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Original Article

Concordance of diffusion tensor imaging alterations with EEG lateralization in MR negative refractory temporal lobe epilepsy

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Abstract

Aim: In this study, we aimed to investigate the occult microstructural changes in both temporal lobes and their localization concordance with electroencephalogram (EEG) lateralization side in MR negative refractory temporal lobe epilepsies using diffusion tensor imaging (DTI).

Material and Methods: Clinical files of 200 adult patients diagnosed with temporal lobe epilepsy and followed by neurology department were reviewed. A total of 32 patients who had uncontrolled seizures despite antiepileptic medication and had normal MR findings were included in the study. Using DTI data, symmetric region of interests (ROIs) were replaced on each temporal white matter to calculate parameters including fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD). Mean values of each of these parameters were compared between the epileptogenic lateralization side on (EEG) and opposite temporal lobe.

Results: FA and RD values were significantly different on lateralization side compared to normal side, whereas AD value showed no significant difference between two sides.

Conclusion: The subtle microstructural abnormalities which cannot be discerned on routine conventional MRI practice in brains of refractory TLE patients can be revealed by DTI. The localization of these DTI abnormalities mostly shows concordance with the lateralization side on EEG. Awareness of the existence and degree of these alterations may be useful in determining medical treatment strategies or may be a guide in planning blind antiepileptic surgery.

Keywords: Diffusion tensor imaging; EEG; temporal lobe epilepsy

INTRODUCTION

Epilepsy is one of the commonest neurological diseases which affect nearly 50 million individuals worldwide. Approximately 30% of patients under treatment with antiepileptic medications have uncontrolled seizures (1). More than 40% of whole adult epilepsies are temporal lobe epilepsies (TLE). TLE may be sporadic or with a positive family history. The major detectable causes of TLE include hippocampal sclerosis, vascular malformations, cortical development malformations, benign tumors and post-traumatic or post infectious gliosis (2).

MRI is the most sensitive and useful examination tool for identifying epileptogenic foci and structural abnormalities in patients with focal epilepsies. TLE can be classified as lesional and non-lesional depending on whether there is an identifiable lesion on conventional MRI (3,4). Non-lesional temporal lobe epilepsy (nl-TLE) accounts for 30% of all TLE patients (5).

DTI is a non-invasive MRI technique that can provide either quantitative information about microstructural integrity of cerebral white matter or three dimensional visual information with respect to specific white matter tracts (6). Microstructural pathological changes such as axonal or myelin damage can be identified with this technique (7,8). In DTI, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) are quantified parameters in many neurological diseases (9). FA measures the total magnitude of water directional movement along the axonal fibers reflecting the structural integrity of fiber tracts. MD is the mean measure of diffusion of water molecules in each direction. AD describes the mean water diffusivity along the principle axis of diffusion within a voxel as a marker for

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axonal damage. RD is defined as the mean magnitude of water diffusion perpendicular to the axons as a marker for demyelination (8,10).

After the initial report by Arfanakis et al. on DTI in TLE, particularly in the last decade, growing numbers of studies on DTI and TLE has been published in the literature (11). To the best of our knowledge, there is limited number of studies investigating the correlation of interictal EEG lateralization with DTI in refractory TLE patients. In the current study we aimed to investigate the concordance of DTI findings with interictal EEG lateralization in MR negative refractory TLE patients and to compare the results with the similar studies in the literature.

MATERIAL and METHODS

Patient selection

We examined the clinical records of 200 TLE patients over 18 years old followed by neurology department of our institution. The inclusion criteria were being resistant to medical antiepileptic treatment (persisting seizures for over one month despite administration of at least 2 antiepileptic drugs) and having normal MR findings with lateralization on EEG examination. Patients who were reported to have any parenchymal lesion or epileptogenic focus on MRI were excluded from the study.

This study protocol was approved by the Ethics Committee of Inonu University School of Medicine (IRB authorization number: 2020/682) and conducted in accordance with the ethical principles of the 2013 Declaration of Helsinki and Good Clinical Applications.

Imaging and post processing procedure

Whole MRI procedures of all patients included in the study were performed on 3 Tesla MR scanner (Skyra; Siemens, Erlangen, Germany) without contrast media injection using 20-channel phased-array head coil. In our center diffusion tensor sequence (DTI) is routinely applied in epilepsy imaging protocol. DTI data were obtained by using 30 diffusion encoding directions at b=0 and b=1000 values (s mm^{-2}) with echoplanar sequence (TR/TE: 3100/95 ms, FoV read: 220 mm, matrix: 124 x 128, slice thickness: 5 mm). Imaging data were transferred to a offline working station (syngo.via; Siemens, Erlangen, Germany). T1 MPRAGE (TR/TE: 2300/3 ms; matrix: 240 × 256 ; FoV read: 240 mm; slice thickness: 1 mm) and T2 space da-fl (TR/TE: 4750/387 ms; matrix: 256 x 256; FoV read: 230 mm; slice thickness: 0,9 mm) 3 dimension sagital volumetric images were assessed again for any cortical dysplasia and parenchymal pathology after multiplanar reconstruction in 3 orthogonal planes. After the tensor data of MR negative confirmed patients were registered to high resolution T1 images, ADC and fractional anisotropy (FA) maps were created. Subsequently, anatomic regions for ROI replacement were determined on axial T1 and T2 FLAIR images which were automatically senchronized with these maps since they provide better anatomical resolution. In bilateral cerebral hemispheres, symmetric ROIs of equal size (mean 0.3 cm^2) and number (5 for each side) were replaced on lateral and/or medial temporal white matter regions reciprocally, avoiding CSF contamination. FA, RD and AD parameters were calculated automatically (Figure 1). Mean values of each of these parameters were also calculated separately for both lateralized and opposite normal sides. The obtained mean values were then compared between each sides.

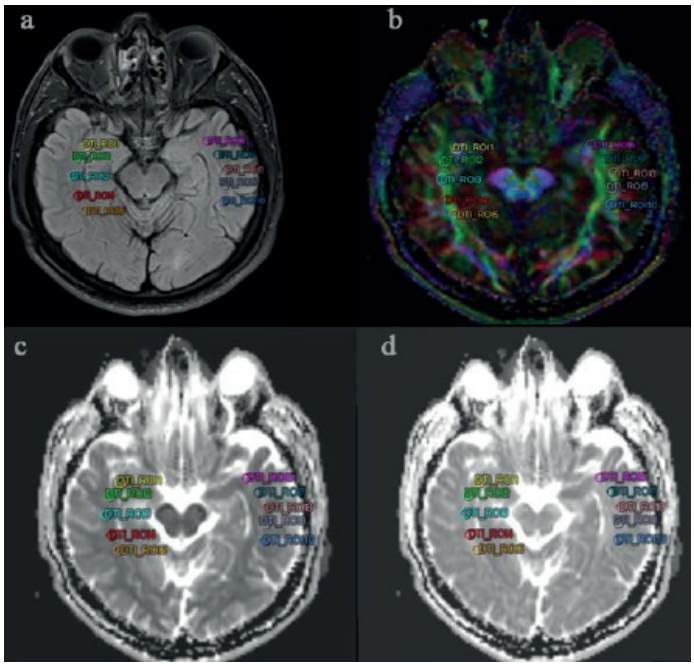

Figure 1. ROI replacement on bilateral temporal lobes on axial T2 FLAIR (a) and corresponding regions on colored FA (b), RD (c), AD (d) maps

Statistical analysis

In order to compare the pathological (according to EEG lateralization) and normal side with 95% confidence level (α = 0.05) and 80% strength (β = 0.20), the minimum number of patients to be included in the study was calculated as 10 considering effect size. The normality of data was checked by Shapiro-Wilk test. Since the data did not show normal distribution the Wilcoxon signed ranks test was used for comparisons. Numerical data are summarized with median, minimum and maximum values and categorical variables with numbers and percentages. The significance level was considered as 0.05 in all tests. IBM SPSS Statistics for Windows version 25.0 (NY, USA) used in the analysis.

RESULTS

According to inclusion and exclusion criteria, 32 patients were included in the study. Of the 32 patients 17 were female (53.1%) and 15 were male (46.9%) with a mean age of 32.5±12.3 years and an age range of 18-64 years.

The number of antiepileptic drugs which the patients were treated was 2 at minimal and 5 at maximal. The disease duration was ranging between 1 and 36 years. On interictal EEG, epileptic activity was in the left temporal side in 26 patients, whereas 6 had on the right temporal side.

The range of FA1 value (pathological side on EEG) was 174,69 - 447,77 with median value of 322,97. The FA2 values (normal contralateral side) were ranging between 149.01-526.00 with median value of 365,82. RD1 (pathological side) and RD2 (normal side) values were ranging between 505.75- 878,03 and 493.03-1,215.47 with median values of 63861 and 668.41, respectively. Finally, AD1 (pathological side) and AD2 (normal side) values were ranging between 976.10 -1287.18 and 946.00-1489.73 with median values of 1154.50 and 1188.68, respectively.

FA values were found statistically significantly lower in lateralization sides compared to those in contralateral temporal white matters (p=0.014). RD values were also significantly higher in lateralization sides (p=0.040). AD values did not show any significant difference between both sides (p= 0.166) (Table 1).

Table 1. Comparison of DTI parameters between bilateral temporal white matters

	Lateralisation side	Opposite side	p
	Median (min.-max.)	Median(min.-max.)	
FA (n=32)	322.97 (174.69-477.77)	365.82 (149.01-526.00)	**0.014**
RD (n=32)	683.61 (505.75-878.03)	668.41 (493.03-1215.47)	**0.040**
AD (n=32)	1154.50 (976.10-1287.18)	1188.68 (946.00-1489.73)	0.166

P ≤ 0.05

DISCUSSION

In the present study we retrospectively examined the diffusion tensor alterations of temporal white matters in MRI negative refractory TLE patients and revealed that DTI parameters including FA and RD showed statistically significant difference in the laterality sides on EEG compared to contralateral temporal white matters. These alterations probably reflect microstructural abnormalities which cannot be detected in routine conventional imaging. Our study presents highly consistent results with the literature.

In some cohort studies it was reported that in TLE, which is one of the most common types of focal epilepsy syndromes, nearly 30 percent of the patients have normal conventional MRI findings (12-14). Surface EEG recording is one of the noninvasive methods for detecting epileptogenic focus (15). Especially video-EEG monitorization is helpful in determining interictal epileptiform activity (16). On the other hand PET, SPECT and, if available, magnetoencephalography (MEG) are useful tools in detecting epileptogenic foci for presurgical evaluation of drug refractory epilepsies (17).

DTI, as a noninvasive MRI technique, has been increasingly used in helping first diagnosis and monitoring epilepsy since the early 2000's. Many DTI studies have revealed that normally appearing cerebral white matter parameters exhibited differences in MR negative TLE patients on conventional MRI (14). In the studies with respect to DTI changes and MR negative TLE, FA is the most congruous parameter that is mostly decreased in the epileptogenic regions. Other tensor parameters usually vary in different studies. In a prospective study comparing MR negative TLE group with healthy controls, Liacu et al. found significantly decreased FA values in hippocampal regions of either intragroup comparison of ipsilateral and contralateral sides of nl-TLE or lateralization sides versus controls whereas MD and other parameters did not significantly altered. As a similar finding with ours, decreased anisotropy (FA) here is a sensitive marker of breakdown of structural integrity (18). Another study investigating DTI abnormalities and anatomic concordance with MEG dipole cluster on MR negative pediatric patients, had similar but stronger results revealing 100 percent of the MR negative group showed significantly decreased FA values and % 68 lobar concordance to the epileptogenic zones defined with MEG . Abnormality of MD was also lobar concordant with MEG dipole cluster in the study (19).

The ability of DTI application to give information about microstructural changes is not limited to temporal lobes in lesional and nl-TLE, the extent of these changes to other structures out of temporal lobe such as corpus callosum may also be assessed by this method. Lyra et al. studied 42 patients with hippocampal sclerosis and 30 healthy controls with DTI. They revealed that HS patients displayed decreased FA and increased MD and RD in the anterior, mid-posterior and posterior CC segments, compared to controls but no differences in AD (20). Thalamic DTI abnormality is another example of extratemporal interactions in TLE. Thalamus has been studied with DTI since it has anatomical connectivity with medial temporal lobe and has role in seizure modulation by Kim et al. They found significantly higher MD values in epileptogenic sides of lesional and nl-TLE groups compared to controls and also decreased FA in seizure side in nl-TLE group but no group differences (21). A recent study compared 12 TLE patients who were undergone temporal lobectomy and amigdalohippocampectomy surgery (6 were lesional and 6 were nl-TLE) with age-sex matched controls and revealed that there were diffusion tensor alterations in both pathologic and contralateral sides but more pronounced in ipsilateral epileptogenic side suggesting that DTI could be a useful tool for presurgical evaluation to determine the laterality of TLE, including patients with "normal" MRI.

Current study has also several limitations. This was a retrospective based study, namely, uncontrolled variables may have effected the results. Secondly, small sample size and lacking of comparison to healthy controls may be another effect that change statistical value of the study.

CONCLUSION

Despite the lacking of comparison with age and sex matched controls our results with respect to DTI alteration

were nearly similar to those in the literature. Especially FA decrease seems to be more reliable marker of breakdown of microstructural integrity. With its high concordance of laterality on EEG, DTI is a useful noninvasive imaging technique detecting visually indiscernible microalterations in white matter and may contribute to presurgical planning of nl-TLE patients with this aspect.

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

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Ethical approval: This study protocol was approved by the Ethics Committee of Inonu University School of Medicine (IRB authorization number: 2020/682).

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