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Research Article

Uncinate Fasciculus in Temporal Lobe Epilepsy

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Abstract

Background and purpose: Temporal lobe epilepsy is the most common focal intractable epilepsy. Uncinate fasciculus is a white fiber bundle that connects the orbitofrontal cortex with the anterior temporal lobe, and is implicated in most of the superior mental functions. There is evidence of uncinate fasciculus as a propagation pathway of seizures from temporal lobe. The aim of the study is to determine uncinate fasciculus alterations in patients with temporal lobe epilepsy, through fractional anisotropy.
Methods: Thirty-three patients with temporal lobe epilepsy (10 right and 23 left) were studied. All of them were right-handed and had left hemisphere dominance for language. A 1.5 T MR imaging scanner was used to obtain diffusion tensor imaging (DTI). Fractional anisotropy of uncinate fasciculus was calculated through TBSS (Tract Based Spatial Statistics). Statistical analysis was done using IBM SPSS (v. 25).
Results: Fractional anisotropy was higher in right uncinate fasciculus, regardless of epilepsy side. Right uncinate fasciculus, at the insula level, showed lower fractional anisotropy in patients with right temporal lobe epilepsy.
Conclusions: Results support the evidence of uncinate fasciculus as a pathway of propagation in temporal lobe epilepsy, specially at insular level.

Key words: temporal lobe epilepsy, uncinate fasciculus, diffusion tensor imaging

Introduction

Epilepsy is one of the most common neurologic disorders, affecting around fifty million people all over the world (World Health Organization, 2019). International League against Epilepsy (ILAE) defines epilepsy as a condition with two or more recurrent electrical seizures in 24 hours, without any identified cause. Among more than forty clinical epilepsy syndromes, temporal lobe epilepsy (TLE) is the most frequent and also represents two thirds of the surgical-required intractable epilepsy (Cendes, 2005) (Ladino, et al., 2014) (Allone, et al., 2017), with mesial temporal sclerosis being a hallmark, although not always present. However, some evidence suggests that TLE is rather a brain network disorder, with adjacent white matter fiber bundles microstructural changes, particularly uncinate fasciculus (UF), arcuate fasciculus, cingulum and external capsule (Rodríguez-Cruces & Concha, 2015). UF is a major fiber tract that connects orbitofrontal cortex with anterior temporal lobe, linking rostral portions of amygdala and temporal gyri with the gyrus rectus, because of this connectivity and localization, it is considered part of the limbic system and has been implicated in emotion, memory, behavioral process patterns, social situational awareness, language (Papagno, et al., 2011) (Nomura, et al., 2013) (Von der Heide, et al., 2013), and notably in temporal lobe epilepsy as an important pathway of seizure activity spread (Kim, et al., 2011). Microstructural changes in these white matter fiber bundles are evaluated with magnetic resonance imaging by using fractional anisotropy (FA), a parameter of diffusion tensor imaging sequence. It is an assessment of restriction and directionality of water molecules movement, with values ranging between 0 (no anisotropy) and 1 (maximus anisotropy) (Beaulieu, 2002) (Alexander, et al., 2007). It is also an assessment of white matter fiber integrity (Diao, et al., 2015), but is affected by fiber crossing within a voxel or partial volume effect (Chanraud, et al., 2010). Reported values of FA for the UF varies among 0.32 y 0.48 (Von der Heide, et al., 2013). However, there is discrepancy about side dominance, with some authors reporting right dominance (Rodrigo, et al., 2007) (Park, et al., 2004), specially at insular and temporal portions; and other reporting left dominance (Diehl, et al., 2008). Methodological variations in imaging acquisition or assessment are supposed to explain these discrepancies. Regarding microstructural changes in UF of TLE patients, some authors found FA values alteration of UF, suggesting fiber damage (Rodrigo, et al., 2007), specifically ipsilateral to epileptogenic focus (Diao, et al., 2015) (Diehl, et al., 2008) (Ahmadi, et al., 2009) (Concha, et al., 2012). The aim of this study is to determine UF alterations by depicting it in three major segments, through FA assessment, in patients with temporal lobe epilepsy.

Materials and methods

Subjects

Patients with TLE were selected among those who fulfill the following

inclusion criteria: 1) epilepsy side consistently defined by clinic, MRI findings, FDG-PETCT and EEG, 2) left hemispheric dominance for language, and 3) right-handedness. Patients with brain malignancy and those who received radiation treatment for brain, head and/or neck, were excluded. Two groups were formed for analysis, right TLE and left TLE patients.

Image acquisition and analysis

Images were obtained from a 1.5-T Signa MR scanner (GE Medical Systems, Milwaukee, WI), including a DTI sequence with 35 diffusion gradient directions, b value of 1000 s/mm^2, 22 cm FOV, 128 x 128 acquisition matrix, 48 slices and Z resolution of 3 mm. DTI was analyzed in and independent work station and FA was calculated using TBSS (Tract Based Spatial Statistics) from FSL (Functional Magnetic Resonance Imaging of the Brain´s Software Library) (Smith, et al., 2004) for iMac, this tool improves sensibility, objectivity and interpretability for DTI group analysis (Smith, et al., 2006).

FA was calculated automatically in each UF using the JHU White-Matter tractography Atlas. Additionally, FA was calculated in three different right and left UF segments (frontal, insular and temporal). Then, the automatically obtained values were compared within each group and the three segments FA values were compared between both groups. Non-parametric U-Mann Whitney test was used. Age, sex, educational level and epilepsy time duration was compared between both groups, using *t* student test. Statistical analysis was done with IBM SPSS v25, and $p < 0.05$ was considered significant.

Results

Thirty-three patients were selected, 10 were right TLE patients and 23 were left TLE patients. Female sex accounted for the 60% of patients. Most common age range was among 20-29 years old. Epilepsy time duration has a mean of 24.8 ± 11.7 years with a range of 5 to 44 years. There were no statistical differences for age, sex, educational level and epilepsy time duration between right and left TLE groups. Table 1.

	Right TLE (n=10)	**Left TLE (n=23)**	***p***
Sex			0.92
Female	6	14	
Male	4	9	
Age (years)	38.4 ± 9	34.1 ± 10	0.26
Epilepsy time duration (years)	25.5 ± 13	24.5 ± 11	0.82

The analysis within groups showed side-to-side asymmetry with greater FA values in right UF, in both groups ($p < 0.01$). Table 2.

Table 2. Uncinate fasciculus FA in right TLE patients			
	Mean	**SD**	*p*
Right UF-FA	0.27	0.07	0.00
Left UF-FA	0.24	0.03	
Uncinate fasciculus FA in left TLE patients			
	Mean	**SD**	*p*
Right UF-FA	0.29	0.08	0.00
Left UF-FA	0.25	0.06	

The analysis between groups, for each segment of UF, showed statistical difference only for the insular segment, with lower FA values in right UF in patients with right TLE ($p < 0.05$). Table 3.

Table 3. Three segments UF FA and epilepsy side		
	Right TLE	**Left TLE**
Right frontal UF-FA	0.28 ± 0.07	0.30 ± 0.09
Left frontal UF-FA	0.27 ± 0.08	0.32 ± 0.10
Right insular UF-FA*	0.43 ± 0.11	0.49 ± 0,12
Left insular UF-FA	0.50 ± 0.12	0.49 ± 0.14
Right temporal UF-FA	0.18 ± 0.04	0.16 ± 0.04
Left temporal UF-FA	0.19 ± 0.04	0.18 ± 0.06

Discussion

Seizure pathways in TLE has motivated a great amount of experimental studies, including *in vivo* models using electrophysiological recordings, kindling and metabolic studies. This data suggests a "single focus" that primary spread to parahippocampal cortex, then perirhinal, piriform and insular cortex toward frontal motor cortex (McIntyre & Gilby, 2008). However, there is evidence of additional temporal and extratemporal changes in TLE patients. In this sense, a "model network" has been proposed, considering several cortical and subcortical structures anatomically and functionally connected, with the same vulnerability to seizure activity (Palmigiano, et al., 2012). Regardless of a known seizure onset zone in TLE, diffuse changes in white matter tracts connecting temporal lobe with other regions are described. Also, evidence using FA to assess specific white matter fiber bundle suggests changes due to damage, particularly in UF. In this way, Rodrigo (2007), Diehl (2008), Ahmadi (2009), Concha (2012) and Diao (2015) have previously described FA values alteration of UF in TLE patients. In our study, we analyzed FA of UF in two groups of TLE patients categorized by epilepsy side, with no statistical differences among age, sex and epilepsy time duration. Table 1. Some variability between each side UF was found, with greater FA in right UF in both groups. Table 2. These results suggest a right UF dominance, as was described previously by Park (2004) and Rodrigo (2007), particularly at insular and temporal segments. Furthermore, Highley (2002) in a postmortem study, found that right UF was 27% larger and contained 33% more fibers than left UF. However, the reason for this asymmetry remains to be elucidated. Three different segments of UF were evaluated between both groups, these were at frontal, insular and temporal segments, from which only insular segment showed difference, with lower FA values ipsilateral to the epilepsy side in right TLE patients. According to animal models of McIntire & Gilby (2008), insular, perirhinal and piriform cortex are and important component to seizure spread and recruitment of motor neurons; so, we can assume insular UF portion as having the major role in seizure spread. As FA represents a combination of volume, density, myelination and coherence of fibers bundles (Park, et al., 2004); our results suggest that right TLE patients have microstructural injuries in ipsilateral UF, particularly at insular segment. These changes ipsilateral to epileptogenic focus would be the result of gliosis or microdysgenesis, findings commonly found in hippocampi of intractable TLE patients (Kasper, et al., 2003). Wallerian degeneration has also been implicated as a consequence of progressive neuronal loss in chronic epilepsy (Beaulieu, 2002). Interestingly, Diehl (2008) found bilateral UF values alterations in right and left TLE patients, demonstrating remote diffusion abnormalities to the presumed seizure focus, as was described previously by Concha (2005). Moreover, some other entities may alter FA values in greater or lesser degree, and these can be epilepsy related conditions such as postictal state (Diehl, et al., 2005), or other not related conditions such as cytotoxic or vasogenic edema, encephalopathy, psychiatric disorders and inflammation (Assaf & Pasternak, 2008). Unfortunately, we did not consider time interval between last seizure and magnetic resonance imaging, as the study was retrospective, which can originate pitfalls in FA values. Also, the lack of a control group and the small number of patients are significant limitations of this study.

Conclusions

Our results support the evidence of right dominance for the UF. Also, confirm changes in FA of UF ipsilateral to the TLE side, even though this white matter fiber bundle is not directly related to TLE, but more studies with bigger samples are needed to confirm these findings.

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