Received: 7 June 2024 | Revised: 15 September 2024 | Accepted: 13 October 2024

DOI: 10.1002/lio2.70026

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Prognosis of asymptomatic endolymphatic hydrops in healthy volunteers: A five-year cohort study

Takahiro Kimura MD, PhD[1] | Tadashi Kitahara MD, PhD[1] | Tadao Okayasu MD, PhD[1] | Masaharu Sakagami MD, PhD[1] | Tomoyuki Shiozaki PhD[1] | Hiroshi Inui MD, PhD[1] | Toshizo Koizumi MD, PhD[2] | Mariko Kakudo MD, PhD[3]

[1]Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, Nara, Japan

[2]Department of Otolaryngology-Head and Neck Surgery, Nippon Life Hospital, Osaka, Japan

[3]Department of Otolaryngology, Takai Hospital, Nara, Japan

Correspondence
Tadashi Kitahara, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan.
Email: tkitahara@naramed-u.ac.jp

Funding information
JSPS KAKENHI (2022–2024) from the Japan Agency for Medical Research and Development, Grant/Award Number: 23K08915; Ministry of Health, Labour and Welfare of Japan, Grant/Award Number: 22dk0310117h0001

Abstract

Background: This study aimed to clarify the prognosis of asymptomatic endolymphatic hydrops (EH) in healthy volunteers via five-year follow-ups with inner ear magnetic resonance imaging (MRI).

Methods: Inner ear MRI was performed on 115 participants recruited as controls in a previous study on Meniere's disease. The endolymphatic space was visualized using Naganawa's method of contrast-enhanced MRI with intravenous gadolinium injection and evaluated using Nakashima's method of 2D imaging analysis.

Results: Cochlear or vestibular EH was present in 7.0% of participants ($n = 8$), with all cases being unilateral (laterality), moderate (severity), and asymptomatic (onset). Only cochlear-localized EH, only vestibular-localized EH, and both EH were present in 1.7% ($n = 2$) (C group), 4.3% ($n = 5$) (V group), and 0.9% ($n = 1$) (CV group) of participants, respectively. Conducting inner ear MRI after 5 years showed that EH had almost disappeared in two participants in the C and V groups (4/8, 50.0%). EH was still present in three participants in the V group and one in the CV group (4/8, 50.0%). One participant in the V group and another in the CV group presented with residual inner ear EH and developed typical symptomatic Meniere's disease (2/8, 25.0%).

Conclusions: Approximately 7% of healthy participants showed asymptomatic EH. Therefore, EH is not the definitive marker for making a diagnosis of Meniere's disease or the suitable predictor for the development of Meniere's disease. Among these participants, 25% maintained EH and subsequently developed typical Meniere's disease within the next 5 years. Schellong-positive participants maintained persistent

EH in the inner ear, and participants with higher scores on the self-rating depression scale developed Meniere's symptoms after 5 years.

Level of evidence: 2a

KEYWORDS

asymptomatic endolymphatic hydrops, autonomic nervous dysregulation, depression, healthy controls, inner ear gadolinium-enhanced MRI, Meniere's disease

1 | INTRODUCTION

Meniere's disease (MD) is characterized by repeated symptoms of rotatory vertigo attacks, sensorineural hearing loss, and tinnitus.[1] In 1938, the otopathology of MD was first revealed as endolymphatic hydrops (EH) by Dr. Yamakawa[2] and Dr. Hallpike[3] through temporal bone studies. Since then, EH has been considered a histological marker of MD,[4] and several neuro-otologic examinations, such as the glycerol test,[5,6] electrocochleogram,[6,7] and furosemide test,[8] have been established to diagnose EH.

In 2007, the otopathology of MD was first demonstrated by Nakashima and Naganawa,[9] who used delayed enhancement magnetic resonance imaging (MRI) after a transtympanic gadolinium injection. Since then, the intravenous injection of gadolinium with delayed acquisition of MRI sequences has permitted the visualization and classification of EH.[10,11] By using this technique, the Nara Medical University group revealed for the first time in 2016 that the EH-positive ratios in patients with definite MD were significantly higher than those in the control participants,[12] followed by the findings of the Nagoya University group in 2018.[13]

EH is considered an essential and reliable diagnostic tool for certain MD by the American Academy of Otolaryngology-Head and Neck Surgery in 1995[14] and by the Japan Society for Equilibrium Research in 2021.[15] However, histopathological[4] and imaging reports[12] showed some cases of asymptomatic EH. The present study aimed to clarify the prognosis of asymptomatic EH in healthy volunteers via 5-year follow-ups with inner ear MRI.

2 | MATERIALS AND METHODS

2.1 | Participants

Healthy human volunteers were originally recruited in the previous MD study as controls[12,16] and those with asymptomatic EH were picked up in this 5-year cohort one. Subjects with vertigo, hearing loss, middle or inner ear diseases, cranial disease, head trauma, renal disease, heart disease, or gadolinium allergy were excluded. This study was approved by the Medical Ethics Committee of Nara Medical University Hospital (certificate number: 0889). Written informed consent was obtained from all the subjects, and this study was performed in compliance with the Declaration of Helsinki.

A total of 115 subjects aged 20–83 years (mean age: 55.6 years) were enrolled in this study. Among these, 51 were men and 64 were women. They underwent the first inner ear MRI in a previous study on MD between May 2014 and April 2020 (Table 1). Those with positive EH results were scheduled to undergo a second imaging exam 5 years later (Table 2).

2.2 | Inner ear MRI

Naganawa et al. used MRI to show that the 4 h after the intravenous injection of Gd is a tool for imaging EH.[10,11] Briefly, in the current study, MRI measurements were performed 4 h after intravenous administration of a single dose (0.2 mL/kg or 0.1 mmol/kg body weight) of Gd-labeled diethylenetriaminepentaacetic acid bismethylamide (Magnescope; Guerbet, Tokyo, Japan). Imaging was performed on a 3 T MRI unit (MAGNETOM Verio; Siemens, Erlangen, Germany) by using a 32-channel array head coil. Special sequences for the differentiation of endolymphatic and perilymphatic fluids were adopted as proposed by Naganawa et al.[10,11]

All patients underwent the following: heavily T2-weighted (hT2W) MRI cisternography as an anatomical reference for the total lymph fluid; hT2W 3D fluid-attenuated inversion recovery sequences with an inversion time of 2250 ms, resulting in positive perilymph images (PPIs); and hT2W 3D inversion recovery with an inversion time of 2050 ms, resulting in positive endolymph images (PEIs). After acquiring these images, we obtained a hybrid of the reversed image of the positive endolymph signal and the negative image of the positive perilymph signal after motion correction by subtracting PEI from PPI, as proposed by Naganawa et al.[10,11] This protocol estimated pixels with negative values to represent the EH.

2.3 | MRI evaluation

Two otolaryngologists who were blinded to the patients' clinical progress evaluated the MRI findings. If the evaluations differed, a third otolaryngologist made the final decision. The cochlear and vestibular EH degree was classified as none, mild, or significant according to the criteria reported by Nakashima et al.[9] An axial slice near the modiolus was used to evaluate the cochlear EH. To evaluate the vestibular EH, one axial slice that displayed the vestibule to the maximum extent

TABLE 1 Characteristics of the 8 healthy participants with asymptomatic endolymphatic hydrops (EH) at the first inner ear magnetic resonance imaging.

First MRI	Age	Gender	Coch sympt	Vest sympt	EH laterality	CochEH	VestEH	AveHL	Schellong	SDS	Figures
Case-1	40	Female	No	No	R	+	−	N/A	N/A	N/A	Figure 1A
Case-2	42	Female	No	No	L	+	−	N/A	N/A	N/A	
Case-3	44	Male	No	No	L	−	+	N/A	N/A	N/A	
Case-4	48	Male	No	No	R	−	+	N/A	N/A	N/A	Figure 1B
Case-5	52	Male	No	No	R	−	+	N/A	N/A	N/A	Figure 1C
Case-6	50	Female	No	No	L	−	+	N/A	N/A	N/A	
Case-7	55	Female	No	No	L	−	+	N/A	N/A	N/A	Figure 1D
Case-8	46	Male	No	No	R	+	+	N/A	N/A	N/A	Figure 1E

Abbreviations: aveHL: four-tone-averaged hearing levels; cochEH: cochlear endolymphatic hydrops; Coch symptoms: cochlear symptoms; EH laterality: laterality of endolymphatic hydrops; Schellong: Schellong test; SDS: self-rating depression scale; vestEH: vestibular endolymphatic hydrops; vest symptoms: vestibular symptoms.

TABLE 2 Characteristics of the same eight participants as in Table 1 at the second inner ear magnetic resonance imaging.

Second MRI	Age	Gender	Vest sympt	Coch sympt	EH laterality	CochEH	VestEH	AveHL	Schellong	SDS	Figures
Case-1	45	Female	No	No	R	−	−	N/A	+	40	Figure 1A′
Case-2	47	Female	No	No	L	−	−	N/A	−	35	
Case-3	49	Male	No	No	L	−	−	N/A	−	50	
Case-4	53	Male	No	No	R	−	−	N/A	−	40	Figure 1B′
Case-5	57	Male	No	No	R	−	+	N/A	+	48	Figure 1C′
Case-6	55	Female	No	No	L	−	+	N/A	+	42	
Case-7	60	Female	Yes	Yes	L	−	+	18.8	+	69	Figures 1D′ and 2A
Case-8	51	Male	Yes	Yes	R	+	+	28.8	+	55	Figures 1E′ and 2B

Abbreviations: aveHL, four-tone averaged hearing levels; cochEH, cochlear endolymphatic hydrops; Coch symptoms, cochlear symptoms; EH laterality, laterality of endolymphatic hydrops; Schellong, Schellong test; SDS, self-rating depression scale score; vestEH, vestibular endolymphatic hydrops; vest symptoms, vestibular symptoms.

was adopted, but the ampulla of the semicircular canal was excluded from the evaluation.

Patients with no EH in the cochlea did not show Reissner's membrane displacement. Patients with mild cochlear EH showed displacement of the Reissner's membrane, but the area of the endolymphatic space did not exceed that of the scala vestibule. In patients with significant cochlear EH, the endolymphatic space area exceeded that of the scala vestibule. A higher grade was assigned when the EH grade differed between the basal and upper turns of the cochlea. In the vestibule, grading was determined from the ratio of the area of the endolymphatic space to that of the vestibular fluid space. Patients with no, mild, and significant EH in the vestibule had a ratio of ≤1:3, 1:3 to 1:2, and >1:2. In the present study, mild and significant EH were defined as "positive."

2.4 | Schellong test

All participants with positive EH on the first inner ear MRI underwent the Schellong test at the time of the second MRI after 5 years. Daily autonomic status can be easily measured in the clinic using the Schellong test to check changes in blood pressure (BP) or pulse rate (PR) as patients stand up from the supine position. A positive range was defined as systolic BP decrease >21 mmHg and/or PR increase >21 beats/min before and immediately after standing.[17]

2.5 | Self-rating depression scale (SDS) scoring

All participants with positive EH on the first inner ear MRI completed questionnaires on the SDS at the time of the second MRI 5 years later. Patients with SDS scores >40 (possible range 20–80) were classified as having depression. As seen in Table 3, the SDS comprises 10 positively and 10 negatively worded items that inquire about the symptoms of depression. These scores were used to define the following categories of depression: not having significant depression (≤40 points) and having significant depression (≥41 points). The SDS has been translated into Japanese, and its validity in the Japanese version has been confirmed.[18]

TABLE 3 Self-rating depression scale (SDS).

1. I feel downhearted and blue.
2. Morning is when I feel the best.
3. I have crying spells or feel like it.
4. I have trouble sleeping at night.
5. I eat as much as I used to.
6. I still enjoy sex.
7. I notice that I am losing weight.
8. I have trouble with constipation.
9. My heart beats faster than usual.
10. I get tired for no reason.
11. My mind is as clear as it used to be.
12. I find it easy to do the things I used to.
13. I am restless and can't keep still.
14. I feel hopeful about the future.
15. I am more irritable than usual.
16. I find it easy to make decisions.
17. I feel that I am useful and needed.
18. My life is pretty full.
19. I feel that others would be better off if I were dead.
20. I still enjoy the things I used to do

Note: SDS is a short self-administered survey to quantify the depressed status of a patient. There are 20 items on the scale that rate the four common characteristics of depression: the pervasive effect, the physiological equivalents, other disturbances, and psychomotor activities. There are 10 positively worded and 10 negatively worded questions. Each question is scored on a scale of 1–4 (a little of the time, some of the time, good part of the time, most of the time). The scores range from 25 to 100: 25–49, normal range; 50–59, mildly depressed; 60–69, moderately depressed; 70 and above, severely depressed.

2.6 | Statistical analysis

Fisher's exact and Mann–Whitney *U* tests were used in this study. Statistical significance was set at $p < .05$. All statistical analyses were performed using SPSS version 25.0 software (IBM Inc., Armonk, NY, USA).

3 | RESULTS

Among the 115 participants who underwent inner ear MRI, either cochlear or vestibular EH was present in 7.0% ($n = 8$), and all cases were unilateral (laterality), moderate (severity), and asymptomatic (onset) (Table 1 and Figure 1A–E). Only cochlear-localized EH was present in 1.7% ($n = 2$) (C group), only vestibular-localized EH in 4.3% ($n = 5$) (V group), and both EH in 0.9% ($n = 1$) (CV group).

Five years later, by using inner ear MRI again, EH almost disappeared in two participants in the C group and two participants in the V group (the EH reduction group) (4/8, 50.0%) (Table 2 and Figure 1A′–E′). EH was still present in three participants in the V group and one in the CV group (the persistent EH group) (4/8, 50.0%). One participant belonging to the V group and another belonging to the CV group presented with residual inner ear EH and developed typical symptomatic types of Meniere's (the EH/MD developed group) (2/8, 25.0%) (Figure 2).

Schellong tests were performed on all eight patients only once during the second MRI after 5 years (Table 2). In this examination, 5 showed positive results (5/8, 62.5%): 1 positive out of 4 in the EH reduction group (1/4:25.0%), 3 positive out of 4 in the persistent EH group (3/4:75.0%), and 2 positive out of 2 in the EH/MD developed group (2/2:100.0%). The OD positivity rates were relatively higher in the persistent EH group than in the EH reduction group (Fisher's exact test: $p = 0.07$). The OD-positive rates were almost the same in the EH/MD group as in the other groups (Fisher's exact test: $p = .36$).

SDS scoring questionnaires were administered to all 8 patients only once during the second MRI after 5 years (SDS scores: range 35–69, median 45.0) (Table 2). The SDS scores were relatively higher in the persistent EH group than in the EH reduction group (Mann–Whitney *U* test, $p = .08$). The SDS scores were significantly higher in the EH/MD group than in the other groups (Mann–Whitney *U* test: $p = .04$).

4 | DISCUSSION

First of all, we would like to discuss the controversial relationships between EH and MD. In our previous study of the inner ear MRI, it was revealed that EH could be detected in 80% and not detected in 20% of clinically diagnosed definite MD.[12] In the present study, EH could also be detected in 7% and not detected in 93% of healthy volunteers with no audiovestibular symptoms. By comparing the EH positive rates between these two studies, it is no doubt that the inner ear MRI could be one of the most reliable exams to make definite diagnosis as MD. However, the previous Harvard temporal bone study also reported that EH is detected in some cases with non-MD,[4] resulting in the supportive data for the present inner ear MRI study. Therefore, EH might not be the definitive marker for a certain diagnosis as MD. Okuno et al. reported in their Pittsburgh temporal bone study that EH is most frequently detected in otolithic organs in MD.[19] Noij et al. focused on functional abnormality in vestibular evoked myogenic potentials (VEMP)[20] and Bachinger et al. insisted on radiological hypoplasia of vestibular aqueduct[21] as predictors of bilateralization in unilateral MD. van der Lubbe et al. concluded in their review article that asymptomatic EH should be individually evaluated by not only detailed inner ear images but also various kinds of neuro-otologic exams during long-term follow-ups.[22] Nowadays, as neuroscientific relationships between EH and MD have not elucidated yet, hydropic ears, regardless of accompanied symptoms, should be treated modestly not as a definitive marker of MD but as an epiphenomenon of MD. When asymptomatic EH is detected, it should be better to take inner ear images together with various kinds of neuro-otologic exams for predicting the subsequent onset during long-term follow-ups. At least from the present study, it can be said that ~25% of cases with asymptomatic EH who never developed symptoms before could have Meniere's symptoms within the next 5 years. Further studies with much more cases and much more detailed audiovestibular exams are needed.

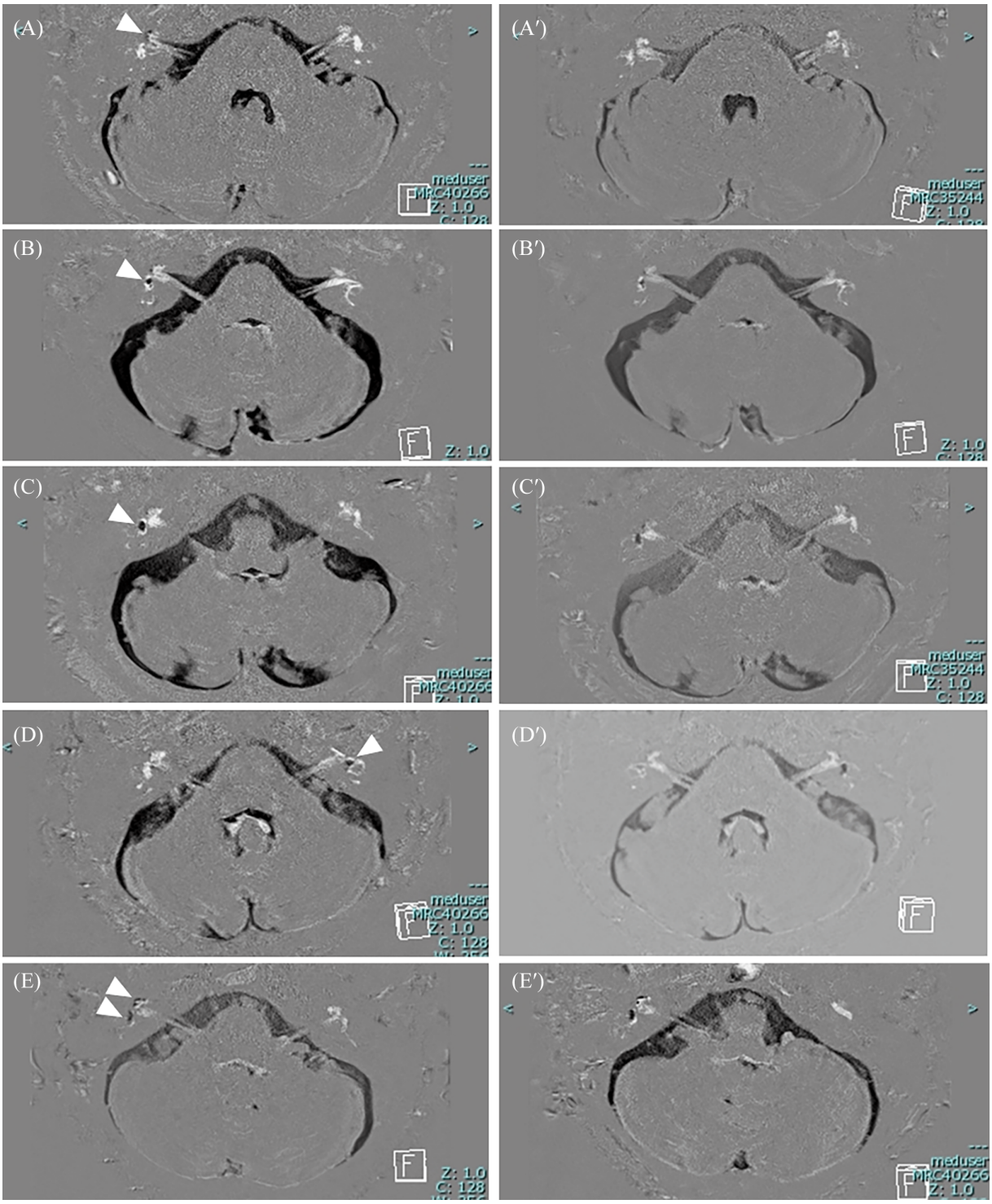

FIGURE 1 Representative participants with asymptomatic endolymphatic hydrops (EH) at the first inner ear magnetic resonance imaging (MRI) (A–E) and changes in the EH at the second inner ear MRI (A′–E′). Compared with the inner ear defects of 8 participants with asymptomatic EHs on the first MRI (A–E), EH almost disappeared in participants A′ (Case-1 in Tables 1 and 2) and B′ (Case-4 in Tables 1 and 2) 5 years later. EH persisted in participants C′ (case-5 in Tables 1 and 2), D′ (Case-7 in Tables 1 and 2), and E′ (Case-8 in Tables 1 and 2) 5 years later. Participant C′ showed no symptoms of Meniere's disease, but participants D′ and E′ developed typical symptoms of Meniere's disease. White arrowheads indicated EH in figures at the first inner ear MRI.

In the present study, 8 out of 115 healthy volunteers, that is, ~7% of normal participants, showed unilateral asymptomatic EHs on inner ear MRI. We should keep this rate of false-positive findings in mind when using inner ear MRI[12,16] and consider accompanying inner ear symptoms in diagnosing MD. EHs in 4 of the above 8 false positives remained unchanged, and EHs in 2 of these 4 participants

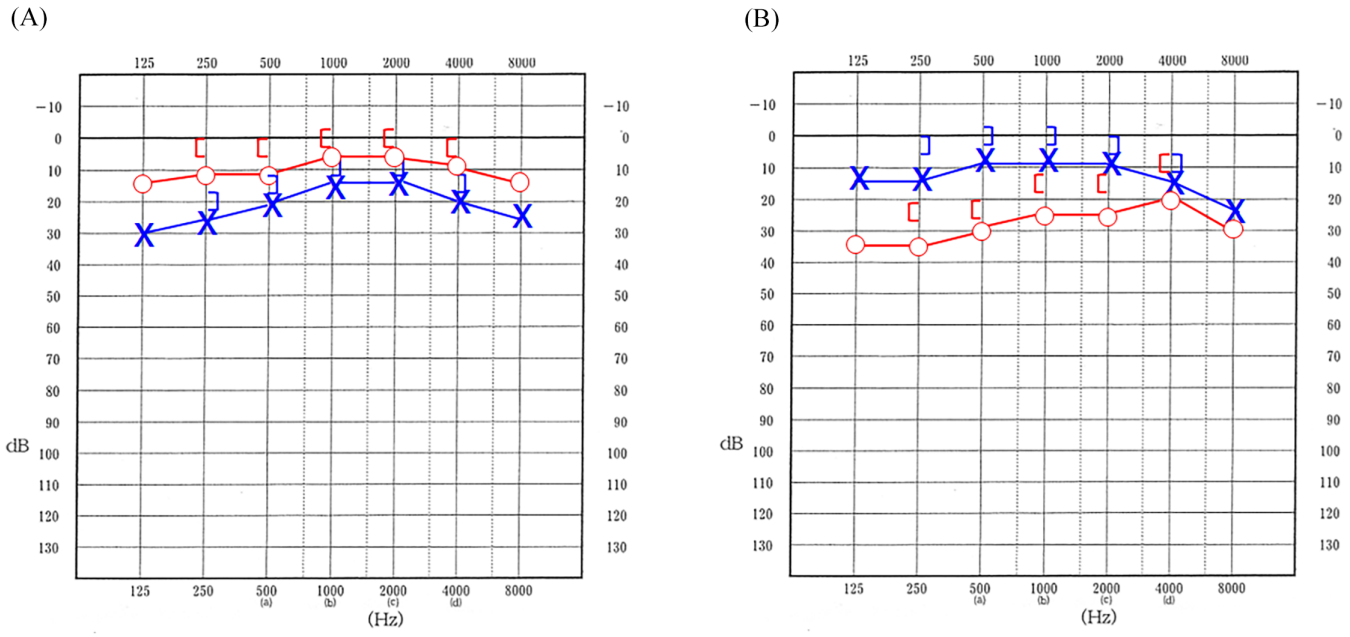

FIGURE 2 Pure tone audiometry charts in developed participants 7 (A) and 8 (B). Two patients with asymptomatic endolymphatic hydrops (EH) developed typical symptomatic Meniere's disease (MD), resulting in unilateral low-tone sensorineural hearing loss (SNHL). (A) Case-7 (Tables 1 and 2): This patient presented with left asymptomatic EH 5 years ago and developed left MD with repeated vertigo and left low-tone SNHL. (B) Case-8 (Tables 1 and 2): This patient presented with right asymptomatic EH 5 years ago and developed right MD with repeated vertigo and right low-tone SNHL.

developed symptoms within the next 5 years. The two participants with unchanged asymptomatic EHs may indicate their own physiological endolymphatic space and the other two who developed symptomatic EHs may imply the preliminary stage of MD at the first MRI. The possibility of the asymptomatic EHs detected using inner ear MRI from disappearing, remaining with no symptoms, and developing into Meniere's symptoms may be 50.0%, 25.0%, and 25.0% within the next 5 years, respectively. Recently, 3D quantitative analysis of the ratios of endolymphatic space volume out of total inner ear fluid space volume (ELS%) was used to diagnose MD, resulting in an accurate evaluation method of >27.5% in the vestibule, >16.2% in the cochlea, and >18.8% in the semicircular canals with a sensitivity of 0.84 and specificity of 0.92 (area under the curve: 0.88).[23] Further inner ear MRI research is needed to assess the quantitative relationship between symptom onset and ELS% in patients with MD.

The detailed mechanisms of EH generation and the onset of MD remain unknown. MD occurs specifically in white-collar workers in developed nations, that is, civilization is menierization, and psychogenic rather than physical stress may have a greater influence on inner ear pathology in MD.[24] Additionally, MD showed significant positive correlations with EH volume and stress level under psychological distress.[25] In the present study, we confirmed that Schellong-positive participants tended to maintain persistent EHs in the inner ear and that participants with higher scores on the SDS developed Meniere's symptoms 5 years later. Basic studies in rodents[26–28] and human[29–31] revealed that the dysregulation of adrenergic and vasopressinergic cells in the inner ear might collapse the inner ear fluid homeostasis, resulting in the production of EH. Overall, these results suggest that long-term autonomic system dysfunction can generate EH, and subsequent psychogenic stress in mental disorders could develop into the onset of MD.

This study had some limitations. The total number of participants with asymptomatic EH was small, and none of them underwent any other otology/neurotology examinations at the first visit, according to previous study designs.[12,16] Schellong tests and SDS scoring questionnaires were also performed just at the time of the second MRI and might not explain the conditions of the autonomic nervous system and mental stability during this five-year study. Future progress in magnetic resonance and MRI software quality is needed to clarify the neuroscientific relationships between psychogenic stress, EH, and MD.

5 | CONCLUSION

EH is not the definitive marker for making a diagnosis as MD because 7% of healthy participants showed asymptomatic EH by means of the present inner ear MRI study. EH is not a suitable predictor for the development of MD because 75% of healthy participants with asymptomatic EH showed no audiovestibular symptoms in the next 5 years by means of the present 5-year cohort study. Asymptomatic EH might lead to the onset of Meniere's symptoms through an autonomic imbalance and/or mental distress thereafter.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Michiko Shuto, a registered statistician (certificate number: 62720218), for the helpful advice on the statistical analyses and Professors Shinji Naganawa and Toshiaki Taoka (Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan) for their technical support. This study was partly supported by a Grant-in-Aid for Research on Intractable Vestibular Disorder from Japan AMED (2022–2024) and JSPS KAKENHI (Grant 2022–2024).

FUNDING INFORMATION

This study was supported in part by JSPS KAKENHI (2022–2024) from the Japan Agency for Medical Research and Development (Grant No. 23K08915) and AMED under Grant Number (22dk0310117h0001) from the Ministry of Health, Labour and Welfare of Japan.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Tadashi Kitahara https://orcid.org/0000-0002-5260-6202
Tadao Okayasu https://orcid.org/0000-0002-0811-1405
Hiroshi Inui https://orcid.org/0000-0002-3703-5288
Toshizo Koizumi https://orcid.org/0000-0002-2682-4329

REFERENCES

1. Sajjadi H, Paparella MM. Meniere's disease. *Lancet*. 2008;372:406-414.
2. Yamakawa K. Uber die pathologische Veranderung bei einem Meniere-Kranken. *J Otolaryngol Jpn*. 1938;44:2310-2312.
3. Hallpike CK, Cairns H. Observations on the pathology of Meniere's syndrome. *J Laryngol Otol*. 1938;53:625-655.
4. Merchant SN, Adams JC, Nadol JB Jr. Pathophysiology of Meniere's syndrome: are symptoms caused by endolymphatic hydrops? *Otol Neurotol*. 2005;26:74-81.
5. Klockhoff I, Llindblom U. Endolymphatic hydrops revealed by glycerol test. *Acta Otolaryngol*. 1966;61:459-462.
6. Mori N, Asai H, Suizu Y, Matsunaga T. Comparison between electrocochleography and glycerol test in the diagnosis of Meniere's disease. *Scand Audiol*. 1985;14:209-213.
7. Yoshie N. Diagnostic significance of the electro-cochleogram in clinical audiology. *Audiology*. 1973;2:504-539.
8. Futaki T, Kitahara M, Morimoto M. The furosemid test for Meniere's disease. *Acta Otolaryngol*. 1975;79:419-524.
9. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. *Laryngoscope*. 2007;117:415-420.
10. Nakashima T, Naganawa S, Pyykko I, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. *Acta Otolaryngol Suppl*. 2009;5-8:5-8.
11. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid after intravenous administration of single-dose gadodiamide. *Magn Reson Med Sci*. 2012;11:145-150.
12. Ito T, Kitahara T, Inui H, et al. Endolymphatic space size in patients with Meniere's disease and healthy controls. *Acta Otolaryngol*. 2016;136:879-882.
13. Yoshida T, Sugimoto S, Teranishi M, et al. Imaging of the endolymphatic space in patients with Meniere's disease. *Auris Nasus Larynx*. 2018;45:33-38.
14. Committee on Hearing and Equilibrium. Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg*. 1995;113:181-185.
15. Iwasaki S, Shojaku H, Murofushi T, et al. Committee for Clinical Practice Guidelines of Japan Society for Equilibrium Research. Diagnostic and therapeutic strategies for Meniere's disease of the Japan Society for Equilibrium Research. *Auris Nasus Larynx*. 2021;48:15-22.
16. Inui H, Kitahara T, Ito T, Sakamoto T. Magnetic resonance 3D measurement of endolymphatic space in 100 control human subjects. *J Int Adv Otology*. 2021;17:536-540.
17. Horinaka A, Kitahara T, Shiozaki T, et al. Head-up sleep may cure patients with intractable benign paroxysmal positional vertigo: a six-month randomized trial. *Laryngoscope Investig Otolaryngol*. 2019;4:353-358.
18. Fukuda K, Kobayashi S. A study on a self-rating depression scale. *Seishin Shinkeigaku Zasshi*. 1973;75:673-679.
19. Okuno T, Sando I. Localization, frequency, and severity of endolymphatic hydrops and the pathology of the labyrinthine membrane in Menière's disease. *Ann Otol Rhinol Laryngol*. 1987;96:438-445.
20. Noij KS, Herrmann BS, Guinan JJJ, Rauch SD. Predicting development of bilateral Menière's disease based on cVEMP threshold and tuning. *Otol Neurotol*. 2019;40:1346-1352.
21. Bachinger D, Schuknecht D, Dlugaiczyk J, Eckhard AH. Radiological configuration of the vestibular aqueduct predicts bilateral progression in Meniere's disease. *Front Neurol*. 2021;12:674170.
22. von der Lubbe MFJA, Vaidyanathan A, Rompaey VV, et al. The "hype" of hydrops in classifying vestibular disorders: a narrative review. *J Neurol*. 2020;267:197-211.
23. Ito T, Inoue T, Inui H, et al. Novel magnetic resonance imaging-based method for accurate diagnosis of Meniere's disease. *Front Surg*. 2021;8:e671624.
24. Watanabe I. Ménière's disease with special emphasis on epidemiology, diagnosis and prognosis. *ORL*. 1980;42:20-45.
25. Fujita H, Ueda K, Kageyama K, Shiozaki T, Inui H, Kitahara T. Relationships between stress levels and endolymphatic space volume in Meniere's disease. *Auris Nasus Larynx*. 2023;50:866-873.
26. Minteguiaga C, Clerget MS, Huy PT, Elalout JM. Beta2-adrenergic but not vasopressin V2 receptor mRNAs are expressed in the stria vascularis of the rat inner ear. *Pflugers Arch*. 1998;436:940-947.
27. Inamoto R, Miyashita T, Akiyama K, Mori T, Mori N. Endolymphatic sac is involved in the regulation of hydrostatic pressure of cochlear endolymph. *Am J Physiol Regul Integr Comp Physiol*. 2009;297:1610-1614.
28. Kakigi A, Egami N, Uehara N, et al. Live imaging and functional changes of the inner ear in an animal model of Meniere's disease. *Sci Rep*. 2020;10:12271.
29. Birgerson L, Friberg U, Rask-Andersen H, Widenfalk B. Adrenergic innervation of the human endolymphatic sac. *Acta Otolaryngol*. 1994;114:529-532.
30. Kitahara T, Doi K, Maekawa C, et al. Meniere's attacks occur in the inner ear with excessive vasopressin type-2 receptors. *J Neuroendocrinol*. 2008;20:1295-1300.
31. Kim BG, Kim JY, Jung JS, et al. Beta1- and beta2-adrenergic stimulation-induced electrogenic transport by human endolymphatic sac epithelium and its clinical implications. *Sci Rep*. 2017;7:42217.

How to cite this article: Kimura T, Kitahara T, Okayasu T, et al. Prognosis of asymptomatic endolymphatic hydrops in healthy volunteers: A five-year cohort study. *Laryngoscope Investigative Otolaryngology*. 2024;9(6):e70026. doi:10.1002/lio2.70026