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Original Article

Magnetic resonance imaging study of morphological and microstructural changes in the trigeminal nerve in trigeminal neuralgia due to neurovascular compression

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Abstract: This study aimed to observe the morphological and microstructural changes in the trigeminal nerves in patients with trigeminal neuralgia (TN) resulting from neurovascular compression (NVC), using magnetic resonance imaging (MRI). Twenty-five healthy volunteers and 50 TN patients with unilateral NVC were divided into three groups: healthy controls (HC), symptomatic side (NVC with TN), and asymptomatic side (NVC without TN). MRI data, including three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA), three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA), and diffusion tensor imaging (DTI) were collected from them. The correlation between morphological and quantitative parameters was analyzed by measuring the trigeminal nerve cross-sectional area (CSA) in 3D-TOF-MRA images, fractional anisotropy (FA), and apparent diffusion coefficient (ADC) in the root entry or exit zone (REZ) of the bilateral trigeminal nerve in DTI images. The mean CSA and FA were significantly lower in symptomatic side group than that in the HC and asymptomatic side groups. Linear correlation analysis showed moderate correlation among CSA, ADC, and FA (r=-0.59, p=0.000 and r=0.58, p=0.000) and good consistency between CSA, reflecting trigeminal nerve atrophy caused by NVC morphologically, and DTI, displaying nervous demyelination quantitatively. The symptomatic side group had significantly lower CSA and FA, and higher ADC than the HC and asymptomatic side groups. The CSA, FA, and ADC had certain relevance; however, there were no marked differences between FA values in grades I and II, and ADC values in different classifications of NVC.

Keywords: Magnetic resonance imaging, diffusion, trigeminal nerve, microvascular compression

Introduction

The most prevalent theory of trigeminal neuralgia (TN) etiology is neurovascular compression (NVC); the trigeminal nerve is compressed by NVC and trigeminal nerve morphological atrophy and nerve fiber demyelination occurs [1-3]. Many methods, such as three-dimensional time-of-flight magnetic resonance angiography sequence (3D-TOF-MRA) and three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA), have been used to study the morphology of NVC induced by nerve atrophy clinically [4-7].

Recently, some quantitative studies using diffusion tensor imaging (DTI) have found that the symptomatic side of the trigeminal brainstem segment in patients of TN (REZ) had decreased fractional anisotropy (FA) values [8-12], but the correlation between changes in trigeminal nerve fiber morphology and local demyelination has rarely been studied in TN patients with different degrees of NVC. Hence, the aim of this study was to investigate the changes in and correlation between morphological atrophy and nerve fiber demyelination in different degrees of NVC in TN patients using 3D-TOF-MRA, 3D-FIESTA, and DTI.

Materials and methods

Subjects

Twenty-five healthy volunteers (13 men and 12 women; mean age, 55 years) and 50 patients with unilateral TN (29 men and 21 women; mean age, 54 years) were admitted to the Zhejiang Central Hospital of Huzhou and examined using magnetic resonance imaging (MRI)

from January 2013 to December 2015. The inclusive criteria of TN patients were as follows: patients with typical clinical TN in accordance with the diagnostic criteria of World Health Organization (WHO) and patients not undergoing any therapy, such as microvascular decompression or radiofrequency ablation. The exclusion criteria were as follows: presence of non-classic TN; trigeminal neuropathy; presence of chronic pain, such as toothache and sinusitis; temporomandibular joint disorder syndrome caused by misdiagnosis of patients at the early stage of TN; and high-field MRI contraindications. In all 50 patients, there were different clinical manifestations, such as the involvement of the first (V1) trigeminal nerve in 2 cases, the second trigeminal nerve (V2) in 8 cases, the third trigeminal nerve (V3) in 6 cases, both V1 and V2 in 4 cases, both V1 and V3 in 9 cases, both V2 and V3 in 12 cases, and V1, V2, and V3 in 9 cases. All volunteers and patients provided informed consent before the examination. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with the approval from the Ethics Committee of Huzhou Center Hospital. Written informed consent was obtained from all participants.

Imaging protocol

All imaging was performed using a 3.0-T superconducting magnetic resonance instrument Discovery MR 750 (GE Healthcare, Waukesha, American) with an 8-channel head coil. The parameters of each technique used were as follows: (1) axial 3D-TOF-MRA (TR/TE, 4.1/1.0 ms; FOV, 20 cm×20 cm; matrix, 320×256; NEX, 2; section thickness, 1 mm; section interval, 0 mm; flip angle, 15°); (2) axial 3D-FIESTA (TR/TE, 6.3/1.5 ms; FOV, 20 cm×20 cm; matrix, 256×192; NEX, 2; section thickness, 1 mm; section interval, 0 mm; flip angle, 60°); and (3) axial DTI using single-shot spin-echo echo planar sequence (SS-SE-EPI), (diffusion-sensitive gradient directions, 20; b value for 0 and 800 s/mm^2; TR/TE, 6000/80 ms; FOV, 20 cm×20 cm; matrix, 128×128; section thickness, 1 mm; section interval, 0 mm; FAT pressure fat; scan time, about 4 min). The scanning was performed from the base area of the skull for the trigeminal nerve, with accurate and symmetrical positioning and without any movement; it was ensured that the canthomeatal line was perpendicular to the ground as far as possible.

Grade standard of NVC in morphology

According to the grading standard of NVC morphologically [13], NVC was classified into three stages according to the degree of NVC: the first stage involved slight contact between blood vessels and nerves, the second stage involved vascular compression not exceeding 20% of the nerve circumference, and the third stage involved vascular compression exceeding 20% of the perimeter of the nerve.

Image analysis and data measurement

All 3D-TOF-MRA, 3D-FIESTA, and DTI data were stored in the GE AW4.6 image processing workstation, and morphology and the relationship between the bilateral trigeminal nerve and its peripheral vascular space was displayed. Further, the workstation was used to assess the degree of vascular and nerve compression using the Functool (GE Healthcare) software package on the background of 3D-TOF-MRA or 3D-FIESTA by means of DTI.

In the cross-section of 3D-TOF-MRA, vascular nerve compression 3D-FIESTA image measurement of the bilateral trigeminal nerve area (CSA), a region of interest (ROI) measurement was performed at the trigeminal nerve compression level to avoid partial volume effects in the data. For the DTI measurement of FA and ADC values, the ROI was most commonly in the brainstem segment of the trigeminal nerve, and manual delineation around the ROI area was about 10 mm^2; the FA value of the threshold was set from 0.2 to 0.6, in order to avoid the interference by the cerebrospinal fluid, brain tissue around the fiber bundle, and bones. In accordance with the principles of a blind study, two trained and experienced doctors in the radiology department manually sketched the ROI and obtained the average of the results of the measurement, in order to reduce the manual delineation of the area of interest caused by leakage and noise errors.

Statistical analysis

All data were processed by the medical statistical software MedCalcV12.7.0 and displayed as mean ± standard deviation (SD) for CSA, FA, and ADC values. First, a normality test was performed for statistical results. If the results followed a normal distribution, a *t*-test was performed on the average of a group of healthy

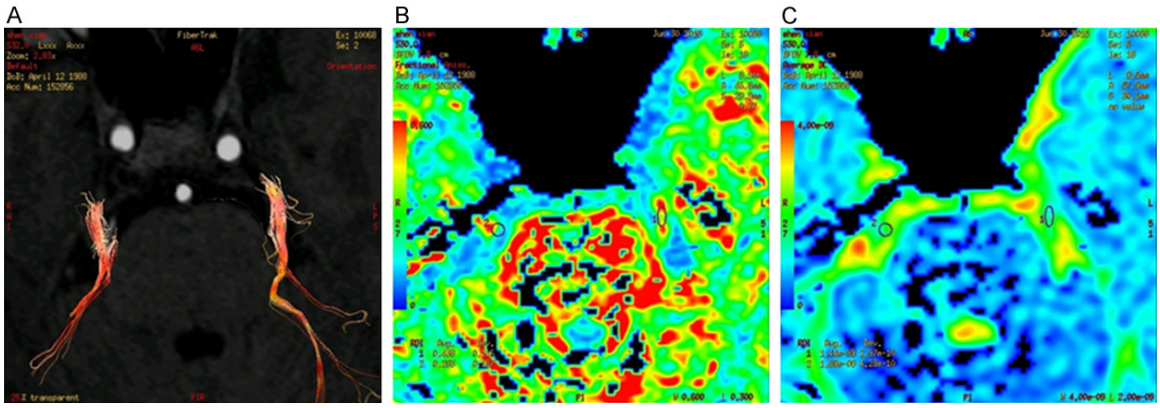

Figure 1. Trigeminal neuralgia symptoms in adults, male, aged, right superior cerebellar artery compression of trigeminal REZ segment. (A) Fusion 3D-TOF-MRA background image of the DTT reconstruction images, showing the right superior cerebellar artery compression of the right side of the trigeminal nerve, the fiber bundle is not smooth, there is pressure on. (B and C) are respectively DTI grayscale image and fractional anisotropy (FA) images, display the measured location of the bilateral trigeminal nerve by ROI.

Table 1. CSA values, FA values and ADC values of healthy volunteers and TN patients in symptomatic and asymptomatic groups

Parameters	HC	NVC with TN	NVC without TN	HC vs. NVC with TN	HC vs. NVC without TN	NVC with TN vs. NVC without TN
CSA (mm^2)	5.15±0.07	3.99±0.44	5.02±0.32	P=0.000 (t=8.82)	P=0.079 (t=1.78)	P=0.000 (t=9.96)
FA	0.45±0.06	0.36±0.04	0.44±0.05	P=0.000 (t=7.99)	P=0.589 (t=0.54)	P=0.000 (t=9.18)
ADC ($\times 10^{-3}$ mm^2/s)	1.55±0.07	1.77±0.12	1.54±0.07	P=0.000 (t=8.49)	P=0.859 (t=0.18)	P=0.000 (t=11.27)

Note: CSA: cross-sectional area; FA: anisotropy; ADC: apparent diffusion coefficient; HC: healthy volunteers; NVC: neurovascular compression; TN: trigeminal neuralgia.

volunteers and normal side, the symptomatic side, and asymptomatic side of TN patients. The average value of different NVC grades in TN patients were compared using the Student-Newman-Keuls (SNK) method. If the statistical results did not conform to the normal distribution, non-parametric tests and Pearson linear regression analysis were conducted and the correlation between the FA, ADC, and CSA values were calculated. The difference was considered statistically significant if p-value was <0.05.

Result

Microvascular decompression

Among all TN patients with NVC (left, 28 cases; right, 22 cases), the classification of blood vessels in different NVC were as follows: grade I for 10 cases (6 cases with anterior superior cerebellar artery, 3 cases with anterior inferior cerebellar artery, 1 case with posterior cerebellar artery); grade II for 15 cases (12 cases with anterior superior cerebellar artery, 2 cases with the anterior inferior cerebellar artery, 1 case with posterior cerebellar artery); grade III for 25 cases (19 cases with anterior superior cerebellar artery, 4 cases with anterior inferior cerebellar artery, 1 case with posterior cerebellar artery, and 1 case with vertebral artery).

CSA, FA, and ADC value

No obvious NVC signs were observed on the raw data images of 3D-TOF-MRA, 3D-FIESTA, and the reconstructed images of scans from all healthy volunteers. Unilateral NVC was observed in all TN patients (**Figure 1**). **Table 1** shows the CSA, FA, and ADC values of healthy volunteers, symptomatic side of TN patients, and asymptomatic side TN patients. The symptomatic side of TN patients group presented with lower average CSA and FA values and higher average ADC values than the asymptomatic side of TN patients group and healthy volunteers, with marked statistical difference between the groups. There was no statistical dif-

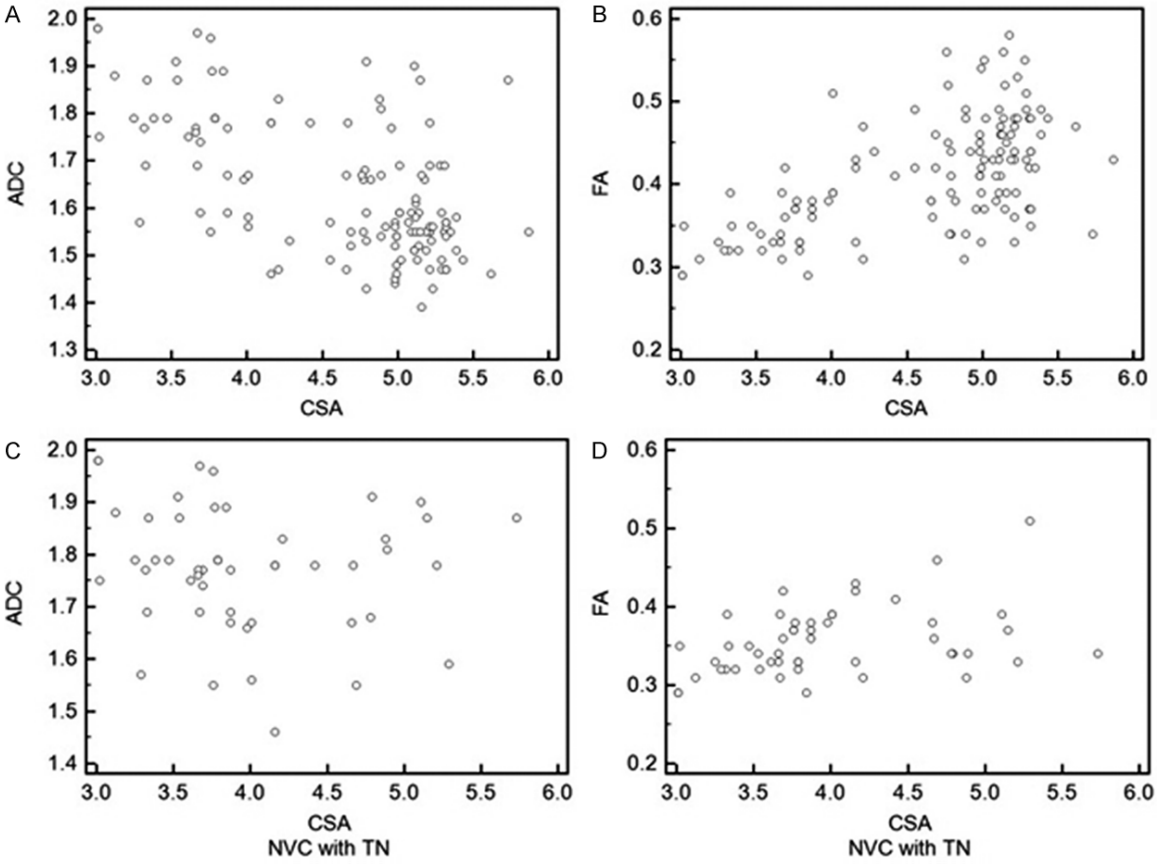

Figure 2. A. Correlation analysis between CSA and ADC value of volunteers and patients with TN; B. Correlation analysisbetween CSA and FA values in volunteers and patients with TN; C. Correlation Analysis of CSA value and ADC value in symptomatic patients with TN; D: Correlation between CSA and FA value in symptomatic TN patients.

ference between average CSA, FA, and ADC values between the asymptomatic side of TN patients group and healthy volunteers. Linear regression analysis showed that CSA negatively correlates with ADC (r=-0.59, p=0.000) (**Figure 2A**), while CSA positively correlates with FA (r=0.58, p=0.000) (**Figure 2B**).

CSA, FA, and ADC values of different morphological NVC grades

Table 2 shows the CSA, FA and ADC values for the symptomatic side in TN patients with different morphological NVC grades. The value of CSA and FA decreased whereas the CSA values increased with the NVC grade; mostly, the CSA and FA values are significantly different among groups I, II, and III, but there is no significant difference in FA values between groups I and II. The ADC value increases with the increase in NVC grade, but there is no significant difference between the groups I, II and III. Linear regression analysis shows a weak negative correlation between CSA and ADC (r=-0.119, p=0.410) (**Figure 2C**), and CSA values were positively correlated with FA values (r=0.373, p=0.008) (**Figure 2D**).

Discussion

NVC for long durations can lead to degeneration and atrophy of the trigeminal nerve [6, 7, 14]. DTI can be used to assess the pathophysiology of nerve demyelination by assessing quantitative parameters, such as FA values [12]. Previous studies have shown that in TN patients the ipsilateral trigeminal nerve area REZ has FA values lower than that of the contralateral side, and this difference is significant [7, 15], while the pressure point CSA in TN patients decreases significantly [6]. However, a study on the correlation among FA, ADC, and CSA values of TN patients with NVC has not yet been reported. Therefore, this study focuses on eval-

Table 2. The average CSA value, FA value and ADC value of the different morphological NVC classification in patients with symptomatic TN

Parameters	Grade I	Grade II	Grade III	Grade I vs. II	Grade I vs. III	Grade II vs. III
CSA (mm^2)	4.79±0.55	4.14±0.53	3.56±0.37	P=0.009 (t=2.85)	P=0.000 (t=7.69)	P=0.000 (t=4.21)
FA	0.38±0.04	0.37±0.05	0.34±0.03	P=0.507 (t=0.67)	P=0.003 (t=3.23)	P=0.035 (t=2.19)
ADC ($\times 10^{-3}$ mm^2/s)	1.75±0.16	1.76±0.10	1.79±0.11	P=0.824 (t=0.23)	P=0.406 (t=0.84)	P=0.413 (t=0.83)

Note: CSA: cross-sectional area; FA: anisotropy; ADC: apparent diffusion coefficient; NVC: neurovascular compression; Grade classification.

uating the changes and correlations of trigeminal nerve atrophy and nerve fiber demyelination, and tries to further investigate whether there is consistency between different grades of NVC and morphological atrophy and nerve fiber demyelination.

The results of this study have further confirmed that the compression point of the symptomatic side in TN patients presents with significantly lower CSA and FA values and increased ADC values than those in healthy volunteers and on the asymptomatic side in TN patients ($p<0.05$), which means that the symptomatic side of TN patients has undergone morphological and microstructural changes in the nerve after nerve fiber demyelination. Liu et al [16] have verified that the symptomatic side of TN patients has higher radial diffusivity (RD) than the asymptomatic side and healthy volunteers, by plurality of diffusion index of DTI, such as FA value, axial dispersion coefficient (AD), and vertical diffusion coefficient (RD), indicating the presence of NVC without statistical differences in AD values, which explains why they did not undergo demyelination and axonal damage. In this study, Pearson linear regression analysis showed the morphological parameters of CSA in healthy volunteers and patients with TN, and ADC and FA values have moderate correlation (r=-0.59, p=0.000; r=0.58, p=0.000), suggesting that there is a good correlation between morphological parameters and microstructural parameters of nerve bundles.

According to the morphological classification of NVC, our results show that morphological parameters of CSA values gradually decreased with decreases in grade and with statistically significant differences between any two groups. The FA value gradually decreased with decreases in grade without, with statistical differences between all group except groups I and II. There was also little difference in ADC values, which means that trigeminal nerve demyelination with signs of NVC signs is so mild that it cannot cause TN.

Lin et al [2] have conducted an NVC analysis for trigeminal nerve compression symptoms in healthy volunteers and measured FA, AD, and RD values in these patients. They found no significant differences, which means that signs of trigeminal nerve NVC are not the only factor causing TN [17]. This may be due to nerve fiber degeneration being a chronic demyelinating process rather than a result of acute nerve fiber damage [10, 18, 19]; only long-term compression will cause demyelination of the trigeminal nerve and result in a decreased FA value. During the analysis of TN patients, our study shows a decreased correlation among CSA, ADC, and FA values, which may be because morphological changes of grade I and II NVC are difficult to distinguish with respect to trigeminal nerve demyelination [20, 21].

There are some limitations in this study, such as low sample-size for different NVC classifications, which may bias the statistical results, and subjectivity of DTI scanning methods, parameters, ROI values, and analysis methods.

Disclosure of conflict of interest

None.

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