Microstructural changes of the vestibulocochlear nerve in patients with Ménière’s disease using diffusion tensor imaging

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Objective: To evaluate the microstructural changes of the vestibulocochlear nerve in patients with Ménière’s disease.

Methods: A total of 26 subjects, 13 patients with MD and 13 healthy controls, underwent diffusion tensor imaging (DTI) on a 3T scanner. The independent sample \( t \)-test was used to compare the differences in fractional anisotropy (FA) and apparent diffusion coefficient (ADC) between the two groups. A Pearson correlation was used between DTI and the dizziness handicap inventory (DHI) scores.

Results: There was a significant decrease in FA and an increase in ADC of the vestibulocochlear nerve in MD patients compared with healthy controls (\( P = 0.04, P = 0.001 \)). FA had negative correlations with the DHI score (\( r = -0.62, P = 0.02 \)) and DHI-functional score (\( r = -0.64, P = 0.02 \)).

Conclusion: These results are the first evidence of possible changes in the microstructure of the vestibulocochlear nerves in patients with MD. DTI is a potential technique for evaluating the vestibulocochlear nerve in patients with MD.

Keywords: diffusion tensor imaging, Ménière’s disease, vestibulocochlear nerve, microstructure, fractional anisotropy (FA)

Introduction

Ménière’s disease (MD) is an inner ear disease and characterized by episodic attacks of vertigo, fluctuating hearing loss, tinnitus, aural pressure, and a progressive loss of audiovestibular functions (1). Endolymphatic hydrops (EH) was discovered and correlated with MD in 1938 (2). Recently, developments in gadolinium chelate (GdC)-enhanced MRI have provided a tool for visualizing endolymphatic hydrops non-invasively (3–6). With these new imaging techniques, EH can be used to confirm the diagnosis. However, there was no evidence that shown the correlation between EH and
the severity and frequency of vertigo attacks (7–9). Currently, decreased hippocampal volume was found in Meniere’s disease patients, and the volume was significantly correlated with severity of hearing and vestibular function of affected side (10). It indicates that MD may not only affect the inner ear. The syndromes of MD include vestibular function and hearing loss, and the vestibulocochlear nerve is a complex of cochlear and vestibular nerves. Thus, this research hypothesized there may be subtle changes in the vestibulocochlear nerve in MD patients and aimed to detect them with diffusion tensor imaging (DTI).

DTI can show the movement of neural fiber bundles under living conditions by describing and quantifying the extent and direction of water molecule diffusion (11, 12). In the healthy neural fiber bundles, the local water molecules that diffuse along the axon encounter smaller obstacles than those perpendicular to the axon (13, 14). Among the DTI parameters, the fractional anisotropy (FA) is a measure that essentially represents the SD of the eigenvalues, and the apparent diffusion coefficient (ADC) quantifies the amount of diffusion in all directions (15, 16). An FA is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero means that diffusion is isotropic it is unrestricted (or equally restricted) in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. FA is a measure often used in diffusion imaging where it is thought to reflect fiber density, axonal diameter, and myelination in white matter. ADC is a measure of the freedom of water molecular diffusion in the tissue environment. Research on cytotoxic edema suggests that the ADC is sensitive to a small change in the distribution of water between intra- and extra-cellular environments, and can be viewed as a probe of cell fluid electrolyte homeostasis. DTI has been used as a technique for various pathologies investigations, including stroke, amyotrophic lateral sclerosis, multiple sclerosis, and epilepsy in the central nerve system (17–20). Recent works evaluated the auditory pathway and facial nerves by DTI successfully, which indicated that DTI may be a potential tool for evaluating the integrity of the vestibulocochlear nerve by obtaining quantitative information (21–23). DTI parameters even can detect the development of white matter lesions before quantifiable changes in normal-appearing white matter (24). Moreover, it was reported that DTI parameters correlated strongly with neurophysiological measures in chronic inflammatory demyelinating polyneuropathy and lumbar spinal nerves (25, 26).

In this research, DTI was used to evaluate the vestibulocochlear nerve in MD, and the relation, between DTI parameters (FA and ADC) and clinical syndromes was also detected. The severity of vertigo was measured by the dizziness handicap inventory (DHI) scores. The outcomes of this research may contribute to the diagnosis of MD and understanding the pathogenesis of MD.

Materials and methods

Participants

With ethical approval and written informed consent, 13 patients with definite MD (7 female; mean ± SD age, 55.08 ± 12.72 years) and 13 healthy adults (7 female; mean ± SD age, 50.08 ± 12.91 years) who were balanced in years and sexuality were recruited in our hospital for this study. The healthy control group were excluded if they had a history of vestibular symptoms or cochlear symptoms. Definite MD: Two or more spontaneous attacks of vertigo, each lasting 20 min to 12 h; audiometrically documented fluctuating low- to midfrequency sensorineural hearing loss (SNHL) in the affected ear on at least 1 occasion before, during, or after 1 of the episodes of vertigo; fluctuating aural symptoms (hearing loss, tinnitus, or fullness) in the affected ear; other causes excluded by other tests. All the patients were enrolled within 48 h of the vertigo attacks.

MRI data acquisition

All MRI DTI data were acquired from all subjects on a 3T Siemens Verio clinical MRI scanner (Siemens Healthcare). T2*WI: thickness = 0.5 mm, TR = 1500 ms, TE = 289 ms, FA = 120°, FOV = 200 mm, matrix = 384 × 384. DTI sequence: slice thickness = 2.0 mm, FOV = 220 mm, matrix = 128 × 128, fractional anisotropy (FA) = 90°, b0 images = 65, diffusion gradient directions = 31, b-value = 1,000 s/mm², TR = 10,500 ms, TE = 82 ms.

Assessment of vestibular symptoms

The degrees of severity of dizziness were evaluated using the dizziness handicap inventory (DHI). The DHI is a 25-item questionnaire addressing the self-perceived handicapping effects of vestibular disease in terms of the patient’s quality of life emotionally, physically, and functionally (27). Each score is evaluated by the patients separately. The DHI scores were 53 ± 20.76, DHI-functional were 23.69 ± 9.33. Currently, FA and ADC maps were generated using the same software. FA and ADC maps were generated using the same software. FA and ADC maps were generated using the same software. FA and ADC maps were generated using the same software. FA and ADC maps were generated using the same software. FA and ADC maps were generated using the same software.

Data analysis

The diffusion tensor data was measured using a dedicated workstation (Ziosoftstation2, Ziosoft Inc., https://ziosoftinc.com). FA and ADC maps were generated using the same software. This software provides a novel technique that can counterpoint the T2 map with the FA/ADC map by spatial location automatically. The 3D T2 image was rigidly registered to the DTI data automatically and midsagittal plane were transformed.
FIGURE 1
Vestibulocochlear nerve (arrows) and facial nerve (triangle) were separated on the T2-weighted axial (a) and sagittal (b) images from a representative subject.

FIGURE 2
FA/ADC measurement. VCN was located on the T2 map (a,e), registered to FA (b,d) map and ADC map (c,f) automatically, measured on FA/ADC map in the MR axial (a–c) and sagittal (d–f) images.

Accordingly, FA and ADC values were obtained from the vestibulocochlear nerve (VCN). To determine whether the DTI parameters deviate from the normal range of values, the facial nerve (FN) was also measured. VCN and FN showed up clearly on the T2 image (Figure 1). They were located on the T2 map and measured on the FA map and ADC map by multi-points (an average of five points per nerve, Figure 2). The measurement was operated separately by two senior radiologists who were blinded between the control subjects and the MD patients. The average of each metric was taken forward into further analysis.

Statistical analysis

Data were analyzed using SPSS 25 (IBM Corp). The FA and ADC values per nerve were compared using two sample t-tests to investigate the differences in patients and controls. The FA and ADC values from the side with hearing loss were compared separately against the other side to investigate whether there was a difference between the two sides in patients with unilateral deafness. A Pearson correlation coefficient analysis was performed on DTI parameters and DHI scores to examine the correlation between VCN changes and the degrees of dizziness. The receiver operating characteristic (ROC) curve was used to analyses the diagnostic efficacy of FA and ADC values. The statistical significance was set at \( P < 0.05 \). Data are presented as mean ± SD in the text.

Results

DTI of the interested nerves

The FA and ADC values of VCN and FN are shown in Tables 1, 2. In healthy controls, FA and ADC values of these nerves showed no significant difference in the left and right side.
TABLE 1  Clinical information and diffusion tensor imaging (DTI) parameters of MD patients.

| MD  | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Sex | M   | F   | F   | F   | M   | F   | F   | M   | F   | M   | F   | M   | M   |
| Age | 51  | 51  | 68  | 58  | 32  | 65  | 56  | 54  | 27  | 66  | 59  | 64  | 65  |
| Disease course | 2 years | 4 years | 20 years | 2 years | 4 years | 10 years | 2 months | 15 years | 7 months | 2 years | 2 weeks | 1 years | 6 months |
| DHI | 40  | 46  | 64  | 84  | 32  | 40  | 70  | 96  | 66  | 32  | 42  | 40  | 38  |
| DHI-functional | 18  | 20  | 24  | 32  | 16  | 24  | 32  | 36  | 26  | 16  | 20  | 24  | 20  |
| DHI-emotional | 12  | 20  | 30  | 36  | 16  | 4   | 16  | 32  | 20  | 12  | 14  | 10  | 14  |
| DHI-physical | 10  | 6   | 10  | 14  | 0   | 12  | 22  | 28  | 20  | 4   | 8   | 6   | 4   |
| Stage of MD | I (R, L) | II (R) | III (R) | I (L) | II (R) | III (R) | I (L) | III (R, L) | I (L) | I (R, L) | I (R) | I (R) | I (R, L) |
| Frequency of attacks | Weeks | Months | Years | Months | Months | Years | Months | Months | Months |
| Number of attacks in last 3 months | 10 | 2 | 1 | 3 | 2 | 1 | 6 | 1 | 2 | 1 | 2 | 1 |
| FA of VCN (R) | 0.19 | 0.14 | 0.15 | 0.14 | 0.33 | 0.20 | 0.13 | 0.17 | 0.26 | 0.29 | 0.24 | 0.16 | 0.28 |
| FA of VCN (L) | 0.21 | 0.20 | 0.15 | 0.13 | 0.25 | 0.24 | 0.16 | 0.13 | 0.26 | 0.22 | 0.31 | 0.25 | 0.14 |
| ADC of VCN (R) | 2.39 | 3.11 | 3.04 | 1.85 | 2.61 | 2.33 | 2.54 | 2.62 | 2.82 | 1.66 | 3.05 | 2.33 | 2.38 |
| ADC of VCN (L) | 2.56 | 3.00 | 2.65 | 2.80 | 2.88 | 3.04 | 1.97 | 2.57 | 2.91 | 2.90 | 1.81 | 1.90 | 3.15 |
| FA of FN (R) | 0.23 | 0.29 | 0.19 | 0.21 | 0.20 | 0.22 | 0.33 | 0.24 | 0.20 | 0.32 | 0.20 | 0.20 | 0.19 |
| FA of FN (L) | 0.24 | 0.19 | 0.23 | 0.32 | 0.24 | 0.24 | 0.45 | 0.18 | 0.43 | 0.37 | 0.30 | 0.18 | 0.18 |
| ADC of FN (R) | 2.42 | 2.89 | 2.83 | 2.92 | 3.03 | 2.42 | 1.43 | 3.51 | 3.60 | 2.79 | 3.17 | 2.49 | 2.88 |
| ADC of FN (L) | 2.45 | 2.51 | 2.56 | 2.25 | 3.42 | 3.33 | 1.97 | 3.84 | 2.97 | 3.07 | 2.69 | 2.35 | 2.90 |

FA, fractional anisotropy; ADC, apparent diffusion coefficient (10^-3 mm²/s); VCN, vestibulocochlear nerve; FN, facial nerve; R, right side; L, left side.

TABLE 2  Diffusion tensor imaging (DTI) parameters of healthy controls.

| Healthy controls | Sex | Age | FA of VCN (R) | FA of VCN (L) | ADC of VCN (R) | ADC of VCN (L) | FA of FN (R) | FA of FN (L) | ADC of FN (R) | ADC of FN (L) |
|------------------|-----|-----|---------------|---------------|----------------|----------------|---------------|---------------|----------------|----------------|
| 1                | F   | 43  | 0.27          | 0.15          | 2.22           | 2.30           | 0.18          | 0.33          | 2.91           | 1.82           |
| 2                | M   | 32  | 0.25          | 0.18          | 1.67           | 1.18           | 0.23          | 0.28          | 2.65           | 2.32           |
| 3                | M   | 41  | 0.24          | 0.28          | 2.26           | 2.32           | 0.18          | 0.21          | 2.45           | 2.35           |
| 4                | F   | 41  | 0.24          | 0.26          | 2.46           | 2.49           | 0.19          | 0.26          | 2.85           | 1.86           |
| 5                | F   | 46  | 0.24          | 0.20          | 2.79           | 3.29           | 0.27          | 0.19          | 2.13           | 2.64           |
| 6                | M   | 68  | 0.18          | 0.24          | 2.95           | 2.67           | 0.19          | 0.16          | 2.88           | 3.10           |
| 7                | M   | 48  | 0.21          | 0.35          | 2.23           | 2.21           | 0.18          | 0.31          | 2.53           | 2.55           |
| 8                | F   | 67  | 0.25          | 0.19          | 1.06           | 2.91           | 0.35          | 0.18          | 2.31           | 2.90           |
| 9                | F   | 60  | 0.26          | 0.28          | 2.54           | 1.81           | 0.27          | 0.16          | 2.10           | 3.18           |
| 10               | M   | 58  | 0.34          | 0.26          | 1.76           | 1.03           | 0.27          | 0.36          | 2.62           | 1.74           |
| 11               | M   | 61  | 0.24          | 0.23          | 1.92           | 1.30           | 0.21          | 0.30          | 1.14           | 1.78           |
| 12               | F   | 28  | 0.37          | 0.25          | 1.80           | 2.30           | 0.39          | 0.27          | 2.02           | 1.55           |
| 13               | F   | 58  | 0.30          | 0.18          | 1.00           | 1.18           | 0.41          | 0.27          | 2.45           | 2.16           |

FA, fractional anisotropy; ADC, apparent diffusion coefficient (10^-3 mm²/s); VCN, vestibulocochlear nerve; FN, facial nerve; R, right side; L, left side.

Comparison of DTI parameters

FA of VCN was lower in patients (0.21 ± 0.01) compared with controls (0.24 ± 0.01, P = 0.04, Figure 3). ADC of VCN was higher in patients (2.59 ± 0.09) compared with controls (2.06 ± 0.13, P = 0.001, Figure 4). No differences were detected in FA and ADC values from FN, CN, and VN in the patients and healthy controls. Further, the FA of VCN was significantly lower than that of the facial nerve (0.24 ± 0.08, P = 0.02). Eight patients showed unilateral hearing loss, FA and ADC of the vestibulocochlear nerve showed no significant difference between the deafness side and the other side (P = 0.73, P = 0.56). Based on ROC curve analysis, the FA cutoff point was 0.18, with the area under the ROC curve (AUC) 0.68.
FIGURE 3
Comparison of FA values (VCN) between MD patients and healthy controls (HC).

FIGURE 4
Comparison of ADC values (VCN) between MD patients and healthy controls (HC).

sensitivity 0.42, specificity 1; the ADC cutoff point was $2.56 \times 10^{-3}$ mm$^2$/s, with AUC 0.73, sensitivity 0.62, specificity 0.81 (Figure 5).

DTI parameters correlate with assessment of vestibular symptoms

The DHI score and FA of VCN showed a negative correlation ($r = -0.62$, $P = 0.02$), so as the DHI-functional score and FA value ($r = -0.64$, $P = 0.02$, Figure 6), which indicates the more serious of the dizziness, the lower the FA was detected.

Discussion

In this work, we have used diffusion tensor to investigate the microstructural properties of the vestibulocochlear nerve. A lower FA and a higher ADC were found in the vestibulocochlear nerve in MD patients compared with healthy controls. The decrease in FA and increase in ADC were presented on both the deafness side and the other side. Further, the FA and DHI had a negative correlation in patients with MD.

FA is highly sensitive to the change in microstructure, decreased FA was related to changes of neural fiber integrity, myelin, and axonal integrity (23, 28, 29). The increase in ADC
was shown to be associated with inflammation, edema, and axonal injury (30–32). In summary, the decreased FA and increased ADC may indicate microstructural changes occurred in vestibulocochlear nerves, which may be edema, inflammation, the damage of neural fiber integrity, myelin, or axonal integrity in active MD.

In this research, DTI parameters were analyzed by the affected side or the average value of the two sides in bilateral MD patients. The FA of VCN was lower than that of FN in MD, while they showed no difference in the healthy control group. This suggested that DTI acquisition could provide stable DTI measures in the cisternal segment. FA and ADC showed alterations in VCN may be associated with its special anatomical structure, the cisternal segment of the vestibulocochlear nerve is the transition pathway from the central nerve to the peripheral nerve, and the nerve sheath is thin and easily damaged.

In patients with unilateral deafness, DTI parameters showed no difference on both sides in MD, which indicated that the alteration may originate from both the vestibular nerve fibers and the cochlear nerve fibers. On one hand, recent work on patients with unilateral hearing loss showed FA decrease on both sides, indicating bilateral changes in microstructure of the auditory nerve and auditory pathway in unilaterally deaf subjects (21, 23). On the other hand, the attack of vertigo is always associated with abnormal vestibular signals, whether there were subtle changes in vestibular nerve fibers was unknown. In our research, the decreased FA had negative correlation with DHI and DHI-functional scores. There was no correlation between FA and DHI-emotional, so as FA and DHI-physical. The DHI is very commonly used to qualify the life measure for vestibular disorders and is quite efficient in evaluating the severity of dizziness (33). It means that patients with higher DHI and DHI-functional scores had lower FA, which could indicate a change in vestibular nerve fibers.

Limitations

The sample size in this study was small, which may affect the result of whether there was a DTI parameter difference between the two sides. However, alterations in FA and ADC were found in vestibulocochlear nerve in patients, suggesting that there were
possible changes in the microstructure of the vestibulocochlear nerves in patients with MD. The pathophysiological mechanism of the alterations in DTI was unclear. The separation of the different nerves was processed on T2 map, the counterpoint was processed by the Ziosoft automatically and could be manually corrected. Since the nerve cross-section is small, the software cannot observe FA and ADC values with multi-points. To more specifically image the vestibulocochlear nerve, a high-resolution T2WI with 0.5 mm slice thickness, and a DTI technique with 31 directions were used.

Conclusion

Decreased FA and increased ADC were detected in the vestibulocochlear nerve in patients with MD, and the change in FA was correlated with DHI, these results indicated possible changes in the microstructure of the vestibulocochlear nerve in MD. DTI may be a potential imaging biomarker for the diagnosis of MD.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

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Author contributions

XY: design and conceptualization of study, acquired data, and drafted the manuscript. ZC: design and conceptualization of study and revised the manuscript for intellectual content. XL: design and conceptualization of study and supervision. ZY: resources and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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