Deep White Matter Track Record of Functional Integrity in Childhood Absence Epilepsy

PURPOSE: It is unknown whether white matter abnormalities exist in childhood absence epilepsy (CAE), a syndrome of idiopathic epilepsy (IGE). Diffusion tensor imaging (DTI) can noninvasively quantify white matter integrity. This study used DTI to investigate abnormal changes in white matter of untreated CAE patients. METHODS: Subjects included nine patients with untreated CAE and nine age-and sex-matched healthy controls. Diffusion tensor imaging parameters were voxel based and statistically compared between patients and controls. The correlations between DTI parameters in regions of interest (ROIs) and age of seizure onset or duration of epilepsy were analyzed. RESULTS: Untreated CAE patients had a significantly higher fractional anisotropy (FA) value in the bilateral thalamus, anterior corpus callosum and upper brainstem, while also displaying a lower FA value in prefrontal white matter, anterior cingulate, and bilateral posterior limbs of the internal capsule compared to control subjects. An increase in mean diffusivity (MD) value was observed in parietal lobe white matter, prefrontal white matter, and posterior cerebellar hemispheres, in addition to subcortical structures including bilateral putamen and posterior limb of internal capsule. There were MD significant correlations between ROI diffusion parameters and the duration of the disease or the age of onset. CONCLUSIONS: The results showed white matter integrity impairment in the basal ganglia thalamocortical circuit of drug-naïve CAE patients. These abnormalities in white matter may be related to increased cortical excitability and cause cognitive, linguistic, and behavioral/emotional deficits both during and between seizures.

Commentary
The ability to demonstrate the extent of a white matter connected epileptic circuit is possible by utilizing diffusion-based magnetic resonance (MR) imaging. Such MR sequences have a long history of detecting seizure-related changes in white matter associated diffusion. These MRI abnormalities have been shown to occur both interictally, and during complex partial status epilepticus (1). Diffusion weighted MR imaging (DWI) sequences measure the magnitude of water movement by applying an additional directional gradient to standard T2-weighted echo planar imaging sequences. These standard imaging sets acquire the data in the three cardinal planes (XYZ) and average the data to get an estimate of the total diffusion within a voxel. The result can be expressed as the apparent diffusion coefficient (ADC). So, the magnitude of diffusion, or mean diffusivity (MD) in DWI is the average of the ADC. Diffusion tensor imaging (DTI) is an evolution of this technique, capable of demonstrating seizure-associated changes in the directionality of water diffusion not possible with DWI and fluid attenuation inversion recovery (FLAIR) sequences (2–4).

The recent review by Yang et al. demonstrates DTI-related differences in extensive deep cerebral, bilateral thalami, brainstem, and cerebellar white matter circuits in a small cohort of newly diagnosed drug-naïve children with childhood absence epilepsy (CAE) compared with age- and sex-matched controls. Furthermore, the article attempts to suggest a causal relationship of such DTI-related changes with cognitive and emotional deficits often seen in these children.

From an imaging technology perspective, DTI is based on the knowledge that the diffusion of water molecules within brain white matter is not equal in all directions. Diffusion is typically restricted by cell membranes of myelinated neurons, called anisotropic diffusion, or fractional anisotropy (FA). FA represents a measure of the directionality of water diffusion. Water does not diffuse across intact axonal fibers but rather along their major axis. So, intact brain white matter promotes anisotropic diffusion, whereas anisotropy indices tend toward 1. Conversely, isotropic diffusion, where water diffuses in no apparent direction, represents altered or disrupted white matter pathways. In this scenario, the FA index approaches zero. The MD, or trace, is a measurement of the amplitude of the diffusional motion, putatively reflective of cell hydration.

Chronic changes seen with DTI following years of focal-onset seizures have been well described in the literature. For example, the usual pattern in mesial temporal sclerosis and cortical dysplasia is a reduced FA and increased MD on the
involved side (3, 5). In support of secondary epileptogenesis in humans, chronic DTI-related changes are not confined to the ipsilateral hippocampus alone but are often seen contralaterally (6, 7), as well as in the relay pathways of the thalamus (8). In longstanding temporal lobe epilepsy, a significantly reduced FA is often seen in the posterior corpus callosum in patients compared with controls. This finding suggests widespread changes owing to chronic influences from distant connected epileptic sources.

Conversely, transient postictal changes in FA compared with interictal DTI measures can be utilized to visualize transient subcortical remnants of the directionality of an epileptic circuit recruited by partial-onset seizures (2, 9). These transient postictal measures are not typically useful in those patients in whom secondarily generalized seizures have occurred immediately prior to postictal MRI. Such widespread propagation pathways become too complex to analyze.

DTI-related alterations as demonstrated by Yang et al. in recently diagnosed drug-naïve children with typical absence epilepsy are relatively new in the literature. Yang et al. found significantly increased FA in the thalamus, bilaterally and upper brainstem of untreated CAE patients. The study also demonstrated increased FA in the anterior corpus callosum. This finding is in contrast to reduced FA observed in the posterior corpus callosum, robustly implicated in temporal lobe epilepsy. This information reinforces the presence of an overactive neural circuit in the anterior corpus callosum of CAE patients compared with normal controls. These data suggest intact anterior corpus callosum integrity with increased axonal bundle diameters. The findings support the use of corpus callosotomy to potentially disrupt the bulk of interhemispheric communication of intractable epileptic circuits shared by the localization-related frontal lobe and generalized epilepsies. Yang et al. also demonstrated a reduced FA in the prefrontal white matter, anterior cingulate, and posterior limbs of the internal capsule bilaterally compared with normal controls. This finding is suggestive of disrupted axonal integrity in those regions. In addition, the authors found an increased MD in the putamen bilaterally, an indirect measure of increased subcortical neuronal hydration. These data suggest that the basal ganglia pathways are, in part, associated with the generation of epileptic activity in CAE seen as generalized spike-wave discharges on scalp EEG. Of interest, the authors reported an increased MD extending to the cerebellum. This structure has consistently been associated with both transient hyper- and hypo-perfusion–related alterations reported in the ictal single photon emission computed tomography (SPECT) literature. The electrophysiological connection of the cerebellum as a deep brain modulator of epileptiform activity is well established. However, its complete role in the epilepsies remains unknown.

Evaluating functional connectivity patterns in infants and children along with longitudinal follow-up has not been well studied until recently (10). Information gained from DTI can begin to decipher the extensive network underpinnings of cognitive differences between unimpaired children without epilepsy and those with absence epilepsy. Yang et al., however, suggest causality of cognitive and behavioral relationships with DTI in the absence of close neuropsychological and psychiatric assessment in the patient cohort.

As diffusion tensor models evolve, improved visualization of affected neural circuits will be likely introduced in the diagnostic evaluation of widespread epileptic networks. For example, the magnitude and direction of the principal eigenvector within a DTI voxel will be better utilized to mathematically produce colorized fiber orientation maps. As a result, improved fiber tracking with an ability to resolve crossing fiber tracts will generate better modeling of deep cerebral epileptic networks extending throughout the brain.

The neuroimaging information presented by Yang et al., even though lacking robust statistical power, sets the stage for attempting to better understand structural changes in extensive epileptic circuits. Using DTI with larger patient cohorts will contribute toward understanding neurocognitive deficits in children with a common childhood epilepsy syndrome.

by Marvin A. Rossi, MD, PhD

References

Disclosure of Potential Conflicts of Interest

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