



Diffusion tensor imaging of microstructural alterations in the trigeminal nerve due to neurovascular contact/compression

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Abstract

Background Several recent studies have focused on microstructural changes in the trigeminal nerve in trigeminal neuralgia using diffusion tensor imaging (DTI). However, alterations after microvascular decompression (MVD) have rarely been investigated. Furthermore, the trigeminal nerve of asymptomatic individuals also presenting with neurovascular contact/compression (NVC) has not yet been studied.

Methods Thirty-four patients suffering from trigeminal neuralgia and 34 healthy age-matched controls, who were identified as having unilateral NVC signs, underwent both DTI and high-resolution magnetic resonance imaging (MRI) for comparison. All trigeminal neuralgia patients underwent a post-surgical MRI scan after 7 days and a follow-up MRI scan within 6–8 months after surgery. The apparent diffusion coefficients (ADCs) and fractional anisotropy (FA) values were measured from coronal images in which the nerves from the root exit point to the distal segment were clearly shown.

Results In 34 trigeminal neuralgia patients, the absolute FA value was significantly lower on the affected side (mean FA, 0.34 ± 0.03) than on the unaffected side (mean FA, 0.37 ± 0.05 , $p < 0.001$). The FA ratio was also significantly different between the trigeminal neuralgia group (R_{SFA} , 0.92 ± 0.06) and the control group (R_{SFA} , 0.99 ± 0.09) ($p = 0.001$). The absolute ADC value between the two sides in patients and the ratios of ADC between the trigeminal neuralgia and control groups did not show any significant differences ($p = 0.21$ and 0.29 , respectively). However, in 34 healthy subjects presenting with signs of NVC, neither the FA value nor the ADC showed a difference between sides ($p > 0.05$). The FA ratio of patients showed a significant increase on two follow-up MRI scans compared to the preoperative FA ($p = 0.02$ and 0.002 , respectively), while the ADC ratio showed a significant decrease at 6 months after MVD ($p = 0.004$).

Conclusion This study of trigeminal neuralgia due to NVC found that DTI indexes could reflect alterations in the affected trigeminal nerve. Furthermore, a reversible change after MVD surgery could be potentially valuable for monitoring the change in white matter of the trigeminal nerve.

Keywords MRI · Diffusion tensor imaging · Trigeminal neuralgia · Neurovascular contact/compression · Microvascular decompression

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Abbreviations

| | |
|------|-------------------------------------|
| ADC | apparent diffusion coefficient |
| AICA | anterior inferior cerebellar artery |
| DTI | diffusion tensor imaging |
| FA | fractional anisotropy |
| MRI | magnetic resonance imaging |
| MVD | microvascular decompression |
| NVC | nerve vascular compression/contact |
| SCA | superior cerebellar artery |

Introduction

Trigeminal neuralgia is a unique form of neuropathic pain characterized by brief, severe, paroxysmal, stabbing pain. Trigeminal neuralgia is typically unilateral and occurs in the distribution of one or more branches of the trigeminal nerve [1]. The most widely proposed pathophysiology is mechanical irritation of the trigeminal nerve resulting from neurovascular compression/contact (NVC) at or near the root entry/exit zone [2]. Since compression causes focal axonal degeneration and demyelination of the nerve, microvascular decompression (MVD) is the gold-standard treatment for the majority of trigeminal neuralgia patients [3, 4].

To date, the decision to perform MVD for trigeminal neuralgia has been based on high-spatial-resolution magnetic resonance imaging (MRI) and MRI angiography, which can be used to detect anatomical compression and exclude other causes of trigeminal neuralgia before surgery [5, 6]. Recently, microstructural changes in the trigeminal nerve of trigeminal neuralgia have been investigated by using diffusion tensor imaging (DTI) [7], which is sensitive to the diffusion of water molecules. However, only a few studies have investigated the structural change in the nerves after MVD by DTI. More importantly, studies have revealed that NVC signs are present not only on the affected nerves but also in asymptomatic individuals [1]. Therefore, conventional MRI is challenged by NVC signs not being a specific finding, and there is value in investigating whether DTI can differentiate pathological from occasional NVC.

Thus, the purpose of this study was to assess microstructural changes using DTI to identify pathological features resulting from NVC primarily in trigeminal neuralgia patients and to detect the microstructural changes in the nerves after the relief of pain by MVD.

Methods

Patient enrolment

This study was approved by the institutional review board, and a retrospective review was performed between January

2011 and February 2012. Trigeminal neuralgia patients and a population with hemifacial spasm as controls were enrolled in this study. The inclusion criteria for trigeminal neuralgia patients were as follows: (1) diagnosis of classical trigeminal neuralgia, (2) unilateral NVC identified in the trigeminal nerve and tumor-induced trigeminal neuralgia excluded by conventional MRI, and (3) MRI with DTI sequence performed one time before surgery and twice after MVD treatment. The inclusion criteria for the controls were as follows: (1) no facial pain syndrome, (2) unilateral NVC signs identified in the trigeminal nerve by conventional MRI, and (3) MRI with DTI sequence performed.

Finally, 34 consecutive trigeminal neuralgia patients (16 men and 18 women; age range, 52–81 years; mean age \pm SD, 61.47 \pm 8.42 years) who had been suffering from pain for 3 months to 10 years were enrolled along with 34 age-matched controls (14 men and 20 women; age range, 53–73 years; mean age \pm SD, 60.76 \pm 4.31 years). All participants were identified as having unilateral NVC by conventional MRI. All 34 patients underwent MVD and were verified to have NVC during surgery. Additionally, all patients underwent a postoperative MRI scan after 7 days and a follow-up MRI scan within 6–8 months after MVD.

Imaging protocol

Imaging was performed using a 3.0-T MRI system (Signa HDx 3T; GE Healthcare, Milwaukee, WI, USA) equipped with an eight-channel head coil. The following high-spatial-resolution sequences were performed: (a) a spin-echo single-shot echo-planar DTI sequence with a coronal view (echo time/repetition time, 4000/min ms; matrix, 160 \times 160; field of coronal view, 240 \times 240 mm; section thickness, 3 mm; direction, 25; *b* value, 1000 s/mm²), (b) MR tomographic angiography with an axial view (echo time/repetition time, 18/5 ms; flip angle, 15°; matrix, 320 \times 320; field of coronal view, 18 mm; section thickness, 1 mm), and (c) 3D fast imaging employing a steady-state sequence with an axial view (echo time/repetition time, 4.9/1.8 ms; flip angle, 60°; matrix, 320 \times 320; field of coronal view, 18 mm; section thickness, 1 mm).

Image processing and analysis

DTI data were processed using FuncTool software (GE Medical Systems, Milwaukee, WI, USA). After a motion-correction algorithm was applied to correct for head motion and image distortion due to eddy current artifacts, the fractional anisotropy (FA) value and apparent diffusion coefficient (ADC) for each voxel and color-coded map were automatically calculated and displayed. A region of interest of approximately 0.89 mm² (range, 0.76–0.94 mm²) was positioned on the coronal FA maps of four continuous slices in which the trigeminal nerve from the root exit point to the distal cisternal

segment was clearly shown. All regions of interest were marked by two neuroradiologists, and the abovementioned measurements were performed three times. The FA values and ADCs were successfully obtained for the trigeminal nerve bilaterally in all subjects (Fig. 1).

The average FA value and ADCs of four continuous slices were calculated as absolute values, and the standardization of FA values and ADCs was defined by ratios (Rs) as relative values, which were calculated according to the following formulas proposed by Fujiwara et al.: $RS_{FA} = FA_{\text{affected side}} / FA_{\text{unaffected side}}$; $RS_{ADC} = ADC_{\text{affected side}} / ADC_{\text{unaffected side}}$ [8].

The results of MR tomographic angiographic and fast imaging employing steady-state sequence data were reconstructed with multi-planar reconstruction parallel and perpendicular to the trigeminal nerve to obtain sagittal and coronal images, respectively. NVC was defined according to the criteria [4], including simple contact and compression with nerve dislocation. Another criterion was the contact between the vessel and the brainstem close to the nerve origin in the pons without direct contact with the nerve itself. Additionally, the distance between the site of vascular contact/compression and the origin of the nerve in the brainstem was measured.

Statistical analysis

Using a paired-sample two-tailed *t* test, the mean FA values and ADCs were compared between the affected and unaffected sides in both the trigeminal neuralgia patients and healthy controls, while the pre- and postoperative FA and ADC ratios were compared in the trigeminal neuralgia patients. Additionally, the FA and ADC ratios were compared between the patients and the healthy controls using an independent *t* test. Correlations of the FA and ADC ratios with the illness

duration and the distance from the site of vascular contact/compression to the origin of the nerve in the brainstem were examined using Spearman's rank-correlation coefficient; $p < 0.05$ was considered to indicate a significant difference. All statistical analyses were performed using SPSS software (SPSS for Windows, version 16.0; SPSS, Inc.).

Results

Patient characteristics and surgical findings

Table 1 shows the clinical characteristics of the trigeminal neuralgia patients and asymptomatic controls. The MRI diagnosis of the responsible vessels in 32 patients matched the surgical findings, while the MRI diagnosis partially matched the NVC findings in only two cases. Of these two cases, MRI identified the superior cerebellar artery (SCA) as the responsible vessel, while MVD revealed that the vessels compressing the nerve were the SCA and anterior inferior cerebellar artery (AICA). The sensitivity of preoperative MRI was 94.12%. After surgery, 31 of 34 patients became pain-free at early time points without medication. Two patients became pain-free with reduced medication, and only one patient did not achieve any pain relief after MVD.

Pre-surgical DTI findings

In 34 patients, the absolute FA value was significantly lower on the affected side (mean FA \pm SD, 0.34 ± 0.03) than on the contralateral unaffected side (mean FA \pm SD, 0.37 ± 0.05) ($p < 0.001$). Although the absolute ADCs were greater on the affected side (mean ADC \pm SD, $2.12 \times 10^{-9} \pm 0.21 \text{ mm}^2/$

Fig. 1 FA values and ADCs of the bilateral trigeminal nerve obtained from coronal DTI images. Axial **a** FA map, **b** ADC map, **c** $b = 0$ DTI map, and **d** fiber tracking map. Images **a–c** are focused on zone(s) of interest

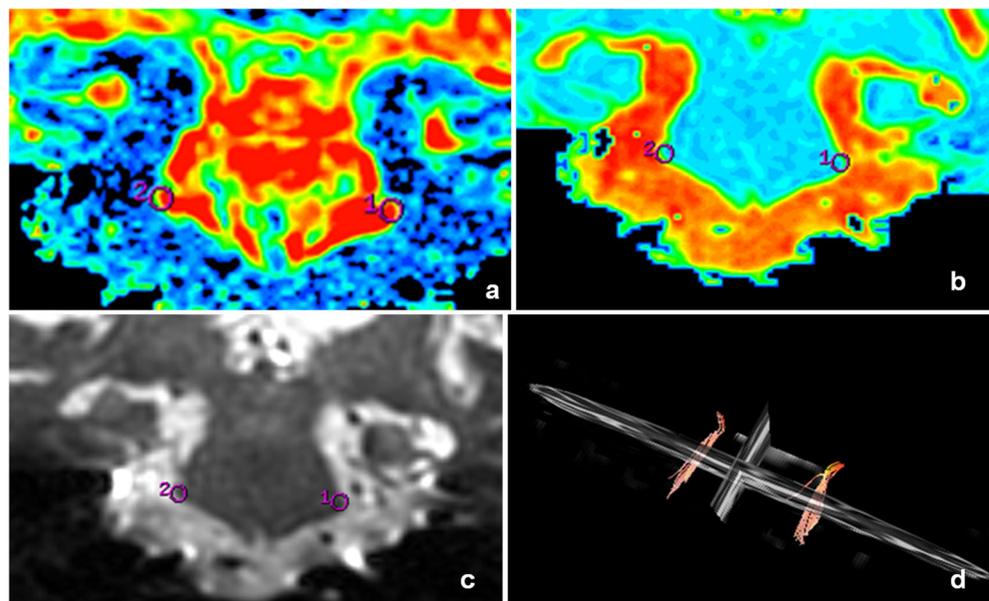


Table 1 Clinical characteristics of the trigeminal neuralgia patients

| Factor | | Value |
|------------------|----------|--------------------|
| Age | | 61.47 ± 8.42 years |
| Sex | Male | 16 (47.06%) |
| | Female | 18 (52.94%) |
| Disease duration | | 3.85 ± 2.80 years |
| Affected side | Right | 18 (52.94%) |
| | Left | 16 (47.06%) |
| Affected vessel | SCA | 20 (58.82%) |
| | AICA | 6 (17.65%) |
| | VA | 1 (2.94%) |
| | SCA+AICA | 7 (20.59%) |
| Nerve branch | V2 | 6 (17.65%) |
| | V3 | 4 (11.76%) |
| | V1+2 | 8 (23.53%) |
| | V2+3 | 16 (47.06%) |
| Distance | | 1.73 ± 1.21 mm |

SCA, superior cerebellar artery; AICA, anterior inferior cerebellar artery; VA, vertebral artery; Distance, distance between the compression site and the pons measured on MRI. Numerical data are presented as mean ± SD

s) than on the unaffected side (mean ADC ± SD, $2.00 \times 10^{-9} \pm 0.29 \text{ mm}^2/\text{s}$), the difference was not significant ($p = 0.21$). However, in the normal controls, neither the FA value nor the ADCs differed between the two sides.

Compared to the normal controls ($R_{\text{FA}} \pm \text{SD}$, 0.99 ± 0.09), the trigeminal neuralgia patients showed a significantly decreased FA ratio ($R_{\text{FA}} \pm \text{SD}$, 0.92 ± 0.06 , $t = 3.44$, $p = 0.001$). The ADC ratio was not different between the two groups ($t = 1.07$, $p = 0.29$) (Fig. 2).

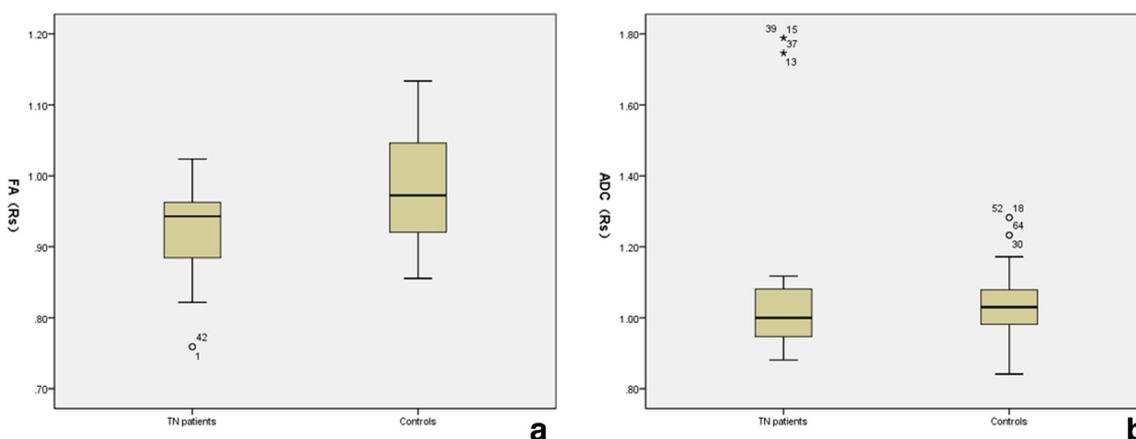


Fig. 2 Boxplots illustrating a comparison of the DTI indexes for the trigeminal nerve between control subjects and patients with trigeminal neuralgia due to NVC. **a** The FA ratios (R_{SFA}). **b** The ADC ratios (R_{SADC}). The variance of FA ratios was significantly lower in trigeminal neuralgia patients than in normal controls ($t = 3.44$, $p = 0.001$). No significant difference was observed in ADC ratios between the two

There was no significant correlation between the FA ratio and the disease duration ($r = 0.43$, $p = 0.10$) or the distance from the compression point to the pons ($r = -0.01$, $p = 0.97$).

Post-surgical DTI findings

All 34 trigeminal neuralgia patients underwent two MRI scans after MVD, one at 7 days and another at 6–8 months after the surgery. Compared to the preoperative FA ratio ($R_{\text{SFA}} \pm \text{SD}$, 0.92 ± 0.06), the FA ratios at 7 days ($R_{\text{SFA}} \pm \text{SD}$, 0.97 ± 0.10 , $t = 2.44$, $p = 0.02$) and 6–8 months after surgery ($R_{\text{SFA}} \pm \text{SD}$, 1.00 ± 0.09 , $t = 3.44$, $p = 0.002$) were both significantly increased. Compared to the preoperative ADC ratio ($R_{\text{SADC}} \pm \text{SD}$, 1.09 ± 0.26), the ADC ratio at 7 days after the surgery was not significantly different ($R_{\text{SADC}} \pm \text{SD}$, 1.02 ± 0.27 , $t = 1.84$, $p = 0.068$); however, the ADC ratio at 6–8 months after surgery was significantly decreased ($R_{\text{SADC}} \pm \text{SD}$, 0.98 ± 0.03 , $t = 3.12$, $p = 0.004$) (Figs. 3 and 4). In one patient who showed no pain relief after MVD, both the FA and ADC ratios were similar preoperatively and at both postoperative follow-ups (R_{SFA} , 0.98, 0.95, and 0.98; R_{SADC} , 0.95, 0.98, and 0.96, respectively).

Discussion

In our study, lower FA values were observed on the affected side than on the unaffected side of trigeminal neuralgia patients. Furthermore, even though NVC signs were identified in both groups by anatomical MRI, decreased FA values were also found in trigeminal neuralgia patients compared to those in asymptomatic individuals. In patients who underwent effective MVD, the FA value showed a significant increase at

groups ($t = 1.07$, $p = 0.29$). Values more than 1.5 interquartile ranges (IQRs) but less than 3 IQRs from the end of the box are labeled as outliers (O), and values more than three IQRs from the end of a box are labeled as extreme (*). The thick line in the box < median. The upper and lower borders of the box indicate the 75th and 25th percentiles, respectively. The whiskers indicate the maximum and minimum

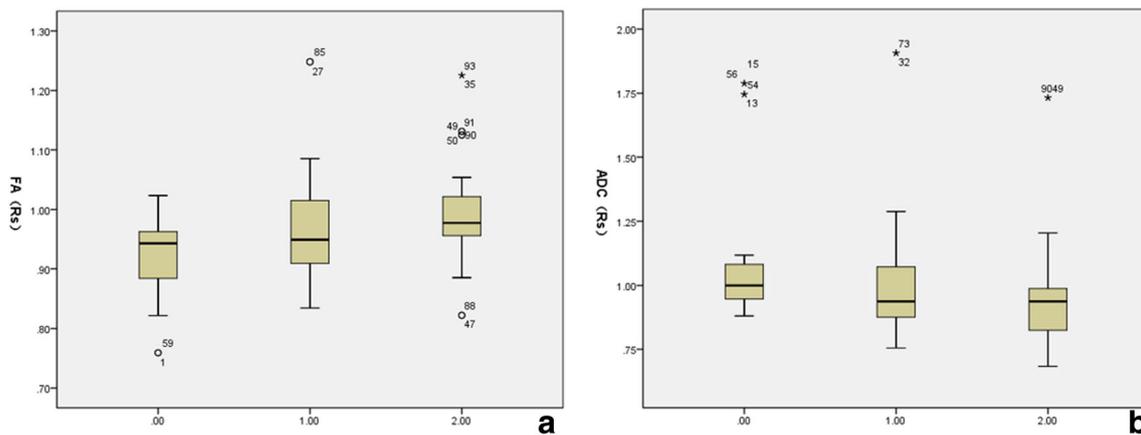


Fig. 3 Boxplots of the DTI indexes before and after surgery. **a** The FA ratios (Rs). **b** The ADC ratios (Rs). Compared to the preoperative FA ratio, the FA ratios at 7 days and 6–8 months postoperatively were

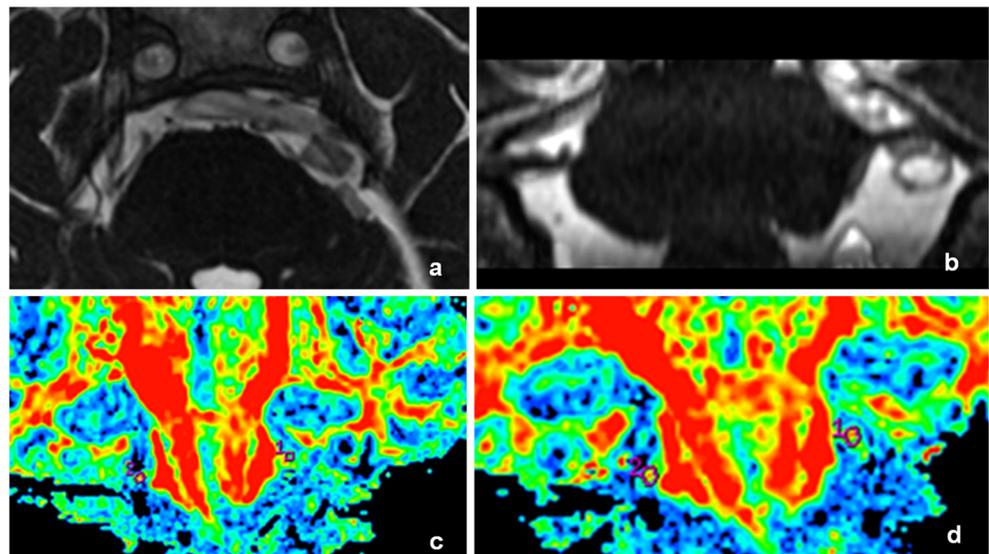
significantly different ($p = 0.02$ and 0.002), but only the ADC ratio at 6–8 months postoperatively showed a significant difference ($p = 0.004$). 0, pre-operation; 1, 7 days after MVD; 2, 6–8 months after MVD

the early postoperative time point, while the ADC showed a notable decrease at 6–8 months postoperatively, which might reflect the microstructural recovery of the trigeminal nerve.

The preoperative values of DTI-derived parameters in trigeminal neuralgia patients have been previously studied, and the findings of such studies have demonstrated that DTI can identify microstructural changes resulting from the loss of myelin and axonal membranes in the trigeminal nerve [9, 10]. In line with previous studies, decreased alterations in the FA values were present in the affected nerve of patients with NVC-induced trigeminal neuralgia, and these alterations corresponded to the underlying pathologic changes of demyelination. This finding is also consistent with a previous finding showing that nerve atrophy is associated with decreased FA values, as demonstrated by Leal et al. [11], indicating that cellular changes may also result from degradation of the nerve structure in trigeminal neuralgia. Although the ADCs on the

affected side were slightly higher than those on the unaffected side, the difference was not significant in our study. This result was not in line with other studies except for Fujiwara [8]. One major possible explanation could be that the loss of myelin and axonal membranes in the trigeminal nerve quantified by the reduced directionality of diffusion (i.e., FA) may be more sensitive than diffusivity being averaged in all spatial directions (i.e., ADC) [12]. This still warrants sufficient evidences and further investigations. Another possible reason includes the usage of a 2D diffusion model and the relatively small sample size in this study. Recent studies further investigated 3D information on the diffusivity of water molecules and demonstrated that both axial diffusivity and radial diffusivity from the 3D features of the ADC value were higher in patients with NVC-induced trigeminal neuralgia than in controls [7]. A 3D diffusion ellipsoid model to assess the white matter of the trigeminal nerve is needed in a large-scale study. In addition to NVC, there are

Fig. 4 One 57-year-old male with trigeminal neuralgia underwent a follow-up examination at 7 days after MVD. Conventional MRI **a** axial 3D-fast imaging employing steady-state sequence image and **b** reconstruction showed the region between the nerve and vessel on the left side after MVD. DTI **c** FA map before MVD (affected side/unaffected side, 0.305/0.327) and **d** FA map after MVD (affected side/unaffected side, 0.321/0.320) showing that the FA value of the affected nerve increased after successful surgery



other etiologies for trigeminal neuralgia, such as primary demyelination lesions, brainstem infarction, and nerve root infiltration by a tumor affecting the trigeminal pathway [9, 13–15]. Our results are also similar to those of other investigators with regard to patients of other known causes, such as tumor infiltration and multiple sclerosis. Thus, the changes on DTI in the trigeminal nerve reflect the degeneration of white matter, which may explain the involvement of focal demyelination in the pathogenesis of trigeminal neuralgia.

To the best of our knowledge, few studies have focused on the DTI features of the trigeminal nerve in asymptomatic individuals who also present with NVC signs [16]. Although some researchers have reported that dislocation of the nerve by a vessel could be a diagnostic clue for trigeminal neuralgia because such a variant has rarely been observed in asymptomatic populations, it was still difficult to distinguish the signs of NVC between trigeminal neuralgia patients and normal controls based solely on anatomical MRI [17]. In this study, we enrolled participants who presented with NVC signs but had no history of facial pain as healthy controls to investigate the functional changes occurring in NVC. In contrast to the significantly decreased FA values in trigeminal neuralgia patients, the DTI parameters in the healthy controls showed no differences between the affected and unaffected sides, which is in line with Lin et al.'s findings [16]. These supplementary findings provide evidence that DTI-derived FA values could reveal the pathological role played by NVC in patients compared with normal controls. In a future study, it would be interesting to follow the DTI and clinical manifestations of NVC in these normal individuals to track whether damage in the form of focal myelin loss occurs.

Furthermore, DTI alterations at the trigeminal root entry/exit zone after effective neurosurgical treatment have been reported [7, 9, 11, 12, 14]. In a cat model of pressure-mediated optic nerve demyelination, remyelination was observed at approximately 6 weeks after the cessation of pressure and indicated recovery at approximately 11 weeks after the cessation of pressure [18]. Herweh et al. observed that the initial reduction in the FA value of the affected nerve of trigeminal neuralgia patients had been resolved at 5 months after successful MVD [19]. Partially, in line with previous studies, we investigated the alteration of the white matter of the trigeminal nerve by using two follow-up MRI scans in patients with NVC-related trigeminal neuralgia. At 7 days after MVD, the FA value presented a reversible increase, which suggested that FA may be sensitive to neural tissue recovery with remyelination. However, the ADC value did not show a significant change at first, even when the patients experienced symptom relief, but the ADC presented a reversible decrease at the second follow-up, 6–8 months postoperatively. There is no change of ADC at first; the possible reason could be that because the ADC may be less sensitive than the FA value, changes in the ADC occurred over a longer period of time. We also hypothesize that since ADC characterizes the overall mean-squared displacement of molecules and the overall presence of

obstacles to diffusion [6, 20], the ADC values' recovery suggested that there will be adjustment in the synaptic circuitry of the trigeminal nerve and reorganization of myelin after withdrawal of chronic pulsatile compression [21]. Recently, Zhang et al. employed a 3D diffusion model to assess 3D characteristics from ADC (e.g., λ_{\perp} and λ_{\parallel}). The authors found that at 6 months after treatment, the recovery was due to a predominant reduction in λ_{\perp} , which is in line with remyelination, while the diffusion recovery at 1 week after treatment was mainly due to the decrease in λ_{\parallel} , corresponding to axonal membrane stabilization, which appears to support our results [15]. In particular, only one patient did not achieve any pain relief in the present study, and the preoperative FA values and ADCs of this patient were similar to the postoperative values at both follow-ups. Our study demonstrates that DTI indexes could potentially provide new insight into monitoring the structural change in the trigeminal nerve with neuralgia after MVD. Additionally, we investigated whether DTI-derived indexes are associated with other clinical data, such as the disease duration and the distance from the contact/compression site to the pons measured on MRI. Unfortunately, we did not find any correlations between the DTI-derived parameters and the above data. However, Lee et al. found that the baseline FA value was associated with the symptom duration, and further study is warranted [22].

There are some limitations to our study. First, a region of interest was positioned on the coronal FA maps in which the trigeminal nerve can be delineated more clearly and precisely. But, even if image distortion artifacts of coronal-view DTI are minimized by improving the resolution of DTI parameters and EPI correction in this study, the coronal view of DTI still has more partial volume effect from imaging with the cerebrospinal fluid signal and the small size of anatomical structures versus the size of the region of interest. Further studies with high-spatial-resolution MRI and DTI are needed. Using a diffusion ellipsoid model to represent the 3D characteristics of white matter should also be applied in future investigations. Second, the standardization used to estimate the severity of compression was incomprehensive. This study included only the disease duration and the distance between the pons and the compression point as clinical indexes, and not the responsible vein, which may also affect estimations of the compression severity. In addition, the effects of surgical changes, such as residual blood or Teflon around the nerve, were not considered in this study. Third, although DTI could be helpful for differentiating pathological and occasional NVC, it does not seem to influence the neurosurgeon's decision to perform MVD on patients directly. Long-term follow-up studies of these populations to track whether trigeminal neuralgia occurs within several years would be an interesting means to investigate the pathological role of NVC. Fourth, the sample size was relatively small, which may have limited the statistical power for detecting significant correlations between diffusivity features and clinical data. Further studies with larger patient cohorts will be needed to confirm our results.

Conclusion

Alterations in diffusivity parameters of the trigeminal nerve were found in patients with NVC-induced trigeminal neuralgia, reflecting microstructural demyelination, but were not found in asymptomatic individuals with NVC signs. Moreover, reversible DTI changes occurred after an effective operation, demonstrating that these parameters have potential as supplementary indicators. We demonstrate that DTI is a valuable tool for estimating the functional characteristics and monitoring the alteration of trigeminal neuralgia in patients after treatment, providing equivocal clinical or imaging findings; however, a larger sample is needed to assess the accuracy of these parameters in determining the severity of trigeminal neuralgia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the institutional review board.

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