Original Article

Longitudinal variation of endolymphatic hydrops in patients with Ménière's disease

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Background: The relationships of endolymphatic hydrops (EH) and perilymphatic enhancement (PE) with Ménière's disease (MD) remains unclear. This study aimed to describe the dynamic variation of EH and PE for MD patients over 2 hospitalizations by applying magnetic resonance imaging (MRI) to further clarify the relationships of EH and PE with MD.

Methods: A total of 77 MD patients who underwent inner ear MRI after intravenous administration of gadolinium and pure-tone average (PTA) testing during a first and second hospitalization were included. The degree of EH and PE were evaluated via MRI, and the duration and frequency of vertigo attacks and PTA were collected and recorded. The PTA, EH, and PE for the 2 hospitalizations were compared, and the relationships of EH and cochlear PE with the MD stage were investigated.

Results: There was no difference between the 2 hospitalizations for duration of vertigo attacks or frequency of vertigo attacks. However, there were significant differences in PTA ($Z=-3.02$, $P=0.003$). Additionally, the cochlear and vestibular EH in the asymptomatic ear at the second hospitalization was significantly worse than that of the first hospitalization ($Z=-2.33$ and -2.49, $P=0.020$ and 0.013, respectively), while there were no differences in EH and PE in the affected ear (all $P>0.05$). Moreover, the degree of cochlear and vestibular EH was correlated with MD stage (both $P<0.01$).

Conclusions: Although EH and PE in the affected ear were unchanged over 2 hospitalizations, an underlying EH in the asymptomatic ear and hearing loss in the affected ear for MD patients developed longitudinally with the duration of disease, and EH varied with the natural course of MD whereas PE did not. Therefore, EH instead of PE is necessary but insufficient to cause the clinical symptoms of MD.

Keywords: Ménière's disease (MD); endolymphatic hydrops (EH); magnetic resonance imaging (MRI)

Submitted Nov 21, 2022. Accepted for publication Jan 06, 2023. Published online Jan 11, 2023.
doi: 10.21037/atm-22-6313
View this article at: https://dx.doi.org/10.21037/atm-22-6313

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Introduction

Ménière's disease (MD) is an inner ear condition that is not fully understood. MD has an estimated prevalence of 0.19–0.27% (1,2) and is characterized by symptoms of fluctuating low-frequency sensorineural hearing loss, vertigo, tinnitus, and aural fullness (3). The clinical symptoms of MD can overlap with other clinical entities and commonly fluctuate, while the clinical phenotype and severity of symptoms of MD vary among patients. Accordingly, MD can be a controversial and difficult disease with respect to diagnosis, pathogenesis, and optimal treatment (4,5). Initially, endolymphatic hydrops (EH) was assumed to be causative in MD as a result of research by Hallpike and Cairns cementing the association of MD with EH in 1938 (6). However, doubts have subsequently been raised regarding this hypothesis. Nadol (7) suggested that EH represents the end-stage of many damaging processes rather than a single disorder, while Merchant *et al.* (8) depicted EH as an epiphenomenon. However, in a meta-analysis of 541 hydropic temporal bones, Foster *et al.* (9) theorized that a combination of vascular disease with EH, a preexisting anatomic lesion, may cause MD. In addition, a scoping review found that MD is a multifactorial disease caused by structural dysfunction, immunologic damage, and genetic susceptibility, with EH a crucial pathophysiology for MD (10). Regardless, the association between EH and MD remains ambiguous.

Currently, while the cause of MD remains undetermined and controversial, a pathophysiological substrate is known for EH. Distension in the endolymphatic space of the membranous labyrinth, partially or fully occupying the usual perilymphatic space, has been reported based on temporal bone studies (6). Moreover, some studies have proposed perilymphatic enhancement (PE) as an additional discriminating parameter for MD (11-14). Recently, gadolinium contrast-enhanced magnetic resonance imaging (MRI) has been used to acquire *in vivo* imaging of EH and PE, allowing an assessment of the degree of EH and PE presented in the vestibule and cochlea (12,15-17). Moreover, the 2020 revised diagnostic criteria (18) for MD reported by Japan demonstrated that the MRI examination is necessary to diagnosis the MD. With these, there is potential for improving our understanding of the relationships of EH and PE with MD and the natural history of the disease and assess changes in response to treatment (12,15-17). It is known that MD is a chronic condition. Early detection of EH and PE by MRI and dynamic monitoring of longitudinal variation in EH and PE are very important for understanding the relationship of EH and PE with MD. However, longitudinal studies regarding the evolution of EH and PE in MD are scarce (19-23). Studies with small groups of patients have assessed changes in EH during or after treatment by using delayed intravenous contrast-enhanced MRI (19-23). Moreover, these studies compared EH before and after a particular therapy. Therefore, there may be some bias in these results. Additionally, to our knowledge, no prior studies have been performed to assess the serial changes in PE. The assessment of longitudinal changes in EH and PE is important for developing an understanding of the relationships of EH and PE with MD.

Therefore, in the present study, we aimed to explore how EH and PE behaved longitudinally in a larger group of patients with MD over 2 hospitalizations and determine the relationships of EH and PE with MD. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6313/rc).

Highlight box

Key findings

- Asymptomatic endolymphatic hydrops at the second hospitalization was significantly worse than that of the first hospitalization, while endolymphatic hydrops and perilymphatic enhancement in the affected ear were not.

What is known and what is new?

- Endolymphatic hydrops and perilymphatic enhancement were discriminating parameters for Ménière's disease.
- Increased perilymphatic enhancement is an incidental imaging biomarker and unique for Ménière's disease.

What is the implication, and what should change now?

- Endolymphatic hydrops instead of perilymphatic enhancement is necessary but insufficient to cause the clinical symptoms of Ménière's disease.

Methods

Patients

To obtain detailed and complete clinical data, 77 patients with definite unilateral MD according to the 2015 revised diagnostic criteria of the Bárány Society (24), twice admitted to the Department of Otolaryngology at Shandong Provincial ENT Hospital between August 2018

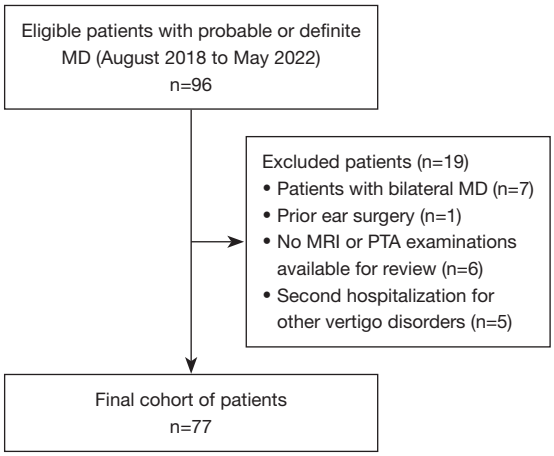

Figure 1 Flow chart showing patient inclusion in the study. MD, Ménière's disease; MRI, magnetic resonance imaging; PTA, pure-tone average.

and May 2022, were enrolled in this study. The selection criteria were as follows: (I) diagnosis of definite unilateral MD in 2 hospitalizations; and (II) 2 MRI and pure-tone average (PTA) examinations, respectively, performed at the 2 hospitalizations. The exclusion criteria were as follows: (I) physical trauma or neoplasm; (II) prior ear surgery or treatment with chemotherapeutic agents or other immunosuppressive drugs; (III) magnetic resonance (MR)-related contraindications; and (IV) second hospitalization for other vertigo disorders. This retrospective study was approved by the ethics committee of Shandong Provincial ENT Hospital (No. 20220112) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the research, the requirement for informed consent was waived. A flowchart of patient enrollment is provided in *Figure 1*. At the time of diagnosis, all patients underwent MRI and PTA (GSI-61). All patients then received continuous medication or surgery. A second MRI and PTA examination were performed at the second hospitalization.

MR experiments and intravenous gadobutrol injection

All scans were performed on a 3-tesla MR system (Discovery 750w, GE Healthcare, Waukesha, WI, USA) equipped with a 19-channel phased-array head and neck coil or a 3-tesla MR system (MAGNTOM Prisma, Siemens Healthineers, Erlangen, Germany) with parallel transmit technology (TimTX TrueShape, Siemens Healthineers) and a 64-channel array head and neck coil. The 3D-FLAIR or 3D-SPACE real IR (3D-real IR) imaging sequence was applied 6 hours after intravenous injection of a double-dose (0.4 mL/kg body weight) of gadoteridol (ProHance, Singen, Germany), as per a previous study (25). Meanwhile, 3D T2-weighted image (T2WI) or 3D-SPACE T2WI was performed to obtain reference anatomic images of the labyrinthine fluid space. The parameters of 3D-SPACE T2WI sequences were: field of view (FOV) =162 mm × 82 mm, repetition time (TR) =1,200 ms, echo time (TE) =125 ms, slice thickness =0.5 mm, and acquisition time (TA) =3 min 47 s. Parameters of 3D-real IR protocol were: FOV =162 mm × 80 mm, TR =8,000 ms, TE =491 ms, inversion time (TI) =2,250 ms, slice thickness =0.6 mm, and TA =15 min 12 s. The parameters of 3D-FLAIR sequence were: TR =9,000 ms, TE =130 ms, TI =2,500 ms, echo train length (ETL) =140, bandwidth =36 kHz, slice thickness =1.6 mm, overlap =50%, FOV =210 mm × 160 mm, and TA =5 min 46 s. The parameters of 3D-T2WI sequence were: TR =2,500 ms, TE =102 ms, ETL =120, bandwidth =42 kHz, slice thickness =1.0 mm, overlap =50%, FOV =210 mm × 160 mm, and TA =2 min 41 s.

Data collection and analysis

Clinical data collection

Clinical data including age, sex, duration of disease (defined as the time since the onset of the first disease-related symptom, e.g., vertigo or hearing loss), duration of vertigo attacks (the longest duration of vertigo attacks before the hospitalization), frequency of vertigo attacks (the mean number of vertigo episodes in 1 month before the hospitalization), the time interval between the 2 hospitalizations, and PTA were collected and recorded. The PTA (500 Hz, 1, 2, and 4 kHz), low-frequency (125, 250, and 500 Hz), middle-frequency (1 k and 2 k Hz), and high-frequency (4 and 8 kHz) hearing thresholds were evaluated. Staging was based on the three-tone average of the pure-tone thresholds at 0.5, 1 and 2 kHz of the worst audiogram during the interval 6 months before MRI scanning (26).

Imaging analysis

All MR images were evaluated with the ADW 4.7 workstation (GE Medical Systems) in different sessions by 2 independent radiologists with 10 and 15 years of working experience, respectively, and blinded to the clinical data. The time interval between reading sessions for the 2 radiologists was more than 3 days. The 2 MR images were

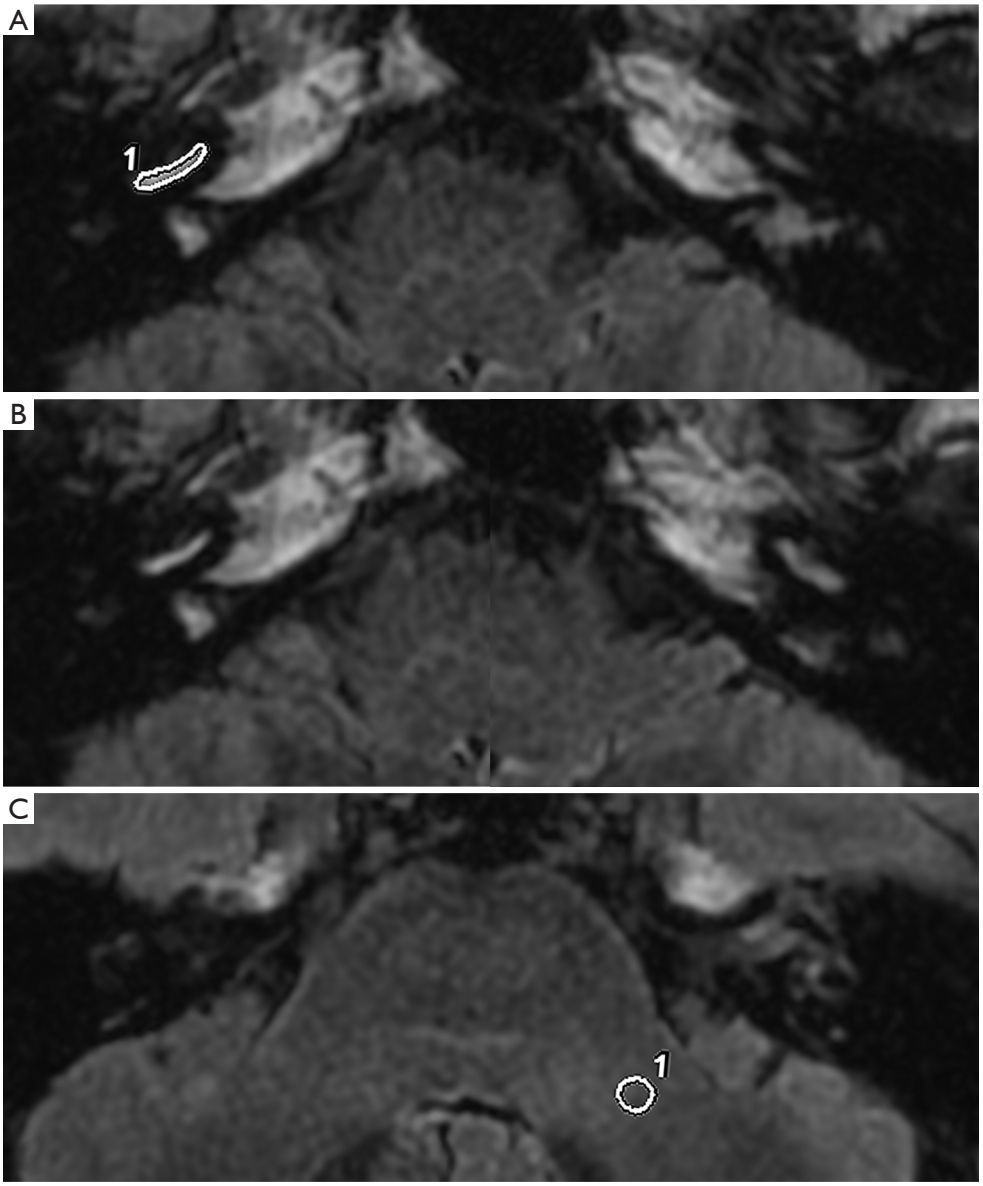

Figure 2 Axial 3D-FLAIR images after intravenous gadolinium of a patient with definite unilateral right-sided Ménière's disease (A-C). (A,B) At the level of the cochlear basal turn are the same images. (B) Shows a visually increased perilymphatic enhancement in the right cochlea compared with the left cochlea (score 2). (C) Was at the level in the left middle cerebellar peduncle. Measurements of signal intensity were performed by drawing an oval region of interest along the edge of the cochlear basal turn (A, oval #1) and a circular region of interest at the left middle cerebellar peduncle (C, circle #1) to calculate the signal intensity ratio.

randomly evaluated. Finally, any discrepancies between the 2 radiologists were resolved by another radiologist with 20 years of experience.

The degree of EH in the cochlea was classified into 3 groups: none, grade I, and grade II, according to criteria described previously (12,17). In the vestibule, degree was classified into 4 groups: none, grade I, grade II, and grade III. PE in the 77 affected cochlea was visually assessed with a 2-point score system: 1, equal or lower signal intensity (SI) compared with the asymptomatic ear; and 2, higher SI compared with the asymptomatic ear (*Figure 2*) or similar to the SI of patients with acute blood-labyrinth barrier (BLB)

Table 1 Characteristics of the study population (n=77)

Variable	Value
Age (years)[a]	50.73±12.95
Sex	Male 45; female 32
Ear affected	Right 32; left 45
Disease duration (m)[b]	18 [5.5, 48]
The time interval between 2 hospitalizations (m)[b]	10 [2, 20]
Medical treatment	Medication 50; surgery 27
Stage 1 (n)	
1	13
2	20
3	37
4	7
Stage 2 (n)	
1	9
2	14
3	41
4	13

Staging was based on the pure-tone average at the thresholds of 0.500–2 kHz. Stage 1 was the staging of first hospitalization, and stage 2 refers to the second hospitalization. [a], values are presented as mean ± standard deviation; [b], values are presented as M [P_{25}, P_{75}].

breakdown (12,14). For patients with MRI examinations at 2 hospitalizations with the same MR system, we quantified the PE using a modified version of the method by van Steekelenburg (14). The signal intensity ratio (SIR), a quantitative index of PE, was calculated with an oval region of interest (ROI) along the edge of cochlear basal turn (SI_{peri}) divided by a reference measurement of 10 mm^2 circular ROI in the left middle cerebellar peduncle (SI_{lmcp}, *Figure 2C*). Radiologists measured each ROI twice for each patient and averaged these SIs for analysis.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM, Chicago, IL, USA). Interobserver agreement was tested using kappa (κ) statistics. The Wilcoxon signed-ranks test or paired Student's *t*-test was performed to evaluate differences between the 2 hospitalizations. Kendall's tau-b correlation analysis was conducted to explore the correlation between the MD stage and the degree of EH in the cochlea and vestibule. Spearman's correlation coefficient was used to investigate the relationship between SIR and MD stage. Statistical significance was set at P<0.05.

Results

Population

The baseline clinical characteristics of the study cohort are summarized in *Table 1*. There were 45 male and 32 female patients with a mean age of 50.73±12.95 years (range, 28–79 years). Disease duration ranged from 0.33–240 months (median, 18 months), and the time interval between 2 hospitalizations was 1–44 months (median, 10 months).

Vertigo and PTA

The median for duration of vertigo attacks at the first hospitalization was 3 hours, and that of the second hospitalization was 2 hours. Consequently, there was no difference in duration of vertigo attacks [d=0.00, 95% confidence interval (CI): −1.50 to 1.29, *Z*=−0.21, P=0.834]. In addition, there was no significant difference in the number of vertigo episodes per month (d=0.25, 95% CI: −0.50 to 1.50, Z=−0.75, P=0.451).

The medians for PTA, low-frequency, middle-frequency, and high-frequency hearing thresholds at the first hospitalization in the affected ear were 48.75, 46.67, 45.00, and 57.50, respectively, and that of the second hospitalization were 55.00, 50.00, 55.00, and 65.00, respectively. Consequently, there was a significant difference between the 2 hospitalizations (Z=−3.02, −1.96, −2.73, and −3.05, respectively, P=0.003, 0.049, 0.006, and 0.002, respectively), while there was no significant difference in the asymptomatic ear (all P>0.05) (*Table 2*, *Figure 3*).

EH

All patients had a notably high signal in the perilymph space of the cochlea, vestibule, and semicircular canal, whereas the endolymphatic space showed a low signal with a clear outline of the cochlea, saccule, and utricle. Kappa values evaluating interobserver agreement for cochlear and vestibular hydrops and score of visually cochlear PE are listed in *Table 3*.

The percentage of EH in affected and asymptomatic ears at the second hospitalization was higher than that of the

Table 2 The PTA at 2 hospitalizations in 77 patients with Ménière's disease

Side	PTA	First hospitalization[a]	Second hospitalization[a]	d (95% CI)	Z value	P value
The affected side	Pure-tone average (dB)	48.75 (30.63, 63.13)	55.00 (37.50, 66.25)	5.00 (1.89 to 8.75)	−3.02	0.003
	Low-frequency hearing thresholds (dB)	46.67 (30.83, 59.17)	50.00 (37.50, 60.83)	4.17 (0.00 to 8.33)	−1.96	0.049
	Middle-frequency hearing thresholds (dB)	45.00 (27.50, 58.75)	55.00 (35.00, 63.75)	5.00 (1.25 to 10.00)	−2.73	0.006
	High-frequency hearing thresholds (dB)	57.50 (35.00, 77.50)	65.00 (50.00, 81.25)	6.25 (2.50 to 10.00)	−3.05	0.002
The asymptomatic side	Pure-tone average (dB)	17.50 (7.50, 25.00)	17.50 (10.00, 27.50)	0.63 (−0.63 to 2.50)	−1.22	0.221
	Low-frequency hearing thresholds (dB)	11.67 (6.67, 15.00)	11.67 (8.33, 19.16)	0.83 (−0.83 to 2.50)	−1.43	0.154
	Middle-frequency hearing thresholds (dB)	12.50 (7.50, 21.25)	15.00 (7.50, 25.00)	0.00 (−1.25 to 2.50)	−0.97	0.331
	High-frequency hearing thresholds (dB)	30.00 (12.50, 52.50)	30.00 (10.00, 53.75)	1.25 (−1.25 to 2.50)	−1.13	0.259

[a], values are presented as M (P_{25}, P_{75}). PTA, pure-tone average.

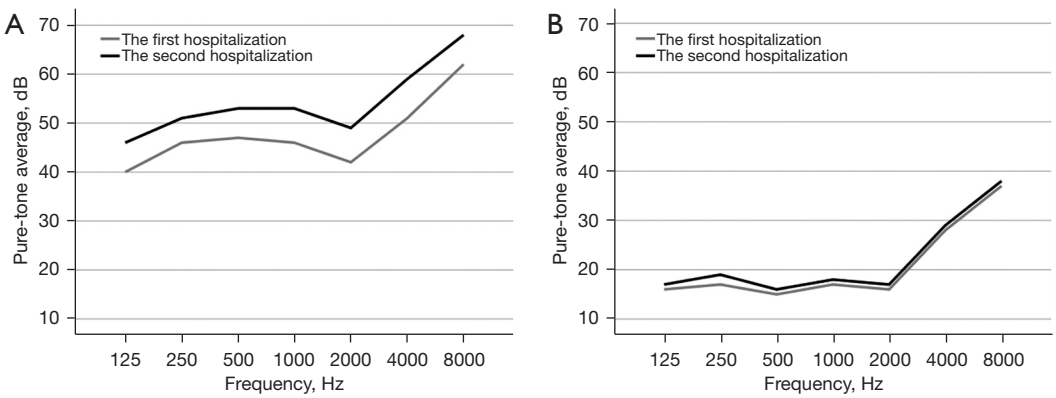

Figure 3 Pure-tone average at the first and second hospitalization in the affected (A) and asymptomatic (B) inner ear.

Table 3 Interobserver agreement

Side	Variable	Kappa value	
		First hospitalization	Second hospitalization
Affected side	Cochlear hydrops	0.91	0.95
	Vestibular hydrops	1.00	1.00
Asymptomatic side	Cochlear hydrops	1.00	1.00
	Vestibular hydrops	1.00	1.00
Affected side	Visually cochlear PE	0.86	0.88

PE, perilymphatic enhancement.

Table 4 Number and percent (%) distribution of cochlear and vestibular EH grading at 2 hospitalizations in 77 patients with Ménière's disease

Side	Grade of EH	First hospitalization, n (%)	Second hospitalization, n (%)	Wilcoxon signed-ranks test	
				Z value	P value
The affected side	No cochlear EH	11 (14.3)	7 (9.1)	−1.59	0.112
	Cochlear EH (I)	21 (27.3)	20 (26.0)		
	Cochlear EH (II)	45 (58.4)	50 (64.9)		
	No vestibular EH	10 (13.0)	7 (9.1)	−1.71	0.087
	Vestibular EH (I)	10 (13.0)	12 (15.6)		
	Vestibular EH (II)	37 (48.1)	29 (37.7)		
	Vestibular EH (III)	20 (26.0)	29 (37.7)		
The asymptomatic side	No cochlear EH	70 (90.9)	65 (84.4)	−2.33	0.020
	Cochlear EH (I)	4 (5.2)	4 (5.2)		
	Cochlear EH (II)	3 (3.9)	8 (10.4)		
	No vestibular EH	70 (90.9)	65 (84.4)	−2.49	0.013
	Vestibular EH (I)	5 (6.5)	4 (5.2)		
	Vestibular EH (II)	2 (2.6)	7 (9.1)		
	Vestibular EH (III)	0 (0.0)	1 (1.3)		

EH, endolymphatic hydrops.

first hospitalization (19.48% *vs.* 11.69%, P=0.014), whereas that in the affected ear was comparable (96.2% *vs.* 92.2%, P=0.083). The percentages of no cochlear EH, cochlear EH (I), and cochlear EH (II) in the asymptomatic inner ear were 90.9% and 84.4%, 5.2% and 5.2%, and 3.9% and 10.4% at the first and second hospitalizations, respectively. The percentages of no vestibular EH, vestibular EH (I), vestibular EH (II), and vestibular EH (III) were 90.9% and 84.4%, 6.5% and 5.2%, 2.6% and 9.1%, and 0.0% and 1.3%, respectively (*Table 4*). The cochlear and vestibular EH in the asymptomatic ear at the second hospitalization was significantly worse than that in the first hospitalization (Z=−2.33 and −2.49, P=0.020 and 0.013, respectively, *Figure 4*). However, there was no difference between the 2 hospitalizations in cochlear and vestibular EH in the affected ear (*Z*=−1.59 and −1.71, P=0.112 and 0.087, respectively) (*Table 4*, *Figure 4*).

The relationships between MD stage and degree of cochlear and vestibular EH at the first and second hospitalizations are illustrated in *Figure 5*. Interestingly, the degree of cochlear and vestibular EH was correlated with MD stage (first hospitalization: cochlear EH, Kendall's tau-b =0.440, P<0.001; vestibular EH, Kendall's tau-b =0.341, P=0.001; second hospitalization: cochlear EH, Kendall's tau-b =0.282, P=0.006; vestibular EH, Kendall's tau-b =0.270, P=0.007).

PE

The scores for visually PE in the 77 affected cochleae of patients with MD are listed in *Table 5*. There was no difference between the 2 hospitalizations in scores for the cochlea in the affected ear (Z=−1.60, P=0.109). There were 38 patients with MRI examinations at the 2 hospitalizations with the same MR system. For these patients, the mean SIR values of the affected cochleae were 4.18±3.84 and 4.09±3.27 at the first and second hospitalizations, respectively. Consequently, there was no significant difference between the 2 hospitalizations in the SIR values (d=0.09, 95% CI: −0.43 to 0.62, *t*=0.36, P=0.721). Meanwhile, the visual or quantitative PE in the affected cochlea was not related to the MD stage (all P>0.05).

Discussion

In this study, we explored how EH and PE behave longitudinally in a larger group of patients with MD over 2 hospitalizations to understand the relationships of EH

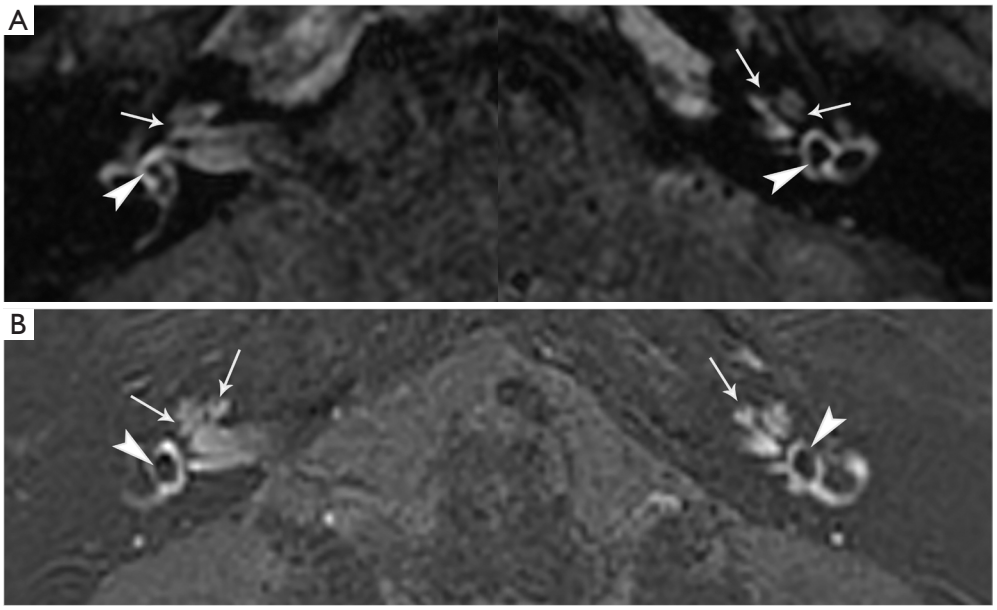

Figure 4 A 3D-FLAIR (A) and 3D-real IR (B) MRI of a 71-year-old man with definite unilateral left-sided Ménière's disease at the first and second hospitalization, respectively. There is no apparent change in the degree of cochlear hydrops (arrows) in the bilateral inner ear or vestibular hydrops (arrowhead) in the left inner ear, whereas the degree of vestibular hydrops (arrowhead) in the right inner ear progressed. MRI, magnetic resonance imaging.

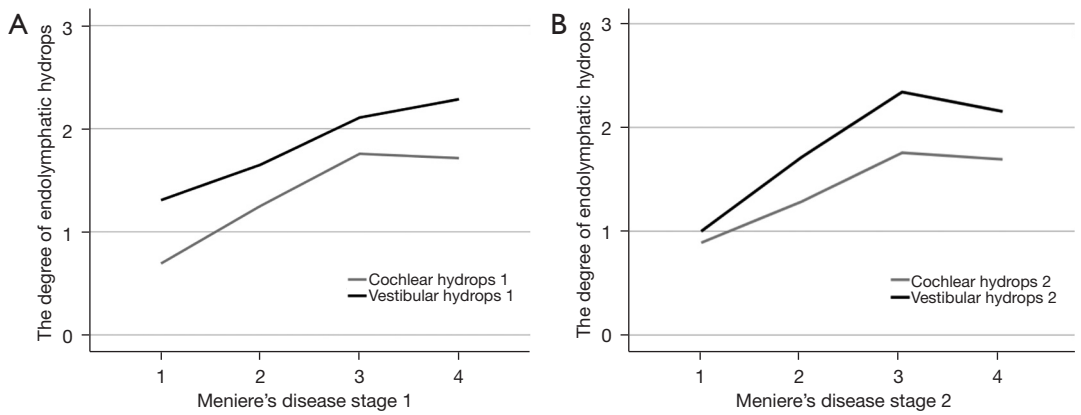

Figure 5 Correlation between the Ménière's disease stage and degree of EH in the affected cochlea and vestibule at first (A) and second (B) hospitalization. Stage 1 refers to the first hospitalization, and stage 2 refers to the second hospitalization. EH, endolymphatic hydrops.

with MD stage. Alternatively, Sun *et al.* only analyzed once examination showing the relationship between EH and MD stage, which was consistent with our vestibular EH at the first hospitalization. Although the prevalence and severity of EH have been demonstrated to progress with the duration of MD (40) and correlate with the worsening of audio vestibular function (32,33), the degree of EH decreased with MD stage when it changed from stage 3 to 4 at the second hospitalization in this study. The reasons for this result are unclear but may be because of the rupture and repair of Reissner's membrane (41,42) due to overdistension of the endolymphatic compartment with the duration of MD. This leads to an intermixing of a certain amount of endolymph and perilymph, causing a modest decrease in degree of EH and hearing loss to deteriorate (43). Alternatively, the decrease in endolymph is due to abnormally osmotic gradients (44)

Table 5 Score for visually perilymphatic enhancement on the 77 affected ears of patients with Ménière's disease

Location and time of PE	Score		Wilcoxon signed-ranks test	
	1[a]	2[a]	Z value	P value
$Cochlea_f$	32 (41.56)	45 (58.44)	−1.60	0.109
$Cochlea_s$	26 (33.77)	51 (66.23)		

[a], values are presented as numbers (percent, %); f and s refer to the first and second hospitalization, respectively. PE, perilymphatic enhancement.

and PE with MD. We concluded that EH and PE assessed by MRI remained unchanged in the affected ear, and EH developed in the asymptomatic ear in MD patients over 2 hospitalizations. Additionally, the degree of EH varied with stage of MD.

EH and vertigo

The results of our analysis demonstrated that the duration of vertigo attacks, frequency of vertigo attacks, and EH in the affected inner ears showed no differences between 2 hospitalizations, whereas EH developed in the asymptomatic ears. The EH assessed by MRI was unchanged in the affected inner ear between 2 examinations, which is in concordance with previously published studies (19,23). Currently, the functional role and evolution of EH during the natural course of MD remains controversial (8,9). EH is usually expected to change in association with vertigo episode changes if EH alone generates and correlates with the clinical symptoms of MD (22). However, the duration of vertigo attacks, frequency of vertigo attacks, and EH in the affected inner ears remained unchanged over 2 hospitalizations in the present study. Moreover, vertigo attacks recurred in all 77 patients. This result was likely due to 4 possible causes: (I) The change of clinical symptoms in these patients may have been a coincidence related to normal symptom fluctuation (21,27). (II) An acute increase in the endolymphatic space which was too small to be shown by MRI caused the vestibular disorder (28,29). (III) EH developed independently of MD vestibular symptoms. Previous studies have reported that vertigo control during or after treatment was not always a result of the reduced EH (19,22,23,30). (IV) One or more additional (unknown) cofactors, such as vascular risk factors, other than EH related to the MD symptoms (9). This was proven by the finding that EH and MD were found in association in 100% of 163 cases when the definition of MD was strictly applied. In addition, Gürkov *et al.* (31) speculated that EH was necessary but insufficient for the display of the full symptom triad of MD.

EH and PTA

We demonstrated that PTA remained unchanged in the asymptomatic ear and worsened in the affected ear of MD patients over 2 hospitalizations, while the degree of EH was unchanged in the affected ear and worsened in the asymptomatic ear. Several reports have shown that the degree of EH is correlated with loss of audiovestibular functions (32,33). However, the association between hearing loss and EH is not uniform in each patient (31). It may be that changes in EH precede that in hearing loss. One study reported that the displacement of basilar membrane, an essential part of the mechanoelectrical transfer function of the hearing system, caused by EH led to hearing loss (34). Moreover, the previous study indicated that hearing in patients with intractable MD worsened gradually over 2–13 years (35). Alternatively, EH is necessary but not sufficient to cause hearing loss. A prior study has noted that EH is very often present in the asymptomatic ear (36). Although the percentage of EH in asymptomatic inner ears in this study was lower than that found in previous research (36), EH in the asymptomatic ear at the second hospitalization was significantly worse than that of the first hospitalization, whereas PTA was not. This suggested that there were some additional cofactors that convert asymptomatic EH into symptomatic MD (9). Furthermore, the incidence of symptomatic and functional involvement of the asymptomatic ear in typical unilateral MD increases almost linearly with the length of observation (31). In addition, it has been well acknowledged that unilateral MD is highly likely to progress to bilateral MD over time (37), and this results in a bilaterality rate of almost 50% at 30 years after onset of unilateral MD (38).

The degree of EH varied with MD stage. Interestingly, the degree of vestibular EH increased with MD stage at the first hospitalization. However, degree of cochlear EH decreased with MD stage when it changed from stage 3 to 4, as did degree of cochlear and vestibular EH at the second hospitalization. However, our results were not entirely consistent with a previous study (39). This may have been because Sun *et al.* (39) analyzed the relationship between total EH index and MD stage and did not separately analyze the relationship of cochlear EH index or vestibular EH index

at the terminal MD stage, or the endolymphatic sinus is enlarged due to excess of endolymph volume, leading to an amount of endolymph being displaced from the sinus into the endolymphatic sac (45).

Consequently, EH is necessary for MD. As the diagnostic guidelines for MD published in Japan in 2020 (18), identification of EH in the affected ear by contrast-enhanced MRI is a necessary condition for the diagnosis of certain MD. Therefore, contrast-enhanced MRI examination is recommended to the diagnosis of MD. It can not only detect EH, but also exclude the tumor or tumorlike lesions in cerebellopontine angle-internal auditory canal and labyrinth.

PE

Increased PE in the affected inner ear of patients with MD has been demonstrated in previous MRI studies (11,12,17,46), which support the theory that increased BLB permeability may be a biomarker of disease status in MD. Moreover, Pakdaman *et al.* (46) deemed PE complementary to clinical evaluation when assessing the effectiveness of various treatments. In the present study, however, the visual or quantitative PE in the affected inner ear remained unchanged between the 2 hospitalizations. Tagaya *et al.* (11) and Zhang *et al.* (47) concluded that there was a positive correlation between the cochlear SIR and grade of cochlear hydrops in the affected ear. Accordingly, as the EH assessed by MRI was unchanged in the affected ear between 2 examinations in this study, the cochlear PE remained unchanged. Alternatively, the BLB permeability had a change too small to appear on MRI in patients with terminal MD stage (stage 3 and 4). In fact, most patients (57.14% and 70.13% at the first and second hospitalizations, respectively) included in this study had a terminal MD stage. Another reason may be that PE in the affected cochlea was unrelated to the MD stage, which was shown in this study. In addition, previous studies have noted that increased PE was seen in patients with sudden hearing loss (48,49), and therefore increased PE could be an incidental imaging biomarker and unique for MD.

Our study had some limitations. The primary limitation of this study was that for some patients, the 2 MRI examinations were not performed using the same MR system. Although the 2 MR imaging techniques have comparable resolution, use of the same MR system over 2 hospitalizations is needed to confidently compare changes in EH and PE. Second, the time interval between the 2 hospitalizations (median, 10 months) was short and varied. In addition, EH and PE were evaluated only twice via MRI during this period. A longer and more standardized observation period and more frequent evaluations of EH and PE by MRI are necessary to better understand the chronic course of MD. Third, this study included only MD patients with 2 hospitalizations rather than all MD patients admitted to our hospital, which biased the results somewhat. With the feasibility of assessing EH by nonenhanced MRI (50), in future studies, all MD patients will be followed for changes in EH to validate our conclusions.

Conclusions

Vertigo episodes and hearing loss in MD patients did not ameliorate, but rather vertigo attacks recurred and hearing loss in the affected ear worsened in this study. Although EH and PE in the affected inner ear were unchanged over 2 hospitalizations, the degree of EH in the asymptomatic ear for MD patients developed, and the degree of EH in the affected ear varied with the natural course of MD whereas PE did not. Therefore, EH instead of PE is necessary but insufficient to cause the clinical symptoms of MD.

Acknowledgments

Funding: This study was supported by the National Natural Science Foundation of China (No. 8190040190).

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6313/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6313/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6313/coif). WD is an employee of GE Healthcare.The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the ethics committee of Shandong

Provincial ENT Hospital (No. 20220112), and conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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(English Language Editor: A. Muijlwijk)

Cite this article as: Li J, Wang L, Hu N, Li L, Song G, Xu H, Xu T, Dou W, Li C, Yan W, Sun L, Gong R. Longitudinal variation of endolymphatic hydrops in patients with Ménière's disease. Ann Transl Med 2023;11(2):44. doi: 10.21037/atm-22-6313