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Microstructural abnormalities in the trigeminal nerves of patients with trigeminal neuralgia revealed by multiple diffusion metrics

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ABSTRACT

Objective: To investigate microstructural tissue changes of trigeminal nerve (TGN) in patients with unilateral trigeminal neuralgia (TN) by multiple diffusion metrics, and correlate the diffusion indexes with the clinical variables.
Methods: 16 patients with TN and 6 healthy controls (HC) were recruited into our study. All participants were imaged with a 3.0 T system with three-dimension time-of-flight (TOF) magnetic resonance angiography and fluid attenuated inversion recovery (FLAIR) DTI-sequence. We placed regions of interest over the root entry zone of the TGN and measured fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). The mean values of FA, MD, AD and RD were compared between the affected and unaffected sides in the same patient, and to HC values. The correlation between the side-to-side diffusion metric difference and clinical variables (disease duration and visual analogy scale, VAS) was further explored.
Results: Compared with the unaffected side and HC, the affected side showed significantly decreased FA and increased RD; however, no significant changes of AD were found. A trend toward significantly increased MD was identified on the affected side comparing with the unaffected side. We also found the significant correlation between the FA reduction and VAS of pain ($r = -0.55$, $p = 0.03$).
Conclusion: DTI can quantitatively assess the microstructural abnormalities of the affected TGN in patients with TN. Our results suggest demyelination without significant axonal injury is the essential pathological basis of the affected TGN by multiple diffusion metrics. The correlation between FA reduction and VAS suggests FA as a potential objective MRI biomarker to correlate with clinical severity.

1. Introduction

Trigeminal neuralgia (TN) is characterized by recurrent episodes of sudden, severe, electric shock-like, stabbing pain localized to the sensory supply areas of trigeminal nerve (TGN). Currently, it is thought to be caused by neurovascular compression of the TGN at its root entry zone (REZ), and microvascular decompression (MVD) is considered the most effective treatment [1–3]. However, the exact pathogenesis of TN is unclear since neurovascular contact can also be present in the form of an anatomic variant in healthy subjects or on the unaffected side in patients with TN. Microstructural damages of the TGN, such as axonal loss and demyelination, are regarded as the possible underlying pathogenesis of TN [4,5].

Diffusion-tensor imaging (DTI) quantifies the amount of non-random water diffusion within tissues and provides unique in vivo information about the pathological processes that affect water diffusion as a result of microstructural damage [6,7]. Several recent studies [4,8–10] reported diffusion changes in TN. However in their studies the results were controversial, and only fractional anisotropy (FA) or mean diffusivity (MD) was analyzed. FA reflects the degree of directionality of cellular structures, while MD represents the diffusion in the noncolinear direction or free diffusion. They are believed to provide a general, nonspecific measure of tissue alteration. The directional diffusivity metrics axial diffusivity (AD) and radial diffusivity (RD) of white matter tracts have been

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hypothesized to more specifically differentiate axonal injury from demyelination in white matter tracts, respectively [11–13].

Thus, the aim of our study was to evaluate possible microstructural tissue changes of TGN in patients with unilateral TN by multiple diffusion metrics (FA, MD, AD and RD), and correlate the diffusion indexes with the clinical variables.

2. Materials and methods

2.1. Participants

We recruited 16 patients (7 males, 9 females, mean age ± SD: 50.0 ± 7.8 years) with a history of two to twelve years of TN. All patients were diagnosed with primary TN according to the International Classification of Headache Disorders criteria (second edition) [14] for classic primary TN and treated with MVD at Department of Functional Neurosurgery, Xuanwu Hospital, Capital Medical University. Visual analogue scale (VAS) of pain was assessed at the same day as the MR scan taken. Table 1 presents the main demographic and clinical characteristics of the study participants. To ensure the validity of the study, 6 healthy controls (HC) (3 females and 3 males), with ages ranging from 30 to 52 years, were also included in the study. HC had no history of significant facial pain. Written informed consent was obtained from each participant and this study was approved by the institutional review board of Xuanwu Hospital, Capital Medical University.

2.2. Data acquisition

All participants were imaged with a 3.0 T system (Trio Tim, Siemens, Erlangen, Germany). A standard head coil was used with foam padding to restrict head motion. The following protocol was applied. First, a three-dimension time-of-flight (TOF) magnetic resonance angiography was acquired to display the anatomic relationship between the vessels and trigeminal nerve and for the localization of the slice position of the DTI sequence. Second, a fluid attenuated inversion recovery (FLAIR) DTI-sequence was used to avoid obscuration from CSF signal; repetition time/echo time/inversion time 8700/106/2500, field of view 240 mm × 240 mm, matrix 128 × 128, $b = 0$ and 1000 s/mm^2 with diffusion gradients applied in twelve non-collinear directions, twenty 3-mm-slices without gap, acquisition time: 11:46 min. The localizing procedure allowed prescribing a 3 mm axial slice to cover both TGNs including the root entry zone at the pons and the proximal part of the cisternal course to avoid partial volume effects.

2.3. Data processing

The data of DTI were transferred to the workstation (Leonardo syngo 2003A, Siemens) and analyzed by two experienced neuroradiologists. A motion correction algorithm was applied to correct for patient motion and image distortions due to eddy current artifacts. The diffusion tensor was calculated for each voxel, and was diagonalized to yield eigenvectors and values from which the FA, MD, AD and RD values were calculated for each voxel.

Regions of interest (ROI) for quantitative assessment of FA, MD, AD and RD were positioned on the root entry zone of the TGN to avoid potential partial volume effects (Fig. 1). The difference between both sides is given as percentage in relation to the unaffected side. These DTI parameters were calculated independently by two observers, who were blinded to the side of the face with symptoms. The inter-observer coefficients of variation for the average MD, FA, AD and RD were less than 5%. For statistical analysis we utilized the mean values of the two observers.

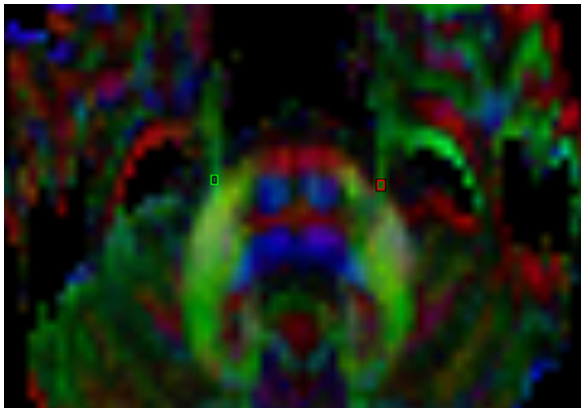

Fig. 1. Color FA image with example of box-shaped regions of interest used for quantitative analysis of FA in the TGN root entry zone.

2.4. Statistical analysis

The mean values of MD, FA, AD and RD were compared among the affected and unaffected sides in the same patient, and HC by using a one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. Therefore, $p < 0.005$ was considered to indicate a significant difference. Pearson correlation analysis was used to assess correlation between the side-to-side diffusion metric difference and clinical variables (disease duration and VAS). All statistical calculations were performed with SPSS12 software (SPSS, Inc., Chicago, IL).

3. Results

The left side was affected in 8 patients, and in the other 8 patients, the right side was involved. Neurovascular contact at the root entry or exit zone of the TGN on the affected side was observed in 12 patients (12/16, 75.0%). In more than half of the patients (9/16, 56.3%), contact with the superior cerebellar artery (SCA) was identified; other patients had nerve contact with other arteries including the posterior cerebellar artery (PICA), veterbral artery (VA), and anterior inferior cerebellar artery (AICA) (Table 1).

In all the patients and HC, the TGNs could be delineated on both sides. FA was significantly decreased on the affected side ((mean ± std): 0.32 ± 0.08; −28.2%) than on the contralateral unaffected side ((mean ± std): 0.45 ± 0.07) ($p = 4.4 \times 10^{-6}$), while RD was observed to be significantly increased on the affected side ((mean ± std): $(1.72 \pm 0.34) \times 10^{-3}$ mm^2/s; 36.3%) compared to the contralateral unaffected side ((mean ± std): $(1.34 \pm 0.33) \times 10^{-3}$ mm^2/s) ($p = 0.002$). We observed a trend toward increased MD on the affected side ((mean ± std): $(2.11 \pm 0.40) \times 10^{-3}$ mm^2/s; 21.4%) compared to the contralateral unaffected side ((mean ± std): $(1.83 \pm 0.39) \times 10^{-3}$ mm^2/s) ($p = 0.05$). There were no significant differences in AD between the affected side ((mean ± std): $(2.90 \pm 0.57) \times 10^{-3}$ mm^2/s; 7.6%) and the unaffected side ((mean ± std): $(2.82 \pm 0.54) \times 10^{-3}$ mm^2/s) ($p = 0.72$) (Table 2).

Compared with the mean diffusion metrics of both sides of the healthy controls, the affected side showed significantly decreased FA, increased MD and RD ($p < 0.005$), without significant difference in AD ($p = 0.34$). No significant differences in all the diffusion indexes were found between the unaffected side and the mean value of both sides of HC ($p > 0.01$) (Table 2).

We examined the relationships between the VAS, disease duration and DTI metrics differences. The only significant correlation which we found was between the FA reduction and VAS ($r = -0.55$, $p = 0.03$). The other correlations were all less than ±0.28 ($p > 0.09$).