


# Longitudinal Up-Regulation of Endolymphatic Hydrops in Patients with Meniere's Disease During Medical Treatment

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**Objective/Hypothesis:** Meniere's disease (MD) is a common inner ear disease characterized by repeated episodic vertigo, fluctuating sensorineural hearing loss, and tinnitus. Its pathology is defined as endolymphatic hydrops (EH) in the inner ear and EH has been hypothesized to correlate with the clinical symptoms of MD. We presented the dynamics of in vivo EH in MD patients during medical treatments.

**Study Design:** Prospective, single-arm repeated measures

**Methods:** Eleven MD patients were enrolled. All subjects prospectively underwent gadolinium-enhanced inner ear magnetic resonance (MR) imaging and neuro-otological testing before and after medical treatment. The volume of EH was quantitatively evaluated by processing MR images. All MD patients were administered continuous medication and followed up for more than 12 months.

**Results:** The frequency of vertigo episodes decreased in all patients and vestibular function decreased to 13–91% of the pre-treatment level. The volume ratio of post-treatment EH-to-pre-treatment EH ranged from 1.01–3.22. The total volume of pre-treatment EH was significantly correlated with cochlear symptom disease duration and the affected ear's hearing level.

**Conclusion:** EH in MD patients developed longitudinally with deterioration of inner ear function during medical treatment. The natural course of MD may progress with development of EH at least for a certain period.

**Key Words:** Meniere's disease, endolymphatic hydrops, gadolinium-enhanced inner ear magnetic resonance imaging.

**Level of Evidence:** 2b.

## INTRODUCTION

Meniere's disease (MD) is a common inner ear disease with an estimated prevalence of 0.19–0.27%<sup>1,2</sup> and it is characterized by episodic vertigo, fluctuating sensorineural hearing loss, and tinnitus. The chronic course of MD has been explored in several studies.<sup>3</sup> The vertigo

episodes improve, but both vestibular and hearing function deteriorate. In 1938, MD pathology was reported to be endolymphatic hydrops (EH) in the inner ear, based on temporal bone studies,<sup>4,5</sup> and histologically diagnosed EH was shown to be present in every individual with a clinical MD diagnosis.<sup>6,7</sup> This close association between MD and EH led to the hypothesis that EH causes the clinical symptoms of MD although there exists an opposing opinion that EH is only a histologic marker.<sup>7</sup> Diagnosing MD patients is, thus, identifying the presence of EH. Neuro-otologic examinations such as the glycerol test, furosemide test, electrocochleography, and glycerol vestibular-evoked myogenic potentials are used to prove EH clinically.<sup>8</sup> Treating MD patients in the long-term is the equivalent to reducing EH. Therapeutic agents such as diuretics and betahistine are widely administered.<sup>9</sup> Intratympanic gentamicin (ITG) is the treatment of choice for intractable MD and it is hypothesized to work by damaging the secretory function of vestibular dark cells and thereby reducing EH.<sup>10</sup> Surgery on the endolymphatic sac to improve drainage and decrease EH is another commonly performed option for patients with intractable MD.<sup>11</sup> Thus, EH is now widely recognized as a typical marker for MD, even though this hypothesis has not been conclusively proven.

Recently, 3 Tesla magnetic resonance (MR) imaging, in combination with intratympanic administration of gadolinium (Gd), allowed for successful visualization of EH in MD patients.<sup>12</sup> This new in vivo imaging process

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gives us a chance to understand the pathologic role of EH associated with MD. Episodic vertigo, probably the most disturbing of the main triad of clinical symptoms, has a good prognosis over a long period of time. EH is expected to decrease in association with decreasing vertigo if the symptoms of MD are caused by EH. Visualization of EH using 3T MR imaging 4 h after intravenous administration of Gd is now more routinely performed.<sup>13</sup>

In the present study, we medically treated MD patients and prospectively evaluated the dynamics of EH using Gd-enhanced inner ear MR imaging. To understand the extent to which EH affects diagnostic symptoms, it is necessary to explore how EH behaves longitudinally during medical treatment. In addition, we determined plasma vasopressin to examine a potential role in EH development because it would regulate inner ear homeostasis.<sup>14</sup>

## MATERIALS AND METHODS

### Patients

Eleven consecutive patients with definite unilateral MD<sup>15</sup> and three healthy control subjects were enrolled in this study. The present study was approved by the Ethics Committee of Kansai Rosai Hospital (certificate number: 15D077g). All patients were fully informed about the execution and goals of the study and provided informed consent to participate in this study. At the time of diagnosis, all patients underwent MR imaging and neuro-otological testing. They were not administered continuous medication but anti-emetic effects drugs such as dimenhydrinate and diazepam were allowed only when vertigo attacks occurred. All patients then received continuous medication at least for 8 months and were followed up for vertigo and hearing at least once a month for more than 12 months. Medical treatments included diuretics and/or betahistine, which were considered to be effective for persistent MD symptoms.<sup>9</sup> For example, betahistine mesilate was administered at a daily dose of 36 mg (12 mg three times) and isosorbide, an osmotic diuretic, was administered at a daily dose of 42–63 mg (21 mg two or three times). A second MRI examination was performed after medical treatment and the assessed EH was compared with the pre-treatment examination. Healthy control subjects had never experienced vertigo attacks and their hearing level was normal. They also underwent MR imaging two times at intervals of 12–15 months.

### MRI

MR imaging was performed as previously described.<sup>16,17</sup> Briefly, a standard dose (0.2 ml/kg) of intravenous gadodiamide hydrate (Omniscan; Daiichi Sankyo Pharmaceutical Co., Ltd., Tokyo, Japan) was administered and 4 h later, MRI was performed using a 3T MR imaging unit (Magnetom Verio; Siemens, Erlangen, Germany) equipped with a receive-only 32-channel phased-array coil. All patients underwent heavily T2-weighted (hT2W) MR cisternography (MRC) for the anatomical reference of total lymph fluid, and hT2W 3D-FLAIR with inversion times of 2250 and 2050 ms. HYDROPS imaging was used to detect EH<sup>13</sup>. The details of the sequence parameters are described previously.<sup>18</sup>

### EH Image Evaluation

The HYDROPS-Mi2 image was obtained by multiplying the MRC and HYDROPS images using a DICOM viewer OsiriX

(ver. 8.0, Pixmeo SARL, Berne, Switzerland).<sup>19,20</sup> Experienced otologists, who were blinded to the clinical progress of patients, manually placed regions of interest (ROI) contouring of the cochlea and vestibule on the MRC (Fig. 1a upper row) and then they were copied to the HYDROPS-Mi2 image (Fig. 1a lower row). Using the histogram and the area measuring function of OsiriX, we measured the total number of all pixels in the ROI and the number of pixels with negative signal intensity values (which represents EH) in the ROI. The total amount of measured ROI area corresponds to the total inner ear fluid volume. The total EH volume was semi-quantitatively calculated according to the ratio defined as the number of negative pixels for EH in the ROI divided by the total number of pixels in the ROI.

### Functional Examination

Hearing function was measured using pure tone audiometry (PTA) and evaluated based on the four-tone average formulated by  $(a + b + c + d)/4$  (where a, b, c, and d are hearing levels at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz, respectively) according to the modified 1995 AAO-HNS criteria.<sup>15</sup> The worst hearing level during the 6 months before admission to this study was considered to be the pre-treatment hearing level and the worst hearing level during the most recent 6 months after medical treatment was considered to be the post-treatment hearing level. More than a 10-dB difference in hearing levels pre- and post-treatment was considered to be “better,” less than a –10 dB difference was considered to be “worse,” and anything in between was considered to be “no change.”

A definitive dizzy spell lasting more than 20 min was regarded as a Meniere's vertigo episode.<sup>15</sup> The frequency of vertigo was calculated based on the number of vertigo episodes during the 6 months before medical treatment. Frequency after medical treatment was calculated based on the number of vertigo episodes during the latest 6 months after medical treatment. Vestibular function was measured by a caloric test using an electronystagmography (ENG), once before and once after medical treatment. For the caloric test, the external auditory canal was irrigated with 20 mL of cold water at 30°C followed by 20 mL of hot water at 44°C for 10 s. The induced nystagmus was recorded using ENG in a dark, open-eyes situation. Based on the mean maximum slow-phase eye velocity (max-SPEV) on the treated side, the max-SPEV after treatment-to-max-SPEV before treatment ratio was calculated.

### Measurement of Plasma Antidiuretic Stress Hormone Vasopressin (pAVP)

As reported previously,<sup>16</sup> plasma vasopressin was determined using a radioimmunoassay (arginine vasopressin radioimmunoassay kit; Yamasa, Chiba, Japan) before medical treatment. The normal average pAVP level was 1.25 pg/ml, with a range of 0.3–3.5 pg/ml, based on the data acquired by blood samples collected at 08.00–10.00 h from 105 healthy subjects (61 males, 44 females) who provided informed consent and who had no history of vestibular or cochlear disease.

### Statistical Analysis

Data were assessed statistically using JMP version 12.2.0 (SAS Institute, North Carolina, USA). The correlation analysis was performed with the Pearson's correlation coefficient. The Wilcoxon signed-ranks test was performed to evaluate the difference between repeated-measures where subjects are correlated. P-values less than 0.05 were considered significant.

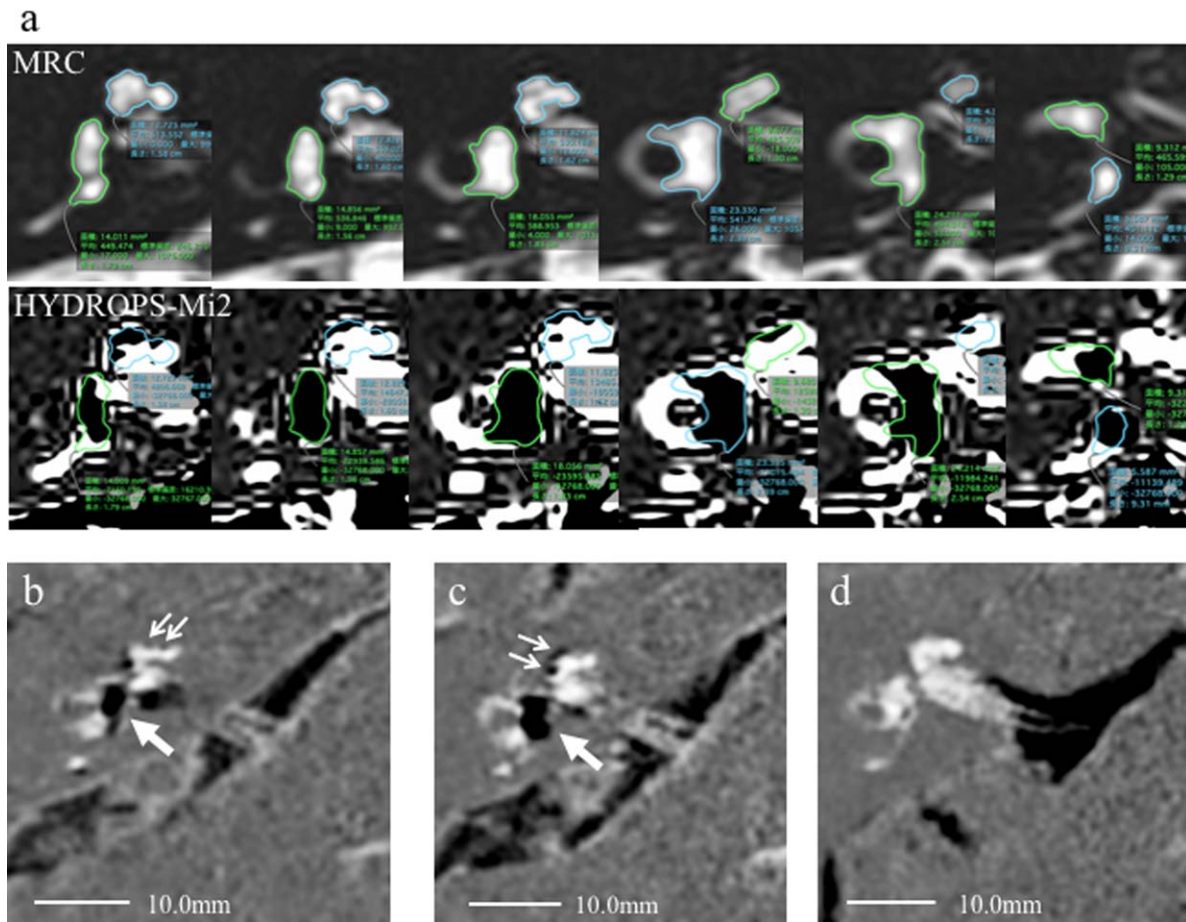


Fig. 1. (a) Upper row: an example of successive series of six MRC images with ROIs including the right cochlea and vestibule. At the mid-modiolar slice, the cochlea is curved, excluding the modiolus. Lower row: the successive series of 6 HYDROPS-Mi2 images with ROIs copied from the above corresponding MRC images. These six images on the right-hand side correspond anatomically to the upper direction of the inner ear. (b) Axial MR image of the right inner ear with EH in MD at the time of diagnosis (Patient 2, pre-EH, HYDROPS image). EH in the cochlea (thin arrows) and in the vestibule (thick arrows). (c) Axial MR image of the right inner ear with EH in MD after medical treatment (Patient 2, post-EH, HYDROPS image). EH in the cochlea (thin arrows) and in the vestibule (thick arrows). (d) Axial MR image of the right inner ear with no evidence of EH (healthy control subject, HYDROPS image). Contrast-enhanced perilymph space is clearly visible. Each scale bar in Figure 1b–d indicates 10.0 mm. EH = endolymphatic hydrops; MR = magnetic resonance; MRC = magnetic resonance cisternograph; ROI = regions of interest

## RESULTS

The clinical characteristics of the study cohort are summarized in Table I. The patient population consisted of five males and six females, with ages ranging from 44 to 77 years (median, 68 years). The duration since cochlear or vestibular symptoms first developed (disease duration) ranged from 1 to 168 months. Shaded columns of PTA in Table I indicate affected side. The mean number of vertigo episodes per month during the 6 months before and after medical treatment was recorded. It decreased in all patients. The disease stage was based on hearing function. Stages I, II, III, and IV correlated with four-tone averages of the worst audiograms in the 6 months before treatment of <25, 25–40, 41–70, and >70, respectively. In this study cohort, there were three patients at stage II, seven patients at stage III, and one patient at stage IV. Hearing function was assessed in seven patients as having “no change,” in two patients as being “worse,” and in two patient as being “better.” Vestibular function in eight of 11 patients was measured

pre- and post-treatment. The caloric response decreased to 13–91% of the pre-treatment level. The total volume of pre-treatment EH varied from 5.3–69.5  $\mu\text{L}$ . The volume ratio of post-treatment EH-to-pre-treatment EH was always more than 1.00 and ranged from 1.01–3.22. The length of follow-up was 13–29 months (median, 18 months). The total volume of pre-treatment EH was significantly correlated with cochlear symptom disease duration and the affected ear’s hearing level (Pearson’s correlation coefficient,  $r = 0.686$  and  $0.638$ , respectively;  $p = 0.0197$  and  $0.0346$ , respectively; Figs. 2a and 2b). The total volume of pre-treatment EH was not correlated with the mean number of vertigo episodes per month. The concentration of the plasma antidiuretic stress hormone vasopressin (pAVP) was significantly correlated with the post-to-pre-EH volume ratio (Pearson’s correlation coefficient,  $r = 0.718$  and  $p = 0.0129$ ; Fig. 2c).

Representative MR images of EH are presented in Figure 1b and 1c. The black areas represent the endolymphatic space in the labyrinth, and the white areas

TABLE I.  
Clinical Characteristics of the Study Cohort.

Case no.	Age, Sex	Disease duration (m) C/V	PTA (dB) R/L	pAVP (pg/ml)	Vertigo attacks Pre (x/mo)	Vertigo attacks Post (x/mo)	Hearing improvement	Caloric response post/pre max-SPEV	Total volume of EH (post, $\mu$ L)	Volume ratio of post/pre EH	Follow-up (m)
1	56, F	26 17	35.0 42.5	2.3	1.5	0.67	worse	0.52	14.8	1.83	17
2	58, F	27 34	33.8 18.8	5.5	30	2.5	worse	0.72	28.6	1.87	29
3	68, M	60 36	35.0 70.0	4.9	1	0	n.c.	0.13	10.0	2.80	16
4	74, M	48 60	42.5 36.3	16.0	1	0	n.c.	-	10.7	3.22	28
5	62, F	28 27	30.0 8.8	2.7	1	0	better	-	14.2	1.37	28
6	66, M	96 19	12.5 65.0	3.8	15	0.5	n.c.	0.54	38.1	2.23	18
7	76, F	168 1	96.3 28.8	4.5	4	2	n.c.	0.32	64.1	1.01	18
8	77, M	30 5	30.0 55.0	2.1	2	0	n.c.	0.90	36.2	1.30	14
9	77, F	60 18	60.0 13.8	3.0	1	0	n.c.	0.47	69.5	1.29	15
10	44, M	120 12	53.8 8.8	3.9	4	0	better	0.91	46.7	1.11	13
11	74, F	1 48	31.3 31.3	3.3	8	2	n.c.	-	5.3	1.66	19

C = cochlear symptom (upper row); V = vestibular symptom (lower row); R = right ear (upper row); L = left ear (lower row); n.c. = no change

represent the perilymphatic space. Figure 1b shows EH in the right inner ear at the time of diagnosis and Figure 1c shows the EH after treatment (Patient 2). Figure 1d shows no EH in the right inner ear of a healthy control subject. The value of total EH volume in healthy control subjects (six ears) is listed in Table II. Each value of upper row corresponds right inner ear and lower row corresponds left inner ear. The time intervals between the first and second MRI examination of healthy control subjects were more than 12 months and the volume of EH was not significantly different between time intervals in six ears (Wilcoxon signed-ranks test,  $p = 0.625$ ). All these three MR images are HYDROPS images.<sup>13</sup>

## DISCUSSION

MD is a chronic disease with recurrent vertigo, tinnitus, and fluctuating hearing loss. Approximately 10–20% of patients have intractable MD and these symptoms persist despite various types of medication. We previously reported long-term results of vertigo control and hearing impairment from intractable MD with either surgery ( $n = 220$ ) or medical treatment ( $n = 66$ ).<sup>21</sup> The complete vertigo control and hearing deterioration in the medical treatment group increased gradually during the 2–13-year follow-up period. In this small study group,

vertigo episodes were completely controlled in six out of 11 patients (54.5%) and hearing function worsened in two of 11 patients (18.2%) (Table I). This study cohort showed better results for vertigo control and hearing deterioration than that of the medical treatment group from intractable MD in our previous study,<sup>21</sup> which suggests that this group belongs to the largest group of patients with non-intractable MD.

In this study, the duration of cochlear symptoms and the hearing level of the affected ear were significantly correlated with the total volume of pre-treatment EH (Fig. 2a and 2b). The duration and the degree of hearing impairment were assumed to affect the volume of pre-treatment EH. Correlation between the duration of MD and the prevalence of EH in the cochlea and semicircular canals was reported in a cross-sectional study.<sup>22</sup> Medical inquiries about the timing of hearing impairment and the hearing level of the affected ear can be helpful to estimate the volume of EH.

In 1938, the pathology of MD was reported by EH,<sup>4,5</sup> and EH is now widely recognized as a typical marker of MD. However, the long-term course of EH has not been well studied because pathologic findings can only be ascertained in post-mortem histologic studies. The finding that histologically diagnosed EH was present in every individual with a clinical diagnosis of MD was reported in a recent study.<sup>7</sup> This close association of

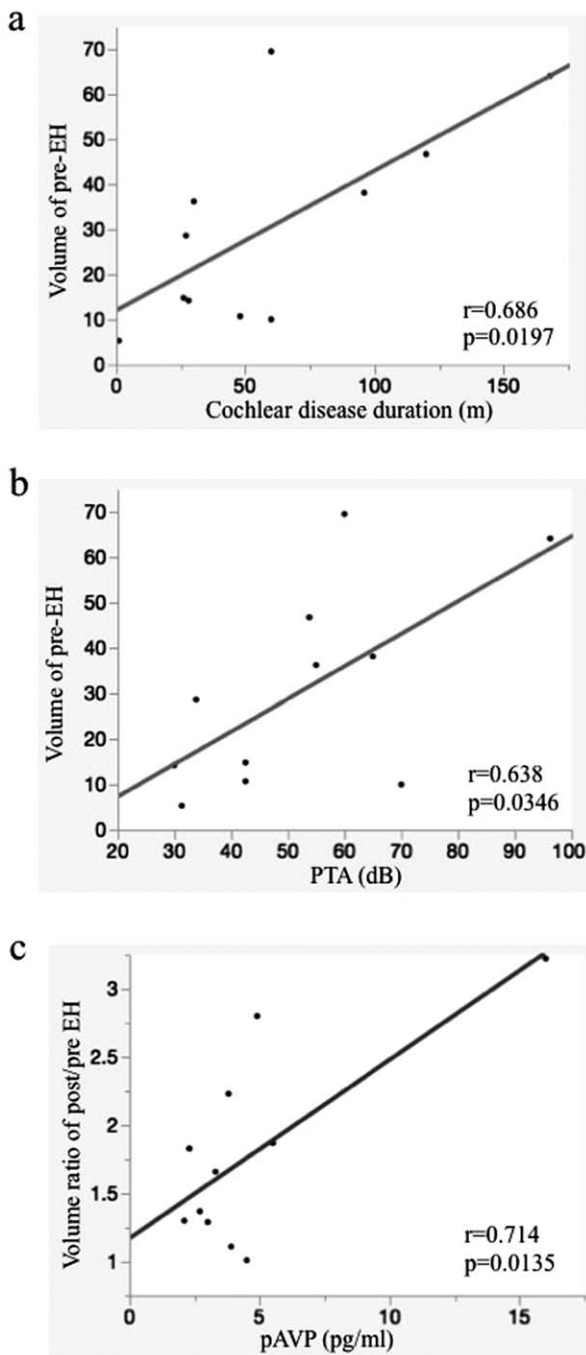


Fig. 2. (a) Correlation between the volume of pre-EH and the duration of cochlear symptoms. (b) Correlation between the volume of pre-EH and hearing loss in the affected ear, expressed as the four-tone average (PTA) at 0.5, 1, 2, and 4 kHz in dB. (c) Correlation between the post-to-pre-EH volume ratio and the plasma vasopressin concentration. EH = endolymphatic hydrops; PTA = pure tone audiometry

MD with EH led to the hypothesis that EH is closely related to the clinical symptoms of MD. Many factors have been proposed as leading to development of EH. In this study cohort, all patients had decreased vertigo and either improved or had an unchanged hearing level in nine of 11 patients after medical treatment (Table I).

Vertigo episodes were well controlled and hearing function was maintained, but despite medical treatment, the volume of EH always increased (Fig. 1b and 1c). In some patients, it increased to more than twice the pre-treatment EH volume. We are interested in how EH behaves during medical treatment because the functional role of EH in MD remains controversial.<sup>7,23</sup> If EH alone generates and correlates with the symptoms of MD, EH is usually expected to decrease as vertigo episodes decrease. In contrast to our expectations, EH developed independently of improving MD vestibular symptoms in this study. It was reported that vertigo suppression after sac surgery was not always a result of the reduced EH.<sup>24</sup> This suggests that EH increased after sac surgery. It corresponds to our findings.

Only diuretics and betahistine are thought to be effective for long-term treatment of MD.<sup>9</sup> Diuretics have widely been used in MD to reduce EH and a decrease in vestibular complaints in MD patients was reported in a crossover placebo-controlled study.<sup>25</sup> Isosorbide, an osmotic diuretic, was shown to reduce EH in an animal model without a rebound increase in EH,<sup>26</sup> and it has been reported to be effective at relieving MD symptoms.<sup>27</sup> Betahistine is a strong H3 antagonist and it increases the dose-dependent cochlear blood flow.<sup>28</sup> It could improve labyrinthine microcirculation and thereby rebalance EH fluid metabolism. The therapeutic benefit of betahistine on vertigo symptoms was shown in a meta-analysis of clinical studies.<sup>29</sup> However, post-treatment EH developed longitudinally in this study. In a recent report, betahistine did not change the degree of EH assessed by MR imaging in 100% of patients ( $n=6$ ) despite decreased vertigo episodes.<sup>30</sup> Additionally, the EH volume assessed by MR imaging did not change in four patients and continued to develop in another four MD patients ( $n=8$  overall) after treatment with ITG.<sup>31</sup> These findings suggest that EH does not decrease during medical treatment, which is a new concept that conflicts with current knowledge about MD.

EH depletion tests have been used clinically to improve the diagnosis of MD. One such test is the glycerol test to reveal cochlear EH associated with audiometry. Another is the furosemide test to reveal vestibular EH associated with caloric stimulation and vestibular-evoked myogenic potentials. However, in a recent study, furosemide administration did not change EH assessed

TABLE II.  
The Value of Total EH Volume in Healthy Control Subjects.

	1st EH volume ( $\mu$ L)	2nd EH volume ( $\mu$ L)	Time intervals (m)
Control 1	11.8	9.7	12
	11.6	10.3	
Control 2	7.8	8.8	15
	7.2	7.5	
Control 3	7.3	6.5	13
	8.2	9.0	

EH = endolymphatic hydrops

by MR imaging in all 12 MD patients.<sup>32</sup> Furosemide has a potent, rapid diuretic effect, which should have a reducing effect on EH. Thus, we suggest that both EH and cofactors are responsible for MD symptoms. EH may still be responsible for MD symptoms because current MR imaging techniques assess EH quantity, but not its quality. It had been suggested that EH consists of different characteristics, such as degenerative hydrops and irritative hydrops.<sup>4</sup>

We suggest that vasopressin (pAVP), an anti-diuretic stress hormone that has a potential role in inner ear homeostasis, plays a role in EH development. It is reported that levels of pAVP were significantly higher in patients who had EH including MD during remission<sup>33</sup> or vertigo episodes,<sup>34</sup> compared with patients who had vertigo related to non-EH causes such as benign paroxysmal positional vertigo and vestibular neuronitis. Systemic injection of vasopressin induces bilateral EH and hearing deterioration in guinea pigs.<sup>35</sup> These findings suggest that a high level of pAVP can induce EH development in MD patients. While one extreme value of 16.0 could be an outlier (Patient 4), plasma vasopressin concentrations significantly correlated with the post-to-pre-EH volume ratio in our preliminary study cohort (Fig. 1c). This direct proportions will reach a plateau because inner ear fluid volumes measured by MRI volumetric assessments in healthy subjects are limited to 195 mm<sup>3</sup> (range, 150–279 mm<sup>3</sup>).<sup>36</sup> We hypothesize that EH developed independently of the improving MD vestibular symptoms as a result of medical treatment, because higher levels of plasma vasopressin concentrations in MD patients might have caused higher increasing rate of EH.

Our study has some limitations. First, the number of MD patients in this pilot study was small. The concept that reduction of EH is not always necessary to treat MD patients is new and needs to be further validated in a study enrolling more patients. Second, the follow-up period (median, 18 months) was short and EH evaluation by MR imaging occurred only twice during this period. A longer observation period and more frequent evaluations of EH by MR imaging are necessary to better understand the long-term course of MD.

## CONCLUSIONS

EH in MD patients did not decrease, but rather it further developed during medical treatment in this study, which was in contrast to our expectations. Though the vertigo episodes ameliorated superficially during medical treatment, an underlying EH in MD patients had developed with deterioration of vestibular and hearing function. The natural course of MD may progress with development of EH at least for a certain period.

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## AUTHOR CONTRIBUTIONS

MF conceived and designed the experiments and wrote the paper. MF, RO, and SA performed the experiments. MF, TK, HI, SN, and NT analyzed the data.

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