

Morphometric evaluation of facial and vestibulocochlear nerves using magnetic resonance imaging in patients with Menière's disease - a retrospective study

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Abstract

Objectives: Several studies proposed a loss of neural structures in Menière's disease (MD). It has also been shown that VIIth and VIIIth cranial nerves are enlarged within MD patients compared to normal controls. We aimed to investigate potential differences in these two nerves in patients with MD. **Setting:** 71 patients with MD were included, 53 showed clinically unilateral affection. Constructive-interference-in-steady-state(CISS) and 3D-FLAIR-inversion-recovery(IR) sequences with two different slice thicknesses were acquired on a clinical 3T magnetic resonance imaging scanner. We evaluated morphometric properties of the VIIth and VIIIth cranial nerves passing from the cerebellopontine angle to the inner ear modiolus. In patients with clinically unilateral MD, we compared the unaffected to the clinically affected side. In addition, we evaluated the morphology of the nerves in correlation to symptom duration. **Results:** The clinically unilateral MD-patients showed no significant differences after Bonferroni correction when comparing the affected side to the non-affected side of VIIth and VIIIth cranial nerves. There was no significant difference between patients with different symptom durations. **Conclusions:** Our data showed no differences in nerve morphometry between the clinically non-affected and the clinically affected side in patients with clinically unilateral MD. There was also no correlation to duration of symptoms, in contrast to previously demonstrated correlations between clinical features and the extent of endolymphatic hydrops. A disease process starting before onset of clinical symptoms could be a potential explanation.

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Keywords:

Menière's disease, MRI, vestibulocochlear nerve, facial nerve, cranial nerve size

Key points:

Menière's disease is characterized by episodic vertigo associated with fluctuating hearing loss, tinnitus, aural fullness and endolymphatic hydrops.

- A loss of neural structures was proposed in Menière's disease, but also a swelling of VIIth and VIIIth cranial nerves compared to normal controls was shown.
- The aim of this observational study was to investigate potential differences in these two nerves in patients with Menière's disease, also considering the duration of the disease.
- The VIIth and VIIIth cranial nerves were measured within the cerebellopontine angle and the branches in their course through the internal auditory canal.
- Furthermore different MRI sequences (two CISS- and two IR-sequences) with different spatial resolution and slice thickness were used for morphometric analysis.

1. Introduction

Menière's disease (MD) is characterized by episodic vertigo associated with tinnitus, fluctuating hearing loss, aural fullness and endolymphatic hydrops (ELH) (1, 2). Several studies proposed a loss of neural structures (such as hair cells or neurons within the spiral ganglion) in Menière's disease (MD) (3). In recent years several studies have evaluated and quantified ELH in patients with MD (4). Only few studies, however, have analyzed morphometric parameters of cranial nerves VII and VIII on MRI (5-8).

The course of cranial nerves VII and VIII from the pons through the cerebellopontine angle and the internal auditory canal (9) make these nerves amenable to morphometric evaluation in anatomical and MRI studies. The VIIIth cranial nerve divides within the IAC into its three branches: cochlear nerve (CN), superior vestibular nerve (SVN) and inferior vestibular nerve (IVN). In the anterosuperior portion of the IAC the facial nerve is found, and inferior to it the cochlear nerve (10). To our knowledge, no morphometric analyses of these nerves have been performed using different MRI sequences with different spatial resolution in patients with clinically unilateral MD in correlation to symptom duration.

We previously demonstrated a swelling of VIIth and VIIIth cranial nerves on MR imaging in patients with MD (8). The aim of this study was to investigate morphometric differences of the VIIth and VIIIth cranial nerve within MD patients using different MR imaging techniques.

2. Methods

Ethical review board approval was provided by the institutional review board for this observational study. All examinations were performed in concordance with the Helsinki Declaration revised 2013.

2.1. Participants

Patients with certain MD according to the AAO-HNS classification (1995)(11) and with MR morphologic confirmation of endolymphatic hydrops (ELH) as an equivalent to the required histopathological findings were included in the study (4, 12-14). All of these patients underwent MRI on a clinical 3 Tesla scanner investigation with a sequence protocol comprising several different MR sequences described below. All patients gave their informed consent for the locally enhanced inner ear MRI (LEIM). Morphometric analysis of the VIIth and VIIIth cranial nerves was performed retrospectively. 24 hours prior to the MRI scan a gadolinium-based contrast agent diluted 8-fold in saline solution, was intratympanically injected (15). After administration, the patient remained in a supine position for another 30 minutes with the head turned approximately 45 degrees toward the contralateral side.

Patient data consisting of CISS-0.6-sequence measurements was compared in our previous study to clinical healthy controls (8). In the current study we compared the affected side with the non-affected side of unilaterally affected MD patients as well as the bilaterally affected MD patients vs. unilateral affected MD patients using the mentioned different MRI sequences.

2.2. Setting with MR Imaging

All MR imaging examinations were performed on a 3T MR unit (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using a commercially available 4-channel flexible surface coil combined with an 8-channel head coil.

The following MR-sequences were acquired of the temporal bone:

CISS-0.6 : A strongly T2-weighted constructive interference in steady state sequence (CISS) with the following parameters was used: TR 7.2 ms, TE 3.16 ms, flip angle of 70°, field of view of 192 x 192 mm², matrix size of 320 x 320, averages 1 and slice thickness of 0.6 mm.

CISS-0.4 : The second CISS had the following parameters: TR 6.24 ms, TE 2.87 ms, flip angle of 70°, field of view of 160 x 160 mm², matrix size of 320 x 320, averages 1 and slice thickness of 0.4 mm.

IR-0.5 : The inversion recovery sequence was acquired using the following parameters: TR 6000 ms, TE 155 ms, flip angle of 180°, field of view of 160 x 160 mm², matrix size of 320 x 320, averages 1 and slice thickness of 0.5 mm.

IR-0.3 : The second inversion recovery sequence had the following parameters: TR 6000 ms, TE 155 ms, flip angle of 180°, field of view of 160 x 160 mm², matrix size of 256 x 256, averages 1 and slice thickness of 0.3 mm.

2.3. Design and analysis

We used a commercially available DICOM-Viewer (OsiriX v.4.0, 64-bit version, Pixmeo, Switzerland) for measuring the diameters of the VIIth and VIIIth cranial nerves. Consistent windowing levels and thin slice thickness were used performing transverse reformats at different locations throughout the course of the nerves from the cerebellopontine angle (CPA) to the internal auditory canal (9) fundus. Locations of the transverse sections were defined as follows:

- VIII – CPA,
- CN, SVN and IVN - meatus of the IAC;
- VII – CPA, meatus of the IAC, fundus of the IAC.

On each transverse section the long diameter (LD), short diameter (SD) perpendicular to LD and cross-sectional area (CSA) were measured. Several dot-markers were positioned on the outline of the examined nerves. These markers were linked and the CSA was calculated. All measurements were performed by the same two readers based on consensus readings. Both readers were blinded for the diagnosis of the patients. All these measurements were made for the CISS-0.4, the CISS-0.6, the IR-0.3 and the IR-0.5 sequences to investigate different nerve sizes depending on the used MRI sequence.

All patients received locally enhanced inner ear MRI (LEIM). The study group was subdivided into two cohorts: The first cohort consisted of unilaterally affected MD patients; the second consisted of bilaterally affected MD patients.

For comparing the affected and the clinically non-affected side a paired samples (dependent) t-test was employed using MedCalc v.12.7.2 (MedCalc Software bvba, Belgium) and SAS v. 9.4 for Windows (Copyright SAS Institute Inc., Cary, NC, USA). After Bonferroni correction $P < 0.05$ was reduced to $P < 0.000595$ for statistical significance. For comparing the subgroups of different symptom duration a two-sided independent samples t-test was used. Furthermore we used Scatterplots, Pearson Correlation Coefficients and Bland-Altman plots for visualization of the degree of correlation as well as measurement differences between the employed MRI sequences.

3. Results

Both ears of the 71 MD patients (27 females, 44 males, mean age 54.4 years, age range 23 - 77 years) were measured and analysed. 53 of these patients were classified as unilaterally affected (20 females, 33 males, mean age 50.5 years, age range 23 - 77 years). Further clinical patient data were also collected, such as symptom duration (range 4 - 252 months, mean 76 months) and four-tone average calculated from hearing at 0.5, 1, 2 and 3 kHz (range unaffected side 2.5 - 31.75 dB, mean 13.87 dB, range affected side 2.5 - 83.5 dB, mean 42.02 dB).

No significant differences were observed when comparing the affected side to the non-affected side of the VIIth and VIIIth cranial nerves in the cohort of clinically unilaterally affected MD patients (table 1) when adjusting for multiple testing. Without adjustment for multiple testing, in order for catering for an explorative approach, significant differences were found following no certain pattern, e.g. $p < 0.05$ could be found for SD at the level of CPA in the VIIIth nerve and LD at level of CPA and fundus of the VIIth nerve. These results were found to be independent of the used MRI sequence (CISS-0.4, CISS-0.6, IR-0.5 or IR-0.3) when adjusting for multiple testing (tables 2 and 3) at the level of the CPA. Without Bonferroni correction significant differences were found in the VIIIth nerve at this level only for SD in CISS-0.4 (table 1) and CSA in IR-0.3 at the level of CPA (table 3), obviously also not following a specific pattern.

Also, no significant differences between the morphometric measurements of the VIIth and VIIIth cranial nerves of the different sides were observed after Bonferroni correction in the cohort of clinically bilaterally affected patients.

When comparing the affected side of the unilaterally affected cohort with the LEIM-assessed side of the bilaterally affected cohort, no significant difference was shown along our measuring points of VIIth and VIIIth cranial nerves (Table 4, cross sectional areas within CISS-0.4, CISS-0.6, IR-0.3 and IR-0.5). Similar results were found investigating the clinically non-affected side of the first cohort and the contralateral ear of the bilaterally affected cohort. These results were again independent of the used MRI sequence.

An overview of the significant p-values without adjustment for multiple testing is summarized in table 5, no specific pattern is recognizable.

We furthermore evaluated the morphometric properties of the VIIth and VIIIth cranial nerves of the first cohort in dependence of symptom duration. We initially divided the cohort of unilaterally affected patients in a subgroup with a symptom duration of a maximum of 12 months ($n = 9$) and compared these to the rest of the group ($n = 26$); we observed no significant differences between the groups neither when comparing the affected sides nor when comparing the non-affected sides. Subsequently, we compared patients with a symptom duration of at least 120 months ($n = 14$) to the patients with a symptom duration of a maximum of 12 months ($n = 9$). Again, there were no significant differences for the morphometric parameters (table 6).

4. Discussion

In our patient cohorts we observed no significant differences between the clinically non-affected side and the

clinically affected side of unilaterally affected patients with MD independently of the used MRI sequence when using the Bonferroni correction for multiple testing.

4.1. Different models of ethiopathogenesis

The pathogenesis of MD is still incompletely understood and the disease can be difficult to diagnose in early stages (2, 13, 16). Autoimmune processes (17) and viral infections, such as latent herpes simplex virus type-1 that may cause vestibular neuritis (18), may play a role in the induction of MD. The involved immunological mechanisms are still not clear, but approximately one-third of the MD cases may have an autoimmune origin (19-21). Further pathophysiological aspects have been discussed, such as genetic predisposition (22), excitotoxicity, chronic otitis media (20), cellular apoptosis and oxidative stress. Reactive oxygen species, specifically nitric oxide generated by nitric oxide synthase, regulate the cochlear blood flow and lead to the release of mitochondrial cytochrome c, which is an important mediator of the intrinsic pathway of apoptosis (23, 24). The presence of hydrops may thus cause neuronal damage in the inner ear via a process of excitotoxicity (1, 25). This neuronal damage could possibly affect the VIIIth and potentially also the VIIth cranial nerve.

Our data, however, demonstrated no differences in nerve diameters when comparing the clinically non-affected to the clinically affected side of unilaterally affected MD patients, possibly pointing toward a more systemic process that leads to subclinical reaction of the contralateral ear in clinically unilaterally affected MD patients. Kariya et al found equal results when comparing the mean number of spiral ganglion cells, the mean loss of inner and outer hair cells in patients and the damage of the stria vascularis with unilateral MD (3). This may support autoimmune processes or genetic predispositions, whereas local processes such as excitotoxicity and reactive oxygen species seem less likely. Moreover, our data did not show a correlation to clinical symptom duration, which again may point toward a very longstanding underlying process prior to the onset of clinical symptoms. On the other hand, it could also indicate that there is no change in the 7th and 8th cranial nerves in MD. However, this contradicts our previous study, which showed thicker nerves in patients with MD compared to a healthy control group (8).

4.2. MRI difficulties

Moreover our data showed different means for the same patients at the same measuring levels in dependence of the employed MRI sequence. These differences occur due to different variable sequence parameters such as slice thickness, different partial volume effects and the relatively small sample size. Where measurements varied largely between VIIth and VIIIth cranial nerve, differences between the 4 employed sequences were small. However, due to the limited sample size, a significant positive correlation could only be shown for the IR-0.3 and IR-0.5 for VIIth and VIIIth cranial nerve. This reflects the difficulty of comparing absolute morphometric parameters in different MRI-studies performed with different sequences on different scanners.

In an explorative approach, without catering for multiple testing, scattered single parameters were found to be significant, these findings showed no specific pattern. Therefore Bonferroni correction was applied.

4.3. Study Limitations

Our study has several limitations that need to be taken into account when interpreting the data. First, our sample size was limited, especially when performing the subgroup analyses. Larger studies are warranted to confirm our results. Second, we did not compare our measurements to an age- and sex-matched healthy control cohort to analyze differences to a clinically unaffected control population. As shown in our previous study (8) only few surveys (5-7, 10) with measurements of the VIIth and VIIIth cranial nerves had been published, mostly in normal hearing patients. The comparison of these published data also showed differences of nerve diameters according to the measuring point and the used MRI sequence.

5. Conclusion

Our data showed no significant differences in diameters and cross-sectional areas of the VIIth and VIIIth cranial nerves between the affected and the clinically non-affected side of unilaterally affected patients with

MD after Bonferroni correction for multiple testing. There was also no correlation to duration of clinical symptoms. This may potentially point toward a systemic process starting long before the onset of first clinical symptoms. On the other hand, it could also indicate that there is no change in the 7th and 8th cranial nerves in MD. However, this contradicts our previous study, which showed thicker nerves in patients with MD compared to a healthy control group (8).

Normative nerve diameters should only be used if comparable MRI sequence parameters are used as our data showed different means for the same patients at the same measuring points depending on the MRI sequences used.

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