze macrostructural changes in the brain (Ashburner and Friston, 2000), and DTI is used for evaluating microstructural WM changes (Smith et al., 2006). Fractional anisotropy (FA) is the most common parameter to be investigated in many neurological disorders including TLE (Focke et al., 2008). WM abnormalities were suggested to differ dependent on the severity or etiology of TLE (Campos et al., 2015; Concha et al., 2009; Labate et al., 2015). Although severe and widespread WM abnormalities are observed in TLE with HS, TLE without HS is often reported to have no WM abnormality (Campos et al., 2015; Mueller et al., 2006).

We hypothesized that TLE with AE would also show a different type of WM abnormalities, reflecting its characteristic neuronal circuits or pathology. In addition, the understanding of the patterns of WM abnormalities in different etiologies can improve our knowledge about brain neuronal networks as well as provide insights for further investigations about various symptoms such as cognitive dysfunctions in TLE. The main purpose of this study was to explore macrostructural and microstructural WM abnormalities in TLE patients with AE compared to normal controls and TLE patients with HS, using VBM and DTI techniques. We also evaluated GM changes and clinical demographics of TLE with AE.

2. Materials and methods

2.1. Participants

As the candidates of TLE with AE, we recruited 67 patients with unilateral TLE (mean ± SD age, 43.8 ± 16.5 years; left/right TLE, 38:29; male:female, 30:37) without any structural abnormalities (but we didn't exclude several cases with possible AE) on visual assessment of conventional MRI, who were examined at our institute between November 2013 and September 2015. Evaluation of AE in this study was based on only volumetry to be described, and therefore the candidates at that point contained patients with no abnormalities on MRI as well as patients with possible AE. The diagnosis of TLE was based on the presence of simple or complex partial seizures consistent with TLE, and focal epileptiform discharge predominantly in a unilateral temporal area as observed on a conventional scalp electroencephalogram. After the diagnosis of TLE, all patients underwent conventional MRI for the visual evaluation of epileptogenic lesions by a single experienced neuroradiologist (N.S.).

Patients with the following criteria were excluded: a significant medical history of acute encephalitis, meningitis, severe head trauma, or ischemic encephalopathy; suspicious epileptogenic lesions (e.g., tumor, cortical dysplasia or vascular malformation) on MRI other than ipsilateral AE at the abnormal electroencephalogram side; or epileptic paroxysms in extra-temporal regions on an electroencephalogram. Subsequently, our selection of TLE patients with ipsilateral AE was performed based on normal control data using automated volumetry of the amygdala as described in a later section.

We also recruited 34 healthy age-matched adults as controls (the control group; mean ± SD age, 42.7 ± 14.5 years; male:female, 17:17) based on the following criteria: no history of neurological or psychiatric diseases; and no medication of central nervous system agents. In addition, 35 patients with unilateral TLE based on seizure semiology and scalp electroencephalogram and ipsilateral HS (mean ± SD age, 45.7 ± 12.0 years; left/right TLE, 16:19; male:female, 18:17) diagnosed in the same period were recruited (the TLE-HS group) for a comparison of the different etiologies. The diagnosis of TLE was the same as that describe above, and the existence of unilateral HS on MRI was determined by the following criteria: ipsilateral reduced hippocampal volume; increased T2 signal on the hippocampus; and abnormal morphology (i.e., a loss of internal architecture of the stratum radiatum, a thin layer of white matter that separates the dentate nucleus and Ammon's horn). No abnormalities were found in extratemporal or contralateral areas.

We also investigated the clinical data of the patients and controls, including gender, age, onset age of epilepsy, duration from onset and number of anti-epileptic drugs being used. The cognitive data of Wechsler Adult Intelligence Scale III were also reviewed. All participants gave written informed consent. The study was approved by the Institutional Review Board at the National Center of Neurology and Psychiatry Hospital.

2.2. MRI acquisitions

The MRI for all participants was performed on a 3.0-T MR system with a 32-channel coil (Philips Medical Systems, Best, The Netherlands). The parameters of the sequences were: three-dimensional (3D) sagittal T1-weighted magnetization prepared rapid acquisition with gradient echo (MPRAGE) images [repetition time (TR)/echo time (TE): 7.12 ms/3.4 ms, flip angle: 10°, number of excitations (NEX): 1, 0.6-mm effective slice thickness with no gap, 300 slices, matrix of 260 × 320, 26 × 24 cm field of view (FOV), acquisition time 4:01 min]; diffusion-weighted images [TR/TE: 6700 ms/58 ms, flip angle: 90°, NEX: 2, 3.0-mm effective slice thickness with no gap, 60 slices, matrix of 80 × 78, 24 × 24 cm FOV, acquisition time 4:13 min]. Diffusion was measured along 15 non-collinear directions using a diffusion-weighted factor b in each direction of 1000 s/mm^2, and one image was acquired with no diffusion gradient.

We also added a routine MRI examination with the following protocols: transverse conventional T1-weighted images [TR/TE: 602/8.0 ms, flip angle: 70°, NEX 1, thickness 3.0 mm with 1.5-mm gap, 34 slices, matrix 256 × 174, 23 × 18 cm FOV, acquisition time 3:33 min]; transverse turbo spin echo T2-weighted images [TR/TE: 4704/80 ms, flip angle: 90°, NEX 2, thickness 3.0 mm with 1.5-mm gap, 34 slices, matrix 368 × 215, 23 × 18 cm FOV, acquisition time 2:49 min]; and coronal fluid-attenuated inversion recovery (FLAIR) images [TR/TE 10,000/120 ms, inversion time 2450 ms, flip angle: 120°, NEX 2, thickness 3.0 mm with 1.5-mm gap, 34 slices, matrix 272 × 144, 23 × 18 cm FOV, acquisition time 3:00 min].

2.3. Volumetry of the amygdala and hippocampus and the selection of TLE patients with AE

We performed an automated volumetric analysis of the amygdala for the selection of TLE patients with AE. We also assessed the hippocampal volumes of all participants to investigate the characteristics of the hippocampus in the TLE with AE cases compared with the TLE-HS group and controls. FreeSurfer software (v.5.3, https://surfer.nmr.mgh.harvard.edu) was used to assess the amygdala and hippocampus volumes based on the 3D T1-weighted MPRAGE images of all the participants. Image processing included the removal of non-brain tissues with a hybrid watershed/surface deformation procedure, automated Talairach transformation, and segmentation of the subcortical structure and cortex. Additionally, we confirmed that the FreeSurfer labelling of amygdala is accurate visually, because amygdala is sometimes partly misclassified by FreeSurfer volumetry.

In our examination of the existence of AE, we obtained the affected and contralateral amygdala volumes in the 67 candidates for TLE with AE, expressed as the laterality index (LI) calculated as follows: (affected side − contralateral side)/(affected side + contralateral side). Then, the higher LI in cases with TLE