

*Research Article*

## The Role of Diffusion Tensor MRI and Fiber Tractography of the Brain in Evaluation of Pediatric Epilepsy

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### Abstract

**Introduction:** Diffusion tensor imaging (DTI) and fiber tractography of the brain plays an important role in evaluation of patients with childhood epilepsy. It shows diffuse white matter abnormalities in patients with pediatric epilepsy. DTI might show the extent of microstructural alterations when the imaging features are normal. **Aim of the work:** To evaluate the diagnostic value of diffusion tensor MRI and fiber tractography of the brain in detection and characterization of white matter abnormalities in patients with pediatric epilepsy. **Patients and Methods:** Our study is a prospective study which included 40 pediatric patients with clinical presentation and EEG changes suggesting childhood epilepsy as a case group and 20 subjects as healthy control group. They all referred from pediatric neurology unit to MRI unit at radiology department, Minia University hospital for children, Minia, Egypt, in the period between June 2019 and July 2020. We examined the effects of epilepsy on 15 major WM tracts. We relied on both FA and MD parameters to characterize the integrity of WM tracts in our analysis. These WM tracts include corpus callosum, forceps minor, forceps major, both corticospinal tracts, both uncinate fasciculi, both cingulum (including cingulate gyrus part and hippocampal part), both superior longitudinal fasciculi and both inferior longitudinal fasciculi. **Results:** The case group (N=40) showed significantly low fractional anisotropy (FA) at all examined tracts excepts right cingulum (cingulate gyrus part) and showed high mean diffusivity (MD) at all examined WM tracts except right cingulum (cingulate gyrus part) and right inferior longitudinal fasciculus. Conventional MRI negative group (N=18) showed significantly low fractional anisotropy (FA) at corpus callosum, forceps minor, left corticospinal tract and left inferior longitudinal fasciculus. High mean diffusivity (MD) was noted at corpus callosum, forceps minor, both uncinate fasciculi and both inferior longitudinal fasciculi.

**Key Words:** DTI: Diffusion tensor imaging, FA: Fractional anisotropy, MD: Mean diffusivity.

### Introduction

Epilepsy is considered a chronic neurological disorder characterized by spontaneous and recurrent seizures. Seizures are caused by excessive, abnormal electrical discharges from the cortical neurons, occurring in about 5 out of 1000 children.<sup>(1)</sup>

The main purpose of neuroimaging in epilepsy patients is to identify underlying structural abnormalities that require specific treatment (i.e. surgery in most instances) and also to aid in formulating a syndromic or etiologic diagnosis. Neuroimaging techniques have advanced the diagnosis, management, and understanding of the pathophysiology underlying the epilepsies.<sup>(2)</sup>

We have intended to explore the utility of diffusion tensor imaging in childhood epilepsy,

and depict the focal and widespread abnormalities in both hippocampal and extra hippocampal cases in our population. The study might establish the diagnostic value of diffusion tensor imaging in epilepsy, and incorporate it in routine protocol. DTI might show the extent of microstructural alterations when the imaging features are normal.<sup>(3)</sup>

### Patients and Methods

#### Study design and population

Our study is a prospective study which included 40 pediatric patients with clinical presentation and EEG changes suggesting childhood epilepsy and 20 subjects as healthy control group. Their ages ranged between 1 and 8 years. They all referred from pediatric neurology unit to MRI unit at radiology department, Minia University hospital for children, Minia, Egypt, in the period between June 2019 and July 2020.

The patients were referred irrespective of treatment status, both previously treated and untreated patients were included in the study.

### **Ethical consideration**

All patients were included after approval of ethical committee of our institution. Parents of the recruited children have signed a written informed consent before MRI examination and before anesthesia.

### **Inclusion criteria:**

1. Pediatric patients clinically presented with epilepsy.
2. Pediatric patients with EEG changes suggesting epilepsy.

### **Exclusion criteria:**

1. Patients with single attack of seizure.
2. Pediatric patients with contraindication to anesthesia as most of our patients undergo light anesthesia before MRI examination.
3. Patients with general contraindication for MRI e.g. cochlear implants.

### **Patient preparation**

Before MRI examination, all patients' parents were routinely questioned about any contraindications for MRI examination such as metallic prosthesis or implants. Patients' parents were asked about any condition to contraindicate anesthesia in patients that need anesthesia. All patients undergo anesthesia using IV anesthetic material (Ketamine 1-2 mg/Kg or Propofol 0.5% 1-2 mg /kg), after complete fasting of the children for at least 6 h before the procedure.

### **MRI technique**

MRI examination was performed for all patients using a 1.5 T Ingenia (Philips Medical Systems, Netherlands), in supine position. Images were acquired in the axial, coronal, and sagittal planes using head coil. A multi planner fast field echo (FFE) localizer was used upon which the remaining pulse sequences were planned (localizing scan).

### **MRI protocol for imaging:**

- 1- **Conventional MRI:** Axial T2WI, Coronal T2WI, Sagittal T1WI and Axial FLAIR.
- 2- **3D T1WI TFE** was done for superimposing over the color coded FA maps.
- 3- **Diffusion tensor imaging (3D medium DTI):** Single-shot spin-echo echo-planar imaging (EPI) and parallel imaging techniques

to achieve motion-free DTI. Diffusion sensitive gradients are applied in 16 directions. The imaging sections were positioned to make the section perpendicular to the anterior commissure-posterior commissure (AC-PC) line.

### **Data processing:**

The data were processed on Philips Research Image-processing Development Environment (PRIDE) software (Philips Medical Systems), which is based on the Fiber Assignment by Continuous Tracking (FACT) method.

Anisotropy was calculated by using orientation-independent fractional anisotropy (FA), and diffusion-tensor MR imaging-based color maps were created from the FA values and the three vector elements. The vector maps were assigned to red (x element, left-right), green (y, anterior-posterior), and blue (z, superior-inferior) with a proportional intensity scale according to the FA. Three-dimensional FT was then achieved by connecting voxel to voxel with the FACT algorithm.

### **Anatomic Landmarks and ROI Locations**

For tracking of the white matter fibers, the region of interest (ROI) method was applied. With knowledge of the fiber pathways, the single or multiple ROIs were placed on the color maps. The plane of the ROI was varied according to the running direction of the white matter fibers (e.g., corticospinal tract on the axial views, corpus callosum on the sagittal views).

### **Image interpretation**

All images were interpreted as regarding the conventional MRI, DTI and FT findings.

### **Statistical analysis**

All data were statistically described in terms of frequency and percentage when appropriate. Relationship between MRI findings and clinical data was calculated using Chi-square test for qualitative data with the significant correlation set at  $p\text{-value} \leq 0.05$ . Continuous data was expressed in form of mean  $\pm$  SD or median (range). Student t-test was used to compare mean of DTI parameters (FA and MD) of the selected WM tracts between the patients and control subjects. A probability value ( $p=0.05$ ) was considered statistically significant. Diagnostic performance of significant DTI parameters was determined by ROC curve. Level of

confidence was kept at 95% hence, P value was significant if  $\leq 0.05$ .

All statistical calculations were done using computer programs IPM SPSS software version 20.0. (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York).

## Results

The study enrolled 40 patients with pediatric epilepsy as case group and 20 healthy control subjects as control group.

The mean age of the case group was  $4.63 \pm 2.21$  years while mean age of the control group was  $4.55 \pm 1.99$  years. 55% (N=22) of the case group were females and 45% (N=18) were males. While 50% (N=10) of the control group were females and 50% (N=10) were males. The majority (45%) of both case and control groups aged between 2 and 4 years. (Table 1)

**Table (1): Demographic data for the studied cases (N=40) and control groups (N=20)**

	Case group (N= 40) N (%)	Control group (N=20) N (%)	P value
<b>Sex</b>			
Male	18 (45)	10 (50)	0.71
Female	22 (55)	10(50)	
<b>Age</b>			
<2 years	4 (10)	1 (5)	0.38
2-4 years	18 (45)	9 (45)	
4-6 Years	7 (17.5)	7 (35)	
6-8 Years	11 (27.5)	3 (15)	
<b>Age (mean <math>\pm</math>SD)</b>	$4.63 \pm 2.21$	$4.55 \pm 1.99$	0.89

The majority 55 % (22 patients) of our cases were presented by seizures only. 22.5% (9 patients) were presented by seizures and developmental delay. Others were presented by other symptoms such as social, behavioral changes, confusion or mental retardation. (Table 2)

The majority 45% (18 patients) of our cases were normal in conventional MRI. 30% (12 patients) of the studied cases show MRI findings suggesting CC dysgenesis. Other cases show findings suggesting metabolic disease, demyelinating disease or lissencephaly. (Table 3).

**Table (2): Clinical presentation of the studied cases (N=40)**

Clinical presentation	No. of cases	Percentage %
Seizures	22	55
Developmental delay	9	22.5
social, behavioral changes	4	10
confusion	3	7.5
mental retardation	2	5

**Table (3): Conventional MRI findings of the studied cases (N=40)**

Conventional MRI findings	No. of cases	Percentage %
<b>Normal</b>	<b>18</b>	<b>45</b>
<b>Abnormal</b>	<b>22</b>	<b>55</b>
○ Corpus callosum dysgenesis	12	30
○ Metabolic disease	4	10
○ Demyelinating disease	5	12.5
○ Lissencephaly	1	2.5

Correlation between DTI indices of the studied cases (N=40) and control group (N=20) was done. The case group (N=40) showed significantly low fractional anisotropy (FA) at all examined tracts excepts right cingulum (cingulate gyrus part) and showed high mean diffusivity (MD) at all examined WM tracts except right cingulum (cingulate gyrus part) and right inferior longitudinal fasciculus.

Correlation between DTI indices of the conventional MRI normal cases (N=18) and control group (N=20) was done. The case group (N=18) showed significantly low fractional

anisotropy (FA) at corpus callosum, forceps minor, left corticospinal tract and left inferior longitudinal fasciculus. High mean diffusivity (MD) was noted at corpus callosum, forceps minor, both uncinate fasciculi and both inferior longitudinal fasciculi.

Receivers operating characteristic (ROC) curves for significant DTI indices (FA and MD) between the conventional MRI normal cases and control groups to determine the cutoff points and diagnostic performance for distinguishing patients with epilepsy from control subjects. (Table 4)

**Table (4): Results of receiver operating curves for significant tracts in distinguishing pediatric epilepsy.**

Tracts	Indices						
	Sensitivity	Specificity	PPV	NPV	Accuracy	Cutoff value	AUC
<b>Corpus callosum (FA)</b>	72.2%	100%	100%	80%	89.4%	$\leq 0.389$	0.894
<b>Corpus callosum (MD)</b>	50%	90%	81.8%	66.7%	64.4%	$> 1.064$	0.64
<b>Forceps minor (FA)</b>	88.89%	100%	100%	90.9%	89.4%	$\leq 0.402$	0.894
<b>Forceps minor (MD)</b>	33.33%	100%	100%	62.5%	62.5%	$> 0.952$	0.625
<b>Uncinate fasciculus (MD)</b>	83.33%	90%	88.2%	85.7%	91%	$> 0.903$	0.911
<b>Cingulum hippocampal part (FA)</b>	83.33%	90%	88.2%	85.7%	85%	$> 0.335$	0.853
<b>Inferior longitudinal fasciculus (MD)</b>	77.78%	100%	100%	83.3%	82%	$> 0.915$	0.822

## Cases

### Case 1

#### Clinical presentation:

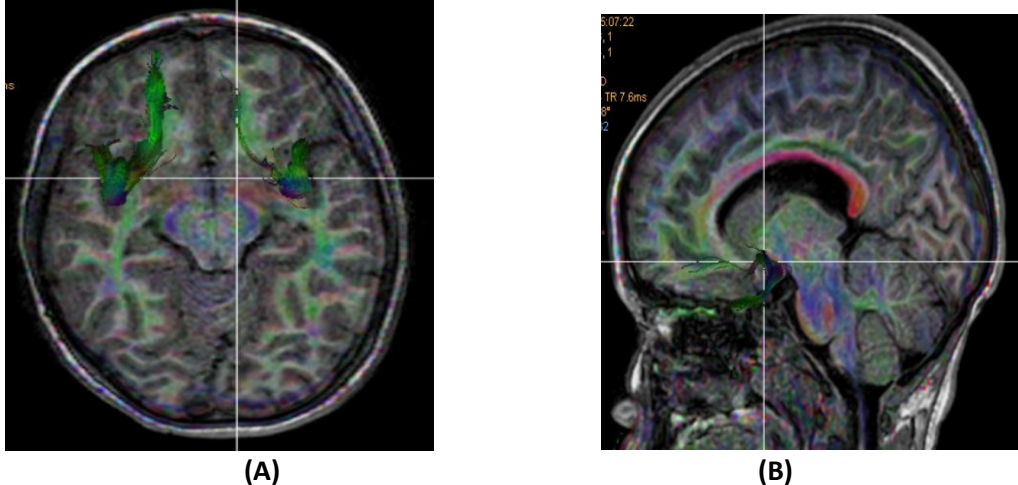
Four years old male presented with seizures as well as social and behavioral abnormalities. Normal motor development.

#### Conventional MRI findings:

Normal conventional MRI findings with no structural abnormalities.

#### DTI and fiber tractography findings:

They showed defect in frontal fibers of the left uncinate fasciculus.



**Figure (1):** (A) 3D FT of both uncinate fasciculi axial image showing defective frontal fibers of the left uncinate fasciculus.

(B) 3D FT of left uncinate fasciculus sagittal image showing defective frontal fibers of the left uncinate fasciculus.

### Case 2:

#### Clinical presentation:

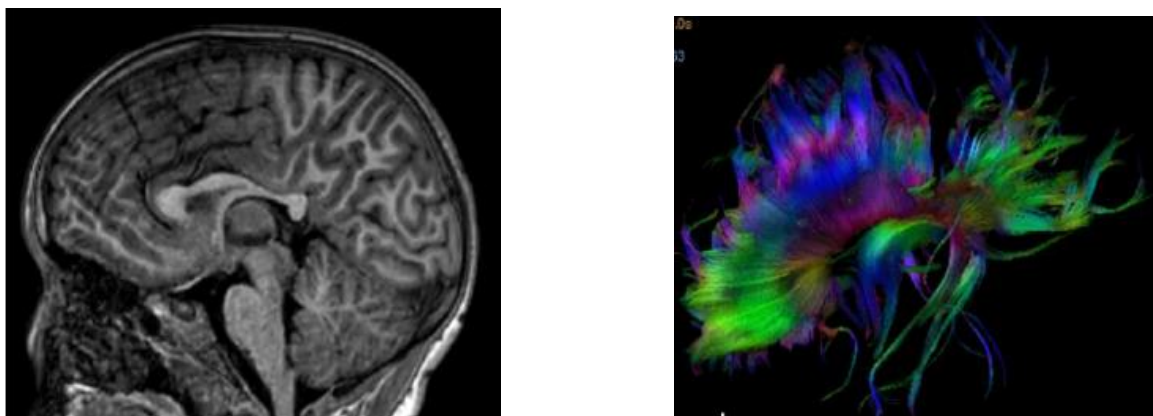
Five years old female with epilepsy with attention defect and hyperactivity disorder. Normal motor development.

#### Conventional MRI findings:

Dysplastic corpus callosum with reduced girth at the posterior segment of body of corpus callosum.

#### DTI and fiber tractography findings:

Fiber tractography (FT) using color map sagittal view showed normal thickness of crossing fibers at the fronto-rostral segment and defective caudal segment at the posterior segment of corpus callosum .



**Figure (2):** (A) 3D T1WI sagittal view showing dysplastic corpus callosum with reduced girth at posterior part of body of CC.

(B) 3D FT of corpus callosum showing normal thickness of the fibers at the fronto-rostral segment and defective caudal segment of corpus callosum.

**Case 3:**

**Clinical presentation:**

Two years old female with seizures and confusion.

**Conventional MRI findings:**

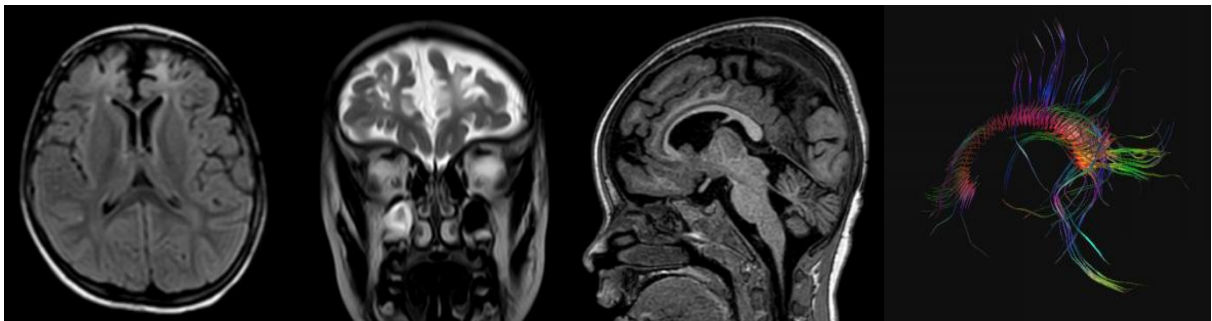
Abnormal signal intensity seen involving both frontal regions, cortical and subcortical in location exhibiting low signal at T1WI and high a T2WI and FLAIR with facilitated diffusion on DWI, suggesting demyelinating disease.

Hypoplastic corpus callosum is also noted with reduced girth at the rostrum and anterior segment of body of corpus callosum.

**DTI and fiber tractography findings:**

- Hypoplastic fronto-rostral fibers of corpus callosum and defective caudal fibers.
- Hypoplastic left inferior fronto-occipital fasciculus.
- Relatively hypoplastic left inferior longitudinal fasciculus.

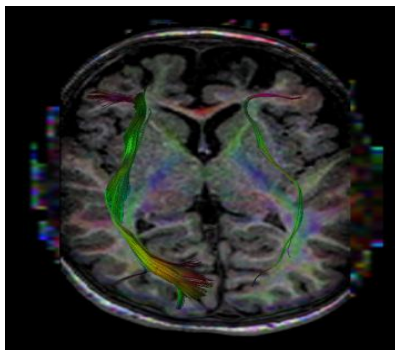
**Figure (3):**



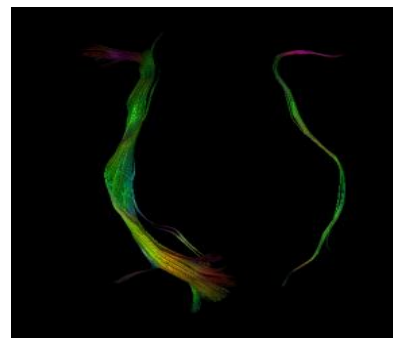
(A&B) FLAIR axial image & T2 coronal image showing abnormal high signal intensity involving both frontal regions, cortical and subcortical with prominent frontal sulci.

(C) 3D T1WI sagittal view show hypoplastic corpus callosum more noted anteriorly.

(D) 3D FT showed marked reduction of callosal fibers.

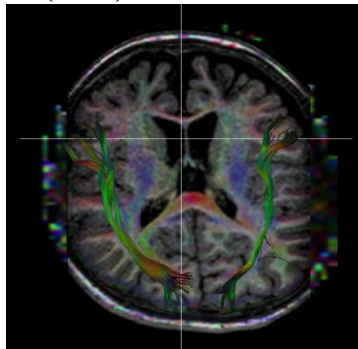


(E)



(F)

(E&F) 3D reconstruction of both IFOT axial image show hypoplastic left IFOT.



(G & H) 3D FT of both ILF axial image show relatively hypoplastic left ILF.



## Discussion

Our study was conducted in the Radiology Department at Minia University Hospitals in the time period between June 2019 and July 2020 to quantify white matter (WM) microstructure changes using DTI and tractography in order to evaluate WM microstructure differences between individuals with pediatric epilepsy and healthy subjects.

Our study is a prospective study that enrolled 40 patients with pediatric epilepsy as case group and 20 healthy subjects as control group. All patients and control were under the age of 8 years with mean age of  $4.63 \pm 2.21$  years for the case group and mean age of  $4.55 \pm 1.99$  years for the control group. The case group had 22 females (55%) and 18 males (45%). While in the control group, 10 cases (50%) were females and 10 cases (50%) were males. It was also noted that the majority (45%) of both case and control groups aged between 2 and 4 years.

The majority of the studied cases (22 patients, 55%) presented by seizures only. Other patients (18 patients, 45%) had other symptoms such as developmental delay, social and behavioral changes, confusion or mental retardation.

In this study, we examined the effects of epilepsy on 15 major WM tracts. We relied on both FA and MD parameters to characterize the integrity of WM tracts in our analysis. These WM tracts include corpus callosum, forceps minor, forceps major, both corticospinal tracts, both uncinate fasciculi, both cingulum (including cingulate gyrus part and hippocampal part), both superior longitudinal fasciculi and both inferior longitudinal fasciculi.

When we compare the DTI indices of fiber tracts between the studied case and control groups (N=60). The case group (N=40) showed significantly low fractional anisotropy (FA) and high mean diffusivity (MD) at most of the examined WM tracts compared to the control group (N=20). These fiber tracts included (corpus callosum, forceps minor, forceps major, both corticospinal tracts, both uncinate fasciculi, left cingulum (cingulate gyrus hippocampal parts) and both inferior fronto-occipital fasciculi as well as both inferior longitudinal fasciculi. This is concordant with Yin et al., 2014 and Meng et al., 2010 who

studied extra temporal white matter abnormalities in children and adolescents with epilepsy and observed reduced FA and increase MD.<sup>(4,5)</sup>

Corpus callosum is the major white matter commissural fiber tract connecting the two hemispheres. The corpus callosum is known to be involved in motor, somatosensory and visual tests of inter hemispheric transfer. Our study revealed statistically significant low FA and high MD values. Kim et al., 2008 and Thivard et al., 2005 studies showed that secondary white matter degeneration of the corpus callosum in patients with intractable temporal lobe epilepsy has reduced FA values in the splenium which agreed with our results.<sup>(6,7)</sup>

In our study, both corticospinal tracts and right cingulum (cingulate gyrus and hippocampal parts) showed no significant change in MD. Left cingulum (hippocampal part) showed reduced MD compared to the control group. Knake et al., 2009, also demonstrated changes in white matter microstructure in patients with TLE and hippocampal sclerosis and observed reduced FA in the genu and body of corpus callosum.<sup>(8)</sup>

The right cingulum (cingulate gyrus part) showed no significant change in FA compared to control group, however, the right cingulum (hippocampal part) showed increased FA compared to the control group.

**The corticospinal** tracts are the major efferent projection fibers that connect the motor cortex to the brain stem and spinal cord. In our study, we observed significantly low FA but no significant changes in MD of both CST. This is concordant with Meng et al., 2010 and Yin et al., 2014 who observed reduced FA in the anterior and posterior limbs of the internal capsule (course of the corticospinal tract). However, they observed an increased MD which may be explained as most of their patients had mesial temporal lobe epilepsy unlike ours, who had variable causes of epilepsy.<sup>(4,5)</sup>

**Uncinate fasciculus** is a major white matter tract connecting anterior temporal and frontal lobes. It is important in the formation and retrieval of memories and is a pathway for seizure spread to the frontal lobe. In our study, both uncinate

fasciculi had reduced FA and increased MD values.<sup>(9)</sup>

Our results agree with what was stated by Diehl et al., 2008, who analyzed the DTI parameters of 28 TLE patients and correlated them with auditory and visual, immediate and delayed memory. They found significant alterations in the diffusion tensor imaging indices in bilateral uncinate fasciculi in patients with left TLE (both medial and lateral).<sup>(9)</sup>

Regarding the cingulum, our results were concordant with Thivard et al., 2005, who observed statistically significant differences in the FA in the left cingulum. However, our study showed no significant change in FA in the right cingulum (cingulate gyrus part) and increased FA at the right cingulum (hippocampal part) and this was against their study.<sup>(6)</sup>

Patients with epilepsy have multiple cognitive impairments like memory, executive functions, language, intelligence and motor speed. Riley et al., 2010 studied the integrity of white matter tracts using whole brain FA and its impact on the cognitive function in 12 TLE patients. They found white matter abnormalities in fornix, uncinate and arcuate fasciculus, inferior longitudinal fasciculus, motor projection fibers and the cerebellum. These abnormalities correlated with the cognitive performance. In our study, we had significantly reduced FA in bilateral inferior longitudinal fasciculi and uncinate fasciculi, in agreement with their study. We did not test the cognitive profiles of our patients.<sup>(10)</sup>

Our results showed that certain white matter tracts show significant changes in FA and MD values although the patients were normal in conventional MRI and had no gross structural abnormalities. This reflects that there are WM microstructural abnormalities in patients with epilepsy even if they have normal conventional MRI findings.

The normal conventional MRI case group (18 patients, 45%) showed significantly lowered fractional anisotropy (FA) at corpus callosum, forceps minor, left corticospinal tract and the left inferior longitudinal fasciculus. While right and left cingulum (hippocampal parts) showed significant increase in FA compared to the control group.

It was also noticed that normal conventional MRI case group showed significant increase in mean diffusivity (MD) at corpus callosum, forceps minor, both uncinate fasciculi, left cingulum (cingulate gyrus part), left inferior fronto-occipital fasciculus and both inferior longitudinal fasciculi.

Our results were agreed with Whelan et al., 2015 who studied white matter alterations in 25 patients with MRI-negative temporal lobe epilepsy and observed significant reductions in FA in the corpus callosum (CC), bilateral superior longitudinal fasciculi (SLF), bilateral inferior longitudinal fasciculi (ILF) and left corticospinal tract (CST). Also, our results agreed with Liacu et al., 2012, who studied DTI abnormalities in the limbic system white matter of patients with temporal lobe epilepsy. They found that 9 patients of the studied cases, with no signal abnormalities on conventional MRI, had DTI abnormalities in the fornix, superior and inferior cingulum and observed that the inferior cingulum was the most affected tract.<sup>(11,12)</sup>

Our results demonstrated positive findings in patients with MRI-negative epilepsy, including significant FA reductions in WM areas of patients, covering widespread parts of the brain, most prominent in the frontal and temporal lobes, corpus callosum, corticospinal tracts and brainstem. This agreed with Hatamleh et al., 2011, Duning et al., 2010 and Chen et al., 2008.<sup>(13, 14, 15).</sup>

### Conclusion & Recommendations

DTI has emerged as a sensitive and excellent tool for demonstration of white matter microstructure changes in epilepsy patients. DTI, through tractography technique, can help assess the cause and effect of epilepsy on the cerebral white matter tracts. It has the potential to provide imaging prognostic markers in chronic patients, highlighting the disease burden on the long run.

**So, we recommend the application of diffusion tensor imaging in routine epilepsy protocol as altered DTI values adds to the diagnosis in equivocal cases and might help as a prognostic measure.**



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