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Structural differences in interictal migraine attack after epilepsy: A diffusion tensor imaging analysis

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ABSTRACT

Objective: Patients with epilepsy (PWE) are more likely to suffer from migraine attack, and aberrant white matter (WM) organization may be the mechanism underlying this phenomenon. This study aimed to use diffusion tensor imaging (DTI) technique to quantify WM structural differences in PWE with interictal migraine.
Methods: Diffusion tensor imaging data were acquired in 13 PWE with migraine and 12 PWE without migraine. Diffusion metrics were analyzed using tract-atlas-based spatial statistics analysis. Atlas-based and tract-based spatial statistical analyses were conducted for robustness analysis. Correlation was explored between altered DTI metrics and clinical parameters.
Results: The main results are as follows: (i) Axonal damage plays a key role in PWE with interictal migraine. (ii) Significant diffusing alterations included higher fractional anisotropy (FA) in the fornix, higher mean diffusivity (MD) in the middle cerebellar peduncle (CP), left superior CP, and right uncinate fasciculus, and higher axial diffusivity (AD) in the middle CP and right medial lemniscus. (iii) Diffusion tensor imaging metrics has the tendency of correlation with seizure/migraine type and duration.
Conclusion: Results indicate that characteristic structural impairments exist in PWE with interictal migraine. Epilepsy may contribute to migraine by altering WMs in the brain stem. White matter tracts in the fornix and right uncinate fasciculus also mediate migraine after epilepsy. This finding may improve our understanding of the pathological mechanisms underlying migraine attack after epilepsy.

1. Introduction

Fifty percent of patients with active epilepsy have comorbid medical disorders. These comorbidities, including migraine, dementia, depression, and anxiety, are associated with poor seizure outcomes and reduced quality of life [1]. Migraine is common in people with epilepsy (PWE), with a prevalence rate of approximately 12% [2]. The correlation between epilepsy and migraine is bidirectional [3]. A recent study indicated that male migraineurs with old age and low income may have higher risk of epilepsy [4]. However, the predisposing risk factors to migraine in PWE are unclear. Moreover, although the link between epilepsy and migraine has long been investigated, data on their relationship are still limited [5].

Epilepsy and migraine are chronic diseases with episodic and recurrent neurological dysfunction [6]. In epilepsy, focal seizures progress to generalized seizures, representing propagation of epileptiform activities [7]. Meanwhile, in migraine, aura represents excitation followed by cortical spreading depression [8]. Epilepsy and migraine share many clinical similarities and may be deeply related to abnormal electric circuits among cortices [9]. Neural tracts provide the structural basis for electric circuits. Using diffusion tensor imaging (DTI), previous studies revealed white matter (WM) alterations in epilepsy and migraine [10,11], but the diffusion tensor characters of PWE with migraine have rarely been reported.

This study aimed to reveal WM differences between PWE with and without migraine, and assess the relationship between diffusion tensor metrics and clinical presentation.

2. Materials and methods

2.1. Patient selection

This study used a cross-sectional cohort design and was conducted from March 2015 to March 2017. Ethical approval was ratified by the Bioethics Committee of The First Affiliated Hospital to Guangxi Medical University. Written consents were obtained from the patients.

Twenty-five PWE were recruited. Only patients who met the following criteria were enrolled in the group with epilepsy and migraine (GEM): (1) the criteria of the International Classification of Headache Disorders for the diagnosis of migraine [12]; (2) migraine after epilepsy onset; and (3) migraine in interictal stage of epilepsy. Patients with epilepsy without migraine were included in the group with epilepsy

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(GE). Patients with epilepsy with severe internal diseases or any signal abnormality under conventional magnetic resonance imaging (MRI) scan (T1-, T2-, and FLAIR-weighted sequences) were excluded.

Clinical data, including (1) age and sex of PWE; (2) duration, frequency, and type of epileptic attack; and (3) duration, frequency, and type of migraine attacks were collected.

2.2. MRI data acquisition

Magnetic resonance imaging data were acquired using a 3.0-T Siemens scanner (Siemens AG, Erlangen, Germany) with a 12-channel head coil. Foam padding was used to minimize head motion. The scanning parameters were as follows: (1) DTI single-shot echo-planar spin-echo sequence with 62-gradient directions [repetition time (TR) = 4900 mm, echo time (TE) = 95 ms, flip angle = 90°, matrix = 128 × 128, b = 0 and 1000 s/mm^2, and 45-axial 3-mm-thick slices without gap].

2.3. Data analysis

The DTI images were processed using PANDA software [13] (http://www.nitrc.org/projects/panda/). Analysis was performed through the following steps:

(1) Preparation. This step included estimating the brain mask, cropping raw images, correcting for the eddy current effect, and calculating diffusion tensor metrics, namely, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).
(2) Diffusion metrics for tract-atlas-based spatial statistics (TABSS) analysis. The mean of all the aligned FA images were created and skeletonized, resulting in a mean FA skeleton. Diffusion metric data from individual subjects were projected onto the skeleton. The ICBM-DTI-81 WM label atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases/) was used to parcellate the entire diffusion metrics on the skeleton into multiple regions of interest (ROIs), and the average values were calculated.
(3) Robustness analysis. In order to check the robustness of our results, we repeated the diffusion analysis by atlas-based analysis and tract-based spatial statistics (TBSS) analysis. For atlas-based analysis, the ICBM-DTI-81 atlases allowed for parcellation of the entire WM into multiple ROIs, and we calculated regional diffusion metrics by averaging the values within each region of the WM atlases. For TBSS-based analysis, the voxel-wise statistical analysis of each metrics on the skeleton was conducted using *fslmaths* and *tbss_skeleton* commands of FMRIB Software Library. Clusters with significant between-group difference ($p < 0.01$) were detected after Conditional Monte Carlo permutation test, and 5000 permutations are used to reduce the uncertainty. More details on this process are presented in Fig. 1.

2.4. Statistical analysis

Data were statistically analyzed using IBM SPSS Statistics 22. The difference between GEM and GE was assessed via unpaired *t*-test or Fisher's exact test ($p < 0.01$). Pearson or Spearman correlation was performed to examine the relationship between diffusion metrics and clinical data. The Bonferroni adjustment was employed to correct for multiple comparisons.

3. Results

3.1. Clinical characteristics

The GE comprised of 13 PWE, whereas the GEM comprised of 12 PWE. The average ages of patients in GE and GEM were 21 and 19 years, respectively ($p = 0.132$). Trends in gender were not evident in the two groups ($p = 1.000$). The PWE in the two groups developed a similar spectrum of seizure duration ($p = 0.927$). Most PWE manifested generalized tonic–clonic seizure (69% in GE and 58% in GEM, $p = 0.688$) and yearly seizure (46% in GE and 58% in GEM, $p = 0.771$). No status epilepticus was reported in the two groups.

Migraine without aura was the most common type in GEM, accounting for approximately 83% of all migraineurs. The duration of migraine was significantly shorter than that of seizure in GEM. Five PWE reported yearly migraine, and 7 PWE reported monthly migraine after epilepsy.

More details are presented in Table 1.

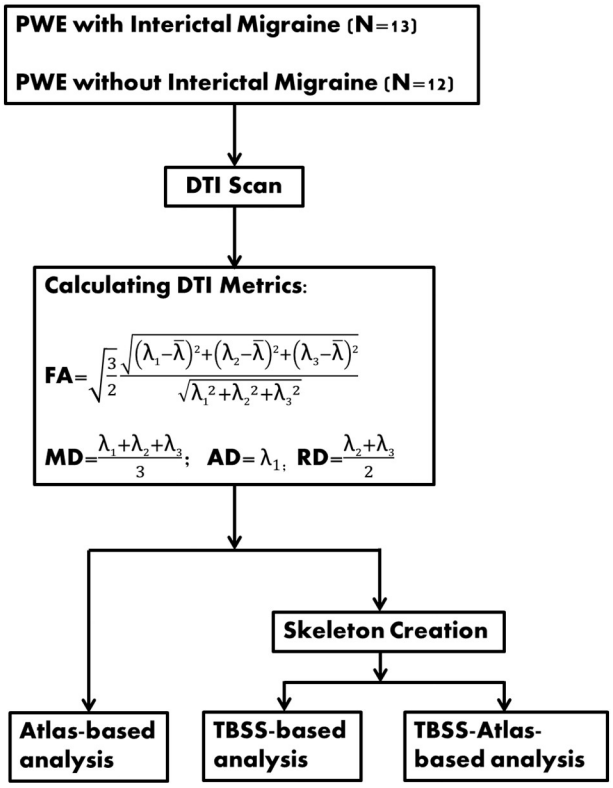

Fig. 1. Flow chart for this study. Definitions of formulae: λ_1 is the long eigenvalue pointing along the axon direction. λ_2 and λ_3 are the long eigenvalues pointing along the vertical axon direction. $\bar{\lambda}$ is the average of λ_1, λ_2, and λ_3.

3.2. DTI assessment

Group analysis showed statistically significant differences in DTI parametric images between PWE with and without interictal migraine. The TABSS-based FA values are presented in Fig. 2A. Patients with epilepsy with migraine showed higher FA value in almost all ROIs compared with PWE without migraine. Relative to GE, patients in GEM had significantly higher FA in the **fornix** ($p = 0.000926$). The TABSS-based MD values are presented in Fig. 2B. Significantly higher MD value in the middle cerebellar peduncle (middle CP) ($p = 0.009$), left superior cerebellar peduncle (superior CP.L) ($p = 0.009$), and right uncinate fasciculus (UC.R) ($p = 0.004$) were detected in GEM. The TABSS-based AD values are presented in Fig. 2C. A trend toward higher AD was noted in the **middle CP** ($p = 0.003$), and the **medial lemniscus** (**ML.R**) ($p = 0.004$). Regions where PWE with migraine had significant RD differences than those without migraine were not noted (Fig. 2D). More detail on WM alterations are presented in Supplementary file 1.

We repeated the diffusion analysis by atlas-based and TBSS analyses to examine robustness. We found that several areas, including **fornix**, **middle CP**, and **UC.R** (Table 2), still showed statistically significant