Characteristics of Abnormal Diffusivity in Normal-Appearing White Matter Investigated with Diffusion Tensor MRI in Tuberous-Sclerosis Complex.

M. Makki[1], D. Chugani[1], H. Chugani[1]

[1]Pediatric Neurology, Children's Hospital of Michigan, Detroit, Mi, United States

Introduction: Tuberous sclerosis complex (TSC) is a neurocutaneous disorder with neurological problems including epilepsy, developmental delay, and cognitive and behavioral problems of varying severity [1]. In the present study, we re-examine the changes in apparent diffusion coefficient (ADC) of normal appearing white matters (NAWM) [2], and we further assess these diffusion changes in NAWM by estimating DTI eigenvalues (major λ_1: parallel to main axis; middle λ_2, and minor λ_3: orthogonal to main axis), apparent diffusion coefficient (ADC) fractional anisotropy (FA), anisotropy index (AI), and relative anisotropy (RA). Understanding those indices may provide some clues to the microstructure changes leading to increased diffusivity in white matter of TSC patients.

Materials and Methods: Six TSC patients (mean age = 10 ± 2 years) and 12 normal control subjects, (mean age = 10 ± 4 years) underwent DT-MRI. Six NAWM brain structures were selected: genu of corpus callosum (GCC), splenium of corpus callosum (SCC), anterior limb of internal capsule (ALIC), posterior limb of internal capsule (PLIC), external capsule (EC), and corona radiate (CR). We also investigated the advantages of using FA, AI, and RA indices in normal control children and patients with TSC, and evaluated their sensitivity to each structure. MRI studies were performed on a 1.5T scanner (GE Healthcare, Milwaukee, WI). Single shot DT SE-EPI consists of one T2W (b=0 [s/mm^2]) image volume of 40 slices (voxel = 1.85x1.85x3 mm^3) followed by 6 gradients in non-collinear directions (b=1000 [s/mm^2]), and 6 averages each. In this study, λ_1, λ_2, and λ_3 were measured to provide a more direct assessment of the directional diffusion changes associated with WM.

Results: The calculated ADC values for all NAWM structures in both hemispheres showed significantly higher values in the TSC group when compared to normal control subjects (Table 1). The GCC had significantly higher λ_1, and λ_2, yielding a significantly higher ADC value when compared to normal control findings. The diffusivity was thus less restricted in the transverse plane and also along the main axon directionality. FA, RA and AI were decreased but not significantly. Similarly, the higher ADC observed in the SCC resulted from a significant increase in the eigenvalues orthogonal to the fibers, while no significant difference was observed in the λ_1. RA was also significantly lower in SCC in TSC patients when compared to normal controls showing that fiber bundle organization was affected also by these changes. The PLIC on the left side in the TSC group had significantly higher λ_3, however, this had no significant effect on the ADC value. On the contrary, the PLIC on the right side in TSC subjects showed significantly higher λ_2 and λ_3 leading to a significantly higher ADC. All eigenvalues of the ALIC in both sides in TSC patients had significantly higher values yielding significantly higher ADC. The EC of the left and right hemispheres had also a significantly higher ADC, derived from a significant increase of the λ_3, and also λ_1 for the right side. In addition the RA values of the two sides were significantly lower in the TSC group. In all structures where we observed increased ADC values, we noticed a reduction in FA, RA and RA values. However, these differences were not significant ($p>0.05$).

Discussion: Significant changes in ADC in NAWM brain structures that are not associated with lesions when compared to a group of age-matched normal control subjects were demonstrated. Further, it was evident that the increase in diffusivity was mainly due to a significant increase in directions orthogonal to the axons (λ_2 and λ_3), and little in the main direction or the axons, (λ_1). Experimental models have revealed that axonal cell membrane account for most of the restriction of water motion in white matter of myelin. Pathologic disruption of cell membranes, loss of myelin, or any process that may alter the integrity of axons would reduce the restriction of water molecules, and therefore, the ADC values would be increased [4]. One possible mechanism for the increased diffusion in the orthogonal direction in TSC patients may be related to recent animal studies of increased astrocyte size and numbers following mutations in TSC1 and TSC2 genes [3, 5]. Uhlmann et al. (2002) reported that heterozygosity for TSC2 resulted in a 1.5 fold increase in the numbers of astrocytes in mice in vivo [5, 6]. Increase cell size and numbers of astrocytes within the large white matter tracts might lead to the observed changes in diffusion in the children with TSC.

Conclusion: The increased mean diffusivity may indicate underlying physiologic processes affected the packing of axonal fibers and increased extracellular space. This may be due to a less restriction of the diffusion process, especially orthogonal to the axons. The increase in ADCs in supratentorial NAWM of patients with TSC may be related to changes in fiber packing density secondary to astrogliosis.

Paired T-Test	CC		CR		PLIC		ALIC		EC	
	Genu	Sple	L	R	L	R	L	R	L	R
λ_1	**0.047**	0.310	0.081	0.066	0.359	**0.044**	**0.017**	**0.013**	0.136	0.069
λ_2	**0.005**	**0.020**	0.053	0.054	0.242	0.155	**0.020**	**0.031**	0.101	0.155
λ_3	0.143	**0.043**	**0.018**	**0.029**	**0.012**	**0.004**	**0.010**	**0.026**	0.083	0.490
ADC	**0.018**	**0.019**	**0.024**	**0.028**	**0.049**	**0.012**	**0.029**	**0.018**	0.097	0.149
FA	0.192	0.055	0.100	0.148	0.690	0.085	0.841	0.951	0.599	0.278
AI	0.139	0.108	0.083	0.142	0.451	0.404	0.599	0.801	0.487	0.245
RA	0.257	**0.021**	0.163	0.217	**0.022**	**0.037**	0.485	0.562	0.573	0.243

Table 1: Statistical analysis of NAWM comparing TSC patients to a group of age-matched normal control subjects. Difference was considered significant when $p < 0.05$., CC Genu and splenium (Sple), CR=corona radiata, PLIC = posterior limb internal capsule, ALIC = anterior limb internal capsule and EC = external capulse. (L means left hemisphere and R means right hemisphere)

References: [1] Curatolo P et al., Eur J Paediatr Neurol; 6:15-23, 2002. [2] Garaci FG, et al., Radiology 232:461-465, 2004. [3] Apicelli AJ et al., GLIA 42:225-234, 2003. [4] Jansen FE et al., Arch Neurol., 60:1580-1584, 2003. [5] Uhlmann EJ et al., Ann Neurol 53; 285-296, 2002, [6] Uhlmann EJ, et al., GLIA 47:180-188, 2004.