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Corpus callosum diffusion abnormalities in refractory epilepsy associated with hippocampal sclerosis

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ABSTRACT

Objectives: To detect by diffusion tensor imaging (DTI) the extent of microstructural integrity changes of the corpus callosum (CC) in patients with hippocampal sclerosis (HS) and to evaluate possible association with clinical characteristics.

Methods: Fourty-two patients with temporal lobe epilepsy (TLE) and HS and 30 control subjects were studied with DTI. We grouped patients according to lesion side (left or right) HS. Mean diffusivity (MD), fractional anisotropy (FA), radial (RD) and axial diffusivity (AD) were extracted from five segments in CC midsagittal section obtained by automatic segmentation. CC DTI findings were compared between groups. We also evaluated association of DTI changes and clinical characteristics.

Results: HS patients displayed decreased FA and increased MD and RD in the anterior, mid-posterior and posterior CC segments, compared to controls. No differences were observed in AD. Patients reporting febrile seizure as the initial precipitating event presented more intense diffusion changes. No differences were seen comparing left and right HS. Age at epilepsy onset, disease duration and seizure frequency were not associated with DTI findings.

Conclusions: This is one of the largest series of TLE-HS patients evaluating CC white matter fiber integrity by DTI, which allowed us to study how some clinical characteristics, such as seizure frequency, disease duration and lesion side, are related to CC integrity. Occurrence of febrile seizure was the only factor that had significant impact on tract integrity. Diffusion changes were not restricted to the posterior part of the CC; we observed the same changes for the anterior part of the CC. Diffusion changes were characterized by an increase in RD, while the AD remained intact for all regions of the CC.

1. Introduction

Diffusion tensor imaging (DTI) allows detection of tissue subtle abnormalities, beyond the detection capability of conventional magnetic resonance imaging (MRI). This technique allows the estimation of the orientation of fiber bundles in white matter on the basis of the diffusion characteristics of water (Le Bihan et al., 1986). Changes in tissue structure can lead to a modification of water diffusion directional preference, which can be detected by DTI (Le Bihan et al., 2001).

Temporal lobe epilepsy (TLE) associated with hippocampal sclerosis (HS) is the most frequent cause of medically refractory epilepsy (Engel 1996; Engel 2001). DTI studies in TLE-HS have disclosed extensive white matter abnormalities, not restricted to the affected temporal lobe (Arfanakis et al., 2002; Assaf et al., 2003; Salmenpera et al., 2006; Yogarajah and Duncan 2008), but also involving extra-temporal and contra-lateral white (Liu et al., 2012; Otte et al., 2012). These findings indicate that structural abnormalities in TLE extend beyond the sclerotic hippocampus and the temporal lobe to involve a larger network of structures.

Corpus callosum (CC) is the largest and the main white matter comissure in the human brain. The CC connects cortical areas of the right and the left cerebral hemispheres, playing a key role in connecting cognitive and sensory information from one hemisphere to the other (Van der Knaap and Van der Ham 2011). As the major commissural

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tract, the CC is also the most important connection for inter-hemispheric epileptic activity propagation (Gloor et al., 1993).

DTI has been used to evaluate CC structural changes in TLE patients, but the available studies are quite variable in both methodology and results. Overall, the studied samples are small (Arfanakis et al., 2002; Gross et al., 2006; Kim et al., 2008; Knake et al., 2009; Meng et al., 2010). In some of them, the patient group is heterogeneous regarding TLE etiology, including patients with HS, neocortical epilepsy, malformations of cortical development and even patients presenting normal MRI (Kim et al., 2008; Meng et al., 2010). Given that HS is a unique disease with characteristics that differ from other etiologies of (Liu et al., 2012), we decided to study a large homogeneous patient series of adult patients with drug resistant TLE associated with unilateral HS, in order to elucidate the involvement of the CC in this particular disease.

The first goal of our study was to detect diffusivity abnormalities along the CC in patients with TLE and unilateral HS. As a secondary goal we aimed to evaluate how these diffusion abnormalities could be related to clinical findings.

2. Material and methods

2.1. Subjects

We studied 42 patients with medically refractory TLE and unilateral HS, confirmed by MRI, and 30 healthy volunteers, matched by age and gender. All patients underwent pre-surgical evaluation that included brain MRI, prolonged video-EEG monitoring, and neuropsychological evaluation. Inclusion criteria were: age between 18 and 55 years, medical refractoriness and brain MRI compatible with unilateral HS. Exclusion criteria were: presence of interictal or ictal epileptiform abnormalities outside the temporal lobes, finding of any additional MRI lesion other than the HS, or presence of any other neurological disease, except primary headache. Controls were also selected according to the same inclusion criteria (where appropriate), and were also required to have a normal brain MRI.

Patients were divided in groups, according to HS side (left or right). Twenty-three out of 42 (54.8%) were women, 25/42 (59.5%) had left HS.

Clinical findings were collected and correlated to DTI data. Recorded clinical data included: age at epilepsy onset (age at onset of recurrent spontaneous seizures), disease duration (time elapsed since the spontaneous or febrile seizure), epilepsy duration (time elapsed since recurrent seizure onset), silent period duration (time elapsed between the initial precipitation event − when present − and onset of recurrent seizures), monthly seizure frequency in the three months preceding video-EEG evaluation, and history of febrile seizures. These clinical features are presented in Table 1.

The study was approved by the Ethics Committee of our institution. The procedures were explained to all subjects and written informed consent was obtained.

Table 1
Patient's clinical features.

	Mean (SD)	n (%)	Median (range)
Age (years)	34.7 (9.6)		32 (20–54)
Sex (Woman)		23 (54.8)	
HS side (Left)		25 (59.5)	
Age at the initial seizure (months)	23.7 (17.3)		24 (2–60)
Initial precipitating event		27 (64.3)	
Febrile seizure occurrence		15 (35.7)	
Age at epilepsy onset (years)	12.6 (7.1)		12.5 (0.2–30)
Duration of epilepsy (years)	22.2 (10.0)		22 (6–48)
Duration of disease (years)	28.8 (11.8)		27 (8–54)
Silent Period (years)	6.6 (7.8)		3.8 (0 − 27)
Monthly Seizures Frequency	7.7 (7.7)		4.5 (1–30)

HS:hippocampal sclerosis.

2.2. MRI acquisition

MRI was acquired with an Intera Achieva 3.0 T system (Philips, Best, The Netherlands), using an eight-channel phased array head coil. All subjects underwent the same protocol including high-resolution T1-weighted volumetric images and a DTI acquisition. T1-weighted images were obtained using a three-dimensional Turbo Field Echo (3DT1-TFE) sequence covering 180 sagittal slices (1 mm thick), with TE = 3.2 ms, TR = 7 ms, FOV = 240 × 240 × 180 mm, matrix of 240 × 240 resulting in an isotropic resolution of 1 mm^3. DTI data were acquired with a diffusion-weighted spin-echo pulse sequence with b value of 1000 s/mm^2 applied in 32 non-collinear diffusion gradient directions. A total of 70 axial slices (2 mm thick) were acquired covering the entire hemisphere and brainstem; with TE = 61 ms, TR = 8500 ms, FOV = 256 × 256 mm, matrix of 128 × 128, resulting in an isotropic resolution of 8 mm^3. Reference images of b = 0 s/mm^2 were also acquired. The diffusion scan was repeated twice to increase signal-to-noise ratio.

2.3. Volumetric post processing

FreeSurfer 5.1.0 software package (http://surfer.nmr.mgh.harvard.edu) was used to obtain segmented CC areas from T1-weighted volumetric images. Using a specific algorithm, based on CC functional and anatomic connectivity (Hofer and Frahm 2006), FreeSurfer segments the midsagittal CC section into five separate labels: anterior (CC1), midanterior (CC2), central (CC3), midposterior (CC4) and posterior (CC5) as shown in Fig. 1. The automated procedures used for cortical and subcortical segmentation were described by Fischl et al. (2002). This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set.

2.4. DTI post processing

DTI datasets were processed with *Bioimagesuite 3.0* (http://www.bioimagesuite.org) and *FSL 5.0* (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) softwares.

The two DTI acquisitions were first corrected for head motion and distortions in diffusion images induced by eddy currents. Afterwards both DTI image sets were co-registered to each other and averaged. The diffusion tensor was then calculated and diagonalized to obtain the eigenvectors (ε_1, ε_2, ε_3), where ε_1 represents the orientation and magnitude of major diffusion in the voxel, and ε_2 and ε_3 represent the diffusion in the other two orthogonal directions. The corresponding eigenvalues, representing the value of diffusion in its direction (λ_1, λ_2 and λ_3) were also calculated. Fractional anisotropy (FA) and mean diffusivity (MD) maps were obtained. FA indicates the degree of directionality of diffusion in a given voxel, it ranges from 0 to 1; 0 indicating fully isotropic diffusion and 1 completely anisotropic diffusion. MD is a measure of the total displacement of water molecules ($\lambda_1 + \lambda_2 + \lambda_3$)/3 in the voxel. Axial diffusivity (AD), given by λ_1, represents the highest diffusion in the voxel and it is assumed to run parallel to the main axon fiber. Radial diffusivity (RD), represents the diffusion perpendicular to the main diffusion direction of the axon fibers and is calculated as ($\lambda_2 + \lambda_3$)/2.

The segmented T1-weighted image of each subject, originated a binary mask of each of the five subdivisions of the CC. Subsequently FA, MD and eigenvalue maps were co-registered with the segmented T1-weighted images, so that it was possible to use the five CC segments as ROI masks onto the DTI maps (Fig. 1). For the process of image registration and motion correction, the tools Brain Extraction Tool (BET) and FMRIB'S Linear Image Registration Tool (FLIRT), both components of FSL (FMRIB software library) were used. FSL consists of a set of tools