

# Evaluation of the relationship between corpus callosum and internal capsule and tuber load in patients with tuberous sclerosis complex by diffusion tensor imaging

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## Abstract

**Aim:** To determine whether there are Diffusion Tensor Imaging (DTI) changes in the white matter pathways such as corpus callosum and internal capsule in patients with Tuberous sclerosis complex (TSC) and to investigate its relationship with tuber load.

**Materials and Methods:** Our study included 17 children with TSC and 15 healthy controls. Total tuber load of the brain was calculated. Correlation between tuber load and ADC (Apparent diffusion coefficient) and FA (Fractional anisotropy) values at corpus callosum (CC) and internal capsule were investigated.

**Results:** When patients with TSC were compared with control, there was a significant difference in ADC and FA values in the corpus callosum and internal capsule. There was a significant difference in FA values between the anterior and posterior limbs of the internal capsule on both sides. The ADC values of CC splenium were positively correlated with the total cerebral tuber load. Also, The FA values obtained from CC splenium were negatively correlated with the tuber load of the right cerebral hemisphere.

**Conclusion:** Relationships between corpus callosum and internal capsule ADC and FA changes and tuber load show that microstructural damage develops in the white matter pathways. DTI parameters can be used as a more sensitive biomarker in the evaluation of the abnormal structure of white matter in patients with TSC. More comprehensive studies are needed to more clearly demonstrate the relationship between DTI properties of white matter and tuber load in TSC patients.

**Keywords:** Corpus callosum; diffusion tensor imaging; tuber load; tuberous sclerosis complex

## INTRODUCTION

In patients with tuberous sclerosis complex (TSC), hamartomatous lesions are most common in the brain (1,2). Two different mutated or deleted genes at 9q34 and 16q13 have been identified, with an autosomal dominant transition. Important neurological symptoms such as epilepsy (90%), mental disability (40%) and autism spectrum disorder (50%) are accompanied (1, 3-5). Cortical tubers and subependymal nodules caused by migration anomalies constitute the most important pathological changes in the brain (1,2). There are findings supporting myelination or migration disorders in cerebral white matter. Tuber load and tuber locations seem insufficient to predict the patient's clinical course (1,2). White matter abnormalities are well-known features in MRI of TSC patients (2,4). White matter changes occur more prominently in patients with more severe neurological phenotype (2,4).

Diffusion tensor imaging (DTI) reveals microstructural features of brain tissue in detail. FA (Fractional anisotropy)

and ADC (Apparent diffusion coefficient) values can be used as biomarkers to identify disease burden in large white matter pathways (3,6). Since the DTI properties of white matter are associated with neurocognitive dysfunctions, it plays an important role in identifying potential disease (7).

The aim of our study is to determine whether there are DTI changes in the white matter pathways such as corpus callosum (CC) and internal capsule (IC) and to investigate its relationship with tuber load.

## MATERIALS and METHODS

Ethics committee approval was received for retrospective study. Our study included 17 children with TSC (10 male, 7 female; 9.18± 3.69 years old) and 15 healthy controls (6 male, 9 female; 9.87±4.48).

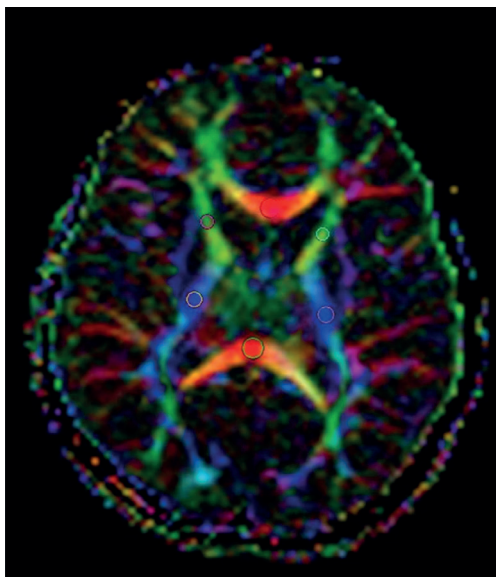
All subjects were examined using the 1.5T MRI (Siemens-Avanto). Routinely MRI protocol included: 3D MPRAGE (TR/TE/TI: 12.5/5/450 ms), axial T2 weighted (TR/TE: 4280/91

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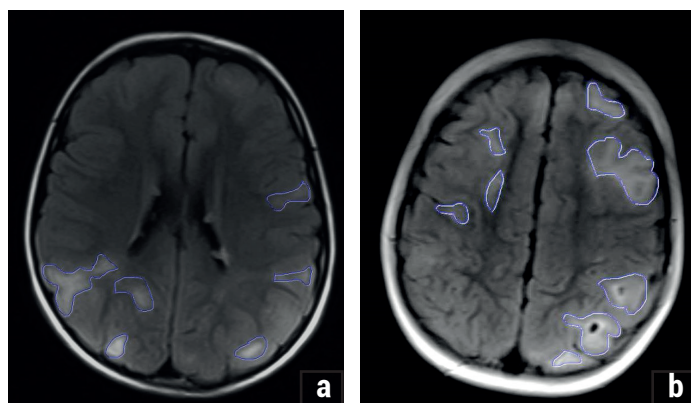
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ms) and T1 weighted (TR/TE: 500/87 ms), axial FLAIR (TR/TE/TI: 8000/118/23.687 ms), coronal FLAIR (TR/TE/TI: 8000/118/23.695 ms), and T2 weighted sagittal (TR/TE: 4810/90 ms) images.

As DTI protocol, SE-EPI image (TR/TE=6.000 /89 ms) containing 5 mm slice thickness and 30 gradient directions was used. ADC and FA maps were created using DTI data on the workstation. Using FA maps, ROIs were placed manually in the CC genu and splenium and anterior and posterior limb of the IC for both hemispheres (Figure 1).



**Figure 1.** The axial color-coded FA maps from a subject with TSC showing placement of region of interest (ROI) on corpus callosum (genu and splenium), anterior and posterior limb of the internal capsule



**Figure 2.** Analysis of tubers volume using by the placement of ROI on axial FLAIR images (2a and 2b)

The volumetric analysis was performed by a 3D semiautomated quantitative assessment of tumor volume in the work station (Siemens workstation, Syngo.via). The cortical and subcortical tuber volumes were outlined and calculated on the axial FLAIR images. Volumetric lesion analysis was performed in a cubic centimeter (cm<sup>3</sup>). Total tuber load of the brain was calculated (Figure 2a and 2b). Correlation between tuber load and ADC and FA values at CC and IC were investigated.

**Statistical Analyses**

Statistical evaluations were performed using SPSS 22.0 version. Kolmogorov Smirnov and Shapiro-Wilks tests were used to evaluate whether the data showed normal distribution. Mann-Whitney U test was used to evaluate the differences the ADC and FA values in CC and IC. The Wilcoxon Ranks Test was used to assess differences in the ADC and FA values of the anterior ve posterior limb of the IC.

**RESULTS**

Tuber load of cerebral hemispheres and FA and ADC values obtained from CC and IC in all subjects are shown in Table 1.

**Table 1. Tuber load of cerebral hemispheres and FA and ADC values obtained from corpus callosum (genu and splenium), anterior and posterior limb of internal capsule in all subjects are shown**

		Patients	Controls
	Tuber volume (right cerebral hemisphere)	21.66±16.35	
	Tuber Volume (left cerebral hemisphere)	29.94±13.87	
	Total Tuber volume	46.60±26.25	
CC genu	ADC	891±61.69	743.33±40.28
	FA	741.53±71.56	480.07±84.36
CC splenium	ADC	887.88±81.09	724.53±35.02
	FA	791.59±56.75	331.40±53.93
Anterior limb of right IC	ADC	803.18±61.72	743.13±28.39
	FA	514.82±86.08	449.27±78.81
Anterior limb of left IC	ADC	824.41±65.49	733.13±31.53
	FA	530.88±101.66	422.53±47.43
Posterior limb of right IC	ADC	797.24±52.09	744.47±39.36
	FA	711.47±33.93	576.13±64.69
Posterior limb of left IC	ADC	801.06±61.83	721.20±34.97
	FA	703.24±57.56	572.67±59.26

**CC; Corpus callosum, IC; Internal capsule, FA; fractional anisotropy ADC; apparent diffusion coefficient (x10<sup>-6</sup>mm<sup>2</sup>/s)**

When patients with TSC were compared with control, there was a significant difference in ADC and FA values in the CC genu and splenium (for each, p; 0,0001). Also, there was also a significant difference in ADC and FA values in the right anterior limb of the IC (respectively; p: 0,003 and p:0,03). An increase in ADC and FA values was detected in the right posterior limb of the IC in patients with TSC. (respectively; p:0,05 and p:0,0001).

Compared to TSC patients and controls, there was a significant difference in ADC and FA values in the left anterior limb of the IC (respectively;  $p:0,0001$  and  $p:0,001$ ). Increased ADC and FA values at left posterior limb of the IC were detected in patients with TSC (for each;  $p:0,0001$ ). There was a significant difference in FA values between the anterior and posterior limb of the IC and was higher in the posterior (right side;  $p:0,0001$ , left side  $p:0,001$ ).

The ADC values of CC splenium were positively correlated with the total cerebral tuber load ( $p:0,106$ ,  $r:0,574$ ) and tuber load of left cerebral hemisphere ( $p:0,106$ ,  $r:0,574$ ). Also, The FA values obtained from CC splenium were negatively correlated with the tuber load of the right cerebral hemisphere ( $p:0,039$ ,  $r:-0,504$ ).

## DISCUSSION

Cortical tubers, subependymal nodules and white matter lesions are the most common MRI findings in TSC patients (2,4). While MRI provides detailed information about brain involvement areas, it does not provide much information in terms of neurobehavioral findings (7). There is a relationship between total tuber load, epilepsy and neurocognitive function. However, the onset of seizures is held responsible as the determinant of neurocognitive dysfunction (7-11). In some locations, it is not easy to predict seizures, cognitive impairment or autism in the presence of a high tuber load (7,11,12).

Normal appearing white matter (NAWM) may show diffuse involvement in patients with TSC due to abnormal cell differentiation, migration and demyelination (13,14). White matter lesions may be associated with neurocognitive dysfunction (13-15). Subcortical white matter lesions may show due to changes in gliosis and heterotopic glia-neurons caused by abnormal cortical migration (5-7).

DTI provides important information to help us better understand abnormalities seen in TSC (7). DTI metrics provide important information about the degree of microstructural damage in white matter. Increased ADC values may decrease in axon number and increase in extracellular fluid due to damage to myelin sheath. A decrease in FA values due to axonal degeneration and demyelination can be observed. In addition, an increase in FA can be seen due to a decrease in axon calibration and an increase in axonal density.

Corpus callosum is the main connecting path between the two hemispheres. Affecting white matter in neurodegenerative events may cause damage to the corpus callosum. It is thought that abnormal diffusion findings in NAWM are caused by widespread abnormal neuronal and axonal organization and hypomyelination (5,14,16,17). Some studies have reported a significant reduction in FA in the IC and CC (14). Decreased FA and increased ADC values may reflect the presence of demyelination and gliosis (18). In our study, ADC and FA values at CC genu and splenium were significantly higher compared to control. We speculate that it develops as a

result of deterioration in myelination due to increased ADC values due to changes in CC microstructure, demyelination, axonal loss, and fluid accumulation in the extracellular distance. Also, increased FA values may be associated with decreased axon caliber and increased axonal density. The microstructural damage of white matter in patients with TSC may be related to demyelination, gliosis, and myelination disorders (19).

In the DTI study conducted by Karadag et al (20), They tried to explain the ADC and FA changes detected in white matter with hypomyelination, heterotopic cells and gliosis. In another study, the authors reported high ADC and low FA values in the CC and IC and external capsules (18,21). In our study, increased ADC and FA values were detected in anterior and posterior limb of the IC of both cerebral hemispheres. FA values were higher in the posterior limb of IC. High ADC values can be explained by demyelination and decrease in axon number due to damage to myelin sheath. FA provides information on axonal integrity and aspects of the organization. Increased FA values in IC may indicate decreased axon caliber and increased axonal density. We think that our results may be interrelated to myelin disorders in NAWM pathways.

While the genu of the CC is associated with prefrontal and premotor white matter pathways, the splenium contains white matter pathways from the parietal, temporal and occipital lobes (2,22,23). ADC values of CC splenium increase with increasing total tuber load in our study. Also, there was a positive correlation between ADC values in the splenium of CC and tuber load of the left cerebral hemisphere. FA values of CC splenium decrease with increasing tuber load of the right cerebral hemisphere. The increase in ADC values in the CC splenium as the tuber load increases in cerebral hemispheres may indicate that demyelination develops in the white matter pathways. Also, as the tubes load increases in the right cerebral hemisphere, FA values decrease in the CC splenium. The relationship between tuber load and ADC and FA values of CC splenium can be accepted as indicative of microstructural changes in NAWM pathways.

There are some limitations to our study. The most important limitation is the low number of patients TSC. Our second limitation is that DTI measurements are made using the ROI based approach. Using voxel-based measurement methods will minimize the margin of error in ADC and FA values. The third limitation is that the relationship between clinical findings observed in TSC patients and tuber burden and DTI findings has not been investigated and neurocognitive functions have not been evaluated.

## CONCLUSION

Relationships between corpus callosum and internal capsule ADC and FA changes and tuber load show that microstructural damage develops in the white matter pathways. DTI parameters can be used as a more sensitive biomarker in the evaluation of the abnormal structure of

white matter in patients with TSC. More comprehensive studies are needed to more clearly demonstrate the relationship between DTI properties of white matter and tuber load in TSC patients.

*Competing interests: The authors declare that they have no competing interest.*

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*Ethical approval: This study was performed with the approval of the local ethics committee (Bezmi'alem Vakif University Faculty of Medicine).*

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