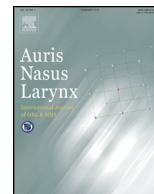




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# Magnetic resonance-based volumetric measurement of the endolymphatic space in patients with Meniere's disease and other endolymphatic hydrops-related diseases

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## ABSTRACT

**Objective:** To employ magnetic resonance imaging (MRI) to measure the volume of the inner ear endolymphatic space (ELS) in patients with acute low-tone sensorineural hearing loss (ALHL), sudden deafness (SD), cochlear Meniere's disease (cMD), and unilateral MD (uMD) compared with control subjects (CS) with chronic rhinosinusitis.

**Methods:** Forty-one patients with ALHL, 82 with SD, 48 with cMD, 72 with uMD, and 47 CS participated in the study. With the exception of all uMD patients, none of the subjects had vertigo. Images of the inner ear fluid space, positive perilymph signal, and positive endolymph signal were acquired using a 3-T MRI scanner. Three-dimensional images were reconstructed semi-automatically by using anatomical and tissue information to fuse the inner ear fluid space images and the ELS images.

**Results:** The cochlear ELS/total fluid space (TFS) volume ratio was  $10.2 \pm 6.7\%$  (mean  $\pm$  standard deviation) in the CS group,  $12.1 \pm 5.7\%$  in ALHL patients,  $15.2 \pm 8.7\%$  in SD patients,  $18.1 \pm 8.2\%$  in cMD patients, and  $21.9 \pm 16.4\%$  in uMD patients. The vestibular ELS/TFS volume ratio was  $17.7 \pm 10.2\%$  in the CS group,  $18.9 \pm 8.3\%$  in ALHL patients,  $19.9 \pm 11.3\%$  in SD patients,  $22.5 \pm 13.7\%$  in cMD patients, and  $35.7 \pm 24.1\%$  in uMD patients. The cochlear ELS/TFS volume ratio in patients with uMD was similar to that in the cMD group and significantly higher than that in the CS, ALHL, and SD groups (CS = ALHL < SD < cMD = uMD;  $p < 0.05$  for CS vs. SD and  $p < 0.01$  for CS vs. cMD). The vestibular ELS/TFS volume ratio in patients with uMD was significantly higher than that in the CS and all other patient groups (CS = ALHL = SD = cMD < uMD;  $p < 0.01$  for uMD vs. all other groups).

**Conclusion:** The cochlear ELS volume of patients with MD and other endolymphatic hydrops-related diseases differed from that of CS. Our results suggest that ALHL may not be caused by endolymphatic hydrops. We confirmed the presence of extended ELS in patients with SD.

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## 1. Introduction

The first report of the visualization of endolymphatic hydrops (ELH) in patients with Meniere's disease (MD) using 3-dimensional magnetic resonance imaging (3D-MRI) was published in 2007 [1]. Since then, many additional studies have

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investigated ELH by 3D-MRI using various routes of gadolinium-based contrast material (GBCM) administration, such as intratympanic versus intravenous injection, and different types of imaging sequences, such as heavily T2-weighted 3D-fluid attenuated inversion recovery sequence (hT2W 3D-FLAIR) and 3D real reconstruction inversion recovery sequence (3D-real IR) [2–5]. Generally, the intravenous route of GBCM delivery is favored since it is less invasive than the intratympanic route and allows both ears to be investigated with a single injection.

Since the original study [1], ELH has been described in many patients with MD and other diseases such as vestibular migraine, acute low-tone sensorineural hearing loss (ALHL), sudden deafness (SD), and atypical MD [6–11]. We have previously used 3D MRI to perform volumetric measurement of the total fluid space (TFS) of the inner ear in MD patients and control subjects (CS) with chronic rhinosinusitis (CRS), and of the endolymphatic space (ELS) in patients without vertiginous or cochlear symptoms [12,13]. The purpose of the present study was to use 3D-MRI to measure and compare the ELS volume in patients with ALHL, SD, cochlear MD (cMD) (all without vertigo), and unilateral MD (uMD) with vertigo.

## 2. Materials and methods

### 2.1. Patients and control subjects

A total of 290 subjects were enrolled in the study; 47 CS (CRS without vertigo), 171 patients with hearing loss without vertigo (41 ALHL, 82 SD, and 48 cMD) and 72 patients with uMD. The ALHL and SD patients were diagnosed between April 2016 and August 2018, the cMD patients were initially diagnosed with SD between August 2006 and June 2018 and were re-diagnosed with cMD between April 2016 and August 2018, and the uMD patients were diagnosed between July 2014 and July 2018. During the first clinic visit, the patients were interviewed to determine the presence of symptoms such as hearing loss, ear fullness, and tinnitus. Hearing levels were measured using an audiometer (Model AA-79; Rion, Tokyo, Japan). The main criteria for ALHL in this study were: (1) acute or sudden onset of cochlear symptoms, including ear fullness, tinnitus, and hearing loss; (2) low-tone hearing loss; (3) absence of vertigo; and (4) unknown cause. The audiometric criteria for low-tone hearing loss were: (1) the sum of hearing levels at low frequencies (0.125, 0.25, and 0.5 kHz)  $\geq 70$  dB and the sum of hearing levels at high frequencies (2, 4, and 8 kHz)  $\leq 60$  dB and (2) recurrent cochlear symptoms. The criteria for SD in this study were: (1) sudden onset of hearing loss without vertigo (patient could state clearly when it appeared and had no recurrence); (2) sensorineural hearing loss, usually severe; and (3) unknown cause. Accessory symptoms included: (1) may be accompanied by tinnitus and (2) no cranial nerve symptoms other than from the eighth nerve. uMD cases were diagnosed according to the criteria of the 1995 American Academy of Otolaryngology-Head and Neck Surgery guidelines [14] and of the Ministry of Health, Labor, and Welfare of Japan issued in 2011. cMD cases were diagnosed according to the criteria of the Ministry of Health, Labor, and Welfare of Japan issued in 2011.

None of the 290 participants had a history of middle ear disease, cranial disease, head trauma, renal disease, severe diabetes mellitus, active gastric ulcer, viral hepatitis, or allergy to gadolinium (Gd). The study was approved by the Medical Ethics Committee of Nara Medical University (certificate number 0889) and was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from each subject.

### 2.2. MRI

Visualization of ELH by MRI following intravenous Gd injection was performed as described by Naganawa et al. [4]. The scans were acquired on a 3-T MR scanner (Magnetom Prisma; Siemens, Erlangen, Germany) using a 32-channel array head coil. Image acquisitions were performed 4 h after administration of a single dose of Gd-diethylenetriaminepentaacetic acid *bis*-methylamide (0.2 ml/kg or 0.1 mmol/kg body weight; Magnescope, Guerbet, Tokyo, Japan). Special sequences were developed to allow for the differentiation of endolymphatic and perilymphatic fluid, as previously proposed by Naganawa et al. [4]. The following image sequences were acquired from all patients: hT2W MR cisternography to obtain an anatomical total lymph fluid reference; hT2W 3D FLAIR sequences with an inversion time of 2250 ms, resulting in a positive perilymph image (PPI); and hT2W 3D inversion recovery sequences with an inversion time of 2050 ms, resulting in a positive endolymphatic image (PEI). The hT2W MR cisternography acquisition parameters were as follows: variable refocus flip angle 3D turbo spin-echo (sampling perfection with application-optimized contrasts using different flip angle evolutions [SPACE]); repetition time, 4400 ms; echo time, 544 ms; constant flip angle mode; matrix size,  $322 \times 384$ ; slices per slab, 104; slice thickness, 1.0 mm; field of view,  $150.9 \times 180.0$  mm; and bandwidth, 434 Hz/pixel.

### 2.3. Image fusion method and MRI evaluation (KIIS technique)

The previously described KIIS technique was used to evaluate the MRI data, with the source inner ear TFS (SPACE sequence) and ELS (PPI-PEI) images being reconstructed on a specialized workstation (Virtual Place; AZE Ltd., Tokyo, Japan) [11]. The inner ear fluid space was manually separated from the surrounding structures using the workstation's object extraction function and cut tool. A high-quality 3D image was then semi-automatically constructed using both anatomical and tissue information to fuse the 3D inner ear fluid space and 3D ELS images. The components of the inner ear were identified using anatomical drawings [11]. The volumes of the inner ear ELS and TFS were measured, and the ratio of the volumes was calculated using the multi-volume software described above. The cochlear and vestibular volumes were also measured.

### 2.4. Statistical analysis

Values are presented as the mean  $\pm$  standard deviation. Volumetric measurements and ratios were compared using one-way analysis of variance. Statistical analyses were performed

using StatMate software (ver. 5.01; ATOMS, Tokyo, Japan). P values <0.05 were considered significant.

### 3. Results

Forty-one ALHL patients (10 men, 31 women) between the ages of 19 and 67 years ( $43.0 \pm 13.6$  years) were included in the study. Twenty-one patients were affected on the right side. The average times from symptom onset to the first audiogram was 6.1 days and from the first audiogram to MRI was 15.6 days. The average TFS in the inner ear, cochlea, and vestibule was  $283.4 \mu\text{l}$ ,  $104.3 \mu\text{l}$ , and  $63.9 \mu\text{l}$  respectively, and the average ELS in the structures was  $44.6 \mu\text{l}$ ,  $12.5 \mu\text{l}$ , and  $12.2 \mu\text{l}$ , respectively.

Eighty-two SD patients (26 men, 56 women) between the ages of 14 and 84 years ( $59.5 \pm 14.7$  years) were included. Of these, 42 were affected on the right side and 40 on the left side. The average times from symptom onset to the first audiogram was 7.2 days and from the first audiogram to MRI was 14.4 days. The average TFS in the inner ear, cochlea, and vestibule was  $275.5 \mu\text{l}$ ,  $100.5 \mu\text{l}$ , and  $61.3 \mu\text{l}$ , respectively, and the average ELS in the structures was  $48.5 \mu\text{l}$ ,  $15.2 \mu\text{l}$ , and  $12.1 \mu\text{l}$ , respectively.

Forty-eight cMD patients (16 men, 32 women) between the ages of 23 and 84 years ( $60.2 \pm 14.3$  years) were included. Of these, 14 were affected on the right side and 34 on the left side. The average times from onset of cMD to MRI was 12.0 months and from onset of SD to MRI in cMD patients was 57.6 months. The average TFS in the inner ear, cochlea, and vestibule was  $289.1 \mu\text{l}$ ,  $105.8 \mu\text{l}$ , and  $61.6 \mu\text{l}$ , respectively, and the average ELS in the structures was  $55.0 \mu\text{l}$ ,  $18.8 \mu\text{l}$ , and  $13.7 \mu\text{l}$ , respectively.

Seventy-two uMD patients (23 men, 49 women) between the ages of 22 and 80 years ( $56.0 \pm 15.0$  years) were included. Thirty-eight patients were affected on the right side and 34 on the left side. The average times from onset of uMD to MRI was 79.3 months and from onset of latest attack to MRI was 1.0 month.

The average TFS in the inner ear, cochlea, and vestibule was  $289.7 \mu\text{l}$ ,  $114.5 \mu\text{l}$ , and  $68.3 \mu\text{l}$ , respectively, and the average ELS in the structures was  $70.5 \mu\text{l}$ ,  $25.6 \mu\text{l}$ , and  $24.3 \mu\text{l}$ , respectively.

The CS group consisted of 47 CRS patients (data from 94 ears) between the ages of 20 and 83 years ( $58.4 \pm 16.3$  years); 25 were men and 22 were women. The average TFS in the inner ear, cochlea, and vestibule was  $281.8 \mu\text{l}$ ,  $113.1 \mu\text{l}$ , and  $69.5 \mu\text{l}$ , respectively, and the average ELS in the structures was  $39.4 \mu\text{l}$ ,  $11.8 \mu\text{l}$ , and  $12.4 \mu\text{l}$ , respectively.

The ELS/TFS volume ratios in each group are shown in Table 1 and Fig. 1. The cochlear ELS/TFS volume ratio in the uMD group was significantly higher than that in the CS, ALHL, and SD groups but was comparable to that in the cMD group. The cochlear ELS/TFS volume ratio was also similar between the CS and ALHL groups (CS = ALHL < SD < cMD = uMD; Fig. 1). The vestibular ELS/TFS volume ratio in the uMD group was significantly higher than that in all other groups, which were similar (CS = ALHL = SD = cMD < uMD; Fig. 1).

### 4. Discussion

Many studies have evaluated ELH in patients with various diseases using the grading system first described by Nakashima et al. in 2009 [15]. Naganawa et al. [5] first described 3D visualization of ELH in living human subjects and generated a 3D reconstructive model in 2010. Following that, Gürkov et al. [16] successfully measured the volumes of normal inner ear components, reporting average TFS volumes in the inner ear, cochlea, and vestibule of  $182 \mu\text{l}$ ,  $68 \mu\text{l}$ , and  $80 \mu\text{l}$ , respectively, and average cochlear and vestibular ELS/TFS volume ratios of 15% and 28%, respectively. Homann et al. [17] reported an average TFS of  $264.73 \mu\text{l}$  in the inner ear and  $102 \mu\text{l}$  in the cochlea of MD patients. Here, we measured TFS and ELS volumes and the ELS/TFS ratio of the inner ear components in CS with CRS and in ALHL, SD, cMD, and uMD patients using the KIIS technique, focusing on the volume rather than the area. Increases in the volume of the cochlear duct extend the ELS, which can be detected by MRI as a black area in the PPI-PEI image, thus allowing accurate quantification of the volume. In our previous study of patients with CRS, we classified the cochlear and vestibular ELS into four categories and described the ELS volume and ELS/TFS volume ratio for each category [13]. The average cochlear and vestibular ELS/TFS volume ratios in CS were 10.2% and 17.7%, respectively. With the current limitation of MRI technology, we confirmed that the normal finding of cochlear ELS was visualized only the upper turn, the normal finding of vestibular ELS was visualized the utricle and the saccule separately.

Among the 47 patients with CRS (CS group), 41 with ALHL, 82 with SD, 48 with cMD, and 72 with uMD selected here, we found that the cochlear ELS increased in the order CS, ALHL, SD, cMD, and uMD. Schuknecht [19] noted that progressive ELH in both human and animal ears may cause degenerative changes in the sensory and neural structures, most severely in the apical region of the cochlea. We confirmed that the origin of the ELS in the cochlea was the upper turn. We found that the ELS/TFS volume ratio was significantly higher in uMD patients than in ALHL patients, and the ELS volume and ELS/TFS volume ratio were similar in the ALHL and CS groups. Yamasoba et al. reported that some patients with ALHL eventually developed typical MD, and their results strongly suggested that ALHL may be caused by ELH [18]. However, our data suggest the opposite; that ALHL may not be caused by ELH. Furthermore, there were no significant ELS volume and ELS/TFS volume ratio differences in the inner ear, cochlea and vestibule between the affected and contralateral ear of the ALHL patients. Further investigation seemed to be necessary. In addition, the ELS/TFS volume ratio in SD patients was significantly higher and significantly lower than that in the CS group and uMD group, respectively. It is not known whether the extended cochlear ELS in patients with SD causes the hearing loss. We observed that the vestibular ELS/TFS volume ratio of the uMD group was significantly higher than that of all other groups, which had similar ratios. Although the ELS/TFS volume ratio tended to be higher in cMD patients than in the CS group, the difference was not statistically significant. Further investigation will be necessary to clarify this finding.

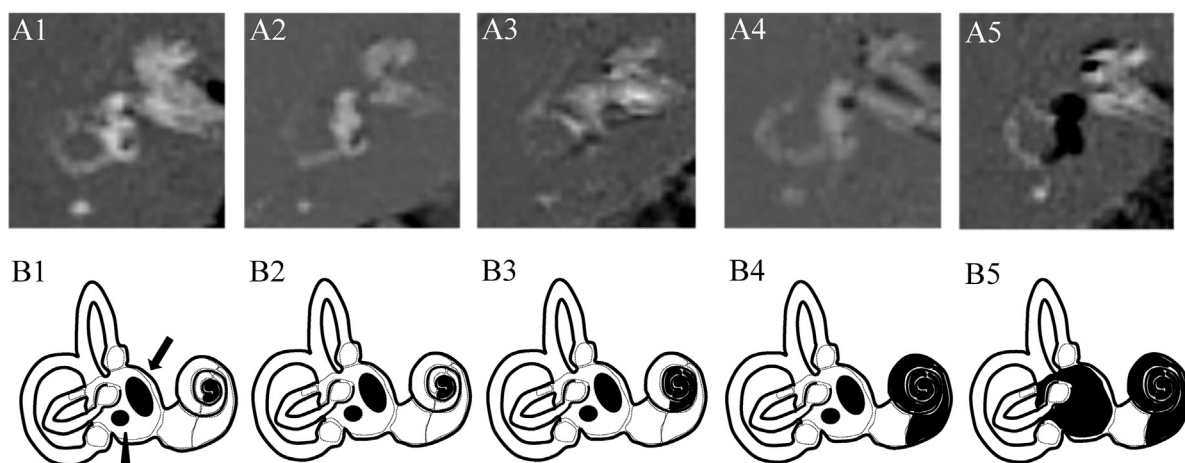
**Table 1**  
ELS/TFS volume ratio of the components of the inner ear.

|                  | Inner ear   |    | ELS/TFS ratio (%) |    | Vestibule   |
|------------------|-------------|----|-------------------|----|-------------|
|                  |             |    | Cochlea           |    |             |
| Control subjects | 13.9 ± 7.9  | *  | 10.2 ± 6.8        | *  | 17.7 ± 10.2 |
| ALHL             | 15.7 ± 5.6  | ** | 12.1 ± 5.7        | ** | 18.9 ± 8.3  |
| SD               | 17.6 ± 6.9  |    | 15.2 ± 8.7        | *  | 19.9 ± 11.3 |
| cMD              | 19.3 ± 8.7  | *  | 18.1 ± 8.2        | ** | 22.5 ± 13.7 |
| uMD              | 24.4 ± 14.8 |    | 21.9 ± 16.4       |    | 35.7 ± 24.1 |

ALHL, acute low-tone sensorineural hearing loss; cMD, cochlear Meniere's disease without vertigo; ELS, endolymphatic space; SD, sudden deafness; TFS, total fluid space; uMD, unilateral Meniere's disease. Values are the mean ± standard deviation.

\*  $p < 0.05$ .

\*\*  $p < 0.01$ .



**Fig. 1.** MR imaging and schematic of the endolymphatic space in the patient groups.

(A) MR imaging.

(B) Schematic of the endolymphatic space.

The black area represents the extended endolymphatic space or endolymphatic hydrops.

(1) Control subjects; (2) acute low-tone sensorineural hearing loss; (3) sudden deafness; (4) cochlear Meniere's disease without vertigo; (5) unilateral Meniere's disease.

The arrow and arrowhead indicate the utricle and the sacculus, respectively.

There were several limitations in this study. We do not know whether the ELS volumes differs between patients diagnosed with definite ALHL and those diagnosed first with ALHL and re-diagnosed later with cMD. In the SD patients, we could not observe a difference in ELS volume from the shape of the audiogram. We do not know the relationship between the duration of MD and the severity of ELS changes in the cMD and uMD patients, and further research is warranted. Yamakawa and Naito [20] described three types of ELH; namely, degenerative hydrops, irritative hydrops, and retention hydrops, in 1954. However, vestibular retention hydrops without abnormal nystagmus cannot be distinguished by MRI alone. Clearly, MRI and clinical symptoms should be taken into account when making a diagnosis.

## 5. Conclusion

We performed MRI-based volumetric measurement of the inner ear ELS in patients with ALHL, SD, cMD, and uMD,

using the KIIS technique to focus on the volume rather than the area. In patients with uMD, the cochlear ELS/TFS volume ratio was significantly higher than that in the CS, ALHL, and SD groups but was comparable to that in the cMD group. The ELS volume of the CS and ALHL groups were also similar ( $CS = ALHL < SD < cMD = uMD$ ). In contrast, the vestibular ELS/TFS volume ratio in uMD patients was significantly higher than that in the other groups ( $CS = ALHL = SD = cMD < uMD$ ). The cochlear ELS volume of patients with MD and other endolymphatic hydrops-related diseases differed from that of CS. Our results suggest that ALHL may not be caused by ELH. We confirmed the presence of extended ELS in patients with SD.

## Disclosure statement

The authors alone are responsible for the content and writing of the paper.



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