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Modulation of hearing function following the downgrading or upgrading of endolymphatic hydrops in Meniere's disease patients with endolymphatic duct blockage

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Abstract

The present study was to investigate the dynamics of endolymphatic hydrops (EH) and hearing function, and explore whether the hearing loss is caused by EH alone and whether the hearing function can be modulated by changes in the EH. The extent of EH visualized by gadolinium (Gd)-enhanced inner ear magnetic resonance imaging, hearing thresholds and the summating potential/action potential ratio (-SP/AP ratio) of electrocochleography (ECochG) were recorded prior to and following surgery in 22 patients with intractable Meniere's disease (MD) who underwent endolymphatic duct blockage (EDB). The difference value of the hearing threshold and -SP/AP ratio was significantly positively correlated with the difference value of the endolymph to vestibule-volume ratio (EVVR) and grading of cochlear hydrops between prior to and following surgery. Among patients with a decreased EVVR, the average hearing threshold and -SP/AP ratio was significantly decreased following surgery, as compared to that prior to surgery. Six out of seven patients with a hearing improvement (≥10-dB decline) and 4/5 patients with a negative conversion of EcochG showed downgrading of their hydrops in the cochlea and/or vestibule. By contrast, among patients with an increased EVVR, the average hearing threshold and -SP/AP ratio tended to increase following EDB, as compared with that prior to surgery. One out of two patients with a hearing deterioration (≥10-dB elevation) showed upgrading of her hydrops in both cochlea and vestibule. The present results showed the downgrading of cochlear and/or vestibular hydrops accompanied by the downregulation of the hearing threshold and -SP/AP ratio of EcochG, as well as the upgrading of cochlear and/or vestibular hydrops that tended to upregulate the hearing threshold and -SP/AP ratio of EcochG; this suggested that hearing loss is likely to be caused by hydrops and that the impaired hearing function be modulated by changes in the hydrops.

Introduction

Meniere's disease (MD) is a well-recognized but inadequately understood condition associated with the classic triad of episodic vertigo, low-tone fluctuating sensorineural hearing loss and tinnitus. Numerous studies have confirmed that virtually all cases of "true" MD present with endolymphatic hydrops (EH) in the inner ear [1–4]. However, certain studies have proposed that the presence of EH in MD may be a mere epiphenomenon, with no direct causal relationship to the disease [5]. The association between EH and Meniere's symptoms has been questioned [6]. Yet, in the last decade, in vivo visualization of EH by MRI has provided compelling evidence linking EH to clinical symptoms of MD [7–10]. A mounting body of evidence from radiologically-proven hydrops has identified a strong correlation between the extent of hearing loss and that of hydrops, particularly in the low tone range [11–15]. However, the way in which the hydrops affects hearing function is not fully understood.

In the present study, the dynamics of EH were evaluated using gadolinium (Gd)-enhanced inner ear MRI, changes in hearing thresholds and summating potential/action potential ratio (-SP/AP ratio) of electrocochleography (ECochG) in a group of patients who had undergone endolymphatic duct blockage (EDB) for the treatment of MD; the aim was to clarify whether or not the change of hydrops is likely to modulate the hearing function and -SP/AP ratio, which would verify a cause-effect relationship between hydrops and auditory physiology.

Materials and methods

Patients

This study was conducted at a large tertiary referral center. Between January 2018 and December 2018, a total of 2,160 patients with vertigo or dizziness were referred to our otology-led vertigo clinic. According to the diagnostic criteria for MD jointly formulated by the Classification Committee of the Bárány Society [16], 62 patients were diagnosed with unilateral definite MD, 8 patients with bilateral definite MD and 18 patients with unilateral probable MD. Out of these 88 patients with definite or probable MD, 39 with intractable MD were hospitalized and referred for 3T MRI of the temporal bone, which demonstrated EH. A total of 26 patients (12 females and 14 males; age range, 30–72 years; mean age, 51.2 years) with intractable MD and MRI-based visualization of unilateral EH underwent EDB for the treatment of MD. Intractable MD in patients was defined as recurrent vertigo/dizziness for ≥6 months, with a failure of systematic medical treatment and psychological management, including appropriate life guidance (i.e., reduction of stress, prevention of overworking and appropriate exercise), as well as oral therapy involving the administration of osmotic diuretic medicine, ameliorants of inner ear circulation, cyanocobalamin and traditional Chinese medicine.

The present study was approved by the Medical Ethics Committee of the Second Xiangya Hospital (certificate number: S452). All participants provided their written informed consent in accordance with the Declaration of Helsinki. Authors had access to information that could identify individual participants during or after data collection.

On the day of the examination, that is, immediately before contrast medium application and 1 day before magnetic resonance imaging (MRI), patients underwent pure tone audiometry (PTA) and extratympanic ECochG either prior to or following surgery. Following the confirmation of both cochlear and vestibular hydrops by Gd-enhanced MRI and once informed consent was obtained, the patients underwent surgery. From February 10 to March 30, 2020, a total of 22 patients were recalled for repeat PTA, ECochG and MRI scans examinations. A total of 4 patients were excluded from the study, due to lack of follow-up Gd-MRI scans, while

22 subjects (11 females and 11 males; age range, 30–65 years; mean age, 50.1 years) met the inclusion criteria.

Hearing function was measured by a pure-tone audiometer and was evaluated based on the four-tone average air-conductive hearing threshold formulated by (a+b+c+d)/4; a, b, c and d represent hearing levels at 0.25, 0.5, 1.0 and 2.0 kHz, respectively. Changes in the hearing levels were defined as worse ($\geq$10-dB elevation), better ($\geq$10-dB decline) or same (-10 dB< x <10 dB).

ECochG

The silver-ball electrode for EcochG was placed on the upper wall of the deepest part of the ear canal near the eardrum, and extratympanic ECochG was recorded bilaterally by averaging 1,000 sweeps after alternating click stimuli (rate: 15/sec) with levels of 100 dB nHL. This test was considered positive at an -SP/AP of >0.40 at our hospital. For further analysis reasons, cases where EcochG traces were unobtainable were classed as negative.

Gd-MRI

MRI was performed using a single-dose (0.2 ml/kg) intravenous administration of gadopente-tate dimeglumine (Magnevist®, Bayer AG) 4 h before the MRI scan (IV-Gd), as well as intra-tympanic administration of 8-fold-diluted Gd (IT-Gd) in both ears or the ear undergoing surgery for the follow-up Gd-MRI, if patients were reluctant to receive intratympanic injections in their healthy ear, 24 h prior to the MRI scan. All scans were performed on a 3T MRI scanner (Magnetom Verio; Siemens AG) using a 12-channel head coil. Three-dimensional real inversion recovery (3D-real IR) sequence MRI images were collected, as previously described [7–9]. Briefly, the parameters for the 3D-real IR sequence were: Voxel size, 0.4x0.4x0.8 mm; scan time, 14 min; repetition time (TR), 9,000 msec, echo time (TE), 181 msec; inversion time (TI), 1,730 msec; slice thickness, 0.80 mm; field of view (FOV), 160x160 mm; matrix size, 3,300x918. The off-label use of IT-Gd-MRI was performed under informed consent.

Image evaluation

All the images obtained by MRI were evaluated by two experienced radiologists who were blinded to the diagnosis of all patients. Analysis of the boundary between the perilymphatic and endolymphatic spaces facilitated the detection of EH, as it was evidenced as an enlarged negative signal expanding into the positive signal of the perilymphatic space confined to the bony labyrinth using 3D-real IR after IT-Gd + IV-Gd. According to the criteria previously described by Nakashima et al and Wesseler et al [9,17], the degree of EH in the cochlea was assessed by visual comparison of the relative areas of the non-enhanced endolymphatic space vs. the contrast-enhanced perilymph space in the axial plane on the mid-mediolar level with regards to a possible dislocation of the Reissner's membrane. The degree of cochlear hydrops was categorized as none (normal finding without EH), grade I (mild EH) or grade II (significant EH) (Fig 1A). An EH of the vestibule was determined by the volume-ratio of endolymphatic space to the total vestibule (endolymph to vestibule-volume ratio, EVVR) using the Syngo.via software package (VB20A; Siemens AG); None, <30% of the vestibular space was filled with endolymph; grade I, 30–50% of the vestibular space was filled with endolymph; grade II, >50% of the vestibular space was filled with endolymph (Fig 1B). According to the suggestion of Wesseler et al [17], this ratio was not estimated based on one section plane alone, but was measured separately in every plane showing the vestibule then using the average of those values calculated as the overall result. The number of planes varied between three and four. The volume of both endolymphatic and perilymphatic space was calculated by

A cEH

| grade 0 (normal finding) | grade I (mild EH) | grade II (significant EH) |

no dislocation of the Reissner's membrane   dislocation of the Reissner's membrane but not reaching over the scala vestibuli   endolymphatic space reachs over the scala vestibuli

B vEH

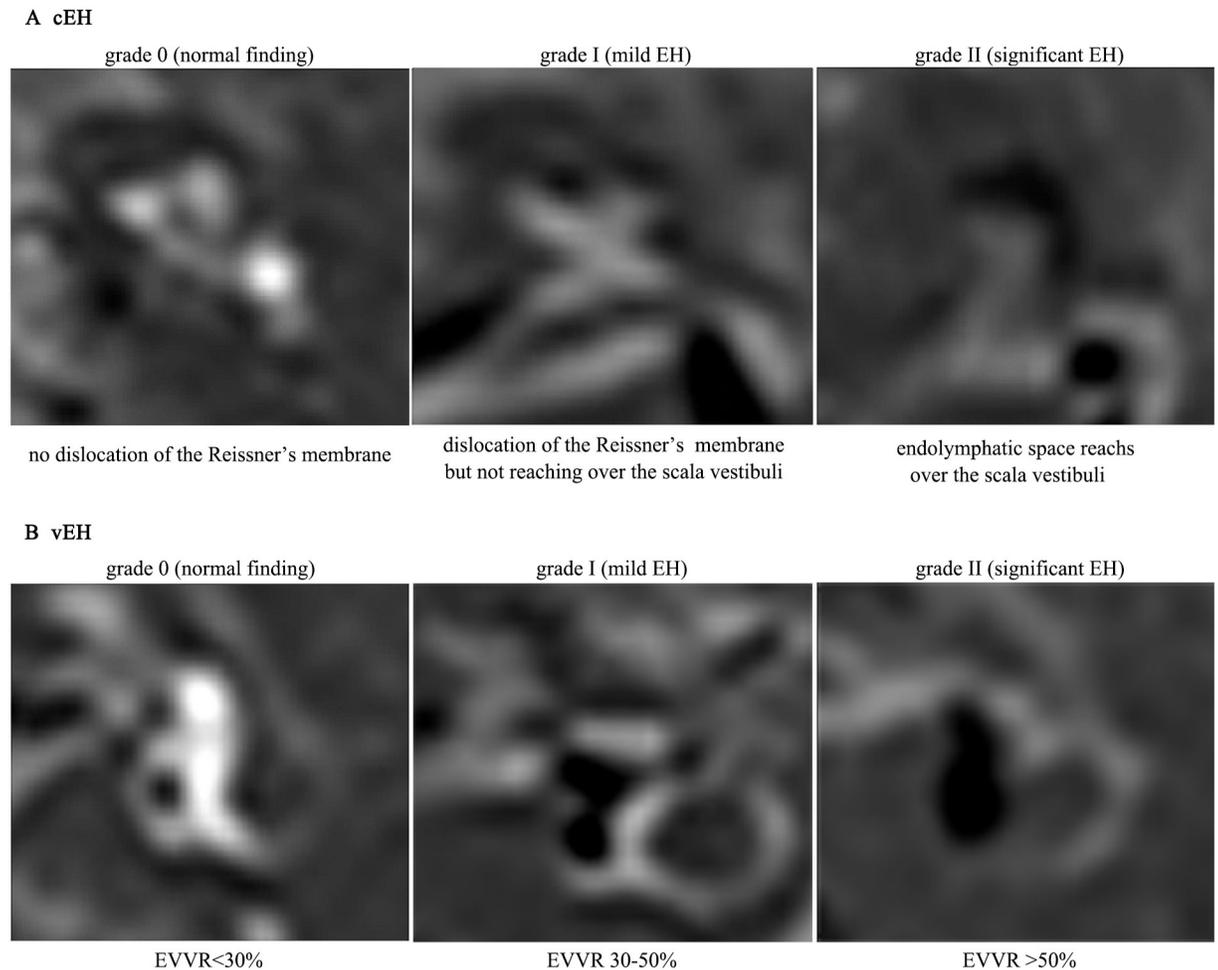| grade 0 (normal finding) | grade I (mild EH) | grade II (significant EH) |

EVVR<30%   EVVR 30-50%   EVVR >50%

Fig 1. Criteria for EH-grading of the cochlea and vestibule in MRI performed 4 h after intravenous and 24 h after intratympanic administration of Gd-based contrast media (IV-Gd + IT-Gd MRI). (A) The criterion for cEH was the dislocation of the Reissner's membrane. (B) The decisive factor for vEH is the EVVR. EH, endolymphatic hydrops; MRI, magnetic resonance imaging; Gd, gadolinium; IV-Gd, intravenous injection of gadopentetate dimeglumine; IT-Gd, intratympanic injection of gadopentetate dimeglumine; cEH, cochlear EH; vEH, vestibular EH; EVVR, endolymph to vestibule-volume.

multiplying the measured surface area (x or y) by the uniform layer thickness of 0.8 mm (a). Thereby, the interpersonal variability in the assessment of an image was minimized. Fig 2 shows and exemplary illustration of this process.

$$\text{Endolymph to vestibule-volume ratio} = EVVR[\%]$$

The enhancement of vestibular hydrops was defined as an EVVR increase of >10 points (%). The reduction of vestibular hydrops was defined as an EVVR decrease of >10 points (%). No change in the vestibular hydrops was defined as an EVVR change of ≤ 10 points (%). The complete reversal of vestibular hydrops was defined as an EVVR of <30 points (%).

Surgical technique

The surgical procedure used for EDB was similar to that described previously [18]. The technical details were as follows: A simple mastoidectomy was performed, clearly exposing the
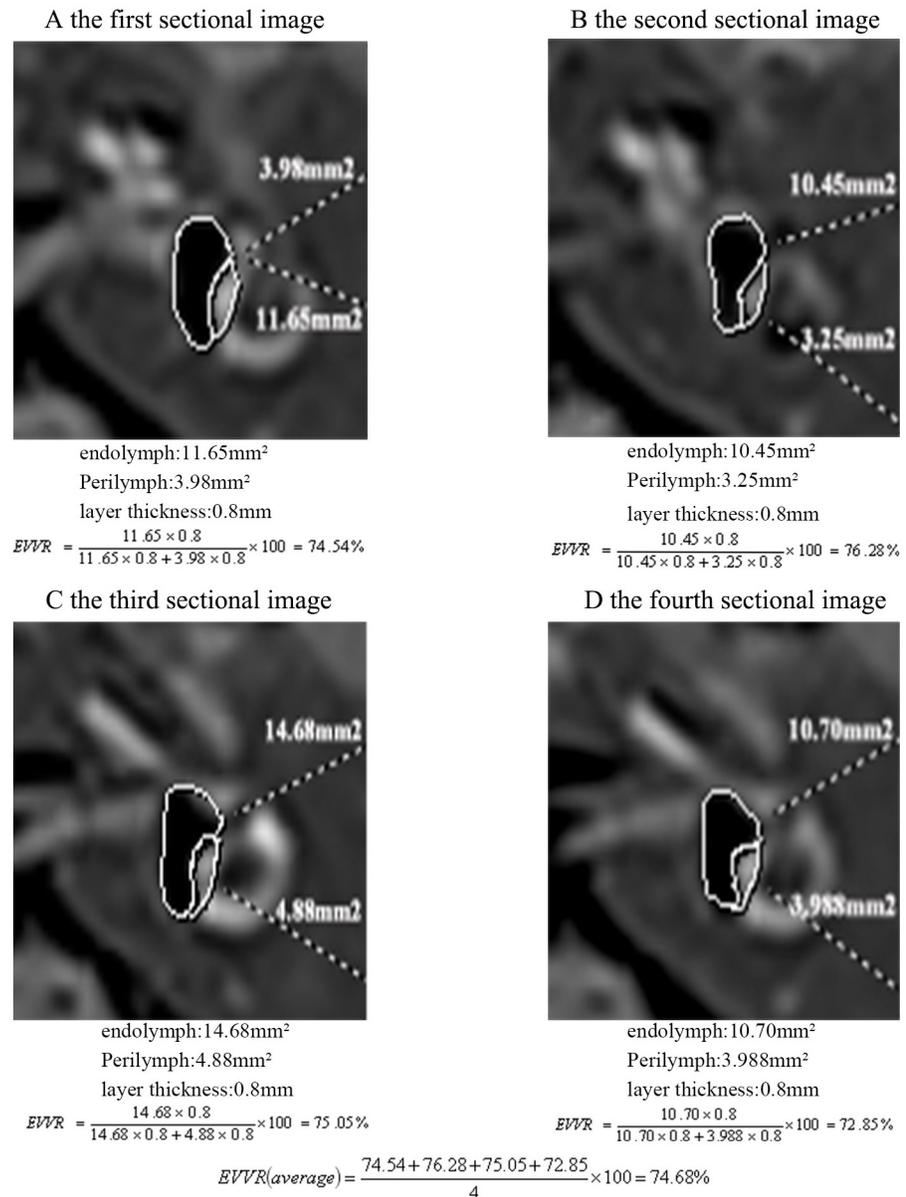
A the first sectional image

endolymph:11.65mm²
Perilymph:3.98mm²
layer thickness:0.8mm

$$EVVR = \frac{11.65 \times 0.8}{11.65 \times 0.8 + 3.98 \times 0.8} \times 100 = 74.54\%$$

B the second sectional image

endolymph:10.45mm²
Perilymph:3.25mm²
layer thickness:0.8mm

$$EVVR = \frac{10.45 \times 0.8}{10.45 \times 0.8 + 3.25 \times 0.8} \times 100 = 76.28\%$$

C the third sectional image

endolymph:14.68mm²
Perilymph:4.88mm²
layer thickness:0.8mm

$$EVVR = \frac{14.68 \times 0.8}{14.68 \times 0.8 + 4.88 \times 0.8} \times 100 = 75.05\%$$

D the fourth sectional image

endolymph:10.70mm²
Perilymph:3.988mm²
layer thickness:0.8mm

$$EVVR = \frac{10.70 \times 0.8}{10.70 \times 0.8 + 3.988 \times 0.8} \times 100 = 72.85\%$$

$$EVVR(average) = \frac{74.54 + 76.28 + 75.05 + 72.85}{4} \times 100 = 74.68\%$$

Fig 2. Assessment of the EVVR. For the EH-grading of the vEH, the overall EVVR was calculated by measuring the area of the xn and yn in every section plane showing the vestibule, and then using the average of those values. The volume of both endolymphatic and perilymphatic space was calculated by multiplying the measured x or y, by the uniform layer thickness of 0.8 mm (a). EVVR, endolymph to vestibule-volume; EH, endolymphatic hydrops; vEH, vestibular EH; xn, endolymph; yn, perilymph; x or y, surface area.

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endolymphatic sac in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal, including the rugose portion. Following the complete skeletonization and decompression of the sac, the bone of the vestibular aqueduct operculum and the posterior fossa dura were dissected from the retrolabyrinthine bone medial to the sac to identify, and to create a region for the insertion of the tips of the forceps to clip the proximal portion of the extraosseous endolymphatic sac. Finally, two small titanium clips were used to block the dissected endolymphatic duct by clipping using the ligating clip applier Small pieces of absorbable
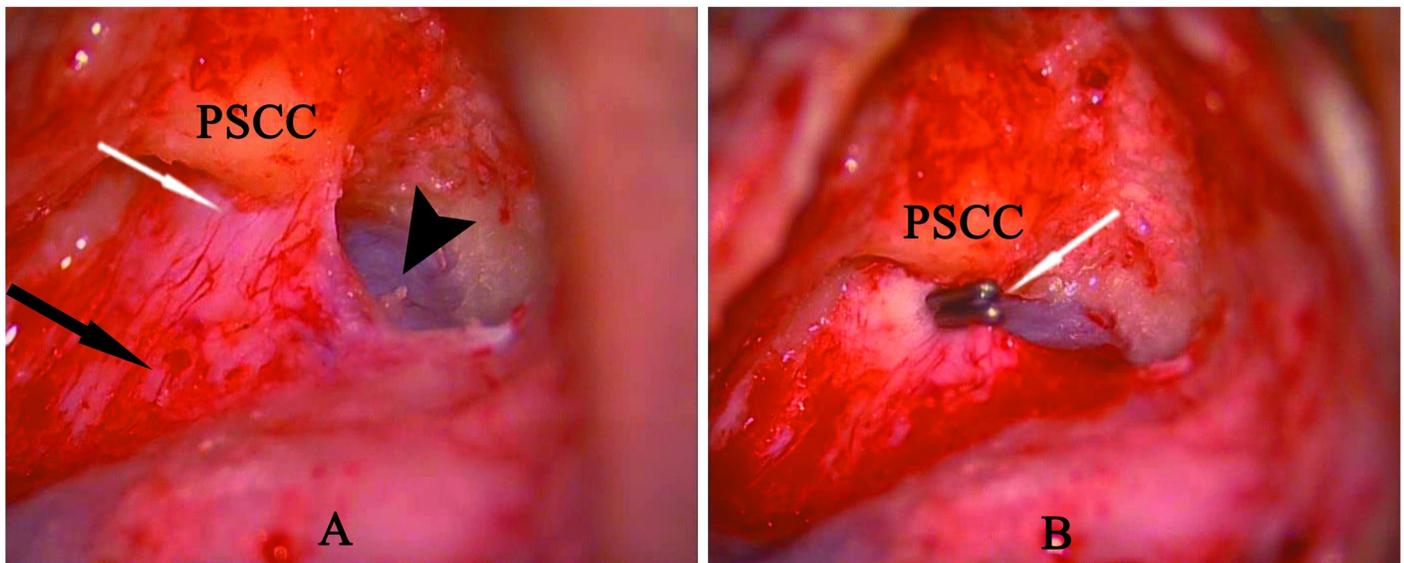
Fig 3. (A) Left ear mastoidectomy and endolymphatic sac dissection showing the intraosseous portion of sac (white arrow), extraosseous portion of sac (black arrow) and posterior fossa dura (arrow head). (B) Two titanium clips (white arrow) blocking the endolymphatic duct behind the posterior semicircular canal (PSCC).

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gelatin sponge soaked in high-concentration dexamethasone were placed on the surface of the sac (Fig 3). Postoperative wound management and postoperative care were similar to those used in other mastoid surgical operations.

Statistical analysis

For statistical analysis, we used paired Student's t-tests for two-group comparisons and Pearson correlations for evaluating the relationship. p values lower than .05 were considered significant. All data were statistically treated with SPSS version 26.0 (IBM Corp., Armonk, NY).

Results

Table 1 shows the clinical profiles of all 22 patients prior to and following surgery, including the results of IV-Gd + IT-Gd MRI, audiometry and ECochG examination in the corresponding periods. Preoperatively, all 22 patients with typical and active unilateral MD showed cochlear and vestibular hydrops in the affected ear; no significantly dilated endolymphatic space could be documented in the asymptomatic contralateral ears. T2-weighted cisternography sequence was used to rule out vestibular schwannoma or endolymphatic sac tumor. No misregistration artifact from motion was noted in any image dataset of the ears. None of the subjects showed no or diagnostically insufficient inner ear contrast. Either prior to or following surgery, PTA was carried out in the whole cohort and EcochG in 95.5% (21/22), as EcochG traces were unobtainable in 1 patient (patient no. 19) with severe hearing loss.

Evaluation of EH on IT-Gd + IV-Gd MRI prior to and following surgery

According to MRI scans, the grade of the cochlear EH in 22 patients was subjectively rated as follows: Mild EH (I) in 13 ears and significant EH (II) in 9 ears prior to surgery, and no hydrops (N) in 2 ears, mild EH (I) in 11 ears and significant EH (II) in 9 ears following surgery. A total of 4 patients showed downgrading of cochlear hydrops and 1 patient showed upgrading (Table 1).

Table 1. Clinical profiles in all 22 patients prior to and following surgery.

Case No.	Age/Sex/Side	Hearing(dB)			-SP/AP ratio			EVVR(%)			Cochlear hydrops			follow-up
		Pre	Post	D-value	Pre	Post	D-value	Pre	Post	D-value	Pre	Post	D-value	(Mon)
1	65/M/L	58.8	55	-3.8	0.66	0.75	+0.09	42.60	46.82	+4.22	I	I	0	21
2	51/M/L	48.8	45	-3.8	1.0	0.85	-0.15	66.78	63.50	-3.28	I	I	0	21
3	37/M/L	55	57.5	+2.5	0.15	0.36	+0.21	56.42	59.55	+1.55	I	I	0	21
4	39/F/R	37.5	25	-12.5	0.60	0.16	-0.44	74.68	15.45	-59.23	I	N	-1	20
5	50/F/R	65	38.8	-26.2	1.61	0.22	-1.39	87.75	26.90	-60.85	II	I	-1	20
6	61/F/L	56.3	66.3	+10.0	0.45	0.55	+0.10	46.55	52.10	+5.55	I	I	0	19
7	47/F/R	46.3	35	-11.3	0.24	0.37	+0.13	53.65	51.50	-2.15	I	I	0	19
8	52/F/L	46.3	58.8	+12.5	0.94	0.78	-0.16	37.85	52.30	+14.45	I	II	+1	18
9	65/F/R	65	73.8	+8.8	1.0	1.45	+0.45	70.22	84.45	+14.23	II	II	0	18
10	46/M/R	55	36.3	-18.7	1.02	0.52	-0.50	82.65	47.45	-35.20	II	II	0	18
11	64/F/R	72.5	65	-7.5	0.57	0.72	+0.15	60.85	62.30	+1.45	II	II	0	17
12	30/F/L	68.8	33.8	-35.0	0.92	0.19	-0.73	49.28	10.35	-39.03	I	N	-1	17
13	48/M/R	56.3	58.8	+2.5	0.42	0.51	+0.09	54.55	46.25	-8.30	I	I	0	16
14	62/F/R	55	26.3	-28.7	0.95	0.22	-0.73	78.73	13.89	-64.84	II	I	-1	16
15	54/M/R	63.8	67.5	+3.7	0.32	0.38	+0.06	76.22	78.35	+2.13	II	II	0	15
16	48/F/L	52.5	33.8	-18.7	0.49	0.42	-0.07	83.50	47.28	-36.22	II	II	0	15
17	48/M/L	43.8	47.5	+3.7	0.63	0.80	+0.17	41.30	45.15	+3.85	I	I	0	15
18	52/M/L	60	56.3	-3.7	1.02	1.22	+0.20	66.82	64.25	-2.57	II	II	0	14
19	60/M/R	80	78.8	-1.2	absence	absence		58.18	52.75	-5.43	II	II	0	14
20	39/M/R	43.8	50	+6.2	0.37	0.62	+0.25	46.88	70.45	+23.57	I	II	+1	14
21	49/F/R	47.5	51.3	+3.8	0.30	0.28	-0.02	50.65	47.48	-3.17	I	I	0	13
22	36/F/L	36.3	35	-1.3	0.50	0.28	-0.22	38.15	41.35	+3.20	I	I	0	13

Including the results of IV-Gd + IT-Gd MRI, audiometry and ECochG examination in the corresponding periods. D-value: Difference of value; EVVR: Endolymph to vestibule-volume ratio; F: Female; M: Male; Pre: Preoperative; Post: Postoperative; L: Left; R: Right; Mon: Month; N: No endolymphatic hydrops; I: Mild endolymphatic hydrops; II: Significant endolymphatic hydrops; 0: No change; +1: Upgrading; -1: Downgrading.

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Based on the EVVR results, the vestibular EH in 22 patients was classified as follows: Mild EH (I) in 7 ears and significant EH (II) in 15 ears prior to surgery, and no hydrops (N) in 4 ears, mild EH (I) in 7 ears and significant EH (II) in 11 ears following surgery. A total of 6 patients showed downgrading of vestibular hydrops and 2 patients showed upgrading (Table 1). The average EVVR was 60.19±15.62 prior to and 49.09±19.25 following surgery in 22 patients, and it decreased significantly following EDB (P = 0.042). With regards to the difference value of the EVVR between prior to and following surgery, 12 patients showed a decreased EVVR value, and 10 patients showed an increased EVVR value. However, a reduction of vestibular hydrops was identified in 6 patients who showed an EVVR decrease of >10 points (-35.20 to -64.84%), and increased vestibular hydrops was detected in 3 patients who showed an EVVR increase of >10 points (14.23 to 23.57%). The other 13 patients showed no change in the vestibular hydrops, as their EVVR changed by ≤10 points (-8.30 to 5.50%). There was a significant positive correlation between the difference value of the EVVR and the grading of cochlear hydrops prior to and following surgery (r = 0.702, P = 0.000), which indicated that the change of hydrops in the vestibule and cochlea was synchronized.

Figs 4 and 5 shows the dynamic changes of EH in patient no. 14, who underwent 4 Gd-MRI scans prior to surgery (October 26, 2018), and 2 weeks (November 8, 2018), 10 months (August 30, 2019) and 16 months (February 29, 2020) after surgery. Axial IT-Gd + IV-Gd MRI
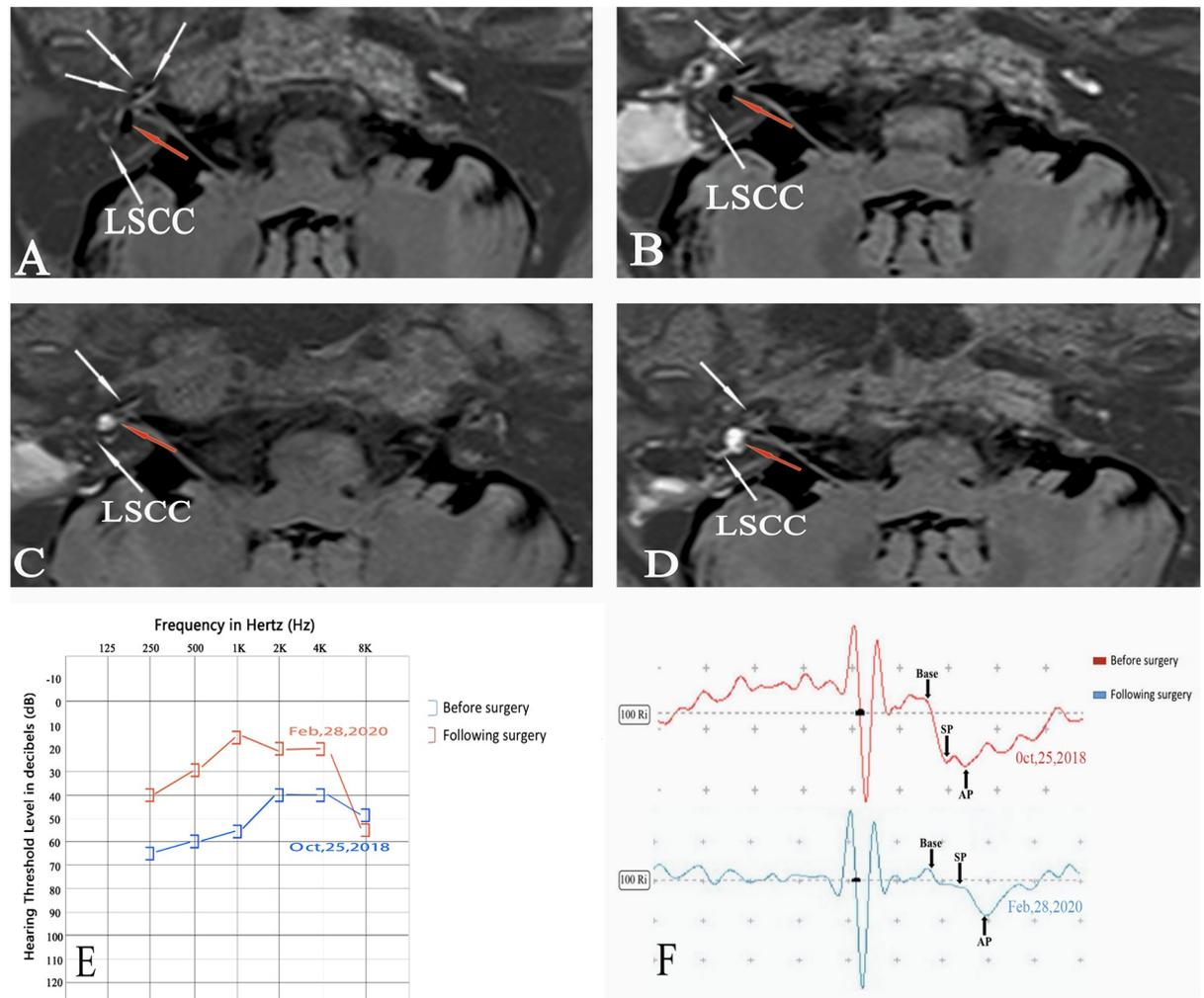
Fig 4. 3D-real IR MRI scans of patient no. 14 (Table 1) with right MD. (A) prior to surgery, (B) 2 weeks, (C) 10 months and (D) 16 months after surgery, as well as changes of the hearing threshold and -SP/AP ratio of EcochG prior to and following surgery. (A) Axial IT-Gd + IV-Gd MRI scan of the right ear showing a significant EH in the vestibule (red arrow) and cochlea (white arrow) and no pathological finding in the left unaffected ear. (B) A significant EH in the vestibule (red arrow) and cochlea (white arrow) remained unchanged 2 weeks after surgery in the right ear. (C) Downgrading of vestibular EH from grade II to none (EVVR, 24.25%) and a remaining grade II EH in the cochlea 10 months after surgery. (D) Axial IT-Gd + IV-Gd MRI showing downgrading of EH from grade II to none (EVVR, 13.89%) in the vestibule (red arrow) and from grade II to I (white arrow) in the cochlea 16 months after surgery in the right ear in the same section plane as in parts A-C. Axial IV-Gd MRI scan of the left unaffected ear showing insufficient contrast in the basal turn of the cochlea. (E) Audiogram showing that the mean hearing threshold of air conduction (0.25, 0.5, 1.0 and 2.0 KHz) decreased from 55 dB before to 26.3 dB after surgery. (F) A negative conversion of EcochG was detected as the -SP/AP ratio decreased from 0.95 before to 0.22 (Table 1) after surgery. LSCC, lateral semicircular canal; 3D-real IR, three-dimensional real inversion recovery; MRI, magnetic resonance imaging; -SP/AP, summating potential/action potential ratio; Gd, gadolinium; EcochG, electrocochleography; EH, endolymphatic hydrops; EVVR, endolymph to vestibule-volume; MD, Meniere's disease; IT-Gd, intratympanic injection of gadopentetate dimeglumine; IV-Gd, intravenous injection of gadopentetate dimeglumine.

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of the right ear showed a significant EH in the vestibule and cochlea prior to surgery (Figs 4A and 5A1-3), an unchanged hydrops 2 weeks after surgery (Figs 4B and 5B1-3), downgrading of vestibular EH from grade II to none (EVVR, 24.25%) and a remaining grade II EH in the cochlea 10 months after surgery (Figs 4C and 5C1-3), and downgrading of EH from grade II to none (EVVR, 13.89%) in the vestibule and from grade II to I in the cochlea 16 months after surgery (Figs 4D and 5D1-3).
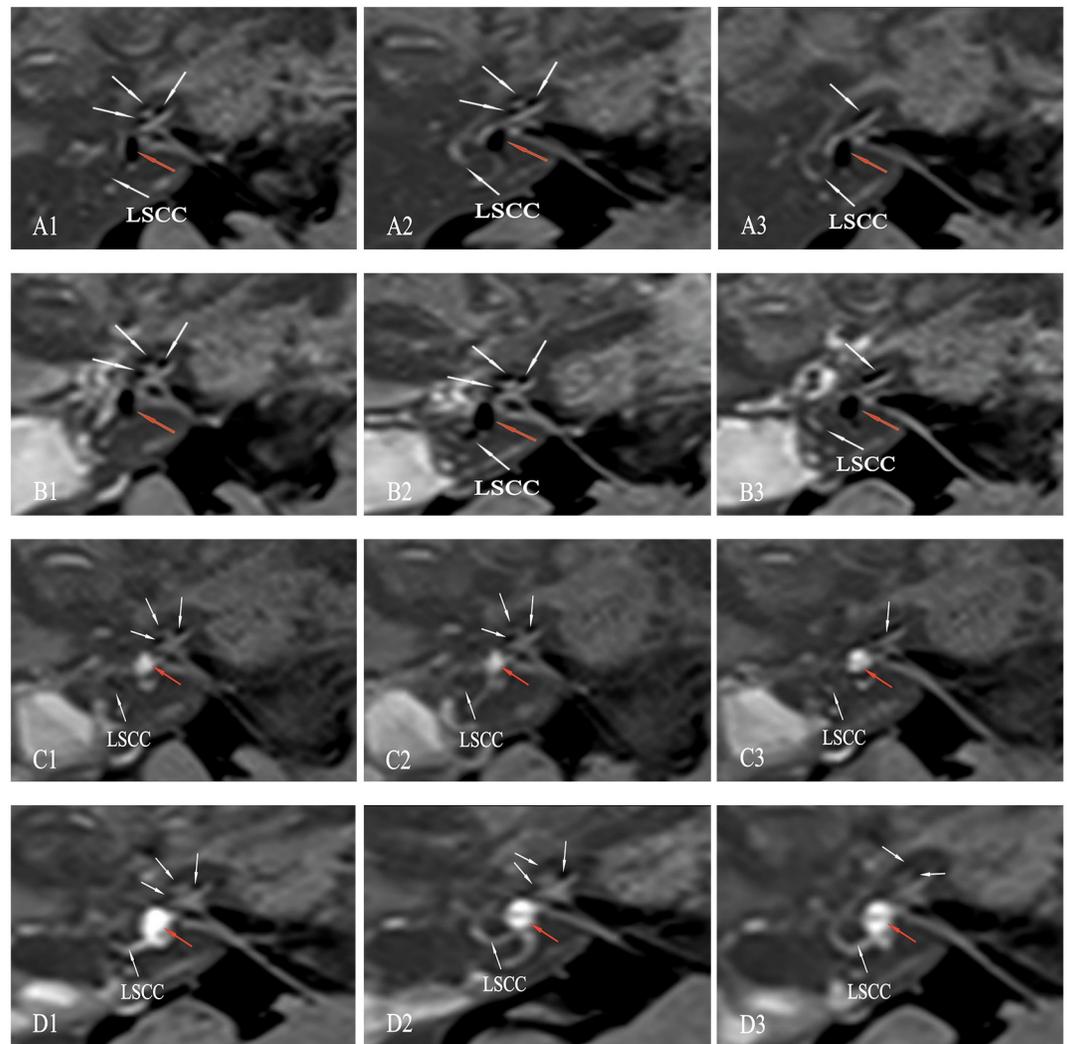
Fig 5. 3D-real IR serial MRI scans of patient no. 14 (Table 1) with right MD. (A1-3) prior to surgery, and (B1-3) 2 weeks, (C1-3) 10 months and (D1-3) 16 months after surgery. (A1-3) Serial MRI scans showing a significant EH in the vestibule (red arrow) and cochlea (white arrow) before surgery. (B1-3) Unchanged EH in the vestibule (red arrow) and cochlea (white arrow) 2 weeks after surgery. (C1-3) Reversal of vestibular hydrops and remaining grade II EH in the cochlea 10 months after surgery. (D1-3) Serial MRI scans showing a disappearance of vestibular EH (red arrow) and the reduction of cochlear EH (white arrow) 16 months after surgery. LSCC, lateral semicircular canal; 3D-real IR, three-dimensional real inversion recovery; MRI, magnetic resonance imaging; EH, endolymphatic hydrops; MD, Meniere's disease.

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Modulation of the hearing threshold following dynamic changes in the hydrops

As shown in Table 1, the postoperative average hearing threshold in 22 patients was 49.80 ±15.39, which was not significantly different (P = 0.067) from that prior to surgery (55.20 ±11.13). However, the difference value of the hearing threshold had a significant positive correlation with the difference value of the EVVR (P = 0.000, r = 0.739) (Fig 6A) and grading of cochlear hydrops (P = 0.000, r = 0.562) (Fig 6B) between prior to and following surgery. Among patients with a decreased EVVR, the average hearing threshold (43.27±15.60) decreased significantly following surgery, as compared to that prior to surgery (56.06±11.33) (P = 0.005) (Fig 7A). Six out of seven patients with a hearing improvement (≥10-dB decline)
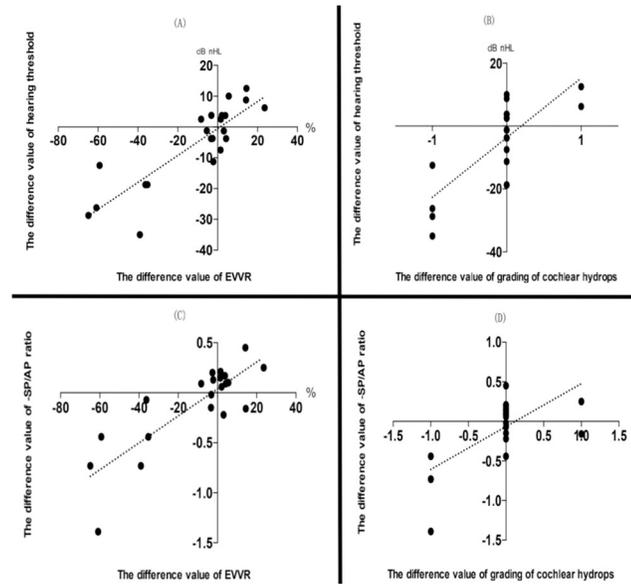
Fig 6. Correlation between the difference value of the hearing threshold, -SP/AP ratio of EcochG, EVVR and grading of cochlear hydrops prior to and following surgery. (A)The difference value of the hearing threshold had a significant positive correlation with the difference value of the EVVR (P = 0.000, r = 0.739). (B) A significant positive correlation was observed between the difference value of the hearing threshold and grading of cochlear hydrops (P = 0.000, r = 0.562). (C) The difference value of the -SP/AP ratio was significantly correlated with the difference value of the EVVR (P = 0.000, r = 0.690). (D) A significant positive correlation was identified between the difference value of the -SP/AP ratio and grading of cochlear hydrops (P = 0.001, r = 0.467). -SP/AP, summating potential/action potential ratio; EVVR, endolymph to vestibule-volume; EcochG, electrocochleography.

exhibited downgrading of their hydrops in the cochlea and/or vestibule (patient nos. 4, 5, 10, 12, 14 and 16) (Table 1). Yet, among patients with an increased EVVR, the average hearing threshold (57.64±11.40) tended to increase following EDB, as compared with that prior to it (54.16±11.40), but there was no significant difference between the two groups (P = 0.115)
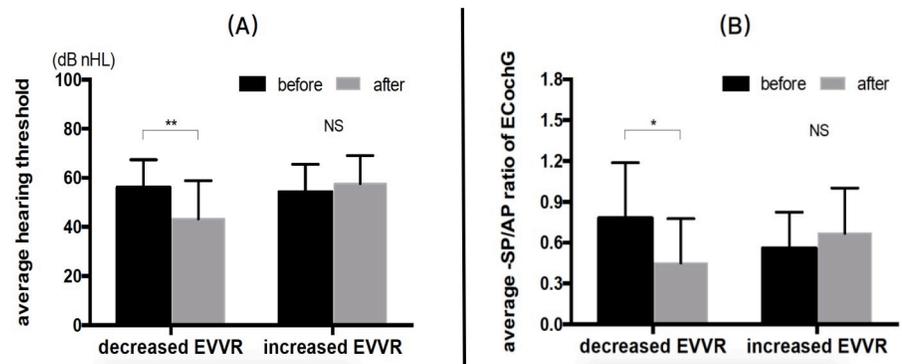

Fig 7. Changes in the average hearing threshold and -SP/AP ratio of EcochG. Among patients with a decreased EVVR, the (A) average hearing threshold (43.27±15.60) and (B) -SP/AP ratio (0.45±0.32) decreased significantly following surgery, as compared with the value prior to surgery (56.06±11.33, P = 0.005 and 0.78±0.41, P = 0.049, respectively). Among patients with an increased EVVR, the (A) average hearing threshold (57.64±11.40) and (B) -SP/AP ratio (0.67±0.33) tended to increase following EDB, as compared with the value prior to it (54.16±11.40 and 0.56 ±0.26, respectively), but there was no significant difference between the two groups (P = 0.115 and P = 0.105, respectively). -SP/AP, summating potential/action potential ratio; EcochG, electrocochleography; EVVR, endolymph to vestibule-volume; EDB, endolymphatic duct blockage; **P < 0.01, paired t-test; *P < 0.05, paired t-test; NS, not significant, paired t-test.

(Fig 7A). One of two patients with hearing deterioration (≥10-dB elevation) showed upgrading of her hydrops in both cochlea and vestibule (patient no. 8) (Table 1).

Modulation of -SP/AP ratio of EcochG following dynamic changes of hydrops

Table 1 shows 73% (16/22) of patients had a positive EcochG (-SP/AP ratio >40%) prior to surgery and 55% (12/22) of patients had a positive EcochG following surgery; there was no significant difference between the two groups (P = 0.190). The mean preoperative SP/AP ratio of ECochG on the affected side was 0.67±0.36, and the postoperative ratio 0.55±0.34, with no significant difference identified (P = 0.217).

However, the difference value of the -SP/AP ratio had a significant positive correlation with the difference value of the EVVR (P = 0.000, r = 0.690) (Fig 6C) and grading of cochlear hydrops (P = 0.001, r = 0.467) (Fig 6D) between prior to and following surgery. Among patients with a decreased EVVR, the average -SP/AP ratio (0.45±0.32) decreased significantly following surgery, as compared with that prior to surgery (0.78±0.41) (P = 0.049) (Fig 7B), and 4/5 patients with a negative conversion of EcochG exhibited downgrading of their hydrops in both cochlea and vestibule (patient nos. 4, 5, 12 and 14) (Table 1). Among patients with an increased EVVR, the average -SP/AP ratio (0.67±0.33) tended to increase following EDB, as compared with that prior to surgery (0.56 ±0.26), but there was no significant difference between the two groups (P = 0.105) (Fig 7B).

Discussion

In vivo visualization of hydrops with Gd-MRI is no longer limited to only showing evidence of the hydrops for the diagnosis of MD. Changes in EH may be used to objectively evaluate the effects of various treatments for patients with MD [19,20]. High-quality imaging is critical for evaluating the dynamics of hydrops, although promising results have been reported using heavily T2-weighted 3D FLAIR sequence following i.v. administration, which has the advantage of not being an off-label use of Gd [21,22]. Yet, the image analysis protocols based on image calculations were too complicated and time-consuming to use for routine diagnostic procedures [23–25]. However, it was difficult to obtain serial MRI scans by this method for evaluating the dynamic changes of EH of "after treatment" and "before treatment" groups. In the present study, the use of IT-Gd + IV-Gd MRI not only improved the effectiveness of imaging and evaluation techniques for EH [26], but also prevented the failure of IT-Gd imaging for ~10% of cases, which would have been caused by an insufficient Gd concentration with anatomic barriers to the round window, such as adhesions, bone dust blockage or thickened round window, when the IT-Gd method alone was used [27,28]. In fact, none of the subjects showed no or diagnostically insufficient inner ear contrast in this study. As shown in Figs 4 and 5, IT-Gd + IV-Gd MRI showed the dynamic changes of EH with serial MRI scans in patient no. 14 prior to surgery, and 2 weeks, 10 months and 16 months after surgery. A discernable reversal of EH accompanied by a hearing improvement and a negative conversion of EcochG could be detected 16 months after surgery.

Although the pathology of MD is well established to be EH. However, the mechanism underlying deafness of MD or idiopathic endolymphatic hydrops is still unknown. The most popular assumption is that the low-tone hearing loss is caused by the displacement of the basilar membrane (BM) from its resting position and the uncoupling of the outer hair cell stereocilia from the tectorial membrane due to hydrops [29–31]; this is known as the mechanical hypothesis. In this theory, the hearing loss in MD is purely due to increased mechanical pressure in the cochlear duct [32]. Yet, it remains unclear whether the hearing loss in MD is caused

by hydrops alone and whether the hearing function can be modulated by changes in the hydrops. A dehydration test via an osmotic diuretic to abruptly diminish hydrops is usually used to observe temporary reversal of hearing loss in MD [33–37]. Diuretic-induced endolymphatic dehydration has been radiologically observed in humans [38], with considerable evidence confirming that glycerol-induced endolymphatic volume load reduction occurs in animals [39–42]. In addition, the reduction of endolymphatic fluids resulting in hearing improvement has been described upon surgical observation; in cases where there was a flow of endolymph following drainage, an improvement in hearing at the low-pitched tone was observed, while in cases where there was no flow of endolymph, no improvement in hearing occurred [43]. The aforementioned findings suggested a likelihood that the hearing loss may be recoverable if the underlying hydrops can be corrected.

Based on a mechanical theory about hearing loss in MD, the low-tone sensorineural hearing loss in MD is caused by the mechanical impact of high endolymphatic pressure [44], which deflects the BM towards the scala tympani and becomes the basis for elevations in the summating potential detected by ECochG. In the present study, among patients with decreased EVVR, the average hearing threshold and -SP/AP ratio decreased significantly; among patients with an increased EVVR, the average hearing threshold and -SP/AP ratio tended to increase following surgery, as compared with the value prior to surgery (Fig 7). These results showed a causative correlation between a disordered hearing function and EH [45], in which the reduction of EH is likely to decrease the direct mechanical impact of high endolymphatic pressure and reverse the displacement of the BM, leading to an improvement in hearing. On the contrary, the increased of endolymphatic volume may give rise to an increase in the displacement of the BM and result in hearing deterioration. Although no significant differences were observed between the postoperative and preoperative average hearing threshold and -SP/AP ratio of EcochG in 22 patients that had undergone EDB, the difference value of the hearing threshold and -SP/AP ratio were significantly positively correlated with the difference value of the EVVR and grading of cochlear hydrops between prior to and following surgery, respectively (Fig 6), which could further strengthen the relationship between the dynamics of EH and changes in the hearing function. In addition, 6/7 patients with a hearing improvement (≥10-dB decline) and 4/5 patients with a negative conversion of EcochG exhibited downgrading of their hydrops in the cochlea and/or vestibule(Table 1), suggesting a downgrading of the cochlear and/or vestibular hydrops accompanied by the downregulation of the hearing threshold and -SP/AP ratio of EcochG. One out of two patients with a hearing deterioration (≥10-dB elevation) exhibited upgrading of the hydrops in both cochlea and vestibule, suggesting that the upgrading of cochlear and vestibular hydrops tended to upregulate the hearing threshold and -SP/AP ratio of EcochG.

Recently, Ito et al reported a positive correlation between the control of vertigo and the decrease in the volume of EH, and no correlation between changes in the hearing function and the volume of EH following sac drainage surgery [46,47]. Higashi-Shingai et al also described that the presence of vestibular EH and the frequency of vertigo attacks significantly decreased following surgery, but no significant improvement in the presence of cochlear EH or the SP/AP ratio of ECochG was observed [48]. The present results showed an obvious difference in the relationship between hearing and -SP/AP ratio, and dynamic changes in the hydrops, as compared with the results of former studies, which could be explained by the varying effects of different methods. In our experience, the reduction in EH could be achieved in certain patients with MD following sac drainage surgery immediately, but there was no improvement in hearing in the majority of these patients who were confirmed with the reversal of hydrops (data not shown), which was consistent with the results of former studies [46–48]. However, in the group of patients who underwent EDB, the reduction of EH could not be observed

immediately following surgery (Fig 4B) and the hydrops remained unchanged 2 weeks after surgery. The reversal of EH could be detected only months after surgery (Fig 4C and 4D), which was more likely to be in accordance with the physiological recovery in the homeostasis of the endolymph. Although the exact role of the EDB procedure on EH remains unknown, the mechanism of action of EDB in MD treatment is expected to be different from that of the traditional ES shunting/decompression procedures [18]. Nevertheless, discussing the difference of these ES surgical procedures was beyond the scope of this study, which focused on evaluating the morphologic-functional correlation between the dynamic change of endolymphatic fluids and hearing function in MD patients following EDB. It was found that there is a great likelihood that hearing loss in MD is caused by EH, and the downgrading or upgrading of EH morphologically holds great potential for modulating hearing function.

The limitation of the present study is the small number of patients. Although fluctuation in the composition and volume of the endolymph is considered to contribute to the fluctuating nature of the symptoms experienced by sufferers of Meniere's. On average, MD stabilizes with no further vestibular attacks by about 8 years after the onset of symptoms; however, hearing loss typically becomes permanent as MD progresses [49]. Nevertheless, by comparing the proportions of the EH ratio of "after treatment" and "before treatment" groups, we could understand the extent to which EH could be reduced to improve hearing. This could facilitate future progress in the field of treatment for MD, especially for maintenance or improvement of hearing in MD.

In conclusion, in the present study, it was first reported that the dynamic change of EH visualized by Gd-MRI was likely to modulate hearing function in 22 MD patients following EDB, highlighting the possibility that the downgrading of cochlear and/or vestibular hydrops could downregulate the hearing threshold and -SP/AP ratio, whereas the upgrading of cochlear and/or vestibular hydrops tended to upregulate the hearing threshold and -SP/AP ratio, suggesting that the hearing loss in MD is likely to be caused by hydrops and this disordered hearing function can be modulated by changes in the hydrops.

Supporting information

S1 File. STROBE statement—Checklist of items that should be included in reports of observational studies.
(DOCX)

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References

1. Lindsay JR. Labyrinthine dropsy. Laryngoscope. 1946; 56: 325–341. PMID: 20994683

2. Altmann F, Kornfeld M. Histological studies of Meniere's disease. Ann Otol Rhinol Laryngol. 1965; 74: 915–943.

3. Schuknecht HF, Gulya AJ. Endolymphatic hydrops. An overview and classification. Ann Otol Rhinol Laryngol Suppl. 1983; 106: 1–20. https://doi.org/10.1177/00034894830920s501 PMID: 6414357

4. Foster CA, Breeze RE. Endolymphatic hydrops in Meniere's disease: cause, consequence, or epiphenomenon?. Otol Neurotol. 2013; 34: 1210–1214. https://doi.org/10.1097/MAO.0b013e31829e83df PMID: 23921917

5. Merchant SN, Adams JC, Nadol JB Jr. Pathophysiology of Meniere's syndrome: are symptoms caused by endolymphatic hydrops?. Otol Neurotol. 2005; 26: 74–81. https://doi.org/10.1097/00129492-200501000-00013 PMID: 15699723

6. Rauch SD, Merchant SN, Thedinger BA. Meniere's syndrome and endolymphatic hydrops. Double-blind temporal bone study. Ann Otol Rhinol Laryngol. 1989; 98: 873–883. https://doi.org/10.1177/000348948909801108

7. Naganawa S, Komada T, Fukatsu H, Ishigaki T, Takizawa O. Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3D-FLAIR sequence at 3 Tesla. Eur Radiol. 2006; 16: 733–737. https://doi.org/10.1007/s00330-005-0046-8 PMID: 16267664

8. Nakashima T, Naganawa S, Sugiura M, Sone M, Hayashi H, Nakata S, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. Laryngoscope. 2007; 117: 415–420.

9. Nakashima T, Naganawa S, Pyykko I, Gibson WP, Sone M, Nakata S, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol Suppl. 2009; 129: 5–8.

10. Pyykko I, Zou J, Poe D, Nakashima T, Naganawa S. Magnetic resonance imaging of the inner ear in Meniere's disease. Otolaryngol Clin North Am. 2010; 43: 1059–80.

11. Gurkov R, Flatz W, Louza J, Strupp M, Krause E. In vivo visualization of endolyphatic hydrops in patients with Meniere's disease: correlation with audiovestibular function. Eur Arch Otorhinolaryngol. 2011; 268: 1743–1748. https://doi.org/10.1007/s00405-011-1573-3 PMID: 21431434

12. Seo YJ, Kim J, Choi JY, Lee WS. Visualization of endolymphatic hydrops and correlation with audio-vestibular functional testing in patients with definite Meniere's disease. Auris Nasus Larynx. 2013; 40: 167–172. https://doi.org/10.1016/j.anl.2012.07.009 PMID: 22867525

13. Wu Q, Dai C, Zhao M, Sha Y. The correlation between symptoms of definite Meniere's disease and endolymphatic hydrops visualized by magnetic resonance imaging. Laryngoscope. 2016; 126: 974–979. https://doi.org/10.1002/lary.25576 PMID: 26333096

14. Jerin C, Floerke S, Maxwell R, Gurkov R. Relationship between the extent of endolymphatic hydrops and the severity and fluctuation of audiovestibular symptoms in patients with Meniere's disease and MRI evidence of hydrops. Otol Neurotol. 2018; 39: e123–130. https://doi.org/10.1097/MAO.0000000000001681 PMID: 29315188

15. Shi S, Guo P, Li W, Wang W. Clinical features and endolymphatic hydrops in patients with mri evidence of hydrops. Ann Otol Rhinol Laryngol. 2019; 128: 286–292. https://doi.org/10.1177/0003489418819551 PMID: 30556402

16. Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandalà M, et al. Diagnostic criteria for Meniere's disease. J Vestib Res. 2015; 25: 1–7.

17. Wesseler A, Óvári A, Javorkova A, Kwiatkowski A, Meyer JE, Kivelitz DE. Diagnostic value of the magnetic resonance imaging with intratympanic gadolinium administration (IT-Gd MRI) versus audio-vestibular tests in Menie're's disease: IT-Gd MRI makes the difference. Otol Neurotol. 2019; 40(3): 225–232. https://doi.org/10.1097/MAO.0000000000002082 PMID: 30550412

18. Saliba I, Gabra N, Alzahrani M, Berbiche D. Endolymphatic duct blockage for Meniere's Disease treatment. Operative Techniques in Otolaryngology—Head and Neck Surgery. 2016; 27: 221–224.

19. Fukushima M, Kitahara T, Horii A, Inohara H. Effects of endolymphatic sac decompression surgery on endolymphatic hydrops. Acta Otolaryngol. 2013; 133: 1292–1296.

20. Gurkov R, Flatz W, Keeser D, Strupp M, Ertl-Wagner B, Krause E. Effect of standard-dose betahistine on endolymphatic hydrops: an MRI pilot study. Eur Arch Otorhinolaryngol. 2013; 270: 1231–1235. https://doi.org/10.1007/s00405-012-2087-3 PMID: 22760844

21. Lingam RK, Connor SEJ, Casselman JW, Beale T. MRI in otology: applications in cholesteatoma and Meniere's disease. Clin Radiol. 2018; 73: 35–44. https://doi.org/10.1016/j.crad.2017.09.002 PMID: 28969854

22. Naganawa S, Yamazaki M, Kawai H, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Meniere's disease with single-dose intravenous gadolinium-based contrast media using heavily T(2)-weighted 3D-FLAIR. Magn Reson Med Sci. 2010; 9: 237–242. https://doi.org/10.2463/mrms.9.237 PMID: 21187694

23. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Meniere's disease after intravenous administration of single-dose gadodiamide: utility of subtraction images with different inversion time. Magn Reson Med Sci. 2012; 11: 213–219. https://doi.org/10.2463/mrms.11.213 PMID: 23037568

24. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Meniere's disease after intravenous administration of single-dose gadodiamide: utility of multiplication of MR cisternography and HYDROPS image. Magn Reson Med Sci. 2013; 12: 63–68. https://doi.org/10.2463/mrms.2012-0027 PMID: 23474961

25. Naganawa S, Yamazaki M, Kawai H, Bokura K, Iida T, Sone M, et al. MR imaging of Meniere's disease after combined intratympanic and intravenous injection of gadolinium using HYDROPS2. Magn Reson Med Sci. 2014; 13: 133–137. https://doi.org/10.2463/mrms.2013-0061

26. Iida T, Teranishi M, Yoshida T, Otake H, Sone M, Kato M, et al. Magnetic resonance imaging of the inner ear after both intratympanic and intravenous gadolinium injections. Acta Oto-Laryngologica. 2013; 133: 434–438. https://doi.org/10.3109/00016489.2012.753640 PMID: 23294239

27. Yoshioka M, Naganawa S, Sone M, Nakata S, Teranishi M, Nakashima T. Individual differences in the permeability of the round window: evaluating the movement of intratympanic gadolinium into the inner ear. Otol Neurotol. 2009; 30: 645–648. https://doi.org/10.1097/MAO.0b013e31819bda66 PMID: 19415042

28. Crane BT, Minor LB, Della Santina CC, Carey JP. Middle ear exploration in patients with Ménière's disease who have failed outpatient intratympanic gentamicin therapy. Otol Neurotol. 2009; 30: 619–624. https://doi.org/10.1097/MAO.0b013e3181a66d2b PMID: 19503016

29. Tonndorf J. The mechanism of hearing loss in early cases of endolymphatic hydrops. Ann Otol Rhinol Laryngol. 1957; 66: 766–784. https://doi.org/10.1177/000348945706600315 PMID: 13488351

30. McCabe BF. Experimental inner ear pressure changes: functional aspects. Ann Otol Rhinol Laryngol. 1961; 70: 541–555.

31. Tonndorf J. Endolymphatic hydrops: mechanical causes of hearing loss. Arch Otorhinolaryngol. 1976; 212: 293–299. https://doi.org/10.1007/BF00453677 PMID: 990091

32. Gibson WP. Hypothetical mechanism for vertigo in Meniere's disease. Otolaryngol Clin North Am. 2010; 43: 1019–1027. https://doi.org/10.1016/j.otc.2010.05.013 PMID: 20713241

33. Klockhoff I, Lindblom U. Glycerol test in Meniere's disease. Acta Otolaryngol. 1967; 63: 449–451.

34. Arenberg IK, Stroud MH, Spector GJ, Carver WF. The salt loading provocative glycerol test for the early diagnosis of auditory endolymphatic hydrops (Meniere's disease) (a preliminary report). Rev Laryngol Otol Rhinol (Bord). 1974; 95: 709–719.

35. Harrison RV, Dauman R, Tavartkiladze GA, Aran JM. Effects of glycerol on cochlear frequency selectivity in patients with Meniere's disease. J Speech Hear Disorders. 1985; 50: 213–217. https://doi.org/10.1044/jshd.5002.213

36. Basel T, Lutkenhoner B. Auditory threshold shifts after glycerol administration to patients with suspected Meniere's disease: a retrospective analysis. Ear Hear. 2013; 34: 370–384. https://doi.org/10.1097/AUD.0b013e31826d0c08 PMID: 23196699

37. Jablonka-Strom A, Pospiech L, Zatonski M, Bochnia M. Dynamics of pure tone audiometry and DPOAE changes induced by glycerol in Meniere's disease. Eur Arch Otorhinolaryngol, 2013; 270: 1751–1756. https://doi.org/10.1007/s00405-012-2246-6 PMID: 23233313

38. Sepahdari AR, Vorasubin N, Ishiyama G, Ishiyama A. Endolymphatic hydrops reversal following acetazolamide therapy: demonstration with delayed Intravenous Contrast-Enhanced 3D-FLAIR MRI. AJNR Am J Neuroradiol. 2016; 37: 151–154. https://doi.org/10.3174/ajnr.A4462 PMID: 26381561

39. Cohen J, Morizono T, Long C. The effect of glycerol on cochlear function and ionic concentration. Arch Otorhinolaryngol. 1985; 241: 285–293. https://doi.org/10.1007/BF00453702 PMID: 4026695

40. Duvall AJ, Hukee MJ, Lindgren BR. The osmotic effect of glycerol on the stria vascularis and endolymph. Acta Otolaryngol. 1987; 103: 241–253.

41. Magliulo G, Della Rocca C, Ungari C, Muscatello M. The effect of glycerol on short-term experimental endolymphatic hydrops. J Otolaryngol. 1991; 20: 188–192. PMID: 1870166

42. Magliulo G, Vingolo GM, Petti R, Cristofari P. Experimental endolymphatic hydrops and glycerol. electrophysiologic study. Ann Otol Rhinol Laryngol. 1993; 102 (8 pt 1): 596–599. https://doi.org/10.1177/000348949310200805

43. Kitahara M, Takeda T, Futaki T, Matsubara H. Pathology of hearing loss in Meniere's disease. 5th Extraordinary Meeting of the Barany Society, At Kyoto, Japan. 1976, Oct: 17–22.

44. Gluth MB. On the Relationship Between Menie're's Disease and Endolymphatic Hydrops. Otol Neurotol. 2020; 41: 242–249. https://doi.org/10.1097/MAO.0000000000002502 PMID: 31746815

45. Takeda T, Takeda S, Kakigi A. A possible mechanism of the formation of endolymphatic hydrops and its associated inner ear disorders. Auris Nasus Larynx. 2020; 47: 25–41. https://doi.org/10.1016/j.anl.2019.09.005 PMID: 31623941

46. Ito T, Inui H, Miyasaka T, Shiozaki T, Matsuyama S, Yamanaka T, et al. Three-Dimensional magnetic resonance imaging reveals the relationship between the control of vertigo and decreases in endolymphatic hydrops after endolymphatic sac drainagewithsteroids for Meniere's Disease. Front Neurol. 2019; 10: 46. https://doi.org/10.3389/fneur.2019.00046 PMID: 30778329

47. Ito T, Inui H, Miyasaka T, Shiozaki T, Fujita H, Yamanaka T, et al. Relationship between changes in hearing function and volumes of endolymphatic hydrops after endolymphatic sac drainage. Acta Oto-Laryngologica. 2019; 139: 739–746. https://doi.org/10.1080/00016489.2019.1630757 PMID: 31274039

48. Higashi-Shingai K, Imai T, Okumura T, Uno A, Kitahara T, Horii A, et al. Change in endolymphatic hydrops 2 years after endolymphatic sac surgery evaluated by MRI. Auris Nasus Larynx. 2019; 46: 335–345. https://doi.org/10.1016/j.anl.2018.10.011 PMID: 30502065

49. Cruz M. Meniere's disease: a stepwise approach. Med Today. 2014; 15: 18–26.