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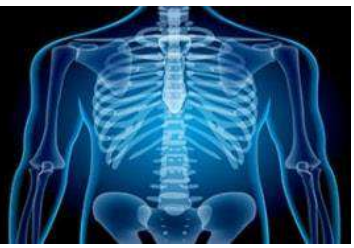

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Extratemporal abnormalities in adults with unilateral temporal lobe epilepsy: A diffusion tensor imaging study

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Abstract
Aims & objectives: To analyse the fractional anisotropy (FA) and mean diffusivity (ADC) of various white matter tracts and the deep grey matter of unilateral temporal lobe epilepsy patients with age matched controls.
Materials and methods: The study was conducted in the department of Radiology, Government Mohan Kumaramangalam Medical College, Salem. This study was done as an analytic, prospective case control study for a period of 2 years from September 2017 to August 2019. Patients with a clinical picture of temporal lobe epilepsy, with either structural abnormalities in temporal lobe on MR imaging or EEG consistent with temporal lobe epilepsy were included. Our control group consisted of 30 adults.
Imaging protocol: The examinations were performed in 1.5T Philips MRI system.
Results: Abnormalities are seen extensively bilaterally in the extra temporal grey and white matter, both ipsilateral and contralateral to the seizure origin.
Conclusion: The findings strongly suggest that microstructural abnormalities are not only restricted to the seizure focus, but also involve ipsilateral and contralateral grey and white matter extensively.

Keywords: temporal lobe epilepsy, diffusion tensor imaging

Introduction
Temporal lobe epilepsy is the most common form of focal epilepsy. The etiology can be varied like hippocampal sclerosis, malformations of cortical development, mass lesions, AV malformations, gliosis etc. Previous studies with diffusion tensor imaging have shown increased apparent diffusion coefficient and decreased fractional anisotropy in the seizure focus [3]. Though the origin of seizure activity is focal, there is widespread propagation of synchronized neuronal firing in seizure disorders via neuronal networks and other cortical and subcortical regions of the brain are affected [9]. These widespread changes may be reflected as altered diffusion tensor imaging metrics.

Hypothesis
1. Mean diffusivity is increased and fractional anisotropy is decreased in hippocampus in patients with mesial temporal sclerosis.
2. Altered diffusion tensor imaging metrics are seen in extra temporal regions in patients with temporal lobe epilepsy.

Aims & Objectives
1. To analyse the fractional anisotropy (FA) and mean diffusivity (ADC) of various white matter tracts and the deep grey matter of unilateral temporal lobe epilepsy patients with age matched controls.

Materials and methods
Study area: The study was conducted in the department of Radiology, Government Mohan Kumaramangalam Medical College, Salem.

Study design and period: This study was done as an analytic, prospective case control study for a period of 2 years from August 2017 to August 2019.

Study population: Patients with a clinical picture of temporal lobe epilepsy, referred to our department for an MRI examination. The patients were referred from neurologists, neurosurgeons and general physicians. Irrespective of treatment status, both previously treated and untreated patients were included in the study.

Cases

Inclusion criteria

Adults, both males and females, with a clinical history of unilateral temporal lobe epilepsy and with either structural abnormalities in temporal lobe on MR imaging or EEG consistent with temporal lobe epilepsy.

Exclusion criteria

1. Presence of intra axial structural abnormalities in locations other than temporal lobe, as it might interfere with the diffusion tensor imaging values.
2. Presence of a major psychiatric disorder, as uncinate fasciculus is shown to be involved in psychiatric disorders.

Of the 39 patients referred to us with a clinical picture of temporal lobe epilepsy, patients with lesions in regions other than temporal lobe and patients with bilateral hippocampal sclerosis were excluded from the study.

Finally, our case group consisted of 30 patients with unilateral temporal lobe epilepsy, 14 males and 16 females, aged between 22 to 49 years, with a mean of 29.9 yrs. 19 (63%) patients had unilateral hippocampal sclerosis, four (13%) had gliosis of the temporal lobe, four (13%) had focal cortical dysplasia, one (3%) had dysplastic neuro epithelial tumour, one (3%) had infiltrative glioma and one (3%) had persistent seizures after temporal lobectomy for hippocampal sclerosis. 18 cases had EEG localised to the ipsilateral temporal lobe. All patients underwent conventional MRI, temporal lobe protocol and diffusion tensor imaging. All of them were seizure free for more than a week at the time of imaging. The duration of seizures ranged from one month to 15 years.

Controls

Our control group consisted of age matched adults with no neurologic deficit and normal by MR imaging.

Our control group consisted of 30 adults, of whom 19 were males and 11 were females, aged between 23 to 46 years, with a mean of 32.9 years.

There was no statistically significant difference between the ages of the two groups.

The control group underwent conventional MRI and diffusion tensor imaging.

Imaging protocol

The examinations were performed in 1.5T Philips MRI system, using the head coil. Our conventional imaging protocol consists of T1W sequence in the sagittal plane, T2W in the axial plane and FLAIR in the coronal plane.

Temporal lobe protocol for epilepsy consists of 3 mm oblique coronal sections orthogonal to hippocampus in T2W, T1 inversion recovery and FLAIR sequences.

DTI images were acquired in the axial plane using spin echo – echo planar imaging sequence using the following parameters.

Diffusion sensitive gradients are applied in 15 directions.

T1W 3D TFE imaging was done for superimposing over the colour coded FA maps. Imaging is performed after a minimum of 7 days after the ictus as ADC values are known to alter in the periictal period.

Imaging analysis

All DTI images were transferred to a workstation where image reconstruction and post processing analysis was performed. ROIs of similar size were placed in colour coded FA map superimposed over isotropic T1W images over bilateral para hippocampal white matter, anterior limb, genu and posterior limb of internal capsule, external capsule, genu, body and splenium of corpus callosum, thalamus, lentiform nucleus and head of caudate nucleus, frontal and occipital regions of superior longitudinal fasciculus, temporal and occipital regions of inferior longitudinal fasciculus, uncinate fasciculus, middle cerebellar peduncle and cingulum. FA and ADC values from each of these ROI was recorded.

The ROIs were placed on the axial images at the level of foramen of Munroe for anterior limb, genu and posterior limb of internal capsule, external capsule, thalamus, lentiform nucleus and head of caudate nucleus. For corpus callosum, frontal and occipital regions of superior longitudinal fasciculus, ROIs were placed on the axial images when the region was maximally seen. For hippocampus, para hippocampal white matter, fornix and uncinate fasciculus coronal images were used. Parasagittal images were used to locate the inferior longitudinal fasciculus.

Statistical analysis

- All the continuous variables were tested for the normality using Shapiro Wilk's test. Variables were normally distributed and expressed as mean ± SD. Categorical variables were expressed either as percentage or proportion.
- Comparison of categorical variables (age) was done by Chi - square test or Fisher's exact test based on the number of observations.
- Comparison of normally distributed continuous variables between cases and controls was done by independent sample T test.
- Comparison of right and left sided variables within controls was done by paired T test.
- All the P values less than 0.05 were considered statistically significant.
- Data entry was done in MS excel worksheet.
- Data analysis was done by SPSS software version 11.0.

Table 1: FA of internal capsule

Site	Cases(30)	Cases(30)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral anterior limb of internal capsule	.68	.12	.65	.12	.211
FA of contralateral anterior limb of internal capsule	.56	.17	.65	.12	.026*
FA of ipsilateral posterior limb of internal capsule	.85	.11	.79	.07	.04*
FA of contralateral posterior limb of internal capsule	.83	.09	.79	.07	.15
FA of ipsilateral genu of internal capsule	.59	.10	.64	.09	.086
FA of contralateral genu of internal capsule	.69	.13	.64	.09	.139

*statistically significant

Compared to controls, patients' contralateral anterior limb of internal capsule had statistically significant reduced FA values. FA of ipsilateral posterior limb of internal capsule was higher. Rest of the values did not achieve statistical significance.

Table 2: ADC of internal capsule

Site	Cases(30)	Cases(30)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
ADC of ipsilateral anterior limb of internal capsule	.81	.22	.73	.13	.11
ADC of contralateral anterior limb of internal capsule	.71	.16	.73	.13	.369
ADC of ipsilateral posterior limb of internal capsule	.62	.14	.69	.10	.03*
ADC of contralateral posterior limb of internal capsule	.63	.09	.69	.10	.036*
ADC of ipsilateral genu of internal capsule	.75	.13	.75	.10	.975
ADC of contralateral genu of internal capsule	.74	.17	.75	.10	.784

*statistically significant

Compared to controls, patients' ADC of bilateral posterior limb of internal capsules had statistically significant lower values. Rest of the regions did not achieve statistical significance.

Table 3: FA & ADC of external capsule

Site	Cases(30)	Cases(30)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral external capsule	.52	.09	.48	.08	.06
FA of contralateral external capsule	.49	.11	.48	.08	.779
ADC of ipsilateral external capsule	.75	.14	.79	.07	.141
ADC of contralateral external capsule	.74	.12	.79	.07	.041*

*statistically significant

Compared to controls, patients' ADC of contralateral external capsule had statistically significant difference. ADC of ipsilateral external capsule was lower, but did not achieve statistical significance.

Table 4: FA & ADC of corpus callosum

Site	Cases(30)	Cases(30)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
FA of genu of corpus callosum	.77	.14	.79	.16	.54
ADC of genu of corpus callosum	.71	.18	.69	.15	.57
FA of body of corpus callosum	.69	.74	.84	.04	.000*
ADC of body of corpus callosum	.83	.11	.71	.13	.000*
FA of splenium of corpus callosum	.81	.11	.84	.09	.32
ADC of splenium of corpus callosum	.74	.17	.72	.16	.69

*statistically significant

Compared to controls, patients' body of corpus callosum had statistically significant values, genu and the splenium did not show statistically significant changes, though the FA was lower and ADC was higher.

Table 5: FA of head of caudate and lentiform nucleus

Site	Cases(30)	Cases(30)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
FA of ipsilateral lentiform nucleus	.29	.04	.26	.12	.09
FA of contralateral lentiform nucleus	.31	.09	.26	.12	.054
FA of ipsilateral head of caudate nucleus	.27	.08	.22	.12	.097
FA of contralateral head of caudate nucleus	.21	.06	.22	.12	.583

*statistically significant

FA of bilateral lentiform nuclei and ipsilateral head of caudate nucleus did not show any significant changes.

Table 6: ADC of head of caudate and lentiform nucleus

Site	Cases(30)	Cases(30)	Controls(30)	Controls(30)	P value
	Mean	SD	Mean	SD	
ADC of ipsilateral lentiform nucleus	.75	.07	.66	.12	.003*
ADC of contralateral lentiform nucleus	.75	.10	.66	.12	.054*
ADC of ipsilateral head of caudate nucleus	.80	.21	.74	.14	.158
ADC of contralateral head of caudate nucleus	.84	.17	.74	.14	.012*

*statistically significant

ADC of bilateral lentiform nuclei and head of contralateral caudate nucleus was higher with statistical significance. ADC of contralateral head of caudate nucleus was higher but did not achieve statistical significance.

Table 7: FA & ADC of thalamus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral thalamus	.40	.09	.38	.07	.352
FA of contralateral thalamus	.40	.09	.38	.07	.503
ADC of ipsilateral thalamus	.70	.16	.74	.06	.226
ADC of contralateral thalamus	.74	.08	.74	.06	.676

Our study did not show any significant alteration in the DTI values between cases and controls in thalamus.

Table 8: FA & ADC of frontal region of superior longitudinal fasciculus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral frontal limb of superior longitudinal fasciculus	.47	.15	.59	.07	.001*
FA of contralateral frontal limb of superior longitudinal fasciculus	.50	.07	.59	.07	.000*
ADC of ipsilateral frontal limb of superior longitudinal fasciculus	.86	.17	.79	.07	.041*
ADC of contralateral frontal limb of superior longitudinal fasciculus	.84	.11	.79	.07	.039*

*statistically significant

Both FA and ADC values of bilateral frontal limbs of superior longitudinal fasciculi showed statistically significant values.

Figure 10. Error bar comparing ADC of bilateral thalami & FA of bilateral frontal superior longitudinal fasciculus of cases and controls

Table 9: FA & ADC of occipital region of superior longitudinal fasciculus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral occipital limb of superior longitudinal fasciculus	.61	.13	.65	.11	.273
FA of contralateral occipital limb of superior longitudinal fasciculus	.59	.09	.65	.11	.045*
ADC of ipsilateral occipital limb of superior longitudinal fasciculus	.77	.09	.77	.12	.842
ADC of contralateral occipital limb of superior longitudinal fasciculus	.80	.12	.77	.12	.315

*statistically significant

Compared to controls, patients' contralateral occipital region of superior longitudinal fasciculus had statistically significant lower FA values. FA of ipsilateral and ADC of bilateral occipital region of superior longitudinal fasciculi did not show significant alterations.

Table 10: FA & ADC of temporal region of inferior longitudinal fasciculus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral temporal limb of inferior longitudinal fasciculus	.44	.20	.63	.09	.000*
FA of contralateral temporal limb of inferior longitudinal fasciculus	.50	.06	.63	.09	.000*
ADC of ipsilateral temporal limb of inferior longitudinal fasciculus	1.05	.39	.87	.11	.027*
ADC of contralateral temporal limb of inferior longitudinal fasciculus	.91	.19	.87	.11	.390

*statistically significant

Compared to controls, patients' FA of bilateral temporal regions and ADC of ipsilateral temporal region of inferior longitudinal fasciculus showed statistically significant altered DTI values.

Table 11: FA & ADC of occipital region of inferior longitudinal fasciculus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral occipital limb of inferior longitudinal fasciculus	.59	.11	.65	.10	.051*
FA of contralateral occipital limb of inferior longitudinal fasciculus	.54	.16	.65	.10	.005*
ADC of ipsilateral occipital limb of inferior longitudinal fasciculus	.81	.09	.77	.09	.065*
ADC of contralateral occipital limb of inferior longitudinal fasciculus	.72	.21	.77	.09	.245

*statistically significant

Compared to controls, patients' FA of bilateral and ADC of contralateral inferior longitudinal fasciculi showed statistically significant reduced FA and increased ADC changes.

Table 12: FA & ADC of uncinate fasciculus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral uncinate fasciculus	.49	.19	.64	.13	.001*
FA of contralateral uncinate fasciculus	.66	.14	.64	.13	.642
ADC of ipsilateral uncinate fasciculus	.90	.39	.69	.17	.010*
ADC of contralateral uncinate fasciculus	.71	.15	.69	.17	.663

*statistically significant

FA & ADC of ipsilateral uncinate fasciculus had statistically significant reduced and increased values respectively, in cases compared to controls.

Table 13: FA & ADC of middle cerebellar peduncle

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral middle cerebellar peduncle	.75	.11	.80	.09	.078*
FA of contralateral middle cerebellar peduncle	.72	.11	.80	.09	.006*
ADC of ipsilateral middle cerebellar peduncle	.67	.15	.65	.09	.476
ADC of contralateral middle cerebellar peduncle	.68	.14	.65	.09	.314

*statistically significant

FA of bilateral middle cerebellar peduncles showed statistically significant reduced values compared to controls, ADC values though higher, did not reach statistical significance.

Table 14: FA & ADC of cingulum

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral cingulum	.67	.09	.77	.06	.000*
FA of contralateral cingulum	.70	.11	.77	.06	.003*
ADC of ipsilateral cingulum	.74	.10	.73	.14	.746
ADC of contralateral cingulum	.73	.14	.73	.14	.447

*statistically significant

FA of bilateral cingulum showed statistically significant reduced values compared to controls, ADC changes were not significant.

Table 15: FA & ADC of parahippocampalgyrus

Site	Cases	Cases	Controls	Controls	P value
	Mean	SD	Mean	SD	
FA of ipsilateral parahippocampalgyrus	.50	.12	.41	.14	.011*
FA of contralateral parahippocampalgyrus	.47	.18	.41	.14	.187
ADC of ipsilateral parahippocampalgyrus	.84	.11	.87	.13	.493
ADC of contralateral parahippocampalgyrus	.89	.18	.87	.13	.564

*statistically significant

FA was higher in the ipsilateral parahippocampalgyrus, contrary to our expectations. Rest of the values showed no statistically significant changes.

Summary of results

Reduced FA was seen in

1. Contralateral anterior limb of internal capsule
2. Ipsilateral external capsule
3. Body of corpus callosum
4. Bilateral frontal regions of superior longitudinal fasciculus
5. Contralateral occipital region of superior longitudinal fasciculus
6. Bilateral temporal regions of inferior longitudinal

fasciculus
7. Bilateral occipital limbs of inferior longitudinal fasciculus
8. Ipsilateral uncinate fasciculus
9. Bilateral middle cerebellar peduncle
10. Bilateral cingulum

Increased FA was seen in
1. Ipsilateral posterior limb of internal capsule
2. Ipsilateral parahippocampalgyrus

Increased ADC was seen in
1. Bilateral posterior limbs of internal capsule
2. Contralateral external capsule
3. Body of corpus callosum
4. Bilateral lentiform nuclei
5. Contralateral head of caudate nucleus
6. Bilateral frontal regions of superior longitudinal fasciculus
7. Ipsilateral temporal regions of inferior longitudinal fasciculus
8. Ipsilateral occipital region of inferior longitudinal fasciculus
9. Ipsilateral uncinate fasciculus

Discussion

Comparison of extra temporal grey matter of patients and controls:

We analysed the FA and ADC values of bilateral thalami, head of caudate nucleus and lentiform nucleus of all our 30 patients and compared them with 30 controls. We observed increased ADC in bilateral lentiform nuclei and the contralateral caudate nucleus. ADC of ipsilateral head of caudate nucleus was higher but did not achieve statistical significance. FA of contralateral head of caudate nucleus was decreased, but statistically insignificant. Our ADC results are in line with Yin *et al*. [9] who got significantly altered values in the caudate nucleus and that of Chen Q *et al*. [13] who concluded that mean diffusivity is more sensitive than fractional anisotropy.

No statistical significance was seen in the thalamus. Thivard *et al*. [17] with statistic parametric mapping explored the whole brain diffusion tensor imaging indices and found no statistically significant changes in the thalami. Our thalamic results concur with their results. Yin *et al*. [9] had insignificant ADC values, which concur with our results, but their FA values showed significant changes.

Comparison of extra temporal white matter of patients and controls:

Though the seizure onset is located within the temporal lobe, through the widespread interaction between cortical and subcortical structures, the epileptic circuitry is widened. Though structural abnormalities were limited to ipsilateral hippocampus and the temporal lobe, widespread diffusion abnormalities were seen in bilateral white matter in our study.

The major extra temporal diffusion abnormalities in our study consists of reduced FA in contralateral anterior limb of internal capsule, ipsilateral external capsule, body of corpus callosum, bilateral frontal regions of superior longitudinal fasciculus, contralateral occipital region of superior longitudinal fasciculus, bilateral temporal and occipital regions of inferior longitudinal fasciculus, ipsilateral uncinate fasciculus, bilateral middle cerebellar peduncle and bilateral cingulum.

Increased ADC values are seen in bilateral posterior limbs of internal capsule, contralateral external capsule, body of corpus callosum, bilateral lentiform nuclei, contralateral head of caudate nucleus, bilateral frontal regions of superior longitudinal fasciculus, ipsilateral temporal and occipital regions of inferior longitudinal fasciculus and ipsilateral uncinate fasciculus.

Our present data are in agreement with Knake *et al*. [28] who observed lower FA values in body/ trunk of corpus callosum, ipsilateral frontal and bilateral temporal lobes. They used both ROI method and whole brain analysis. The results of both methods were complementary to each other. Whole brain analysis picks up confluent changes but is insensitive to small focal changes. ROI method requires precise placement in the predetermined area. We used manually placed ROIs on preselected regions.

Our results of temporal lobe white matter concur with those of Riley *et al*. [16] and Thivard *et al*. [17] who also observed increased diffusivity and reduced anisotropy along the temporal white matter. Thivard *et al*. [17] were the first to describe the extra hippocampal temporal white matter diffusion changes. They found no modification in the FA for the hippocampal/para hippocampal region. In our study, there was significant change in the ADC and FA values of hippocampus, though the para hippocampal region did not demonstrate significant alterations.

We have obtained significant FA and ADC values in bilateral frontal lobe white matter. This shows early and preferential spread to frontal lobes through uncinate fasciculus in nearly all cases. The study by Wang *et al*. [18] with 27 temporal lobe epilepsy patients showed impaired category fluency and other executive functions compared to controls. They concluded that propagation of seizures to frontal lobe, not detected by standard MRI as the reason behind impaired category fluency. Though executive functions were not tested in our patients, frontal white matter involvement implies impaired executive function.

We had statistically significant FA values in bilateral cingulum, a major hippocampal pathway. This is in line with the results of Thivard *et al*. [17] who observed statistically significant differences in the cingulum.

Corpus callosum is the major commissural fibre connecting the two hemispheres. Our study revealed statistically significant changes in both ADC and FA values in the body of corpus callosum. FA was lower and ADC was higher in the genu and splenium, but did not achieve statistical significance. Knake *et al*. [28] observed reduced FA in the genu and body of corpus callosum, Thivard *et al*. [17] found reduced FA in corpus callosum, Meng *et al*. [12] got reduced FA and increased ADC in the splenium, Yin *et al*. [9] had lower FA in genu, body and splenium with higher diffusivity in body of corpus callosum. Kim *et al*. [11] with ten patients of temporal lobe epilepsy found reduced FA values in the splenium, we did not achieve statistically significant altered FA values in the genu/ splenium. These variability in results were observed by various researchers [20] and attributed to variations in methodology, patient selection and duration of the seizures.

Internal capsule is a major projection fibre. We observed statistically significant reduced FA values in contralateral anterior limb and increased ADC in bilateral posterior limbs. Of the previous studies, Meng *et al*. [12] observed

reduced FA and increased diffusivity values in anterior limb, posterior limb and the genu, Yin *et al.* [9] showed lower FA in the anterior and posterior limbs of internal capsule, Wang *et al.* [18] found lower FA in left posterior limb, Meng *et al.* [12] observed increased diffusivity and reduced FA in anterior and posterior limbs.

Reference	Age and number	Seizure type	DTI abnormalities
Assaf *et al.* [2], 2003	12 adults	Unilateral TLE	Increased ADC in ipsilateral hippocampus.
Thivard *et al.* [17], 2005	35 adults	Unilateral TLE	Increased ADC in ipsilateral hippocampus, temporal lobe, reduced ADC in contralateral temporal lobe, reduced FA in ipsilateral extratemporal regions.
Kim *et al.* [11], 2008	10 adults	Unilateral mesial, neocortical TLE	Reduced FA in splenium of corpus callosum
Diehl *et al.* [14], 2008	28 adults	Unilateral TLE	Reduced FA and increased ADC in ipsilateral and contralateral uncinate fasciculi, correlated with visual and auditory memory in left TLE
Knake *et al.* [28], 2009	12 adults	Left TLE	Reduced FA in bilateral temporal lobe white matter, ipsilateral frontal lobe white matter, genu and body of corpus callosum, ipsilateral hippocampus, ipsilateral parahippocampalgyrus.
Kim *et al.* [10], 2010	9 TLE patients with hippocampal sclerosis, 9 TLE patients without hippocampal sclerosis	Unilateral TLE	Increased ADC in bilateral thalami
Meng *et al.* [12], 2010	8 children and adolescents	Unilateral TLE	Reduced FA in bilateral anterior and posterior limbs, genu of internal capsule, splenium of corpus callosum, increased ADC in ipsilateral and contralateral external capsule, anterior and posterior limbs of internal capsule, splenium of corpus callosum.
Wang *et al.* [18], 2012	27 adults	Unilateral TLE	Reduced FA in bilateral thalami, posterior limb of internal capsule, positive correlation between category fluency scores and FA of left frontal lobe and right occipital lobe.
Riley *et al.* [16], 2010	12 adults	Unilateral TLE	Reduced FA in ipsilateral anterior temporal lobe, posterior mesial temporal lobe, cerebellum, contralateral fronto parietal lobe.
Yin *et al.* [9], 2014	20 adults	Unilateral TLE	Reduced FA in internal capsule, external capsule, head of caudate nucleus, lentiform nucleus, thalamus, genu, body and splenium of corpus callosum. Increased ADC in bilateral external capsule, head of caudate nucleus, thalamus, body of corpus callosum.
Our study	30 adults	Unilateral TLE	Reduced FA in contralateral anterior limb of internal capsule, ipsilateral external capsule, body of corpus callosum, bilateral frontal regions of superior longitudinal fasciculus, contralateral occipital regions of superior longitudinal fasciculus, bilateral temporal and occipital regions of inferior longitudinal fasciculus, ipsilateral uncinate fasciculus, bilateral middle cerebellar peduncle and bilateral cingulum. Increased ADC values in bilateral posterior limbs of internal capsule, contralateral external capsule, body of corpus callosum, bilateral lentiform nuclei, contralateral head of caudate nucleus, bilateral frontal regions of superior longitudinal fasciculus, ipsilateral temporal and occipital regions of inferior longitudinal fasciculus and ipsilateral uncinate fasciculus.

Regions in violet represent concurrence with our study.

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 [14]. In our study, ipsilateral uncinate fasciculus had reduced FA and increased ADC values. Diehl *et al.* [14], in 2008 analysed the DTI parameters of 28 TLE patients and correlated them with auditory and visual, immediate and delayed memory. They found significant alterations in diffusion tensor imaging indices in bilateral uncinate fasciculi correlated with memory in patients with left TLE (both medial and lateral). The involvement of uncinate fasciculus in our cases, implies impaired memory, though we did not directly test for memory.

Patients with temporal lobe epilepsy have multiple cognitive impairments like memory, executive functions, language, intelligence and motor speed [16]. Riley *et al.* in 2010 [16] 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 fibres and the cerebellum. These abnormalities correlated with the cognitive performance. In our study, we had significant reduced FA in bilateral middle cerebellar peduncle, temporal and occipital regions of bilateral inferior longitudinal fasciculus, ipsilateral uncinate fasciculus concurring with their study. We did not test the cognitive profiles of our patients, it is an area of future research in our region.

Gross *et al.* [20], in their meta-analysis of 10 studies observed that though the cause and implications of white matter changes are unclear, they represent downstream axonal degeneration secondary to spreading seizure activity. They also observed that the changes are variable between studies in grey and white matter tract involvement and represent variations in patient selection, methodology, duration and propagation of seizure activity. The duration of seizures in our patients ranged from one month to 15 yrs.

In summary, the study concurs with previous studies

demonstrating extensive bilateral white matter DTI abnormalities in patients with unilateral TLE. The majority of association fibres are involved in our cases, only the genu is involved in corpus callosum, scattered areas of involvement is seen in the projection fibres. These findings strongly suggest that structural abnormalities, not depicted on standard MRI involves an extensive bilateral network of structures, rather than limited to the seizure focus. It implicates impairment of memory, cognition and executive functions and reflects the subclinical extent of disease.

The findings suggest that TLE is not a focal disease. Abnormalities are seen extensively bilaterally in the extra temporal grey and white matter, both ipsilateral and contralateral to the seizure origin. Itmay be inferred that propagation of epileptic activity can be blocked by destroying any structure in the epileptic circuit.

Conclusion

1. DTI abnormalities are seen extensively bilaterally in the extra temporal grey and white matter, both ipsilateral and contralateral to the seizure origin. The findings strongly suggest that microstructural abnormalities are not only restricted to the seizure focus, but also involve ipsilateral and contralateral grey and white matter extensively. It shows the extent of spread of subclinical activity and helps in prognostication.

Limitations of Our Study

1. The study was done on patients being ictus free for at least a week, as ictus is shown to affect ADC values. However, subclinical seizures, not identified, could have occurred with impact on our values.
2. In this study, diffusion tensor imaging was done in 15 non collinear directions. Increasing the number of directions might increase the yield of the study.
3. There was technical difficulties in placing the voxel on fornix without contamination from CSF as the size of single voxel was larger than the fornix.
4. The results are population based, so the application as a clinical tool in the management of patients remains unexplored.
5. Duration and compliance with treatment and seizure frequency may affect the FA and ADC values. These were not included as variables in this study.

Recommendations

1. Diffusion tensor imaging can be incorporated in routine epilepsy protocol as altered hippocampal values adds to the diagnosis in equivocal cases. Moreover, there is widespread bilateral alterations in the FA and ADC values, though conventional imaging shows abnormality restricted to ipsilateral temporal lobe.
2. The number of directions may be increased, instead of 15, as it might yield better results.
3. DTI can be done with fluid suppression to avoid CSF contamination for obtaining values from the fornices.
4. Cognition tests can be done from the onset of epilepsy and correlated with DTI, it might help in prognostication.
5. Longitudinal studies can be undertaken in patients with recent onset epilepsy, as it can better define the progression of white matter changes.

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