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Volumetric and shape analysis of hippocampal subfields in unilateral mesial temporal lobe epilepsy with hippocampal atrophy

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ABSTRACT

Objective: The hippocampus consists of several functionally and histologically different subfields that are known to be differentially affected in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE). Using automated MRI analyses, we aimed to investigate atrophy patterns of hippocampal subfields and their relationships with clinical characteristics in a homogenous group of unilateral MTLE.
Methods: Twenty-four left MTLE patients, 23 right MTLE patients, and 41 control subjects were scanned on a 3 T MR scanner. Automated volumetry and shape analysis were used to assess volume and shape changes of hippocampal subfields in MTLE patients relative to controls. Within-group correlations were performed between subfield volumes and clinical variables in patients.
Results: Compared to controls, left and right MTLE patients exhibited significant volume reductions in ipsilateral whole hippocampus and subfields including CA1, CA2–3, CA4–DG, presubiculum, and subiculum (corrected $p < 0.05$). Regional inward shape deformation mainly localized to ipsilateral CA1 and adjacent subiculum was found in left and right MTLE patients relative to controls (corrected $p < 0.05$). Longer disease duration was related to smaller volumes of left CA1, presubiculum, and subiculum in left MTLE, and right CA1 in right MTLE.
Conclusion: We found overall volume reductions in ipsilateral hippocampal subfields in patients with unilateral MTLE, in accordance with known pathologic findings. Our findings of regional atrophy in ipsilateral CA1 and subiculum on shape analysis and an inverse relationship between disease duration and ipsilateral CA1 volume implicate an important role of CA1 and subiculum in the pathogenesis underlying MTLE.

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1. Introduction

Neuronal loss and gliosis of the hippocampus are the histopathological hallmarks of hippocampal sclerosis (HS), the most common cause of intractable mesial temporal lobe epilepsy. Typical MRI features of HS include reduced hippocampal volume and increased T2 signal intensity (Malmgren and Thom, 2012). Quantitative measurement of hippocampal volume using high-resolution MRI provides histologic and clinical information in mesial temporal lobe epilepsy with HS (MTLE). Indeed, smaller hippocampal volume on MRI did correlate well with lower neuronal cell density in the pathologic hippocampus (Malmgren and Thom, 2012; Morita and Cendes, 2010). Previous cross-sectional studies have shown an association between the severity of hippocampal volume reduction on MRI and clinical factors such as duration of epilepsy, seizure frequency, surgical outcome, and neuropsychological functions in patients with MTLE (Jack et al., 1992; Malmgren and Thom, 2012; Morita and Cendes, 2010; Thom et al., 2010).

Pathological classification and grading of HS are determined according to the distinct patterns of neuronal cell loss in the hippocampal subfields. In a classification system for mesial temporal sclerosis proposed by Blümcke et al. (2007), the classical pattern (type 1a, classic HS) is characterized by severe neuronal loss in cornu ammonis 1 (CA1) and moderate loss in CA2–4 and dentate gyrus (DG), while the most common pattern (type 1b, severe HS) consists of severe neuronal loss in all hippocampal subfields (CA1–4, DG). Another clinicopathological study found that duration of epilepsy correlated with pathological HS grade, with longer duration of epilepsy being associated with higher grade HS (Fuerst et al., 2001). Given the differences in surgical outcome (Blümcke et al., 2007; Thom et al., 2010) and memory performance (Pauli et al., 2006) in relation to distribution or severity of neuronal loss in the

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hippocampal subfields, investigation of hippocampal subfield atrophy patterns using quantitative MRI analysis could provide useful information about surgical prognosis and prediction of neurocognitive performance in patients with MTLE.

Studies using manual tracing method may provide more accurate volumetric measurement than automated segmentation of hippocampus, especially in cases of atrophic hippocampus (Pardoe et al., 2009). Nonetheless, manual tracing method requires a high degree of neuroanatomical training, is time-consuming, and is prone to have an operator-dependent bias (Hsu et al., 2002). Moreover, manual delineation of the hippocampal subfields is an extremely laborious procedure, and is therefore not suitable for preprocessing a large MRI dataset. To our knowledge, there is one study that measured hippocampal subfield volumes using manual segmentation in patients with MTLE (Mueller et al., 2009). Recently, automated segmentation techniques have been validated to yield reliable results comparable to those of manual tracing of whole hippocampus as well as subfields (Morey et al., 2009; Van Leemput et al., 2009). Moreover, a recent radiological–pathological study found a significant correlation between neuronal density of CA1 on surgical specimen and MRI-determined volume of CA1 subfield (Schoene-Bake et al., 2014).

Complementary to volumetric measurement, vertex-based shape analysis is another fully automated method that provides useful information about the location and pattern of morphological changes of the subcortical gray matter structures such as hippocampus and thalamus (Kim et al., 2013; Patenaude et al., 2011). Indeed, a few studies have shown a rather consistent finding of ipsilateral CA1 atrophy in patients with unilateral MTLE, but with some discrepancies with regard to involvement of contralateral hippocampus and other ipsilateral subfields such as CA2–4, DG, or subiculum (Bernhardt et al., 2013; Hogan et al., 2004, 2008; Mumoli et al., 2013). Interestingly, a recent study showed that temporal lobe epilepsy patients with normal hippocampal volume had local hippocampal shape changes (atrophy) mainly affecting subicular and hilar/dentate regions, a distinct pattern from the typical CA1 atrophy found in patients with MTLE (Maccotta et al., 2015).

In the current study, we utilized both automated volumetric and shape analysis to explore atrophy patterns of hippocampal subfields and their relationships with clinical variables in a homogenous group of unilateral MTLE.

2. Methods

2.1. Subjects

We prospectively recruited consecutive adult patients with unilateral MTLE from the epilepsy clinic of Korea University Guro Hospital. Inclusion criteria we used were the following: (a) unequivocal unilateral hippocampal atrophy (HA, hippocampal volume of more than 2 SD below the mean volume of controls) and increased T2 signal in the atrophic hippocampus (Jackson et al., 1993); (b) seizure semiology compatible with MTLE; (c) more than 90% of interictal temporal spikes ipsilateral to atrophic hippocampus and/or ictal rhythmic buildup ipsilateral to atrophic hippocampus on video-EEG monitoring; (d) no history of neurological disorders other than MTLE; and (e) no abnormal MRI findings other than HA. All patients showed no focal deficit on neurological examination and were not taking any psychotropic or recreational drugs at the time of study inclusion. Demographic and clinical data including history of febrile seizure, age of seizure onset, duration of epilepsy, frequency of complex partial seizure and secondarily generalized seizure (number of seizures per year), and current antiepileptic drugs were obtained through interviews with the patients and their family members and reviews of medical records.

For group comparison, 41 right-handed healthy volunteers (27 females, mean age = 41.5 ± 9.8 years) matched for age and gender were recruited to serve as control subjects. Control subjects with abnormal or unusual MRI findings were also excluded. The local ethics committee approved the study protocol, and all participants gave written informed consent before study inclusion.

2.2. MRI acquisition

MR images were acquired on a Siemens Trio 3 T scanner (Erlangen, Germany) with a 12-channel phased array head coil. For identification of HA and other structural abnormalities, the following clinical MR images were acquired: axial T2-weighted (4 mm thickness, TR/TE = 4330/104 ms, FOV = 172 mm × 220 mm, matrix = 576 × 410) and FLAIR images (4 mm thickness, TR/TE = 10,000/95 ms, FOV = 151 mm × 230 mm, matrix = 384 × 218), and oblique coronal T2-weighted (3 mm thickness, TR/TE = 3380/114 ms, FOV = 148 mm × 230 mm, matrix = 448 × 288) and FLAIR images (3 mm thickness, TR/TE = 10,000/95 ms, FOV = 151 mm × 230 mm, matrix = 384 × 218) perpendicular to the long axis of hippocampus. For volumetric analysis, high-resolution 3D MP-RAGE sequence was acquired with the following parameters: 176 sagittal slices, TR/TE/TI = 1780/2.34/900 ms, flip angle = 9°, FOV = 256 mm × 256 mm, matrix = 256 × 256, voxel size = 1 mm^3. Diffusion tensor imaging and resting-state functional MR images were also acquired simultaneously but not included in the current study.

2.3. Volumetric analysis

Image preprocessing and volumetric measurement of hippocampal subfields were carried out using FreeSurfer image analysis suite (version 5.3.0, https://surfer.nmr.mgh.harvard.edu). The procedures included removal of non-brain tissue using a hybrid watershed algorithm, automated transformation to the Talairach reference space, and segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2002). The whole hippocampal formation was segmented using the standard segmentation procedure using a probabilistic brain atlas. The estimated intracranial volume (ICV) for each subject was calculated as well. Automated segmentation of the hippocampal subfields was then performed by using Bayesian inference and a probabilistic atlas of hippocampal formation based on manual delineations of subfields in ultra-high resolution T1-weighted images of 10 subjects (Van Leemput et al., 2009). Volumes of the following 7 hippocampal subfields were calculated: fimbria (white matter), fissure (cerebrospinal fluid), CA1, CA2–3, CA4–DG, presubiculum, and subiculum (gray matter). The technical details of the procedures for subfield segmentation are described elsewhere (Hanseeuw et al., 2011; Van Leemput et al., 2009). Briefly, these procedures consisted of delineating the medial border of CA1 by connecting the points of highest curvature on the dorsolateral and ventrolateral edges of the hippocampus, which also constituted the lateral boundary of CA2–3, CA4–DG, and subiculum. The subiculum was separated from the presubiculum through a vertical line drawn from the most medial edge of the fimbria. The medial border of presubiculum was a vertical line at the dorsomedial crown of the parahippocampal gyrus. The lateral boundary of CA1 and the dorsal boundary of CA2–3 was the border between the hippocampus and the temporal horn of the lateral ventricle. A line through the intersection of two points of maximum curvature and perpendicular to the medial boundary of CA1 formed the ventral border of CA2–3 and dorsal boundary for CA4–DG. Finally, the fimbria was defined as the dorsolateral white matter along the entire extent of the hippocampal formation. The voxel measurement of each subfield was 0.5 × 0.5 × 0.5 mm^3. This automated measurement of subfield

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