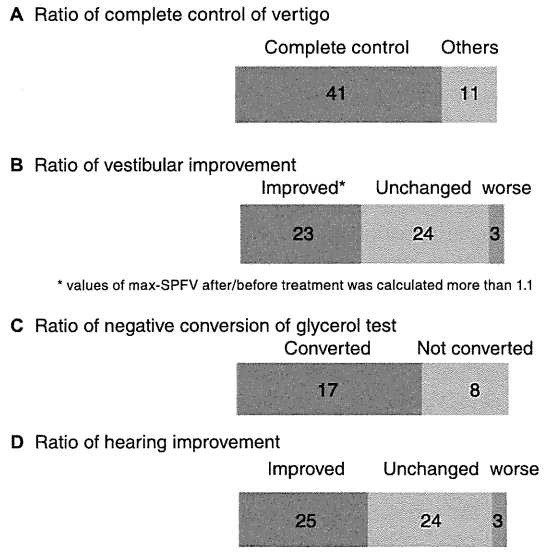


Figure 1. Surgical results including the ratio of the number of patients with complete control of vertigo (A), with vestibular improvement (B), with negative conversion of glycerol test (C), and with hearing improvement (D ).

'worse' and values in between better and worse as 'no change.' The data could be obtained for all the 52 cases.

We performed a glycerol test to detect endolymphatic hydrops twice: during the 6 months before surgery and during the 6 months between 18 and 24 months after surgery [14]. This test is considered positive in pure-tone audiometry if there is a ≥ 10 dB improvement at two or more frequencies between 0.25 and 2.0 kHz. The data could be obtained for 25 of 50 cases, because negative results at the first glycerol test before surgery were found in 15 cases and a lack of paired examinations was found in another 10 cases. Therefore, the positive ratio at the first glycerol test was 62.5% (25/40).

Table I. Two-way table of the ratio of control of vertigo and vestibular function.

| Factors | Complete control | Others |
|---|---|---|
| (a) | | |
| Improved max-SPEV | 20 | 3 |
| Unchanged and worse max-SPEV | 19 | 8 (NS) |
| (b) | | |
| Improved and unchanged max-SPEV | 37 | 10 |
| Worse max-SPEV | 2 | 1 (NS) |

max-SPEV, maximum slow-phase eye velocity; NS, not significant.

Table II. Two-way table of the ratio of control of vertigo and negative conversion of endolymphatic hydrops.

| Glycerol test | Complete control | Others |
|---|---|---|
| + → − | 14 | 3 |
| + → + | 4 | 4 (NS) |

NS, not significant.

### *Statistical analysis*

Data were analyzed using a 2 × 2 contingency table method. Each correlation was assessed using the $\chi^2$ test or Fisher's test. All the data from treatment results were treated statistically with the use of StatView, version 4.0 (SPSS, Chicago, IL, USA). All reported $p$ values were two-sided, and those $< 0.05$ were considered significant.

## Results

Surgical results, including the number of patients with complete control of vertigo (41/52: 77.8%), those with vestibular improvement (23/50: 46.0%), those with negative conversion of glycerol test (17/25: 68.0%), and those with hearing improvement (25/52: 48.1%) are shown in Figure 1. Duration of disease indicates the period between the onset of symptoms and the date of surgery.

As shown in Table I, there was no significant correlation between complete control of vertigo and improvement ($p = 0.1895$) or improvement/preservation ($p = 0.5337$) of max-SPEV (i.e. vestibular function). There was also no significant correlation between complete control of vertigo and negative conversion of the glycerol test ($p = 0.1563$) (Table II). Finally, there was no significant correlation between complete control of vertigo and hearing improvement ($p = 0.1199$) (Table IIIa). Table IIIb shows significant correlation between complete control of vertigo and hearing improvement/preservation ($p = 0.0075$). Additionally,

Table III. Two-way table of the ratio of control of vertigo and hearing function.

| Factors | Complete control | Others |
|---|---|---|
| (a) | | |
| Improved HL | 22 | 3 |
| Unchanged and worse HL | 19 | 8 (NS) |
| (b) | | |
| Improved and unchanged HL | 41 | 8 |
| Worse HL | 0 | 3 ($p < 0.01$) |

HL, hearing loss; NS, not significant.

Table IV. Two-way table of the ratio of (a) vestibular and glycerol test improvements and (b) vestibular and hearing improvements.

| Factors | Glycerol test + → − | Glycerol test + → + |
|---|---|---|
| (a) | | |
| Improved max-SPEV | 14 | 2 |
| Unchanged and worse max-SPEV | 3 | 6 (NS) |
| (b) | Improved HL | Unchanged and worse HL |
| Improved max-SPEV | 18 | 5 |
| Unchanged and worse max-SPEV | 6 | 21 ($p < 0.05$) |

HL, hearing loss; max-SPEV, maximum slow-phase eye velocity; NS, not significant.

there were tendencies in relationships between vestibular and glycerol test improvements ($p = 0.0538$) (Table IVa) and statistical significances in relationships between vestibular and hearing improvements ($p = 0.0217$) (Table IVb).

## Discussion

We examined correlations between the frequency of vertigo and neuro-otologic function in our patients after ESDS to elucidate the mechanisms of the ESDS effects on symptomatic vertigo relief. Judging from Tables I and II, vertigo could be completely controlled after ESDS regardless of the improvement of vestibular function or reduction of endolymphatic hydrops. Uno et al. reported that some patients were still hydrops-positive through the inner ear MRI with intratympanic administration of gadolinium despite complete control of vertigo after ESDS [15]. This finding supports our results that complete control of vertigo does not always depend on improving vestibular function or diminishing endolymphatic hydrops.

We suggest that there are at least three steps by which ESDS can cure intractable Meniere's disease: 1) prevent progression of endolymphatic hydrops; 2) reduce endolymphatic hydrops; 3) improve the function of vestibular hair cells and/or neurons. All three steps have the potential to stop vertigo attacks, but only the third step can facilitate recovery of the caloric response and hearing level. Roughly speaking, according to the present data, ESDS can help 80% of intractable Meniere's patients achieve results via one of these three steps, but in only half of them can the third step be successfully accomplished.

Judging from the data in Table III, complete control of vertigo after ESDS was accomplished following improvement/preservation of the hearing level. Huang and Lin [5], Moffat [6], Gibson [7], Gianoli et al. [8], Kitahara and Goto [9], and Kitahara et al. [10] reported 2-year results with their modified ESDS. They achieved complete control of vertigo in 89%, 42%, 57%, 60%, 85%, and 88% of patients, respectively, and hearing improvement/preservation in 33/54, 15/56, 5/39, 60/22, 32/55, and 49/44% of patients, respectively. These findings indicate that the proportion of patients with hearing improvement/preservation is likely to be similar to the proportion of those with complete vertigo control, except for Moffat's study [6]. After ESDS, the first and second steps outlined earlier would take place most often in the inner ear, resulting in complete control of vertigo and hearing preservation. Judging from the data in Table IV, hearing improvement after ESDS could be accomplished by the direct effect of ESDS on the third step and/or its effect on it indirectly. This might be explained by the diminishing vertigo-induced disease stress and stress-induced plasma vasopressin, resulting in the good condition of the inner ear [16–18]. Altogether, intractable vertigo attacks and progressive hearing loss are controlled when ESDS prevents or reduces the severity of endolymphatic hydrops. The caloric response and hearing level undergo recovery only when ESDS facilitates functional improvement of the inner ear hair cells and/or neurons.

Our study has limitations. First, we have modified the original ESDS [2] to what we used in the present study [10]. Our ESDS includes several interventions not found in the original ESDS protocol. These changes were needed to accomplish an appropriate study design. In later communications, we plan to include several controls to increase data reliability. Second, we have not yet found the best way to evaluate vestibular improvement that obtains international consensus. Based on a previous report of the furosemide test criteria [13], we deemed changes in caloric responses of ± 10% as positive. The third limitation is that both the glycerol test and electrocochleogram have approximately 60% sensitivity at most [14,19]. In recent reports, endolymphatic hydrops imaging was demonstrated using gadolinium-enhanced inner ear MRI [15,19,20]. The sensitivity of this imaging analysis for endolymphatic hydrops was more than 90%, better than that of neuro-otologic exams. Further studies including gadolinium-enhanced inner ear MRI could evaluate the effects of Meniere's treatments on endolymphatic hydrops.

## Conclusion

According to the surgical results and neuro-otologic data, complete freedom from vertigo after ESDS does not always depend on improved vestibular function or a reduction of the severity of endolymphatic hydrops.

## Acknowledgments

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***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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**ORIGINAL ARTICLE**

# Pseudo-anterior canalolithiasis

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**Abstract**

*Conclusion:* Because nystagmus induced by ampullopetal inhibition of the posterior semicircular canal (PSCC) rotates around the axis perpendicular to the plane of the anterior semicircular canal (ASCC) of the other side, when free-floating debris is initially located at the distal portion of the PSCC, a patient showing positional nystagmus appears to have the ASCC type of benign paroxysmal positional nystagmus. We name this 'pseudo-anterior canalolithiasis'. *Objective:* We report on pseudo-anterior canalolithiasis originating in the PSCC and discuss the differential findings between pseudo-anterior and true anterior canalolithiasis by means of three-dimensional (3D) analysis of the positional nystagmus. *Methods:* We performed 3D analysis of the positional nystagmus in a patient with true anterior canalolithiasis and in another patient with pseudo-anterior canalolithiasis. *Results:* In the patient with true anterior canalolithiasis, the direction of positional nystagmus during reverse Epley maneuver was constant and its axis was perpendicular to the plane of the right ASCC three-dimensionally. In contrast, in the patient with pseudo-anterior canalolithiasis, the first positional nystagmus of which the axis was perpendicular to the plane of the left ASCC became a second positional nystagmus of which the axis was perpendicular to the plane of the right PSCC during the reverse Epley maneuver.

**Keywords:** *Three-dimensional analysis, reverse Epley maneuver, rotation vector, time constant*



## Introduction

On the basis of the canalolithiasis hypothesis [1], free-floating debris in the posterior semicircular canal (PSCC) causes the PSCC type of benign paroxysmal positional nystagmus (BPPN) (P-BPPN) [2]. The P-BPPN induced by the Dix-Hallpike (D-H) maneuver [3] in the affected-ear-down head position is composed of both torsional and vertical components (posterior canalolithiasis). The anterior semicircular canal (ASCC) type of BPPN (A-BPPN) is caused by free-floating debris in that canal and is composed of torsio-vertical components in the D-H maneuver in the affected-ear-up head position (anterior canalolithiasis) [4]. The proposed mechanism for canalolithiasis identifies an ampullofugal movement of the free-floating debris in the PSCC during the D-H maneuver that stimulates the PSCC to induce a typical P-BBPN, and also predicts that ampullopetal movement of free-floating debris in the PSCC during the same maneuver inhibits PSCC and induces A-BPPN-like BPPN. We name this 'pseudo-anterior canalolithiasis'.

Here, we report a patient with true anterior canalolithiasis and another patient with pseudo-anterior canalolithiasis who revealed left A-BPPN at

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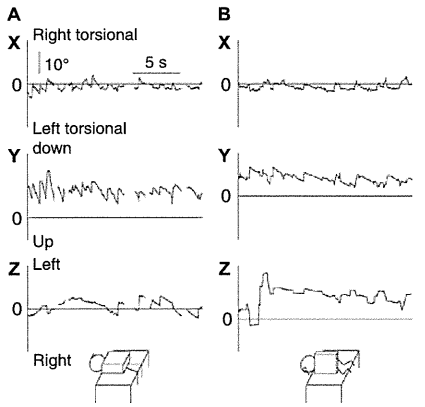


Figure 1. Eye positions in X, Y, and Z components of nystagmus in patient A. (A) Left D-H maneuver; (B) head and trunk turned to the right at the third step of the reverse Epley maneuver. In the X component, 'right torsional' means that the superior pole of the eyeball rotates to the right ear, and 'left torsional' to the left ear.

first and right P-BPPN after the reverse Epley maneuver. We developed a new technique for analyzing the rotation vector of nystagmus in three dimensions with an infrared CCD camera [5]. Using this technique, the affected semicircular canal can be determined by the axis of eye rotation in BPPN, which is perpendicular to the plane of the affected semicircular canal [2,4,6]. We then discuss the differential findings between pseudo- and true anterior canalolithiasis by means of three-dimensional (3D) analysis of positional nystagmus.

## Material and methods

From July 2009 to February 2011, we diagnosed 102 patients with benign paroxysmal positional vertigo (BPPV) following the criteria already described elsewhere [7].

Positional nystagmus of the left eye of patients A and B was recorded on videotape with an infrared CCD camera (*RealEyes*, Micromedical Technologies). In the present study, eye movements were three-dimensionally described by rotation vectors, which characterize the eye positions around a single rotation. An eye position can be reached by rotating the eye from the reference position around a single axis. The eye position is represented by a vector around the axis, of which the length is proportional to the angle of rotation. The reference position was defined as the eye position when the subject was looking straight ahead with the head in an upright position. Straight ahead was defined as looking at a target located horizontally in front of the eye [8]. The method of analysis of the eye rotation vector and its accuracy have already been described elsewhere [5,9].

The videotape images were converted into digital images (720*480 dots) and the space coordinates of the center of the pupil and an iris freckle were reconstructed in three dimensions. The space coordinates were defined as follows. The X axis is parallel to the naso-occipital axis (positive forward), Y axis is parallel to the inter-aural axis (positive left), and Z axis is normal to the X-Y plane (positive upwards). X, Y, and Z components mainly reflect roll, pitch, and yaw components, respectively. The direction of rotation is described from the subject's point of view. In the X component, 'right torsional' means that the superior pole of the eyeball rotates to the right ear, and 'left torsional' to the left ear. The rotation vector $\mathbf{r}$ describing a rotation of $\theta$ around the axis $\mathbf{n}$ is given by the formula $\mathbf{r} = \mathbf{n}\tan(\theta/2)$, with $\mathbf{n}$ being the unit vector, the direction of which represents its axis. We used the Euler angle parameter given as $2^{*}\tan^{-1}$ (magnitude of rotation vector) to represent the eye position as axis angle representations [10,11]. Using the following formula: $\boldsymbol{\omega} = 2 \times (d\mathbf{r}/dt + \mathbf{r} \times d\mathbf{r}/dt)/(1 + \mathbf{r}^2)$, we calculated the eye velocity $\boldsymbol{\omega}$ around X, Y, and Z axes [8]. We then extracted the slow phase eye velocity (SPEV) of the nystagmus by a fuzzy set-based approach [12,13]. Using the least squares method, SPEV in the X component against time was approximated exponentially. Finally, the time constant (TC) was calculated as the reciprocal of the coefficient of time [6]. The recording and analysis of patient eye movements were approved by the Ethics Committee for Medical Research of Osaka University Hospital (no. 10091). Written informed consent was obtained from the patients in this study.

## Results

Of the 102 patients with BPPV [7], only two patients, A and B shown in this study, exhibited A-BPPN.

### *Patient A*

In a 34-year-old male, the left D-H maneuver induced positional nystagmus with a right torsional X component and a downward Y component (right torsional and down-beating nystagmus), suggesting right A-BPPN [4] (Figure 1A). Before the left D-H maneuver, no spontaneous nystagmus was seen in the sitting position as the value of SPEV was almost 0°/s (Figure 2). Patient A was then treated with the reverse Epley maneuver [14] for his right ASCC type of BPPV (A-BPPV, anterior canalolithiasis). The reverse Epley maneuver for right A-BPPV is the same maneuver as the Epley maneuver for left PSCC type of BPPV (P-BPPV). When his head and trunk were rotated to the right (inset in Figure 1B) at the third step of the

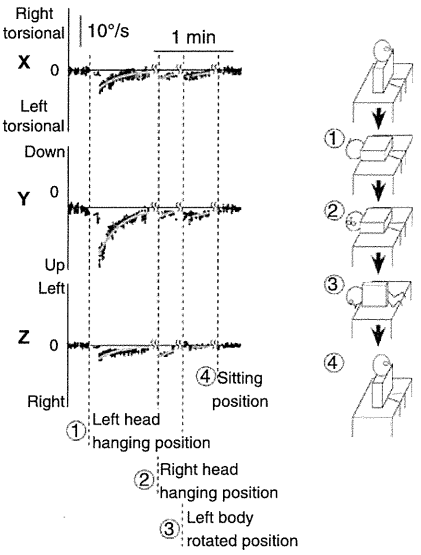


Figure 2. SPEV of nystagmus in patient A during reverse Epley maneuver for treatment of right A-BPPV (anterior canalolithiasis). Upper, middle, and lower recordings are X, Y, and Z components of SPEV, respectively.

reverse Epley maneuver, positional nystagmus with a right torsional X component and downward Y component (right torsional and down-beating nystagmus) still remained (Figure 1B). Figure 2 shows changes in the SPEV of positional nystagmus in patient A during the reverse Epley maneuver. Using the least square method, the SPEV against time (t) was approximated by the following formulas: $-5.8\exp(-t/16.7)$ in the X component, $-14.7\exp(-t/16.7)$ in the Y component, and $-4.2\exp(-t/16.7)$ in the Z component with a TC of 16.7 s at the left D-H maneuver. When TC is 16.7 s, after 50 s ($16.7 \times 3$) the value of SPEV becomes as small as one-twentieth (1/Napier's constant$^3 \approx 1/20$). When SPEV becomes as small as 1/20, practically, we can barely detect nystagmus; thus, we concluded that the duration time of the positional nystagmus was 50 s. At the second step of the reverse Epley maneuver (inset ② in Figure 2), the maximum SPEV was approximately –2.9°/s in the X component, –2.8°/s in the Y component, and –3.6°/s in the Z component with a TC of 13.0 s. At the third step of the reverse Epley maneuver (inset ③ in Figure 2), the maximum SPEV was approximately –1.7°/s in the X component, –2.9°/s in the Y component, and –0.4°/s in the Z component with a TC of 22.0 s.

In Figure 3, SPEVs of the rotation vectors of the positional nystagmus shown in Figure 2 are plotted on XY, XZ, and YZ planes. SPEVs of the rotation vectors of positional nystagmus were in line with the axis perpendicular to the right ASCC plane (Ra) [15]. These findings indicate that, during the left D-H maneuver and the reverse Epley maneuver, the positional nystagmus rotated around the axis perpendicular to the right ASCC plane, resulting in the diagnosis of true anterior canalolithiasis in this patient. His positional nystagmus disappeared at the second visit a week later.

*Patient B*

In this 66-year-old male patient, the right D-H maneuver induced positional nystagmus with a left torsional X component and a downward Y component (left

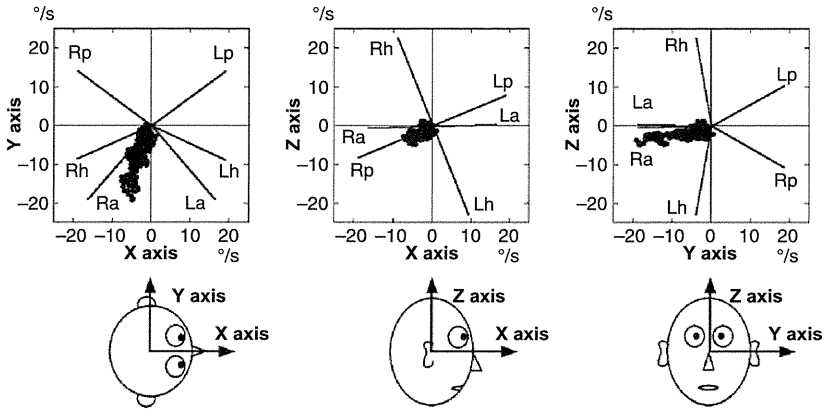


Figure 3. Three-dimensional plotting of the axis angle of the SPEV shown in Figure 2. La, axis perpendicular to the plane of the left ASCC; Lh, axis perpendicular to the plane of the left horizontal semicircular canal; Lp, axis perpendicular to the plane of the left PSCC; Ra, axis perpendicular to the plane of the right ASCC; Rh, axis perpendicular to the plane of the right horizontal semicircular canal; Rp, axis perpendicular to the plane of the right PSCC [15].

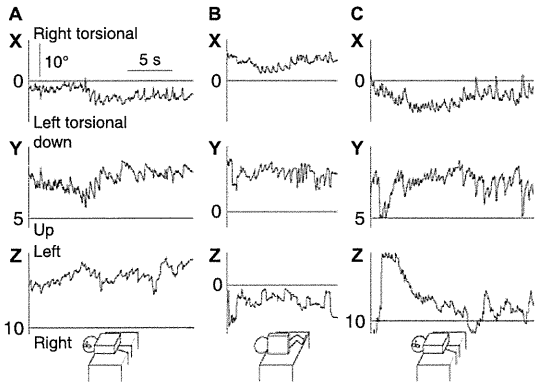


Figure 4. Eye positions in X, Y, and Z components of the nystagmus in patient B. (A) The first right D-H maneuver; (B) head and trunk turned to the left at the third step of reverse Epley maneuver; (C) the second right D-H maneuver after the reverse Epley maneuver.

torsional and down-beating nystagmus), suggesting left A-BPPN (Figure 4A). Before the right D-H maneuver, no spontaneous nystagmus was seen in the sitting position as the value of SPEV was almost 0°/s (Figure 5A). Patient B was then treated with the reverse Epley maneuver for his left A-BPPV (anterior canalolithiasis). The reverse Epley maneuver for left A-BPPV is the same maneuver as the Epley maneuver for right P-BPPV. When his head and trunk were rotated to the left at the third step of the reverse Epley maneuver (inset in Figure 4B), a different positional nystagmus with a right torsional X component and an upward Y component (right torsional and up-beating nystagmus) was induced (Figure 4B). After the reverse Epley maneuver, the positional nystagmus was re-examined in the right D-H maneuver. The nystagmus induced at the third step still remained in the second right D-H maneuver, suggesting right P-BPPN in patient B [2] (Figure 4C).

Figure 5A shows changes in SPEV of positional nystagmus in patient B at the first right D-H maneuver and during the subsequent reverse Epley maneuver, while Figure 5B shows those at the second right D-H maneuver. Using the least square method, the SPEV at the first right D-H maneuver (inset ① in Figure 5) against time (t) was approximated by the following formulas: 11.5exp(–t/9.2) in the X component, –14.5exp(–t/9.2) in the Y component, and 6.0exp(–t/9.2) in the Z component with a TC of 9.2 s. As the TC is 9.2 s, the duration of the positional nystagmus was 28 s (9.2 × 3). The maximum SPEV at the third step of the reverse Epley maneuver (inset ③ in Figure 5) was approximately –11.6°/s in the X component, 17.6°/s in the Y component, and –1.4°/s in the Z component, with a TC of 5.3 s. The maximum SPEV at the second right D-H maneuver (inset ⑤ in Figure 5) was approximately –16.9°/s in the X component, 15.8°/s in the Y component, and –7.1°/s in the Z component, with a TC of 18.2 s (Figure 5B).

In Figure 6, SPEVs of the rotation vectors of positional nystagmus at the first right D-H maneuver (Figure 6A) and those at the second right D-H maneuver (Figure 6B) are plotted on XY, XZ, and YZ planes. Accordingly, at the first right D-H maneuver, SPEVs were in line with the axis perpendicular to the left ASCC plane (La). However, at the second right D-H maneuver, SPEVs were in line with the axis perpendicular to the right PSCC plane (Rp), and because the reverse Epley maneuver failed in the treatment of left anterior canalolithiasis, the diagnosis of right P-BPPV (posterior canalolithiasis) was given to patient B. He was then treated with Epley maneuver for the treatment of right P-BPPV (posterior canalolithiasis) and his positional nystagmus disappeared at the second visit a week later.

## Discussion

In patient A, right torsional and down-beating positional nystagmus with short TC was induced by the left D-H maneuver (Figures 1A and 2), suggesting the diagnosis of right anterior canalolithiasis. The direction of his positional nystagmus was constant

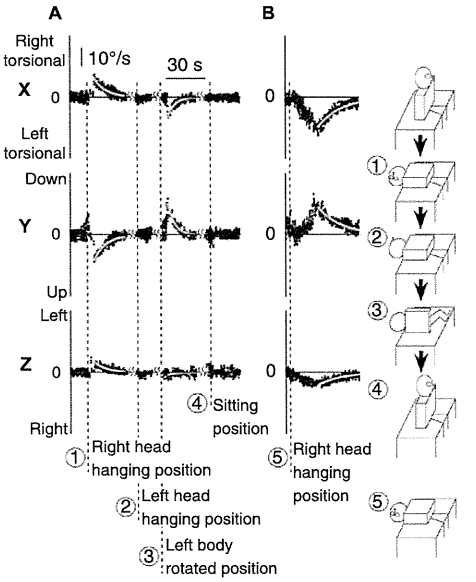


Figure 5. SPEV in X, Y, and Z components of the nystagmus in patient B during the reverse Epley maneuver for treatment of left A-BPPV (anterior canalolithiasis). Upper, middle, and lower recordings are X, Y, and Z components of SPEV, respectively.

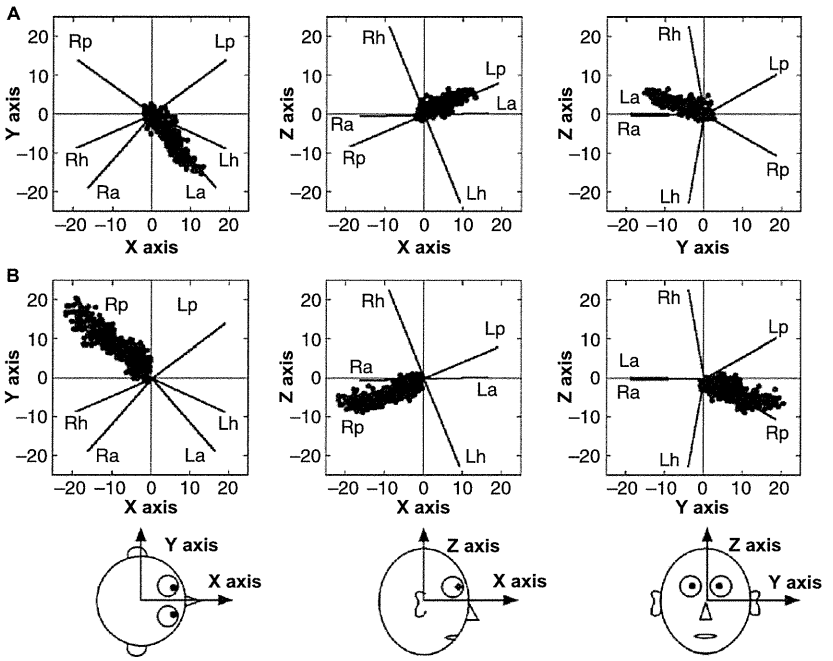


Figure 6. Three-dimensional plotting of the axis angle of SPEV shown in Figure 5. SPEVs of the rotation vectors of positional nystagmus at the first right D-H maneuver (A) and those at the second right D-H maneuver (B) are plotted on XY, XZ, and YZ planes. Abbreviations are the same as for Figure 3.

during the subsequent reverse Epley maneuver for the treatment of right anterior canalolithiasis (Figures 1B and 2) and its axis was perpendicular to the plane of the right ASCC three-dimensionally (Figure 3). These findings indicate that the free-floating debris moved ampullofugally in the right ASCC during the left D-H maneuver and the subsequent reverse Epley maneuver in this patient (Figure 7A), leading to the diagnosis of true right anterior canalolithiasis.

In contrast, in patient B, left torsional and down-beating positional nystagmus with short TC was induced by the first right D-H maneuver (Figures 4A and 5A), suggesting the diagnosis of left anterior canalolithiasis. His positional nystagmus changed to a right torsional and up-beating type at the third step of the subsequent reverse Epley maneuver for the treatment of left anterior canalolithiasis (Figures 4B and 5A). After the reverse Epley maneuver, the nystagmus induced at the third step still remained at the second right D-H maneuver (Figure 4C and 5B). A 3D analysis of his positional nystagmus demonstrated that the axis of the positional nystagmus at the first right D-H maneuver was perpendicular to the plane of the left ASCC (Figure 6A) and that, during the second maneuver, it was perpendicular to the plane of the right PSCC (Figure 6B). Because the reverse Epley maneuver failed in the treatment of left anterior canalolithiasis, the diagnosis of right posterior canalolithiasis was given to patient B. The possible mechanism involved in his positional nystagmus involves an ampullopetal movement of the free-floating debris

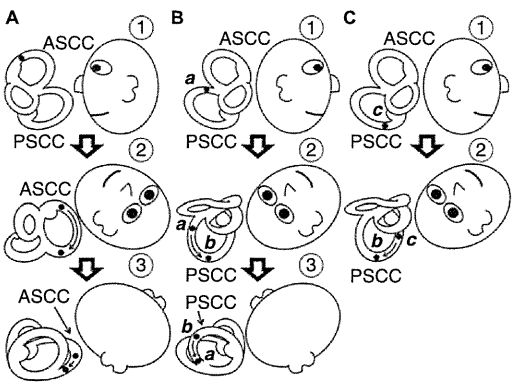


Figure 7. Possible movements of free-floating debris in semicircular canal. (A) A-BPPV (anterior canalolithiasis), ① upright, ② D-H maneuver, and ③ the third step of the reverse Epley maneuver. (B) Pseudo-anterior canalolithiasis with free-floating debris located at the distal portion of the PSCC, ① upright position, ② D-H maneuver, and ③ the third step of the reverse Epley maneuver. (C) P-BPPV (posterior canalolithiasis) with free-floating debris located at the lowest portion of the PSCC, ① upright position and ② D-H maneuver.

located at the distal portion of the right PSCC during the first right D-H maneuver (Figure 7B, *a* to *b*). This is because nystagmus induced by the ampullopetal inhibition of the right PSCC rotates around the axis perpendicular to the plane of the left ASCC [16]. We name this 'pseudo-anterior canalolithiasis'.

The free-floating debris then moved back ampullofugally during the third step of the reverse Epley maneuver for the treatment of left anterior canalolithiasis (Figure 7B, *b* to *a*). Before the re-examination of the positional nystagmus, the free-floating debris possibly fell into the lowest portion of the PSCC in an upright position. Thereafter, the free-floating debris moved ampullofugally in the right PSCC during the second D-H maneuver (Figure 7C, *c* to *b*).

In this paper, we describe a patient with pseudo-left anterior canalolithiasis originating in the right PSCC who showed positional nystagmus that rotated around the axis perpendicular to the plane of the left ASCC in the right D-H maneuver. However, following reverse Epley maneuver for the treatment of left anterior canalolithiasis, a different nystagmus that rotated around the axis perpendicular to the plane of the right PSCC was induced in the second right D-H maneuver. Because nystagmus induced by the ampullopetal inhibition of the right PSCC rotated around the axis perpendicular to the plane of the left ASCC, it is suggested that the free-floating debris was first located at the distal portion of the right PSCC in the patient with pseudo-left anterior canalolithiasis.

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***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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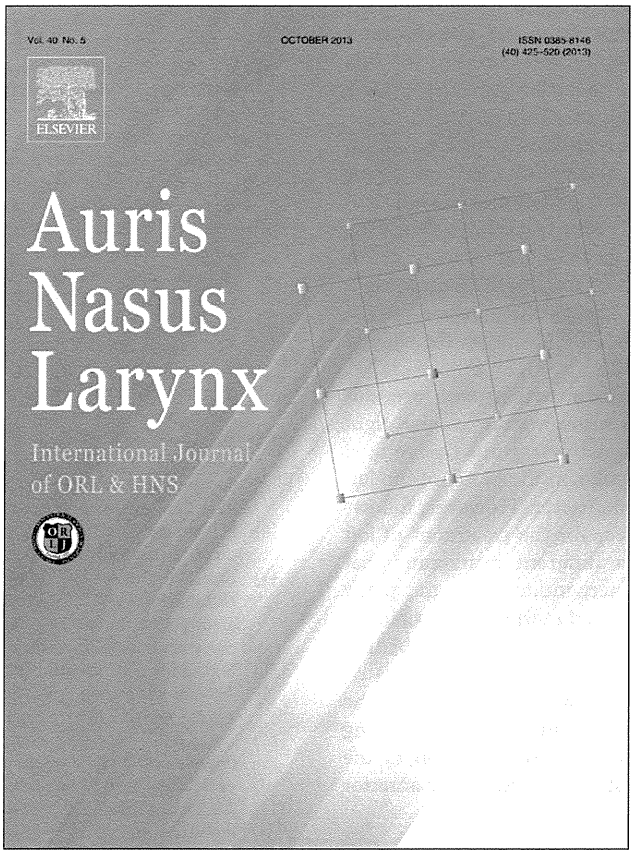

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# Long-term results of endolymphatic sac drainage with local steroids for intractable Meniere's disease

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ABSTRACT

*Objectives:* Meniere's disease is a common inner ear disease characterized by vertigo, hearing loss and tinnitus. Since Meniere's disease is thought to be triggered by an immune insult to inner ear hydrops, we examined endolymphatic sac drainage with intra-endolymphatic sac application of large doses of steroids for intractable Meniere's patients and observed long-term results from 2 years to over a decade until 13 years.

*Methods:* Between 1998 and 2009, we enrolled and assigned 286 intractable Meniere's patients to two groups: group-I (G-I) included patients who underwent endolymphatic sac drainage with steroid instillation and group-II (G-II) included those who declined endolymphatic sac drainage. Definitive spells and hearing improvement in these two groups were determined for 2–13 years after treatment.

*Results:* According to the established criteria, vertigo was completely controlled in 88% of patients in G-I in the 2nd year, in 73% in the 12th year and in 70% in the 13th year. These results in G-I were significantly better than those in G-II for 13 years after treatment. Hearing was improved in 49% of patients in G-I in the 2nd year, in 27% in the 12th year and in 25% in the 13th year. These results in G-I were significantly better than those in G-II for 12 years after treatment, but this was not significant in the 13th year.

*Conclusions:* Endolymphatic sac drainage with intra-endolymphatic sac application of large doses of steroids could improve long-term follow-up results of hearing as well as vertigo control. This means that the drainage with local steroids could also improve patients' long-term quality in the prime of life.



## 1. Introduction

Meniere's disease is a common inner ear disease of 15–50 per 100,000 population and is characterized by repeated episodic vertigo, fluctuating sensorineural hearing loss and tinnitus [1]. 10–20% of Meniere's patients cannot be free from these symptoms in spite of various types of medication. They are prevented from participating in activities of daily life and interaction with their social environment, such as work and schooling, because of frequent vertigo attacks with progressive profound hearing loss and unremitting tinnitus. This type of Meniere's disease is called intractable Meniere's disease and the next therapeutic strategy has not been determined yet.

The definitive pathogenesis of Meniere's disease is still unknown, although the oto-pathology in Meniere's temporal bones was revealed in 1938 to be inner ear endolymphatic hydrops [2,3]. However, it has been reported that Meniere's disease is usually triggered by immune, metabolic, infectious, traumatic or other insults to the inner ear, associated with a small misplaced malfunctioning endolymphatic sac. Among these insults, immune-mediated responses in the inner ear endo-organs, such as the endolymphatic sac, stria vascularis and spiral ligament, are thought to be the main reason for the development of symptoms in Meniere's disease [4]. Therefore, systemic administration and/or local perfusion of corticosteroids into the middle ear have been adopted as an anti-immune or anti-inflammatory therapy for patients with intractable Meniere's disease [5]. These treatments resulted in good relief from vertigo and improvement of hearing in some cases; however, these results, especially for hearing, did not last long enough to discontinue additional repetitive applications of steroids [6]. Since Meniere's disease is characterized by repeated audio-vestibular symptoms, unlike other inner ear diseases without recurrence such as sudden deafness and vestibular neuritis, it is necessary to refrain from repetitive applications of steroids for long-term follow-up with Meniere's patients because of side effects.

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In terms of the inner ear drug delivery system, there is the possibility of the longitudinal route from the endolymphatic sac to the cochlea and vestibule, as suggested by several lines of evidence in animal studies. Morgenstern et al. [7] and Lee et al. [8] demonstrated that intra-endolymphatic sac materials could reach the cochlear endolymphatic site through the vestibular aqueduct route using a test marker and an oto-toxic drug, respectively. Yamasoba et al. suggested the possibility of gene therapy through the vestibular aqueduct route [9]. Recently, in human studies, Colletti et al. showed that intra-endolymphatic sac gadolinium could enhance the cochlear endolymphatic site in MRI imaging through the vestibular aqueduct route [10]. In the present study, we examined long-term results from 2 years to over a decade until 13 years of endolymphatic sac drainage with intra-endolymphatic sac application of large doses of steroids as a new therapeutic strategy for intractable Meniere's disease.

## 2. Materials and methods

The present study was approved by the Ethics Committee of Osaka University Hospital (certificate number: 0421) and registered by ClinicalTrials.gov of the U.S. Food and Drug Administration (certificate number: NCT00500474).

### 2.1. Patients

Patients were eligible for enrollment if they had received a clinical diagnosis of intractable Meniere's disease according to the American Academy of Head and Neck Surgery (AAO-HNS) criteria in 1995 [11]. These criteria can be briefly described as follows. (1) Repeated attacks of vertigo: A definitive spell is spontaneous vertigo lasting at least 20 min. A mixed type of spontaneous nystagmus is observed during attacks. (2) Fluctuating cochlear symptoms: A hearing test usually reveals a marked fluctuation of the threshold in the low and middle tone range. If necessary, we carried out a glycerol test or electrocochleogram to detect endolymphatic hydrops. (3) Exclusion of other causes: To exclude other disorders, a thorough history, and neurological, neurotological and MRI examinations were carried out. Intractable Meniere's disease was designated in cases where various forms of medical and psychological management failed for at least 6 months. Medical management included diuretics, betahistine, diphenidol, dimenhydrinate and diazepam, which are thought to be effective for persistent symptoms in Meniere's disease [12].

### 2.2. Enrollment and assignment

Between April 1998 and March 2009, 286 patients were enrolled and assigned to two study groups at two hospitals, Osaka Rosai Hospital and Osaka University Hospital. Group I (G-I) consisted of 220 patients who underwent endolymphatic sac drainage with steroid instillation into the sac (by the first author, T. Kitahara) and who were followed regularly for at least 2 years. The procedures for steroid instillation into the endolymphatic sac in G-I were performed according to endolymphatic sac drainage with steroid instillation surgery. Medical treatments also kept going on even after surgery and gradually diminished according to the decay profiles of post-operative symptoms. Group II (G-II) consisted of 66 patients who declined endolymphatic sac drainage and thereafter received the best available non-surgical medical treatments mentioned above [12].

The technical details of endolymphatic sac drainage with steroid instillation are as follows. A simple mastoidectomy was performed, clearly exposing the endolymphatic sac in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal. If possible, the sac was exposed including the rugose portion. The sac was opened with an L- (right ear) or backward L- (left ear) shaped incision made along the posterior and distal margins of the lateral wall (Fig. 1A). The sac was then filled with 20 mg of prednisolone (Fig. 1B). While dissolving the volume of prednisolone in the sac, we prepared a bundle of absorbable gelatin films (ca. 4 mm × 20 mm × 0.7 mm × 5 sheets) with fan- and stick-shaped ends. These films were tied to each other with biochemical adhesive (human thrombin combined with human fibrinogen) at the stick-shaped end. The fan-shaped end was then inserted into the sac (Fig. 1C) and small pieces of absorbable gelatin sponge soaked in a high concentration of dexamethasone (32 mg/4 ml) were placed inside and outside the sac lumen, which was expanded with the bundle (Fig. 1D). The sponges containing dexamethasone placed outside the sac were coated with the adhesive so that dexamethasone was slowly delivered into the sac over a long period of time as a natural sustained-release vehicle. The stick-shaped end extending out of the sac was fixed to the front edge of the mastoid cavity with the same adhesive so that the incision into the sac was also expanded for an adequate period of time after surgery. The mastoid cavity was filled with relatively large pieces of absorbable gelatin sponge dipped in steroid antibiotic solution, after which the wound was closed with skin sutures.

### 2.3. Functional examinations

A definitive spell lasting more than 20 min was regarded as a Meniere's vertigo attack according to the 1995 AAO-HNS criteria [11]. The frequency of vertigo was calculated based on the number of vertigo attacks during 6 months before treatment ("before"). The number of attacks in G-II patients who refused endolymphatic sac drainage was also determined. The frequency of vertigo after treatment was calculated as the number of attacks during 6 months before the end of the follow-up period; for example, at the 3rd follow-up year it was calculated based on the number of vertigo attacks during the 6 months between 30 and 36 months after treatment ("after"). The frequency of vertigo in G-II patients at this time point was also determined. "Complete" control of vertigo at the 3rd follow-up year meant no vertigo attacks during that period. The value $0 < \text{after/before} \leq 0.8$ was regarded as "better", $1.2 \leq \text{after/before}$ as "worse" and the other values ($0.8 < \text{after/before} < 1.2$) as "no change".

Hearing function was measured by a pure tone audiometer and was evaluated based on the four-tone average formulated by $(a + b + c + d)/4$ ($a$, $b$, $c$ and $d$ are hearing levels at 0.25 kHz, 0.5 kHz, 1 kHz and 2 kHz, respectively) according to the modified 1995 AAO-HNS criteria. The worst hearing level during the 6 months before treatment was adopted as the hearing level before treatment ("before"). The worst hearing level at follow-up was calculated as the worst hearing level during 6 months before the end of the follow-up period; for example, the worst hearing level during the 6 months between 42 and 48 months after treatment was adopted as the hearing level at the 4th follow-up year ("after"). Higher than 10 dB differences in hearing levels before and after treatment were regarded as "better", lower than −10 dB differences as "worse" and the other values in between "better" and "worse" as "no change".

Vestibular function was measured by a caloric test using an electronystagmogram (ENG). For the caloric test, the external auditory canal was irrigated in turn with 30 °C cold water and 44 °C hot water (20 cc) 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) in the treated side, max-SPEV after treatment/max-SPEV before treatment was calculated and values higher than 1.1 (1.1 indicates 10%

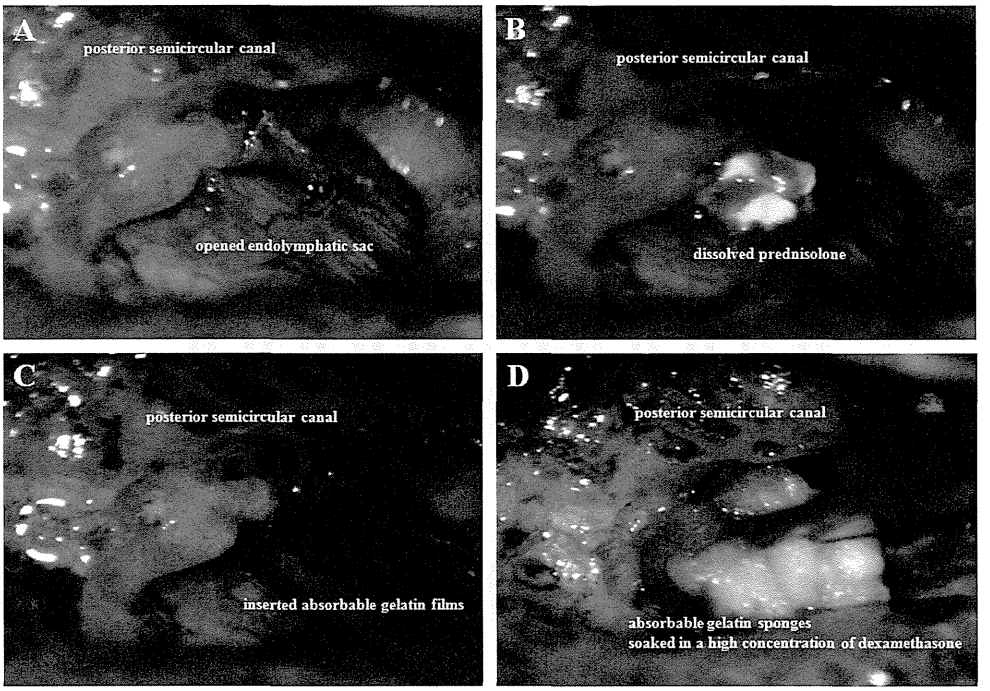


**Fig. 1.** Intra-operative photographs of endolymphatic sac decompression with intra-endolymphatic sac steroids (right ear). (A) The endolymphatic sac was opened with an L-shaped incision made along the posterior and distal margins of the lateral wall. (B) The endolymphatic sac was filled with 20 mg of prednisolone. (C) A bundle of absorbable gelatin films with fan- and stick-shaped ends were prepared and the fan-shaped end was inserted into the sac. (D) Small pieces of absorbable gelatin sponge soaked in a high concentration of dexamethasone were placed inside and outside the sac lumen.

improvement) were recognized as an improvement in vestibular function at the 2nd follow-up year.

### 2.4. Statistical analysis

All the data from treatment results are presented as the ratio of the number of cases and treated statistically with the use of SPSS version 14.0 (Chicago, IL). In each postoperative year result, the chi-square test or Mann–Whitney *U*-test was used to analyze the data between G-I and G-II. All reported *p*-values were two-sided and those under 0.05 were considered as significant.

## 3. Results

The patients' background in these two groups including sex, age at surgery, duration of disease, vertigo frequency before treatment and stage of disease before treatment, are shown in Table 1. The duration of disease indicates the period between the onset of symptoms and the date of treatment. The stage of disease is based on hearing. Stages I, II, III and IV indicate that the four-tone average of the worst audiogram in the 6 months before treatment was <25, 25–40, 41–70 and >70, respectively [18]. There were no significant differences in patients' background between G-I and G-II.

The long-term results in vertigo control and hearing improvement during the 2–13 year follow-up period in G-I and G-II according to the 1995 AAO-HNS criteria [11] are shown in Fig. 2. There were no significant factors of patients' backgrounds influenced on surgical results.

As shown in Fig. 2A, vertigo attacks in G-I were completely suppressed (i.e. vertigo frequency = 0) from 87.6% to 70.0% of patients during the 2–13-year follow-up period after treatment (87.6, 89.1, 85.6, 81.9, 81.5, 78.8, 80.7, 79.5, 75.3, 73.7, 73.2, 70.0%).

**Table 1**
Materials consist of patients with intractable Meniere's disease in groups I ($n = 220$) and II ($n = 66$).

| | Sex | Age (yr ± SD) | Duration (yr ± SD) | Vertigo (α/mo ± SD) | Stage |
|---|---|---|---|---|---|
| Group-I, $n = 220$<br>(G-I: drainage with steroids) | Male = 105<br>Female = 115 | 51.1 ± 14.1 | 8.9 ± 7.4 | 3.7 ± 2.2 | I = 14<br>II = 32<br>III = 112<br>IV = 62 |
| Group-II, $n = 66$<br>(G-II: surgery declined) | Male = 31<br>Female = 35 | 52.8 ± 12.2 | 8.6 ± 6.0 | 3.5 ± 2.2 | I = 4<br>II = 10<br>III = 34<br>IV = 68 |
| *Statistical analysis* | $p = 0.931$ (N.S.)<br>by chi-square | $p = 0.338$ (N.S.)<br>by Mann–Whitney | $p = 0.753$ (N.S.)<br>by Mann–Whitney | $p = 0.448$ (N.S.)<br>by Mann–Whitney | $p = 0.540$ (N.S.)<br>by chi-square |

Age: Age at (or declining of) surgery; duration: duration of disease before (or declining of) surgery; vertigo: mean number of definitive spells per month during the 6 months before (or declining of) surgery; and stage: stages I, II, III and IV, indicating the worst audiogram during the 6 months before (or declining of) surgery, were <25, 25–40, 41–70 and >70, respectively. There were no significant differences in the patients' background between groups I and II (N.S.).

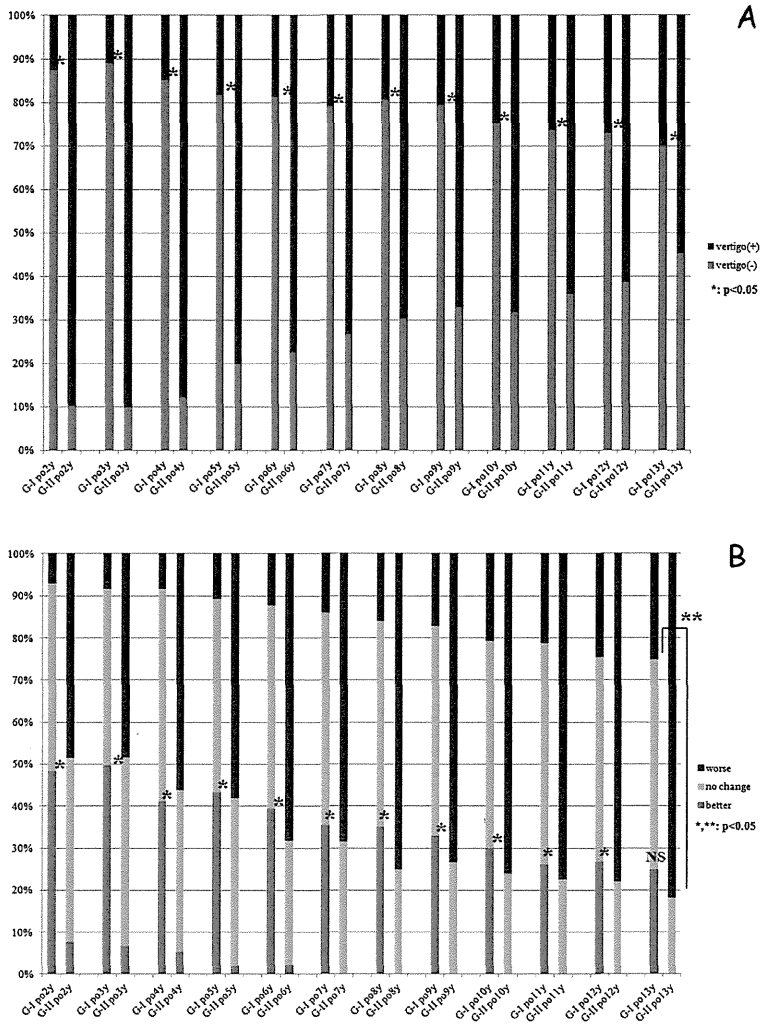


**Fig. 2.** Graphic presentation of long-term results for 2–13 years in patients with intractable Meniere's disease in groups I and II. (A) Vertigo control: Bar graphs were plotted according to every year vertigo result. Red columns (no vertigo) indicate the percentage of patients with no vertigo attacks and blue columns (rec vertigo) indicate the percentage of patients with recurrent vertigo during each period. The results in G-I were significantly better than those in G-II for 13 years after treatment (*). (B) Hearing improvement: All the bar graphs were plotted according to every year hearing result. Red columns (better) show the percentage of patients with higher than 10 dB hearing improvement, blue columns (worse) show the percentage of patients with more than 10 dB hearing deterioration and pink columns (no change) show the other values. The results of hearing improvement (better) in G-I were significantly better than those in G-II for 12 years (*), and the results of hearing preservation (better + no change) in G-I were significantly better than those in G-II for 13 years after treatment (**). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Vertigo attacks in G-II were completely suppressed from 10.6% to 45.5% during the 2–13-year follow-up period (10.6, 10.0, 12.3, 20.0, 22.7, 26.8, 30.6, 33.3, 32.0, 36.4, 38.9, 45.5%).

As shown in Fig. 2B, hearing in G-I was improved for ≥10 dB from 48.6% to 25.0% of patients during the 2–13-year follow-up period after treatment (48.6, 49.5, 41.1, 43.2, 39.2, 35.6, 35.2, 33.0, 30.1, 26.3, 26.8, 25.0%) and was worse for ≤−10 dB from 6.9% to 25.0% during the 2–13-year follow-up period (6.9, 8.4, 8.3, 11.0, 12.3, 14.4, 15.9, 17.0, 20.5, 21.1, 24.4, 25.0%). Hearing in G-II was improved for ≥10 dB from 7.6% to 0.0% during the 2–13-year follow-up period (7.6, 6.7, 5.3, 2.0, 2.3, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0%) and was worse for ≤−10 dB from 48.5% to 81.8% during the 2–13-year follow-up period (48.5, 48.3, 56.1, 58.0, 68.2, 68.3, 75.0, 73.3, 76.0, 77.3, 77.8, 81.8%).

To compare the long-term results between these two groups, 2-year results demonstrated that definitive spells were completely controlled in 87.6% of patients in G-I and 10.6% of patients in G-II (G-I > G-II: Mann–Whitney). Hearing was improved in 48.5% of patients in G-I and 7.6% of patients in G-II (G-I > G-II: Mann–Whitney). Twelve-year results showed that definitive spells were completely controlled in 73.2% of patients in G-I and 38.9% of patients in G-II (G-I > G-II: Mann–Whitney). Hearing was improved in 26.8% of patients in G-I and 0.0% of patients in G-II (G-I > G-II: Mann–Whitney). Thirteen-year results showed that definitive spells were completely controlled in 70.0% of patients in G-I and 45.5% of patients in G-II (G-I > G-II: Mann–Whitney). Hearing was improved in 25.0% of patients in G-I and 0.0% of patients in G-II (G-I = G-II: Mann–Whitney). Thirteen-year results

showed that hearing preservation ("preservation" indicates "better" + "no change") was present in 75.0% of patients in G-I and 18.2% of patients in G-II (G-I > G-II: Mann–Whitney).

Vestibular function was examined in 118 out of 220 cases in G-I just before and 2 years after treatment. Two years after treatment, recovery of vestibular function occurred in only 50% (59/118) of patients. In the 59 patients with improved vestibular function (≥10%), vertigo was completely controlled in 52 (88.1%). In 59 of the 108 patients who did not have improved vestibular function (<10%), vertigo was completely controlled in 48 (81.4%). There were no significant differences in vertigo control between cases with improved or non-improved vestibular function after treatment (chi-square).

## 4. Discussion

Judging from the average age over 50 years at surgery and maximum observation period of 12–13 years, we realize that endolymphatic sac drainage with intra-endolymphatic sac steroids in the present study is a challenging therapeutic strategy for intractable Meniere's patients to improve their long-term quality in the prime of life before retirement. Actually, we demonstrated that endolymphatic sac drainage with intra-endolymphatic sac steroids (G-I) had superior effects to non-surgical treatment of intractable Meniere's patients (G-II), for complete control of vertigo and hearing improvement/preservation for at least 12–13 years.

Systemic administration and/or intratympanic perfusion of corticosteroids have sometimes been adopted as an anti-immune therapy for patients with intractable Meniere's disease. In a number of studies concerned with steroid treatment, only Sennarouglu et al. [5] observed steroid-treated patients for longer than 2 years according to the 1995 AAO-HNS criteria [11]. Sennarouglu et al. reported that intratympanic perfusion of dexamethasone completely suppressed vertigo in 42.0% of patients and significantly improved hearing in 16.0% 2 years after treatment. On the other hand, Silverstein et al. suggested that intratympanic application of dexamethasone showed no significant benefit over placebo in their prospective, randomized, double-blind, crossover trial [6]. In fact, these studies showed that steroid treatment appeared to result in good relief of vertigo and improvement of hearing in some cases. However, there were limitations in the long-term findings of systemic and/or intratympanic steroid application, and additional repetitive applications of steroids for recurrences of symptoms often occurred, especially progressive hearing loss, along with the risk of side effects. On the contrary, hypertension or diabetes mellitus was not contraindication to our surgery, endolymphatic sac drainage with intra-endolymphatic sac steroids.

Endolymphatic sac surgery, which was first performed by Portmann in 1927 [13] is another option for patients with intractable Meniere's disease. Thomsen et al. suggested that endolymphatic sac surgery is no more effective than a placebo [14]. Despite this controversy, endolymphatic sac surgery is still a commonly performed procedure worldwide [15]. This type of conservative surgery is thought to be effective for inner ear decompression against endolymphatic hydrops and several modifications of this surgery have been attempted and reported. Moffat et al. [16] and Gianoli et al. [17] reported 2-year results of their modified endolymphatic sac surgery as follows: there was complete control of vertigo in 43.0% and 60.0% of patients and significant hearing improvement in 19.0% and 60.0% of patients, respectively. Ostrowski et al. followed up Gianoli et al. [17] results for 4–5 years, which resulted in 47.0% of patients having complete control of vertigo and 18.0% having significant hearing improvement [18]. Goin et al. suggested that endolymphatic sac surgery does not modify the natural course of Meniere's disease with respect to hearing [19]. Stahle et al. indicated that Meniere's patients are more annoyed with progressive hearing loss rather than vertigo attacks during long-term follow-up because of spontaneous relief of vertigo over the years [20]. Because of these poor long-term results in hearing with systemic and/or intratympanic application of steroids and endolymphatic surgery, it is necessary to develop methods to improve and maintain inner ear function, especially hearing in patients with intractable Meniere's disease. Surgically opened endolymphatic sac must be closed sooner or later. So, we think that we should do something to improve inner ear function before its closure. We would like to propose the intra-endolymphatic sac steroids as an idea. Since it has not been clarified yet that how much of the steroid was absorbed through an opened-endolymphatic sac in this method, further exams will be needed for stable steroid-effects on the inner ear.

Our study has some limitations. Based on the long and controversial history of evaluation of surgical treatments for intractable Meniere's disease [14], it is necessary to perform a randomized controlled trial to prepare a non-surgical control group when surgical effects are evaluated because of the spontaneous relief of symptoms. However, as mentioned above, endolymphatic sac drainage surgery is a very common strategy for patients with intractable Meniere's disease [15]. Therefore, it would be unethical to not apply drainage to some patients for a perfect randomized controlled trial. Therefore, in the present study, we only included 66 patients in G-II who declined to undergo endolymphatic sac drainage as controls. However, we believe that our data are reliable, because we confirmed that there were no significant differences in the patients' background between G-I and G-II for 13 years. To the best of our knowledge, there are no therapeutic reports for intractable Meniere's disease of such a long-term observation over a decade with a control group.

In the current study, endolymphatic sac drainage with intra-endolymphatic sac steroids in G-I was superior for complete control of vertigo and hearing improvement/preservation compared with non-surgical treatment in G-II. Two years after treatment in G-I patients, definitive spells were completely controlled in 88%, although recovery of vestibular function appeared in just 50% of all cases, such as hearing improvement in 49%. This indicates that recovery of vestibular function is not always necessary for suppressing vertigo attacks, unlike recovery of cochlear function for hearing improvement. Functional recovery of the cochlea is crucial for hearing improvement in the treatment of Meniere's disease. Intra-endolymphatic sac application of large doses of steroids may have the potential for recovery for 12 years after treatment. We hope that the results from this study will ultimately lead to an ideal treatment for intractable Meniere's patients.

## Conflicts of interest

The present study does not include any conflicts of interest.

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ORIGINAL REPORT

# Changes in endolymphatic hydrops after sac surgery examined by Gd-enhanced MRI

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**Abstract**

*Conclusion:* Endolymphatic hydrops could be a reversible inner ear pathological condition. After sac surgery, hydrops was reduced and symptoms went into remission in some cases, although vertigo suppression was not always a result of the reduced hydrops. *Objective:* To examine the changes in endolymphatic hydrops detected by gadolinium (Gd) contrast-enhanced magnetic resonance imaging (MRI) before and 6 months after endolymphatic sac surgery in patients with unilateral Ménière's disease. *Methods:* Fluid-attenuated inversion recovery MRI was obtained 4 h after intravenous administration or 24 h after intratympanic administration of Gd contrast medium. An enlarged negative stain corresponding to the cochlear duct and endolymphatic space of the vestibule was assessed as hydrops. *Results:* Of seven patients with hydrops confirmed by MRI before surgery, both cochlear and vestibular hydrops became negative in two, cochlear hydrops became negative in one, both hydrops were present, but reduced, in one, and there was no change in three patients. The number of vertigo spells was reduced in all cases at 6–12 months after surgery. As for the three cases of negative hydrops, vertigo was completely suppressed. In two cases in which hearing level improved, hydrops became negative after surgery.

**Keywords:** *Ménière's disease, vertigo, hearing, magnetic resonance imaging, inner ear pathology*

## Introduction

Endolymphatic hydrops is widely recognized as a pathologic change in the inner ear related to Ménière's disease (MD). Histopathologic examination initially revealed an enlarged endolymphatic space with no inflammatory change in patients with MD [1,2]. Subsequently, experimental hydrops in animals was developed, and these animals showed inner ear dysfunction [3,4]. Diuretic administration temporarily relieves the hearing impairment caused by MD, probably due to a reduction in hydrops [5]. These accumulated findings support the idea that endolymphatic hydrops is involved in the pathophysiology of MD. Gadolinium (Gd) contrast-enhanced inner ear MRI, introduced by Nakashima and colleagues to clinical practice [6], made it possible to prove that hydrops exists in living patients suffering from MD. We have also observed hydrops in more than 90% of patients with typical and active MD [7,8].

As a treatment option, endolymphatic sac surgery has had a long history since its introduction by Portmann in 1927 [9], but its efficacy has been debated since the 1980s [10]. Our recent modification to the surgery using high-dose steroid instillation into the sac added to a sac-mastoid shunt showed good results in terms of postoperative hearing, as well as vertigo control [11].

In the present study, we examined hydrops by Gd-enhanced MRI before and 6 months after sac

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Table I. Summary of clinical profiles and MRI findings.

| | | | | Hearing* | | Vertigo attack† | | Cochlear hydrops | | Vestibular hydrops | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case no. | Age (years) | Sex | Ear | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| P43 | 47 | F | L | 33.8 | 10 | 9 | 0 | + | – | + | – |
| P34 | 33 | F | L | 46.3 | 28.8 | 17 | 0 | + | – | + | – |
| P36 | 46 | F | R | 61.3 | 80 | 25 | 0 | + | – | + | + |
| P35 | 48 | F | L | 58.8 | 58.8 | 10 | 0 | + | + | + | + |
| P37 | 61 | F | L | 45 | 52.5 | 9 | 0 | + | + | + | + |
| P38 | 47 | M | R | 43.8 | 40 | 16 | 1 | + | + | + | + |
| P33 | 42 | F | R | 78.8 | 87.5 | 13 | 2 | + | + | + | + |

+ Indicates hydrops positive according to the criteria.
*Hearing is expressed as the average of the pure-tone hearing threshold by air conduction at 0.25, 0.5, 1, and 2 kHz.
†Vertigo attack indicates the number of definitive vertigo spells in the 6 months before (Pre) and between 6 and 12 months (Post) after surgery.

surgery in MD patients with frequent episodes of vertigo. We aimed to clarify whether hydrops could be a reversible change, and whether the symptomatic relief after the surgery could be obtained by the resolution of hydrops.

## Material and methods

Seven patients (six females and one male, aged 33–61 years) with unilateral definite MD (AAO-HNS [12]) participated in this study from January to October 2011. All patients had frequent episodes (at least once a month for the last 6 months on average, the maximal interval of two spells was less than 2 months) of definitive vertigo spells defined by AAO-HNS [12], and had developed unilateral hearing impairment. The number of vertigo spells and the hearing level of each case are listed in Table I. After confirmation of both cochlear and vestibular hydrops by Gd-enhanced MRI and giving informed consent, the patients underwent surgery. Some cases used diuretics and vitamin B12 for MD before surgery, but ceased using them within 6 months after the surgery. Other oral medication for diseases other than MD was continued before and after the surgery (cases P37 and P43 for rheumatoid arthritis, P38 for depression). At 6 months after the surgery, MRI was performed again.

We used two types of Gd administration; one intratympanically and the other intravenously. The intratympanic method used Gaddiamide hydrate (Omniscan$^{(R)}$) diluted eightfold in saline, injected into the tympanic cavity with a 23 gauge needle and syringe through the tympanic membrane. The patient stayed in the affected ear up lateral spine position for 30 min, and at 24 h after the injection, MRI was performed [6,7]. The intravenous method used a double dose of gadoteridol compared with general use (Prohance$^{(R)}$ 0.4 ml/kg), injected intravenously, and at 4 h after the injection, MRI was performed [13]. The intratympanic method was only used in early cases (preoperative MRI in cases P34 and P35). Since comparable images could be obtained by the intravenous method, it was used for later cases. The hydrops detection rate was not different between these two methods in our previous study [8].

Images of two-dimensional fluid attenuated inversion recovery (2D-FLAIR) obtained with a 3 Tesla MRI unit (Sigma Excite HD 3T, GE Healthcare) were used for hydrops evaluation. Axial view images of 2 mm thickness were adjusted parallel to the anterior commissure-posterior commissure line the same as a routine MRI. To increase the number of evaluable images, a 2D-FLAIR sequence was done twice with a 1 mm gap in cases P35, P37, P38, and P43.

In the inner ear, only the perilymphatic space was contrast-enhanced by the Gd agent, while the endolymphatic space was evaluable as a low signal intensity area [6,7]. Our criteria for hydrops were basically based on Nakashima et al. [14] but modified to adjust the level of image quality of our device. Cochlear hydrops was qualitatively judged positive when the low intensity signal areas corresponding to the cochlear duct were clearly noticed. The area should be at the edge of the cochlea, and should be distinguished from the bony partition. Vestibular hydrops was judged positive when more than 33.3% of the vestibule was occupied by a low signal area [6–8]. Two of the authors (T.I. and T.K.) independently examined MRI images prepared by others (A.U.) without any information about the clinical course. Outlines of the endolymphatic space were traced on the images (as expressed in Figures 3 and 4) and the

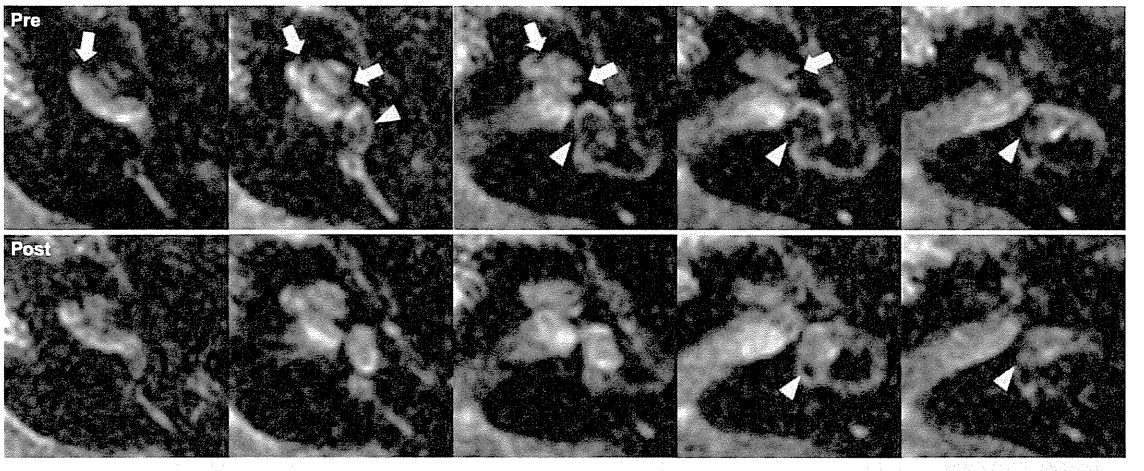


Figure 1. An example of reduced endolymphatic hydrops (case P43). Upper panels are images taken before, and lower panels 6 months after, sac surgery. From the left to the right, caudal to rostral axial views of the inner ear are depicted by Gd-contrasted perilymphatic space. Gd contrast medium was applied intravenously for both examinations. Arrows indicate low signal intensity areas corresponding to the cochlear duct, apparently indicating cochlear hydrops. As for the vestibule, low intensity areas indicated by arrowheads occupy more than 33.3% of the vestibule, indicating vestibular hydrops in the preoperative MRI. The postoperative MRI did not show either cochlear or vestibular hydrops.

proportion of the area in the cochlea or the vestibule was calculated. As the area of the vestibule, the semicircular canals and the ampullae were not included. For comparisons between preoperative and postoperative images in the same case, the extent of hydrops was also assessed, following a positive/negative judgment. Adobe Photoshop CS5 software was used for the image processing.

Our procedure for sac surgery with steroid instillation was described in a previous report [11]. Briefly stated, following an L-shaped incision on the lateral wall of the endolymphatic sac, prednisolone powder

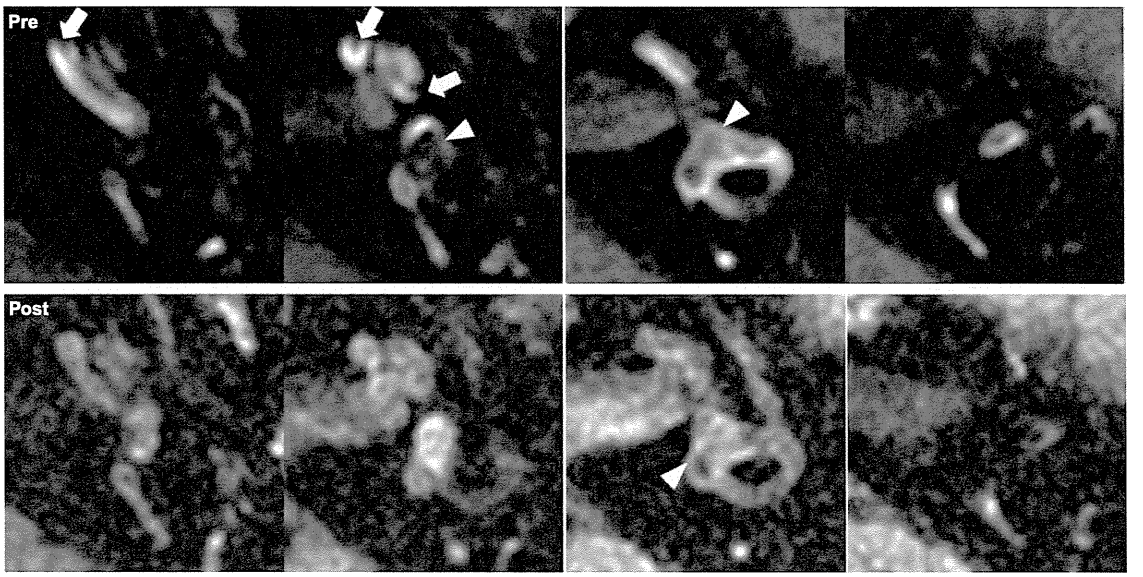


Figure 2. Another example of reduced hydrops (case P34). Upper panels are 2D-FLAIR MR images of Gd contrast medium applied intratympanically before sac surgery. Lower panels are images of Gd contrast medium applied intravenously in the same patient 6 months after surgery. The intratympanic application gave clearer contrast images, but the intravenous application was comparable. Cochlear and vestibular hydrops were clearly seen before surgery, but both disappeared after the surgery. Arrows and arrowheads indicate the endolymphatic space in the cochlea and the vestibule, respectively.

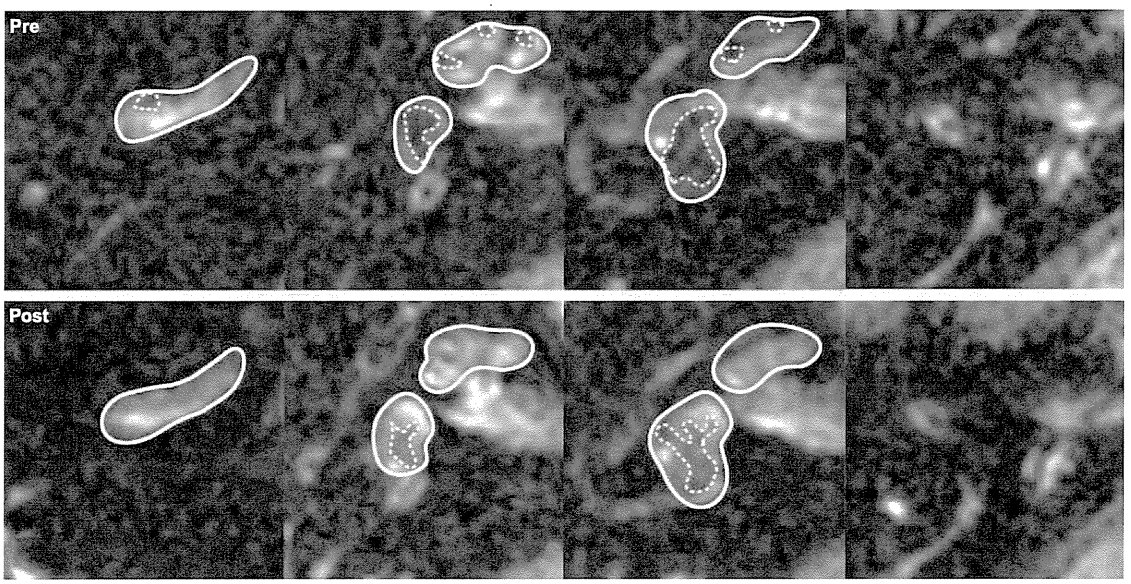


Figure 3. A case where cochlear hydrops became negative and cochlear hydrops remained positive but reduced (case P36). Solid traces indicate outlines of the cochlea and the vestibule; dotted traces indicate the endolymphatic space. The area of endolymphatic space in the vestibule was reduced from 50.5% to 37.2% of the vestibule.



was placed inside, layered gelatin films were inserted, and then small pieces of gelatin sponge soaked in dexamethasone were placed densely in the surrounding area.

This study was conducted under approval of the ethical committee of Osaka University Hospital (IRB #08223, 11341). Some of the preoperative clinical profiles of the cases were presented in a previous report using the same case IDs [8]. All pictures and postoperative case profiles in this article were originally documented.

## Results

Table I shows preoperative and postoperative clinical profiles including the number of vertigo spells 6 months preoperatively and postoperatively for 6–12 months, the worst dB hearing level in the corresponding periods, and MRI results. Preoperatively, all seven patients with typical and active unilateral MD showed cochlear and vestibular hydrops in the affected ear. The proportions of the endolymphatic space in the cochlea and the vestibule were 12.5% (± 5.2%) (mean ± standard deviation) and 50.6% (± 5.5%), respectively. Postoperatively, both cochlear and vestibular hydrops became negative in two cases (P43 shown in Figure 1, P34 in Figure 2). The proportion of the endolymphatic space in the vestibule was changed from 42.3% preoperatively to 19.4% postoperatively in case P43, and from 45.6% to 18.3% in case P34. In these two cases, the postoperative hearing level was improved by more than 10 dB and vertigo spells were completely suppressed. In case P36 (Figure 3), cochlear hydrops became negative, postoperative vestibular hydrops was judged positive according to our criteria (the endolymphatic space >33.3% of the vestibule) but the proportion of the endolymphatic space was reduced from 50.5% to 37.2%. Hearing was worsened by more than 10 dB, but vertigo spells were completely suppressed. In case P35 (Figure 4), both hydrops remained positive after the surgery, but the proportions of the endolymphatic space in the cochlea and the vestibule were reduced from 18.3% to 8.2% and from 50.5% to 37.2%, respectively. In the remaining three cases (P37, P38, P33), postoperative images were quite similar to the preoperative ones, and the proportion of the endolymphatic space for both cochlear and vestibular areas were changed by no more than 10 points (%). Even in these cases, the number of vertigo spells was significantly decreased.

## Discussion

Endolymphatic hydrops was definitively diagnosed only by histopathologic examination after death until Gd-enhanced inner ear MRI was introduced [6]. Histopathologic endolymphatic hydrops was detected at a high rate in patients with MD, regardless of whether MD was still active or not in the last period