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Increase in gray matter volume and white matter fractional anisotropy in the motor pathways of patients with secondarily generalized neocortical seizures

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ABSTRACT

Purpose: Convulsive motor activity is a clinical manifestation of secondarily generalized seizures evolving from different focal regions. The way in which the motor seizures present themselves is not very different from most of the generalized seizures in and between epilepsy patients. This might point towards the involvement of motor-related cortices and corticospinal pathway for wide spread propagation of epileptic activity. Our aim was to identify changes in the cerebral structures and to correlate clinical variables with structural changes particularly in the motor-related cortices and pathway of patients with generalized convulsions from different seizure foci.
Methods: Sixteen patients with focal onset and secondarily generalized seizures were included, along with sixteen healthy volunteers. Structural differences were analysed by measuring grey matter (GM) volume and thickness via T1-weighted MRI, and white matter (WM) fractional anisotropy (FA) via diffusion tensor imaging. GM and WM microstructural properties were compared between patients and controls by voxel- and surface-based analyses. Next, morphometric findings were correlated with seizure severity and disease duration to identify the pathologic process.
Key findings: In addition to widely reduced GM and WM properties, increased GM volume in the bilateral precentral gyri and paracentral lobules, and elevated regional FA in the bilateral corticospinal tracts adjacent to these motor -related GM were observed in patients and with higher statistical difference in the sub-patient group with drug-resistance.
Significance: The increment of GM volume and WM FA in the motor pathway positively correlated with severity and duration of epilepsy. The demonstrated microstructural changes of motor pathways imply a plastic process of motor networks in the patients with frequent generalization of focal seizures.

1. Introduction

Over 70% of patients with focal seizures experience secondary generalization (Forsgren et al., 1996). The ultimate symptoms, including a general stiffening and the jerking of limbs when a focal seizure extensively evolves, indicate the final anatomical involvement of the bilateral motor pathways. Two important neural pathways, including the corpus callosum and the thalamocortical circuit, have been implicated in the regulation of seizure generalization (Marcus and Watson, 1966; Beenhakker and Huguenard, 2009). However, research addressing the anatomical destination of seizure propagation is limited. To prove our hypothesis that there are structural changes in motor pathways involved in the evolution of overt motor activity during generalized convulsions, we analyzed magnetic resonance imaging (MRI) data from patients with secondarily generalized seizures from a focal epileptic source and non-lesional epilepsy.

Size, volume and shape of different brain regions, as well as its structural properties, are commonly analyzed parameters. The original features of the gray matter (GM) and white matter (WM) can be obtained, respectively, by high-resolution T1-weighted MRI and diffusion

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tensor imaging (DTI) for signal processing. An illustrative example concerns juvenile myoclonic epilepsy (JME). The most common and representative syndrome of idiopathic generalized epilepsies (IGEs) manifesting as myoclonic jerks and generalized tonic-clonic seizures, is found to have cortical and subcortical abnormalities diffusely, with maximal differences in the frontal regions (O'Muircheartaigh et al., 2011; Ronan et al., 2012; Koepp et al., 2013). Even the mesial temporal lobe epilepsy (mTLE), one of the most common partial epileptic syndromes, also has alterations of cortical and subcortical structures and not just restricted to the medial temporal region (Focke et al., 2008; Keller and Roberts, 2008). However, studies have not addressed the relationship of motor-related GM and WM with secondary generalization for motor convulsive activity.

In this study, we used two techniques for analyzing brain morphology—voxel-based morphometry (VBM) and surface-based analysis—to characterize the GM volume and thickness, as well as WM FA, in epileptic patients with secondarily generalized seizures from a focus beyond the medial temporal lobe. We then associated the imaging findings with clinical variables. By using these approaches, we sought to identify the corresponding processes causing the structural alterations in these patients.

2. Methods

2.1. Subjects

We retrospectively reviewed the clinical database of Hualien Tzu Chi General Hospital to collect the MR data of patients with secondary generalization of focal seizures. We considered the patients as "non-lesional" if radiologists did not identify any lesions in their MRI scans, such as neoplasms, traumatic lesions, vascular anomalies, or malformations of cortical development. We excluded patients deemed "lesional" when the radiologists identified any undetermined lesions on the MRIs (for example, with possible blurred gray-white matter junctions). In case the radiologist reported possible sclerotic or atrophic changes in the mesial temporal lobe with maximal interictal or ictal epileptiform discharges localized to the temporal lobe, that patient would be excluded. Patients who had conventionally-termed primarily generalized epilepsies with symmetric interictal or ictal epileptiform discharges with non-lateralized presentations of clinical seizures were also excluded. We categorized patients in the drug-resistant group according to the definition proposed by the International League Against Epilepsy in 2009 (Kwan et al., 2010) when patients could not achieve sustained seizure relief even after being treated for over two years with two tolerated and appropriately chosen antiepileptic drugs. We further collected MRI data from age-matched healthy subjects as a control group. The study protocol, which consisted of retrospectively analyzing patient images and collecting images from the control subjects, was approved by the ethics committee of the Buddhist Tzu Chi General Hospital in Hualien, Taiwan, and written informed consent was obtained from each participant.

2.2. MRI acquisition

For each individual participating in this study, a 3T MRI scanner (General Electric, Waukesha, WI, USA) was used to acquire high-resolution, axial, three-dimensional, T1-weighted, fast-spoiled gradient-recalled echo (FSPGR) images (repetition/echo times [TR/TE], 11.812/5.036 milliseconds; 1-mm section thickness without gap; flip angle, 15°; section acquisition matrix, 512 × 512 with 220 × 220 mm^2 field of view [FOV]; and single-shot spin-echo echo-planar whole-brain DTI scans axially [TR/TE], 8000/82.4 milliseconds; 3-mm section thickness without gap; section acquisition matrix, 256 × 256 with 250 × 250 mm^2 FOV; number of excitations, 2; 25 gradient directions with a b value of 1000 s/mm^2, and 1 null tensor image with a b value of 0 s/mm^2).

2.3. Voxel-based analysis

For preprocessing the diffusion-weighted data, we used head motion, eddy current correction and diffusion tensor fitting; we then calculated the fractional anisotropy (FA) map using the FSL 4.0 package (Oxford Centre for Functional MRI of the Brain, Oxford University, Oxford, United Kingdom; http://www.fmrib.ox.ac.uk/fsl) (Koay et al., 2006). Voxel-based analysis was performed using the VBM8 (http://dbm.neuro.uni-jena.de/vbm/) toolbox of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2014a (Mathworks, Natick, MA, USA) to compare the properties of GM and WM between the patients and controls. Each individual SPGR image was registered into the null tensor image space and then reoriented with the original set close to the anterior commissure. The linearly registered SPGR images were segmented into GM, WM, and cerebrospinal fluid using the new segment procedure of SPM8 (Ashburner and Friston, 2005). Referring to a standard Montreal Neurological Institute (MNI) template, GM probability and FA maps were transformed non-linearly and readjusted to the voxel size of 3 × 3 × 3 mm^3 using a high-dimensional DARTEL algorithm (Ashburner, 2007). To account for local compression and expansion caused by linear and non-linear transformations, we modulated the images using the Jacobian determinants of the deformations (Good et al., 2001). In the final step, modulated GM probability and FA maps were smoothed with an isotropic Gaussian kernel having a 4-mm full width at half maximum (FWHM). Comparisons were made between the GM volume and FA of the group; the correlation of GM volume and FA with clinical variables were assessed using the general linear model (GLM) (covariates: age). All the results were corrected for multiple comparisons and the significance levels were set at $p < 0.05$ using AlphaSim correction (combined height threshold $p < 0.05$ and a minimum cluster size = 54 in BrainMask) and the REST software (http://www.restfmri.net/forum/REST V1.7) (Song et al., 2011).

2.4. Surface-based analysis

Cortical thickness was calculated as the average of the distance from the WM surface to the closest point on the pial surface and from that point back to the closest point on the WM surface using the FreeSurfer v5.3.0 software package (http://surfer.nmr.mgh.harvard.edu) (Fischl and Dale, 2000). FreeSurfer was used to spatially register the cortical thickness maps into the FreeSurfer standard space. These maps were then used to perform GLM analysis for group comparisons and to find out the predictors for cortical thickness variations. The thickness maps were smoothed with a 10-mm FWHM Gaussian kernel. The age was used as covariates. Using Freesurfer's built-in GLM tool, Qdec, we compared the cortical thickness between groups and evaluated the association of cortical thickness with clinical variables. All Qdec results were corrected for multiple comparisons used in the assessment of the cluster size p-values. These results, which were cluster-wise corrected for multiple-comparisons, were considered significant for $p < 0.05$. Spearman rank correlation analysis was used to determine associations between the increased significantly GM volume within the motor cortex and the precentral cortical thickness.

3. Results

Ultimately, the MRI data from 16 patients [aged 11–63 years; mean age, 29 years; 5 males and 11 females] fitting our inclusion criteria were collected. Our studied subjects suffered from seizures that originated from the frontal or extratemporal lobe. Eight patients with persistent seizures after treatment with two or more antiepileptic drugs were grouped in the drug-resistant patient group. Demographic and clinical data are summarized in Table 1. In the control group, we included 16 subjects (aged 23–39 years; mean age, 29 years; 5 men and 11 women) having no history of neurological or psychiatric disorders. All the control subjects obtained a maximal score on the mini-mental