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White matter abnormalities in children and adolescents with temporal lobe epilepsy

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Abstract

Background and Purpose: The widespread propagation of synchronized neuronal firing in seizure disorders may affect cortical and subcortical brain regions. Diffusion tensor imaging (DTI) can noninvasively quantify white matter integrity. The purpose of this study was to investigate the abnormal changes of white matter in children and adolescents with focal temporal lobe epilepsy (TLE) using DTI.
Materials and Methods: Eight patients with clinically diagnosed TLE and eight age- and sex-matched healthy controls were studied. DTI images were obtained with a 3-T magnetic resonance imaging scanner. The epileptic foci were localized with magnetoencephalography. Fractional anisotropy (FA), mean diffusivity (MD), parallel ($\lambda_{||}$) and perpendicular ($\lambda_{\perp}$) diffusivities in the genu of the corpus callosum, splenium of the corpus callosum (SCC), external capsule (EC), anterior limbs of the internal capsule (AIC), and the posterior limbs of the internal capsule (PIC) were calculated. The DTI parameters between patients and controls were statistically compared. Correlations of these DTI parameters of each selected structure with age of seizure onset and duration of epilepsy were analysed.
Results: In comparison to controls, both patients' seizure ipsilateral and contralateral had significantly lower FA in the AIC; PIC and SCC and higher MD, $\lambda_{||}$ and $\lambda_{\perp}$ in the EC, AIC, PIC and SCC. The MD, $\lambda_{||}$ and $\lambda_{\perp}$ were significantly correlated with age of seizure onset in the EC and PIC. $\lambda_{||}$ was significantly correlated with the duration of epilepsy in the EC and PIC.
Conclusion: The results of the present study indicate that children and adolescents with TLE had significant abnormalities in the white matter in the hemisphere with seizure foci. Furthermore, these abnormalities may extend to the other brain hemisphere. The age of seizure onset and duration of epilepsy may be important factors in determining the extent of influence of children and adolescents TLE on white matter.

Keywords: Diffusion tensor imaging; Temporal lobe epilepsy; White matter; Children and adolescents

1. Introduction

Epilepsy is the fourth most common neurologic disorders in all ages [1]. Temporal lobe epilepsy (TLE) is the most common form and is the most frequent type of partial epilepsy refractory to medical therapy [2–4]. Sixty percent of surgically treated TLE patients become seizure-free if focal pathology such as hippocampal sclerosis (HS) is identified [5]. The pathological finding underlying the epileptogenic zone in patients with TLE invariably includes hippocampal neuronal loss with associated gliosis (i.e., mesial temporal sclerosis) [6]. Focal cell loss in patients with mesial TLE could be identified in hippocampal formation as well as in the amygdala, parahippocampus and entorhinal cortex. Mesial temporal sclerosis includes prominent neuronal loss in the CA1, CA3, and CA4 hippocampal subfields [7]. Typical TLE is a progressive disorder with focal neuronal loss that may be related to seizure activity and associated with the development of comorbidity, such as neurocognitive decline [7]. Recurrent seizures may directly induce morphological alterations that are proconvulsant and

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increase susceptibility to network synchronization [7]. It has been found that TLE is associated with white matter abnormalities. The white matter abnormalities may represent sequelae of recurrent partial seizure activity, reflecting an abnormal network associated with epileptogenesis. The results of previous reports provide compelling evidence that a neural network of functional and structural reorganization may occur in patients with TLE both ipsilateral and contralateral to the epileptic brain tissue [7]. However, it remains unclear how TLE affects the white matter in the developing brain.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique that can detect in vivo anisotropic diffusion properties in white matter by measuring water diffusion and its directionality in three directions [8–10]. DTI characterizes diffusive transport of water by an effective diffusion tensor D. This symmetric 3×3 tensor is very important, since it contains useful structural information about the tissue. The eigenvalues of D are the three principal diffusivities and the eigenvectors define the local fiber tract direction field [11]. DTI is a significant innovation of diffusion-weighted imaging that identifies areas of altered diffusivity and may show areas of disruption of the microstructural environment. White matter tracts can be reconstructed utilizing the information of directionality of diffusion in each voxel. DTI may be also useful to evaluate direct brain connectivity; a previous study indicated the presence of bilateral limbic system DTI alterations in patients with unilateral TLE [12]. Fiber tracking may be also used to assess white matter abnormalities. It remains to be determined if the use of DTI can increase the specificity and sensitivity of detecting the structural abnormalities in patients with intractable partial epilepsy.

White matter abnormalities in the fornix, cingulum, corpus callosum, internal capsules and external capsules have been reported in patients with TLE [11–13]. It has been found that irreversible structural axonal or myelin abnormalities in the white matter tracts correlate well with the reduced diffusion anisotropy and increased mean and perpendicular diffusivities [14,15]. However, the cerebral mechanisms of diffusion abnormalities in seizures remain largely unknown. The white matter abnormalities might be a direct consequence of seizures (either acute functional or chronic structural changes). It is also possible that the white matter abnormalities represent an underlying predisposing factor in the development of TLE [16,17]. Noteworthily, it is important to investigate the correlations between the age of seizure onset, the duration of epilepsy and the distribution or severity of the diffusion changes.

It has been suggested that the integration of multiple imaging modalities can elucidate functional brain dynamics and cortical connectivity [18,19]. The present study combined DTI and Magnetoencephalography (MEG) to investigate the diffusion characteristics of white matter in children and adolescents with TLE. MEG analysis was used to accurately localize the sources of interictal epileptiform discharges, and DTI analysis provided the unique in vivo information of the whiter matter architecture. To assess the integrity of white matter in the developing brain with epilepsy, the present study was designed to quantify the fractional anisotropy (FA), MD, parallel ($\lambda_{||}$) and perpendicular ($\lambda_{\perp}$) diffusivity. The present study focused on the genu of the corpus callosum (GCC), splenium of the corpus callosum (SCC), external capsule (EC), anterior limbs of the internal capsule (AIC) and posterior limbs of the internal capsule (PIC). We hypothesized that the diffusion of the selected white matter structures would correlate with age of seizure onset and duration of epilepsy.

2. Materials and methods

2.1. Participants

Eight patients with TLE (three girls and five boys) and eight age- and sex-matched healthy controls (three girls and five boys) were retrospectively studied. The mean age of the TLE patients was 11.95 years (range: 5.5–21.0 years); and the mean age of normal subjects was also 11.87 years (range: 5.5–21.0 years). The mean age of seizure onset was 6.7 years (range: 0.5–15 years) and the mean duration of seizures was 5.2 years (range: 1–12 years). Selection criteria for epilepsy patients were: (1) clinically diagnosed TLE; (2) epileptic activity was localized temporal lobe by MEG recordings; (3) no other neurological disorder. Inclusion criteria for healthy controls were: (1) healthy without history of neurological disorder or brain injury; (2) normal hearing, vision, and hand movement; (3) normal magnetic resonance imaging (MRI) scan. This study was approved by the institutional review board at the Cincinnati Children's Hospital Medical Centre (CCHMC).

2.2. Image acquisition

The MR images were acquired on a 3.0-T Siemens Trio MR imaging scanner (Siemens, Erlangen, Germany). A 46-section, diffusion-weighted, spin-echo echo-planar imaging scan was acquired in the axial plane with the following parameters: TR/TE=6000/87 ms, FOV=25.6×25.6 cm, matrix=128×128, section thickness=2 mm, *b* value=1000 s/mm^2 and four repetitions. Diffusion-weighted scans were acquired in 12 optimized directions. Reference T2-weighted images (b=0) were also acquired. The duration of the DTI sequence was 5 min 48 s.

The MEG recordings were obtained in a magnetically shielded room using a whole head CTF 275-Channel MEG system (VSM MedTech Systems, Coquitlam, BC, Canada) in the MEG Center at CCHMC. Before data acquisition commenced, a small coil was attached to the nasion, left and right pre-auricular points of each subject. These three coils were subsequently activated at different frequencies for measuring subjects' head positions relative to the MEG