Bilateral white matter abnormality in children with frontal lobe epilepsy

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Summary

In frontal lobe epilepsy (FLE), interictal discharges and seizures are more likely to spread to contralateral hemisphere and become secondarily generalized. The aim of this study was to assess white matter (WM) integrity in children with FLE using diffusion tensor imaging (DTI). Children with FLE and normal MRI, and healthy controls with no neurological or psychiatric disorders underwent DTI on 3 T MRI. Whole brain fractional anisotropy (FA) and mean diffusivity (MD) maps were compared between right and left FLE with controls. 43 children with FLE, consisting of 28 left and 15 right FLE, and 44 healthy controls were recruited. Patients with left FLE had significant FA reductions in left ($p = 0.002$) and right ($p = 0.003$ and $p = 0.034$) superior longitudinal fasciculi (SLF), genu/body ($p = 0.0002$) and splenium ($p = 0.011$) of corpus callosum. Patients with right FLE had significant FA reductions in left ($p = 0.016$) and right ($p = 0.033$) SLF, genu ($p = 0.001$) and body of corpus callosum ($p = 0.001$ and $p = 0.008$), and significant MD elevation in right thalamus ($p = 0.032$). There was no significant association between FA or MD and clinical seizure parameters. The abnormal WM both ipsilateral and contralateral to seizure focus may be due to seizure activity or abnormal brain development.

Keywords

Frontal lobe epilepsy; Pediatric; Diffusion tensor imaging

Introduction

Frontal lobe epilepsy (FLE) is a common localization-related epilepsy in children (Lawson et al., 2002). The seizure and EEG characteristics of FLE differ from temporal lobe epilepsy (TLE) in ways that go beyond the physical anatomical location. In children with FLE, the interictal discharges arising from a unilateral frontal lobe focus were more likely to spread to both hemispheres and form secondary bilateral synchrony relative to children with TLE (Hu et al., 2012). Children with FLE were also more likely to have secondarily generalized tonic—clonic seizures relative to children with TLE (Hu et al., 2012). Seizure activity within the

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same hemisphere and to the contralateral hemisphere may spread through the white matter (WM) pathways that form the cortico-cortical connections. Children with FLE have demonstrated widespread reduction in cortical thickness both within and beyond the frontal lobe, as well as in the contralateral hemisphere (Widjaja et al., 2011). The reduction in cortical thickness may be a secondary phenomenon related to the propagation of seizure activity to the extrafrontal lobes and contralateral hemisphere, mediated by association fibers that form cortico-cortical connection from the frontal to the extrafrontal lobes of the same hemisphere and by commissural fibers that form cortico-cortical connections to the contralateral hemisphere. Numerous studies in adults and children with TLE have demonstrated abnormal WM in the temporal and extratemporal lobes, using DTI (Arfanakis et al., 2002; Concha et al., 2005, 2007; Gross et al., 2006; Nilsson et al., 2008; Thivard et al., 2005). However, there is no reported study on the integrity of the white matter in children with FLE.

The aim of this study was to assess the WM integrity in children with FLE using DTI. Our hypothesis was that in children with FLE, abnormal WM would be identified both ipsilateral and contralateral to the seizure focus due to the spread of seizure activity through WM tracts.

Methods

This study was approved by the Hospital for Sick Children's research ethics board and written informed consent was obtained from participants. Children with non-lesional FLE who were worked up for epilepsy surgery were recruited into the study. Non-lesional FLE was defined as those with normal 3 T MRI as assessed by the pediatric neuroradiologist. The diagnosis of FLE and seizure lateralization was based on seizure semiology, video electroencephalography and magnetoencephalography in all patients, supplemented by 18F-FDG PET scan in 26 patients. The control group consisted of healthy subjects with no neurological or psychiatric disorders, and was recruited through the hospital's website and poster publications. All control subjects had normal MRI.

MRI

MRI was performed on a Philips 3T scanner (Philips Medical System, Netherlands) using an 8-channel phased array head coil in all patients and controls. DTI was done in both patients and controls using the following parameters: TR/TE = 10,000/60 ms, slice thickness = 2 mm, field of view = 22 cm, matrix = 112×112 , NEX = 2, SENSE factor of 2, $b = 1000$ s/mm², 15 noncollinear directions. Patients had additional imaging including volumetric T1, axial and coronal FLAIR, T2 and PD. Controls had additional volumetric T1 weighted imaging.

DTI analysis

Imaging was processed off-line using FSL FMRIB version 4.1.9 software package (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library, <http://www.fmrib.ox.ac.uk/fsl>) (Smith et al., 2004). First, each diffusion-weighted volume was affine-aligned to its corresponding b0 image using the FMRIBs linear image registration

tool (Jenkinson et al., 2002); this preprocessing step corrects for eddy current distortions and motion artifacts. Prior to fitting the tensor, brain masks of each b0 image were generated using the brain-extraction tool (Smith, 2002). Subsequently, the diffusion tensor was calculated, and FA and MD maps were generated using DTIFit. Voxel-wise statistical analysis of FA and MD data were carried out using TBSS implemented in FSL (Smith et al., 2006). FA images were pre-processed and brain extracted using the Brain Extraction Tool (Smith, 2002; Smith et al., 2006). One representative control case was selected and linearly registered to MNI152 template using FMRIB's linear image registration tool (FLIRT) routine. All FA images were linearly registered to the representative case followed by non-linear registration using FMRIB's nonlinear image registration tool (FNIRT). The transformed FA images were then averaged to create a mean FA image, which was then thinned so that the FA skeleton represented the center of all tracts common to the group. This was thresholded to FA = 0.20 to include the major WM pathways but exclude peripheral tracts where there was significant inter-subject variability and/or partial volume effects with gray matter. Each subject's aligned FA data were then projected onto the skeleton.

A randomization procedure with 10,000 permutations was used to perform the group analysis. A cluster-based thresholding corrected for multiple comparisons by using the null distribution of the maximum (across the image) cluster size was applied, with t value thresholded at 2.3. All the processing performed for FA were used to analyze MD. Anatomic location of the clusters of abnormal FA and MD was determined using John Hopkins University DTI-based WM atlases (Wakana et al., 2004) within FSL.

Correlation with clinical seizure parameters

The relations between clusters of abnormal FA, and clinical seizure parameters such as age of seizure onset, duration of epilepsy, seizure frequency and number of antiepileptic medications were assessed using linear regression analysis. A p -value of <0.05 was considered statistically significant.

Results

Subjects

Forty-three patients with FLE, consisting of 27 females and 16 males, mean age 13.2 years (standard deviation (SD): 3.3 years; age range 6.4–18.5 years) were recruited into the study (Table 1). The mean age at seizure onset was 7.2 years (SD: 4.2 years), the mean duration of epilepsy was 5.9 years (SD: 3.2 years) and the mean seizure frequency was 16.3 per week (SD: 23.3). The mean number of antiepileptic medications was 2.3 (SD: 0.8). Twenty-eight patients had left FLE and 15 patients had right FLE. There were no significant differences in mean age, age at seizure onset, duration of epilepsy, mean seizure frequency and number of antiepileptic medications between those with left FLE and those with right FLE (all $p > 0.05$). Seventeen patients underwent invasive monitoring and surgical resection, and of these twelve were seizure free. Forty-four healthy subjects, 25 males and 19 females, without neurological or psychiatric disorders and normal MRI formed the control group. The mean age of the controls was 12.8 years (SD: 3.6 years; range 6.0–18.8 years). There was no

significant difference in the age ($p = 0.729$) and gender ($\chi^2 = 3.356$, $p = 0.067$) of the patients and controls.

DTI TBSS

(i) Left FLE—Patients with left FLE had clusters of significant FA reductions in the left ($p = 0.002$) and right ($p = 0.003$ and $p = 0.034$) superior longitudinal fasciculi (SLF), genu/body of corpus callosum extending to the right forceps minor ($p = 0.0002$) and splenium of corpus callosum ($p = 0.011$) compared to controls (Fig. 1, Table 2). There was no significant elevation of FA in these patients. There was also no significant elevation or reduction in MD in patients relative to controls.

(ii) Right FLE—Patients with right FLE had clusters of significant FA reductions in the left ($p = 0.016$) and right ($p = 0.033$) SLF, genu of corpus callosum extending to the right forceps minor ($p = 0.001$), and body of corpus callosum ($p = 0.001$ and $p = 0.008$) compared to controls (Fig. 2, Table 2). There was no significant elevation of FA in these patients. There was significant elevation of MD in the right thalamus ($p = 0.032$), but no significant MD reduction in patients relative to controls.

Correlation between abnormal white matter with clinical seizure parameters

(i) Left FLE—There was no significant association between FA of the left and right SLF, genu/body and splenium of corpus callosum with age at seizure onset, duration of epilepsy, seizure frequency, or number of medications (all $p > 0.05$).

(ii) Right FLE—There was no significant association between FA of the left and right SLF, genu and body of corpus callosum, and MD of right thalamus with age at seizure onset, duration of epilepsy, seizure frequency, or number of medications (all $p > 0.05$).

Discussion

We have evaluated children with FLE and had normal MRI, and found reduced FA in the WM of both cerebral hemispheres, affecting the bilateral SLF and corpus callosum in both right and left FLE. The abnormal FA in the SLF and genu and body of corpus callosum likely reflects abnormal structural connectivity of the frontal lobes. The trajectory of the SLF has previously been delineated using DTI tractography (Makris et al., 2005). The SLF is a major association fiber tract composed of four subdivisions. SLF I connects the superior and medial parietal cortex to the supplementary motor cortex and dorsolateral prefrontal cortex (involving the superior and middle frontal, and rostral inferior frontal gyri). SLF II extends from the angular gyrus to the caudal lateral prefrontal cortex (involving superior and middle frontal gyri). SLF III extends from the supramarginal gyrus to the ventral premotor and prefrontal cortex (involving pars opercularis, superior and middle frontal gyri). SLF IV, also known as arcuate fasciculus, extends from the superior temporal gyrus to the lateral prefrontal cortex (involving superior and middle frontal, and rostral inferior frontal gyri). These connections may be bidirectional in nature (Petrides and Pandya, 2002), which has been supported by electrocortical research (Matsumoto et al., 2004).

The genu of corpus callosum connects the prefrontal region. The anterior body of corpus callosum corresponding to region II in Hofer's classification (Hofer and Frahm, 2006) connects the premotor and supplementary motor areas. The posterior body of corpus callosum, corresponding to regions III and IV in Hofer's classification, connects the primary motor cortex and primary sensory areas respectively. The splenium of corpus callosum, corresponding to region V in Hofer's classification, connects the parietal, temporal and occipital lobes.

Fonseca et al. (2012) evaluated 22 adults with FCD presenting with FLE. Patients with right FCD had reduced FA in the ipsilateral forceps minor and contralateral forceps minor and cingulum. Patients with left FCD had reduced FA in the ipsilateral cingulum, forceps minor, anterior thalamic radiation, uncinate fasciculus, inferior frontal occipital fasciculus, superior and inferior longitudinal fasciculus, forceps major, and corticospinal tract; and in the contralateral anterior thalamic radiation, forceps minor and corticospinal tract. The authors have found more extensive reduced FA in patients with FCD. In our study, the reduction in FA was mainly within the SLF and corpus callosum. We have evaluated children with non-lesional FLE. It is possible that some of these children may have had subtle FCD that was not identified on MRI.

Our study was the first to assess the WM in children with FLE and we found abnormal SLF, genu and body of corpus callosum. DTI studies have been reported in patients with epilepsy associated with frontal lobe dysfunction and they have found similar findings. DTI studies in juvenile myoclonic epilepsy, an idiopathic generalized epilepsy with frontal lobe dysfunctions, showed abnormal WM in supplementary motor area, bilateral superior and anterior corona radiata, genu and body of corpus callosum, and multiple superior and middle frontal WM tracts, and thalamofrontal connections (Deppe et al., 2008; Kim et al., 2012b; O'Muircheartaigh et al., 2011). The WM in the frontal lobe has also been examined using DTI in 12 children with drug resistant partial epilepsy (Holt et al., 2011). Using region of interest analysis, reduced FA, reduced ADC and parallel diffusivity was demonstrated in the SLF of children with partial epilepsy compared to controls. Reduced FA has also been demonstrated in the SLF ipsilateral to the seizure focus in children with medically intractable neocortical epilepsy in both right and left focal epilepsy (Kim et al., 2012a). Abnormal WM measured with DTI has previously been shown to correlate with abnormal gray matter metabolism measured with 18F-FDG PET in children with partial epilepsy, suggesting abnormal WM was related to the epileptogenic network (Lippe et al., 2012).

We found no major differences in the abnormal WM between right and left FLE or between the WM ipsilateral and contralateral to seizure focus. Fonseca et al. (Fonseca et al., 2012) found more extensive WM abnormalities in adults with left FLE than right FLE secondary to FCD. DTI studies in patients with TLE have demonstrated differences in abnormal DTI in patients with right and left TLE. Shon et al. (Shon et al., 2010) found patients with left TLE and hippocampal sclerosis showed increased MD in the ipsilateral posterior cingulum, corpus callosum and contralateral occipital and temporal lobes that were not seen in those with right TLE and hippocampal sclerosis. Similarly, increased MD was noted in the ipsilateral posterior fornix and cingulum in patients with left TLE without hippocampal sclerosis, but not in patients with right TLE. Patients with left TLE had more diffuse

abnormal FA than those with right TLE (Ahmadi et al., 2009; Focke et al., 2008), and the changes were more pronounced ipsilateral to the seizure focus (Ahmadi et al., 2009). Differences in our results and the findings in TLE studies and the one study in FLE secondary to FCD were not clear. Thus far, all of the above mentioned studies have been conducted in adults. There has not been any reported study comparing DTI findings in children with right and left partial epilepsy. We postulate that differences in neuronal network in FLE and TLE may contribute to the observed clinical and electrographic differences between these two forms of localization-related epilepsy. Furthermore the underlying substrate responsible for the epilepsy may account for differences in reorganization of the WM pathways and contribute to the observed differences. We have also found elevated MD in the right thalamus in children with right FLE, but not in the left thalamus in children with left FLE. It is unclear why there was elevated MD in the thalamus but no abnormal MD in the WM. It is possible that the abnormal MD in the right thalamus in right FLE was due to noise rather than microstructural changes in the thalamus.

We have found no significant association between abnormal FA in right and left SLF and corpus callosum with age at seizure onset, duration of epilepsy, seizure frequency, or number of medications (all $p > 0.05$) in right and left FLE. There is no consensus in findings on the relation between DTI measures of WM integrity and clinical seizure parameters. Riley et al. (2010) have found earlier age at seizure onset correlated with reduced FA in the corpus callosum in adults with temporal lobe epilepsy. Kim et al. (2012b) found FA reduction in superior and anterior corona radiata, corpus callosum and middle and superior frontal WM tracts correlated with the number of generalized tonic clonic seizures in patients with juvenile myoclonic epilepsy. There is as yet no explanation for the lack of consensus in findings; differences in underlying cause and types of seizures may potentially contribute to some of the differences observed.

In summary, we have found abnormal WM both ipsilateral and contralateral to seizure focus in children with right and left FLE. The abnormal WM may be secondary to seizure activity or underlying abnormal development of the gray matter and WM that predisposed to epilepsy.

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Figure 1.

Patients with left frontal lobe epilepsy show reduced fractional anisotropy (FA) in the left and right superior longitudinal fasciculus, genu and body of corpus callosum extending to the right forceps minor, and splenium of corpus callosum compared to controls. Regions of reduced FA (blue) and white matter skeleton (green) are superimposed on the mean FA image. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 2.

Patients with right frontal lobe epilepsy show reduced fractional anisotropy (FA) in left and right superior longitudinal fasciculus, genu of corpus callosum extending to the right forceps minor, and body of corpus callosum compared to controls. Regions of reduced FA (blue) and white matter skeleton (green) are superimposed on the mean FA image. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Baseline parameters of patients with frontal lobe epilepsy (FLE) and controls.

	Patients		Controls (<i>n</i> = 44)
	Right FLE (<i>n</i> = 15)	Left FLE (<i>n</i> = 28)	
Age (SD) (years)	13.4 (3.2)	13.0 (3.5)	12.8 (3.6)
Sex	12f, 3m	15f, 13m	19f, 25m
Mean age at seizure onset (SD) (years)	7.9 (4.2)	6.8 (4.3)	
Mean duration of epilepsy (SD) (years)	5.6 (3.1)	6.1 (3.2)	
Mean seizure frequency/week (SD)	12.4 (18.6)	18.4 (25.6)	
Mean number of antiepileptic medications (SD)	2.4 (1.0)	2.3 (0.7)	

SD = standard deviation; f = female; m = male.

Significant clusters of reduced fractional anisotropy and elevated mean diffusivity in patients with left and right frontal lobe epilepsy.

Table 2

	Voxel size	Z-MAX	p-value	Z-MAX X	Z-MAX Y	Z-MAX Z
Left FLE						
<i>Regions of reduced fractional anisotropy</i>						
Left superior longitudinal fasciculus	434	0.002		-35	-13	26
Right superior longitudinal fasciculus	374	0.003		41	-8	25
	194	0.034		36	-42	29
Genu/body of corpus callosum	860	0.0002		9	30	-2
Splenium of corpus callosum	273	0.011		-15	-33	28
Right FLE						
<i>Regions of reduced fractional anisotropy</i>						
Left superior longitudinal fasciculus	244	0.016		-38	-25	29
Right superior longitudinal fasciculus	191	0.033		28	-19	26
Genu of corpus callosum	543	0.001		7	22	16
Body of corpus callosum	536	0.001		13	-8	31
	308	0.008		4	-14	25
<i>Region of elevated mean diffusivity</i>						
Right thalamus	238	0.032		0	-11	18

FLE = frontal lobe epilepsy.