Epilepsy & Behavior 70 (2017) 259–264

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Localized shape abnormalities in the thalamus and pallidum are associated with secondarily generalized seizures in mesial temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 16 November 2016
Revised 6 February 2017
Accepted 6 February 2017
Available online 17 April 2017

Keywords:
Secondarily generalized tonic–clonic seizure
Temporal lobe epilepsy
Hippocampal sclerosis
Shape analysis
Medial thalamus
Ventral pallidum

ABSTRACT

Mesial temporal lobe epilepsy (mTLE) is a common type of drug-resistant epilepsy and secondarily generalized tonic–clonic seizures (sGTCS) have devastating consequences for patients' safety and quality of life. To probe the mechanism underlying the genesis of sGTCS, we investigated the structural differences between patients with and without sGTCS in a cohort of mTLE with radiologically defined unilateral hippocampal sclerosis. We performed voxel-based morphometric analysis of cortex and vertex-wise shape analysis of subcortical structures (the basal ganglia and thalamus) on MRI of 39 patients (21 with and 18 without sGTCS). Comparisons were initially made between sGTCS and non-sGTCS groups, and subsequently made between uncontrolled-sGTCS and controlled-sGTCS subgroups. Regional atrophy of the ipsilateral ventral pallidum (cluster size = 450 voxels, corrected $p = 0.047$, Max voxel coordinate = 107, 120, 65), medial thalamus (cluster size = 1128 voxels, corrected $p = 0.049$, Max voxel coordinate = 107, 93, 67), middle frontal gyrus (cluster size = 60 voxels, corrected $p < 0.05$, Max voxel coordinate = −30, 49.5, 6), and contralateral posterior cingulate cortex (cluster size = 130 voxels, corrected $p < 0.05$, Max voxel coordinate = 16.5, −57, 27) was found in the sGTCS group relative to the non-sGTCS group. Furthermore, the uncontrolled-sGTCS subgroup showed more pronounced atrophy of the ipsilateral medial thalamus (cluster size = 1240 voxels, corrected $p = 0.014$, Max voxel coordinate = 107, 93, 67) than the controlled-sGTCS subgroup. These findings indicate a central role of thalamus and pallidum in the pathophysiology of sGTCS in mTLE.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is a common type of focal epilepsy, and is usually accompanied by hippocampal sclerosis. Seizures that occur in TLE with hippocampal sclerosis (TLE–HS) are typically resistant to antiepileptic drugs, which are associated with severe cognitive impairment, affective disorders, and stigmatization [1,2]. Among the seizure types associated with TLE–HS, secondarily generalized tonic–clonic seizures (sGTCS) are the most debilitating type and these in turn put the patients at additional risk of fatal injuries. Additionally, patients with TLE and sGTCS demonstrated worse surgical outcomes after anterior temporal lobectomy compared to those without sGTCS [3,4].

Advancing the treatment strategies of sGTCS requires a detailed and clear understanding of the mechanism as to how the seizures are initiated, propagated, and terminated. However, the mechanism underlying the genesis of the sGTCS in mTLE has not been fully elucidated. Changes of cerebral blood flow (CBF) in the thalamus, basal ganglia, and frontoparietal cortex during the transition from partial seizures to secondarily generalization have been reported in patients with a mixed group of temporal and extra-temporal lobe epilepsy [5]. Some electrophysiological studies suggested that the basal ganglia exert an inhibitory effect against sGTCS in patients with mTLE [6–8]. Also, changes in the blood oxygen level-dependent (BOLD) signals were associated with generalized spike-wave (GSW) activity in the thalamo–cortical network. These were found in both primarily and secondarily generalized epilepsies, using simultaneous electroencephalogram and functional magnetic resonance imaging (EEG–fMRI) [9,10]. These lines of evidence suggest functional involvement of the basal ganglia-thalamo-cortical network in sGTCS. However, it remains unknown whether the structural alterations in these key nodes such as basal ganglia, thalamus, and cortex are involved in the pathophysiological mechanism of sGTCS.

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http://dx.doi.org/10.1016/j.yebeh.2017.02.011
1525-5050/

Clinically, some patients with mTLE have sGTCS despite taking appropriate medication treatment, while some other patients have only partial seizures even though not on medications. This discrepancy in susceptibility to sGTCS might be associated with differences in the epileptogenic network, which may be reflected by morphometric analysis. In the present study, we investigated the relationship between cortical and subcortical gray matter (GM) alterations and the occurrence of sGTCS in a cohort of patients with unilateral TLE-HS. In particular, we initially applied sophisticated morphometric approaches to investigate the regional alterations in cortical volume and the surface shape of the thalamus and basal ganglia in patients with sGTCS versus those without sGTCS (non-sGTCS). Subsequently, we compared the structural alterations in patients with sGTCS that were not controlled by appropriate medical treatment (uncontrolled-sGTCS) versus those with medically controlled sGTCS (controlled-sGTCS).

2. Methods

2.1. Participants

From April 2014 to June 2016, consecutive Chinese patients with unilateral TLE–HS, as confirmed by the clinical workup and imaging findings, were included in this study. Hippocampal sclerosis was defined if both hippocampal atrophy and increased T2 signals were observed on MRI [11]. All the patients were diagnosed by at least two experienced epileptologists based on history, seizure semiology, long-term scalp video-EEG monitoring, neuroimaging findings, and neuropsychological assessments. Some patients who required surgery were diagnosed as unilateral mTLE after stereo-EEG evaluation because their scalp EEG recordings did not provide adequate localizing or lateralizing information. Patients were excluded with: 1) history of brain trauma or surgery, 2) evidence of infectious origin, 3) evidence of secondary lesion that may be contributing to seizures, 4) serious psychiatric disorders, 5) ambiguous history of sGTCS, 6) seizures arising from the temporal lobe which is contralateral to the sclerotic hippocampus, or 7) bilateral mTLE.

A typical sGTCS is characterized by bilateral rigid tonic extremities followed by rhythmic clonic jerks, along with complete loss of consciousness [12]. The seizure type was identified based on the seizure video, and the average seizure frequency was calculated for each patient according to the seizure diaries or family reports. Patients with sGTCS were further divided into two subgroups: 1) controlled-sGTCS subgroup, in which patients had secondarily generalized seizures only at the beginning of the disease course or after the medication was reduced, 2) uncontrolled-sGTCS subgroup, which included patients who had sGTCS events despite appropriate medical treatment with good compliance. Pharmacoresistance was defined as failure to achieve sustained freedom from seizures with adequate doses of two tolerated and appropriately chosen antiepileptic drugs [13]. The clinical variables were analyzed using two-sample independent t tests for continuous variables and Chi-square tests for categorical variables. The significance level was set at $p < 0.05$.

2.2. MRI protocol

MR images were obtained on a 3.0T scanner (MR750, GE Healthcare, USA) with an 8-channel brain phased array coil. High-resolution coronal T2-weighted images perpendicular to the long axis of the hippocampus were acquired using spoiled gradient echo sequence with TR/TE = 5518/176 ms, flip angle = 110°, slice thickness = 2 mm, matrix = 512 × 512. Sagittal 3D T1-weighted images were acquired using brain volume imaging (BRAVO) sequence with TR/TE = 8.2/3.2 ms, TI = 450 ms, flip angle = 12°, slice thickness = 1 mm, matrix = 256 × 256.

2.3. Imaging analysis

It has been reported that hemisphere lateralization of the epileptogetic zone is irrelevant for sGTCS history in patients with TLE [3]. Therefore, images of patients with right mTLE were side-flipped, and brain structures were marked as ipsilateral and contralateral to the epileptogenic zone in the present study.

2.3.1. Shape analysis of the basal ganglia and thalamus

Automated segmentation and vertex-wise shape analysis of the basal ganglia and thalamus were carried out using the FSL-integrated registration and segmentation toolbox (FSL-FIRST) software (v.5.0.0; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/first) installed on a Mac workstation. Briefly, the shape models in the FIRST were constructed from a library of manually segmented images. FIRST automatically searches for the most probable shape illustrations when given the observed intensities from the input images. To normalize the inter-individual head size differences, the segmented subcortical regions including the caudate, putamen, pallidum, and thalamus were reconstructed in the Montreal Neurological Institute space. Comparisons were initially made between non-sGTCS and sGTCS groups, and subsequently made between controlled-sGTCS and uncontrolled-sGTCS subgroups. Group differences were investigated by computing a general linear model, and the model included group (sGTCS/non-sGTCS or controlled-sGTCS/uncontrolled-sGTCS) as an independent factor, and age, gender, and intracranial volume (ICV) as covariates. Permutation testing using "randomize" with 5000 Monte Carlo simulations was used to calculate statistics of the segmented structures, corrected for multiple comparisons by dividing the p-value of 0.05. Clusterwise extent correction was applied, with a threshold of $F > 2.0$. Results from the surface analysis were visualized using Freesurfer's Freeview software [14].

2.3.2. Voxel-based morphometric analysis of cortex

The structural T1WI data were processed using voxel-based morphometry 8 (VBM8, http://dbm.neuro.unijena.de/vbm.html) toolbox of Statistical Parametric Mapping 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) software running on MATLAB R2009b. In the first step, VBM automatically segmented GM, white matter (WM), and cerebrospinal fluid (CSF) in each patient. The volumes of GM, WM, and CSF voxels were determined separately for each patient and summed to calculate ICV. After segmentation, all images were rigidly aligned. Then, a "DARTEL" template of GM was created by nonlinearly aligning the GM images to a common space. The native GM images were normalized to the "DARTEL" template by applying the individual flow fields of all scans, using modulation to compensate for volume changes because of compression and/or expansion. Finally, GM images were smoothed using a Gaussian filter with full-width at half-maximum of 6 mm. Images were visually inspected at each and every processing step. Whole brain voxel-wise two-sample t tests were used to analyze the differences of the GM volume between non-sGTCS and sGTCS groups, with age, gender, and ICV as covariates. The statistical threshold was corrected for multiple comparisons on the cluster levels, which was determined by Monte Carlo simulation (5000 iterations) using AlphaSim as implemented in the REST-toolbox [15]. A combination threshold of $p < 0.0001$ on the voxel level and a cluster size >46 mm^3 voxels was considered significant, which corresponded to a corrected $p < 0.05$. Then, the voxel values from the significant cluster in group comparison were extracted (data not shown).

Subsequently, comparison of voxel values was made between controlled-sGTCS and uncontrolled-sGTCS, using multivariate analysis of covariance (MANCOVA) on age, gender, and ICV. To estimate the impairing effect of epilepsy, partial correlation coefficients were computed between the voxel values and epilepsy duration or frequency of partial seizures, controlling for age, gender, and ICV. To estimate the impairing effect of sGTCS, comparison of voxel values were made