Abnormal Thalamic Diffusivity in Patients With Tuberous-Sclerosis Complex Revealed with Diffusion Tensor MRI.

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Introduction: Tuberous sclerosis complex (TSC) is a neurocutaneous disorder inherited in an autosomal dominant manner, and results from mutations in at least two different genes, TSC1 [1] and TSC2 [2]. Intracranial lesions in TSC include cortical tubers [3,4], subependymal nodules, subependymal giant cell astrocytoma [5] and microscopic abnormalities such as microdysgenesis, heterotopic grey matter, and lamination defects [6]. Recently, further brain abnormalities were detected in supratentorial *normal-appearing* white matter of TSC patients assessed by quantitative diffusion-tensor MRI (DT-MRI) when compared to normal control age matched subjects [7]. To the best f our knowledge no investigation used the benefit of DT-MRI to study gray matter (GM) in TSC patients.

Purposes: In the present investigation, we performed DTI to evaluate changes in GM brain region in particular the head of caudate nuclei (HCN) and the thalamus (TH) which are important in seizure propagation. We measured DTI eigenvalues (λ_1, λ_2, λ_3) to provide a more direct assessment of the directional diffusion changes associated with GM development to understand their microstructure changes. We hypothesized that anisotropy and diffusivity values in the mediodorsal thalamic nucleus would differ between patients with TSC and normal control subjects.

Materials and Methods: We studied six patients (age = [5-17] years, mean = 10 ± 2 years) with established TSC diagnosis and twelve normal control subjects, (age = [7-17] years mean = 10 ± 4 years) with same DT-MRI sequence (1.5T Signa Excite - GE Healthcare, Milwaukee, WI). The clinical protocol includes: *1)* 3D volumetric T1W, *2)* coronal FLAIR, *3)* axial T2W, *4)* coronal T_2*W, *5)* axial T1W with contrast enhanced (Gd-DTPA), and *6)* DTI with dual spin-echo single shot EPI with the following parameters: TR/TE=13000/87 ms, image matrix 128x128, FOV=24 cm, 40 slices of 3mm thickness covering the whole brain. DTI sequence involves an image volume with b=0 [s/mm^2] followed by the acquisition of the same volume in 6 diffusion gradients with b=1000 [s/mm^2]. Six averages were performed to reduce artifacts. Sedation was employed only on patients if necessary, and not on control subjects. We measured all eigenvalues, than we calculated apparent diffusion coefficient, (ADC), fractional anisotropy (FA), anisotropy index (AI), and relative anisotropy (RA) on each ROI.

Results: Comparisons between patients and normal controls (paired t-test) were performed separately in each structure and in each hemisphere. Although there was no significant difference among studied structures between the left and right hemispheres within the two groups, we considered them unpaired and we separately analyzed the left and right areas. In TSC patients the TH in both hemispheres showed significantly higher ADC values (paired t-test) when compared to normal control subjects, whereas no significant change was observed on HCN. Thalamic changes were significantly higher in all eigenvalues in both sides resulting in a significant increase in ADC (Table 1). Anisotropy processed by FA, AI and RA in patients was lower than this of normal control but not statistically significant. It was evident from these finding that the changes in mean diffusivity are not merely explained by changes in brain water content, and more likely reflect microstructural changes in premyelination and myelination, causing increased hindrance to water diffusion perpendicular to the direction of the axonal fibers.

Discussion: Unlike other subcortical GM structures, the TH contains both unmyelinated and myelinated nerves. The unmyelinated nerves consist of intrathalamic relay and connections between the basal ganglia and the brain stem nuclei. The myelinated nerves are the thalamocortical striations, which provide sufficient diffusion restriction to be visible by DTI. The observed increases in thalamic orthogonal diffusivities are most likely due the shorter, unmyelinated interthalamic, striatal, and brainstem projections. On the other hand, increase in parallel diffusivity may be explained by the thalamocortical and corticothalamic projections which are myelinated. Several investigations revealed higher ADC and lower FA in brain zones that appeared normal on conventional MRI [8,9]. Increased thalamic ADC may suggest involvement of the TH in the seizure perhaps due to recruitment of this structure into the epileptic network. DTI has proven to be a sensitive method to detect such remote abnormalities and can be utilized to detect abnormalities in subcortical regions of children with TSC even if structural MRI is negative. Although reduced anisotropy was not significant, it is necessary to perform additional measurements, in order to make a definitive statement about the significance of these changes.

Conclusion: Changes in diffusivity and anisotropy revealed in normal-appearing brain tissue beyond the origin of TSC lesions may be important to help localize lesions in MRI-negative patients and provide more information in detecting potential epileptogenic regions. The increased mean diffusivity may indicate underlying physiologic processes such as loss of myelin and 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 the thalamus of patients with TSC may be caused by loss of tissue organization or by axonal hypomyelination undetectable by conventional MRI exams.

p_value t-test		λ_1	λ_2	λ_3	ADC	FA	AI	RA
TH	**L**	**0.018**	**0.013**	**0.033**	**0.015**	0.443	0.517	0.856
	R	**0.017**	**0.035**	**0.059**	**0.020**	0.552	0.589	0.97
HCN	**L**	0.103	0.092	0.083	0.088	0.874	0.487	0.902
	R	**0.033**	0.121	0.490	0.106	0.115	0.245	0.166

Table 1: Statistical analysis results of paired t-test, where difference was considered significant if $p < 0.05$. TH and HNC refer respectively to thalamus and head of caudate nuclei, L=Left hemisphere and R = right hemisphere.

References : [1] Fryer AE et al., *Lancet; 1, 1987.* [2] Kandt RS et al., *Nat Genet; 2, 1992*. [3] Ferrer I et al., *Clin Neuropathol; 3, 1984*. [4] Huttenlocher PR et al., *Ann Neurol 16, 1984*. [5] Kingsley DPE et al., *Neuroradiology; 28, 1986*. [6] Machado-Salas JP. *Clinical Neuropathol; 3: 1984*.[7] Garaci FG et al., *Radiology 232, 2004.* [8] Arfanakis K, et al.,. *Magn Res Imag 20; 2002*. [9] Rugg-Gunn FJ et., *Brain 1, 2001*.