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Opinion paper

Reduction of ipsilateral thalamic volume in temporal lobe epilepsy with hippocampal sclerosis

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ABSTRACT

The thalamus plays an important role in the modulation of both focal and generalized seizures, but the mechanisms related to seizures may be different among epilepsy syndromes. The aim of this study is to investigate the thalamic atrophy in different epilepsy syndromes. We enrolled a total of 72 patients with epilepsy (22 patients with temporal lobe epilepsy with hippocampal sclerosis, 21 patients with extra-temporal lobe epilepsy, and 29 patients with juvenile myoclonic epilepsy). We analyzed structural volumes of the brain with FreeSurfer 5.1 software, and compared them among subgroups of epilepsy and normal control subjects. Moreover, we quantified correlations between the duration of epilepsy and the structural volumes with age and sex as covariates. The volumes of the ipsilateral hippocampus in temporal lobe epilepsy with hippocampal sclerosis were significantly smaller than those in extra-temporal lobe epilepsy and normal control subjects [analysis of variance (ANOVA), $p < 0.001$]. Although the volumes of the ipsilateral thalamus were not different from those of normal control subjects, the volumes of the ipsilateral thalamus were negatively correlated with duration of epilepsy in temporal lobe epilepsy with hippocampal sclerosis ($r = -0.5$, $p = 0.02$). However, the volumes of interest in extra-temporal lobe epilepsy and juvenile myoclonic epilepsy were not different from those in normal control subjects, and none of these structures were correlated with duration of epilepsy. These findings suggest that the role of the thalamus may be different in thalamo-limbic circuits among epilepsy syndromes.

1. Introduction

Recently, researchers have reached a consensus that epilepsy is a network disease, and the neuronal networks may involve the generation and maintenance of epileptic seizures [1]. There is a considerable amount of compelling evidence that a neuronal network of tightly connected cortical and subcortical brain structures are essential for the generation and maintenance of epileptic activity [2].

In generalized seizures, the cortex and subcortical structures, especially the thalamus, participate in the generation and modulation of seizures mainly involving thalamo-cortical circuits [3]. Previous results from humans and experimental models have demonstrated that cortical and thalamic networks, which generate and maintain certain sleep rhythms, are also critically involved in the production of generalized spike and wave discharges (GSWDs), typically seen in generalized seizures [3]. In addition, in focal seizures, there is evidence of the involvement of subcortical structures, such as the caudate nucleus, putamen, and substantia nigra, in ictus using positron emission tomography (PET) [4]. Moreover, paroxysmal fast activities and slow GSWDs, which are usually seen in Lennox-Gastaut syndrome, are associated with activity in a diffuse network including subcortical structures, such as the brain stem, thalamus, and basal ganglia as well as the cortex [5]. Thus, subcortical structures play a significant role in seizure activity, in terms of cortical seizure threshold, duration, and severity [6].

Of these subcortical structures, a structure of particular interest in the regard is the thalamus, which could play an important role

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in regulating cortical activity [7]. A regulatory role of the thalamus is strongly suggested by the coherence of cortical sleep spindles and alpha activity with thalamo-cortical interplay activity and intra-thalamic feedback [7]. In generalized seizures, the involvement of the thalamus has been well demonstrated [3]. In addition, there have been considerable evidences that the thalamus plays an important role in focal seizures. In resting state-functional MRI (rs-fMRI) study, the thalamus is identified as a common region of brain dysfunction in patients with focal epilepsy, despite individuals with focal seizures having heterogeneous sites of seizure origin [8]. In PET studies, although several authors have reported various subcortical functional changes in patients with focal epilepsy, thalamic changes are the most frequently reported subcortical abnormalities [9,10]. Moreover, bilateral stimulation of the anterior nucleus of the thalamus moderately reduced seizure activities in a randomized trial of 110 patients with focal epilepsy [11]. In addition, the thalamus is involved in controlling seizure activity throughout the brain, regardless of the location of the epileptogenic focus, and it exerts control on the cortex by inducing a stable hyper-synchronization that ultimately leads to seizure termination in focal epilepsy [6,12]. With all evidence taken together, the thalamus is involved in both focal and generalized seizures.

However, few studies have investigated thalamic atrophy according to different types of epilepsy, which could suggest the different role of the thalamus between thalamo-limbic and thalamo-cortical circuits in focal and generalized seizures. On neuroimaging, the progression of epilepsy, in part, refers to a gradual atrophy of a target structure directly involved in an epilepsy network as epilepsy progresses. Thus, correlating a change of volume in a target structure with the duration of epilepsy is a good research tool. The aim of this study is to clarify whether the reduction of ipsilateral thalamic volume is different according to different types of epilepsy.

2. Materials and methods

2.1. Patient subjects

This study was conducted with the approval of our institution's review board. This study was performed in a single tertiary hospital. We enrolled a total of 72 patients with epilepsy, including temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS), extra-temporal lobe epilepsy (ETLE), and juvenile myoclonic epilepsy (JME), from March 2010 to June 2016. Patients with TLE with HS had the following: 1) the typical MRI features of HS, including increased signal intensity on T2-weighted images and reduced hippocampal volume under agreement of three investigators; 2) a history of focal seizures consistent with TLE, such as epigastric aura, staring, oro-alimentary automatism, dystonic posture of the contralateral hand, and head deviation; and 3) ictal or interictal epileptiform discharges originating from the temporal lobe shown by electroencephalography (EEG) (T1/T2, T3/T4, F7/F8, ± T5/T6); and 4) MRI evidence of unilateral HS concordant with the EEG lateralization of the epileptogenic zone and ictal semiology. We excluded patients with bilateral HS or any structural lesions beyond HS on MRI. We also included 21 patients with epilepsy of unknown cause, previously termed as cryptogenic partial epilepsy [1]. The inclusion criteria for these patients were as follows: 1) patients aged 15 or more years; 2) no structural lesions on their brain MRIs; 3) a history of focal seizures that were not characteristic of temporal lobe seizures; 4) ictal or interictal epileptiform discharges that clearly originated from one hemisphere on an EEG; and 5) a normal neurologic examination. We could lateralize but not localize their origin of seizures. Because these patients presumably had their origin of seizures beyond the temporal lobe, we regarded them as ETLE. Moreover, we enrolled 29 patients with a clinical diagnosis of JME [1]. All the patients had the following: 1) age of seizure onset between 10 and 22 years; 2) normal neurologic state and development; 3) the typical seizure history compatible with JME, including myoclonic jerks; and 4) ictal or interictal GSWDs with normal background activity on EEG.

We collected demographic and clinical characteristics including age, sex, age of seizure onset, and duration of epilepsy. The duration of epilepsy was defined as age at the time of MRI minus age of seizure onset. The ipsilateral HS was defined as the side of the hippocampus that was thought to be the primary site of seizure origin, and contralateral HS was the other side. In addition, the ipsilateral side in ETLE was lateralized with ictal or interictal epileptiform discharges on EEG and ictal semiology. Because it is impossible to lateralize the origin of seizures in JME, we defined the right and left sides rather than ipsilateral and contralateral sides. The dosage of antiepileptic drugs (AEDs) was standardized for the AED load. The AED load was defined as the sum of the prescribed daily dose/defined daily dose for each patient, in which the defined daily dose corresponded to the assumed average maintenance daily dose of a drug used for its primary indication (https://www.whocc.no/atc_ddd_index).

2.2. Normal control subjects

The control group consisted of age- and sex-matched healthy subjects (30 normal control subjects were matched for TLE with HS or ETLE, and 24 normal control subjects were independently matched for JME; the mean age in JME was significantly different from that in TLE or ETLE). Of the 30 normal control subjects for comparison with TLE with HS or ETLE, 14 patients (47%) were men and 16 patients (53%) were women. The mean age was 37.6 ± 10.4 years. Of the 24 normal control subjects for comparison with JME, 14 patients (58%) were men and 10 patients (42%) were women. The mean age was 25.8 ± 2.4 years. All subjects were normal on neurological examination and had no medical history of disease. All control subjects had a normal MRI on visual inspection.

2.3. MRI data acquisition

All scans were performed on a 3.0 T MRI scanner (AchievaTx, Phillips Healthcare, Best, The Netherlands) equipped with an 8-channel head coil. All subjects underwent conventional brain MRI protocols, including axial and coronal two-dimensional (2D) T2-weighted images, which were obtained with a turbo spin-echo 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) and axial and coronal 2D T1-weighted images, which were obtained with an inversion recovery sequence [inversion time (TI) = 800 ms, TR/TE = 2000/10 ms, slice thickness = 3 mm, echo train length = 7, FOV = 210 mm, and matrix size = 512 × 512]. Sagittal-oriented high-resolution contiguous three-dimensional (3D) T1-weighted images were obtained with turbo-field-echo sequence (TI = 1300 ms, TR/TE = 8.6/3.96 ms, flip angle = 8°, 1 mm^3 isotropic voxel size). To speed up data acquisition, sensitivity encoding (SENSE) parallel imaging with an acceleration factor of 2 was applied.

2.4. MRI data processing and analysis using FreeSurfer

The FreeSurfer image analysis software version 5.1 was installed on a CentOS (Community ENTerprise Operating System). The processing stream of FreeSurfer consisted of several stages as follows: volume registration with the Talairach atlas, bias field correction, initial volumetric labeling, nonlinear alignment to the Talairach space, and final labeling of the volume. Then, the cortical surface of each hemisphere was inflated to an average spherical

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