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A randomized controlled clinical trial of topical insulin-like growth factor-1 therapy for sudden deafness refractory to systemic corticosteroid treatment

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Abstract

Background: To date, no therapeutic option has been established for sudden deafness refractory to systemic corticosteroids. This study aimed to examine the efficacy and safety of topical insulin-like growth factor-1 (IGF-1) therapy in comparison to intratympanic corticosteroid therapy.

Methods: We randomly assigned patients with sudden deafness refractory to systemic corticosteroids to receive either gelatin hydrogels impregnated with IGF-1 in the middle ear (62 patients) or four intratympanic injections with dexamethasone (Dex; 58 patients). The primary outcome was the proportion of patients showing hearing improvement (10 decibels or greater in pure-tone average hearing thresholds) 8 weeks after treatment. The secondary outcomes included the change in pure-tone average hearing thresholds over time and the incidence of adverse events.

Results: In the IGF-1 group, 66.7% (95% confidence interval [CI], 52.9–78.6%) of the patients showed hearing improvement compared to 53.6% (95% CI, 39.7–67.0%) of the patients in the Dex group ($P = 0.109$). The difference in changes in pure-tone average hearing thresholds over time between the two treatments was statistically significant ($P = 0.003$). No serious adverse events were observed in either treatment group. Tympanic membrane perforation did not persist in any patient in the IGF-1 group, but did persist in 15.5% (95% CI, 7.3–27.4%) of the patients in the Dex group ($P = 0.001$).

Conclusions: The positive effect of topical IGF-1 application on hearing levels and its favorable safety profile suggest utility for topical IGF-1 therapy in patients with sudden deafness.

Trial registration: UMIN Clinical Trials Registry Number UMIN000004366, October 30th, 2010.

Keywords: Dexamethasone, Drug delivery system, IGF-1, Local application, Sudden sensorineural hearing loss

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Background

Sudden sensorineural hearing loss (SSHL), an unexplained unilateral hearing loss with an onset of less than 72 h, is a common disease with acute onset hearing impairment. The incidence of SSHL is reportedly 5 to 20 patients per 100,000 persons per year [1]. Approximately 35,000 patients with SSHL consult a doctor each year in Japan [2]. The standard treatment for SSHL is systemic corticosteroid treatment [3,4]. Hearing improvement after systemic corticosteroids occurs in 50% of the patients, but approximately 20% of the patients show no response [5]. Further, systemic corticosteroid treatment often causes adverse events [6] that can occasionally be life-threatening [7]. As an alternative for systemic corticosteroids, intratympanic corticosteroid treatment by direct injection into the middle ear has recently gained wide popularity because of the low risk for systemic adverse events and because of the potential delivery of high concentrations of a corticosteroid into the inner ear [8]. Intratympanic corticosteroid therapy is commonly used for the treatment of SSHL, after the failure of systemic corticosteroid treatment [9-15]. However, the supporting evidence for its use is weak because of the limitation in the study design and power [16].

A major difficulty in treating sensorineural hearing loss is the poor regeneration capacity of the mammalian cochlea. Therefore, protecting the cochlea from irreversible degeneration is a practical strategy. Several growth factors have been investigated for their protective effects on the sensory hair cells of the cochlea [17,18]. The focus of this study was on insulin-like growth factor-1 (IGF-1), which has been used for the treatment of insulin-resistant diabetes and dwarfism. IGF-1 also plays crucial roles in both the development and maintenance of the cochlea [19,20]. We used a gelatin hydrogel, which enables the sustained release of proteins or peptides, for the delivery of IGF-1 into the cochlear fluid [21]. We previously performed a successful series of animal experiments using this method [21,22]. A prospective, single-armed clinical trial in patients with SSHL refractory to systemic corticosteroids was then performed, the results of which indicated the safety and efficacy of topical IGF-1 therapy in comparison to the historical control of hyperbaric oxygen therapy [23].

The goal of the current study was to investigate the efficacy and safety of topical IGF-1 therapy as a novel therapeutic option for SSHL. We conducted a multicenter, randomized clinical trial to compare topical IGF-1 therapy and intratympanic corticosteroid therapy for treating SSHL refractory to systemic corticosteroids.

Methods

Study design and patients

This was a multicenter, randomized, open, parallel-group trial. The study was conducted from November 2010 through October 2013 at 9 tertiary referral hospitals in Japan. The trial followed the guiding principles of the Declaration of Helsinki. The study protocol, manual of procedures, and informed consent form were approved by the institutional review boards of all participating sites (Ethical Committee of the Graduate School of Medicine, Kyoto University [C470], Ethical Committee of the Graduate School of Medicine, Hirosaki University [2011–145], Ethical Committee of University of Tsukuba Hospital [H23-13], Ethical Committee of Toranomon Hospital [2011-4-15], Ethical Committee of Shinshu University Hospital [1705], Ethical Committee of Nagoya City University Hospital [45-11-0005], Ethical Committee of Kobe City Medical Center General Hospital [1], Ethical Committee of Ehime University Hospital [1105003], and Ethical Committee of the Graduate School of Medicine, Kyushu University [23011]). All patients provided written informed consent. Eligible participants were all adults, 20 years or older, who had SSHL defined as a unilateral sensorineural hearing loss of at least 30 decibels (dB) sound pressure level (SPL) over at least three test frequencies that developed within 3 days. They also met the following eligibility criteria: they had been diagnosed as having SSHL within 25 days of onset; they presented with an abnormality in the distortion product of otoacoustic emissions; and they showed less than 30 dB hearing improvement in the mean hearing level, based on pure-tone audiometry (PTA) at five tested frequencies (0.25 kHz, 0.5 kHz, 1.0 kHz, 2.0 kHz, and 4.0 kHz) after more than 7 days of systemic corticosteroid treatment. Similar to our previous trial [23], we excluded patients with active chronic otitis media, acute otitis media, otitis media with effusion or dysfunction of the auditory tube, malignant tumors, and systemic diseases. All patients underwent imaging examinations to rule out retrocochlear pathology.

Randomization and masking

Patients were randomly assigned (1:1) to receive either topical IGF-1 therapy or intratympanic dexamethasone (Dex) therapy. Randomization was performed centrally with stratification by the study sites and the mean hearing thresholds, based on the PTA at the five frequencies tested at registration (lower than 90 dB SPL vs. 90 dB SPL or higher). The randomization sequence was generated by a third-party contract clinical research organization (independent from the trial investigators). Local investigators used a web-based system during enrolment, which then automatically assigned patients to either treatment group. Besides central randomization, no further masking was used in this open-label study.

Procedures

The treatment was performed within 7 days of enrolment and systemic corticosteroid treatment was completed by

the time of enrolment. Gelatin hydrogels were produced from porcine skin gelatin (Nitta Gelatin Inc., Osaka, Japan), based on a previously described method [23,24]. Mecasermin (Somazon [10 mg for injection]; Astellas Pharma, Inc., Tokyo, Japan), a recombinant human IGF-1, was dissolved in physiological saline at a final concentration of 10 mg/mL. Sixty minutes before application, a 30 μL sample of mecasermin solution was mixed with 3 mg of gelatin hydrogel. After tympanostomy under local anesthesia with 1% lidocaine, the hydrogel (which contained 300 μg of mecasermin) was placed in the round window niche of the middle ear; a single application was used. The control group received four 0.5 mL doses containing 3.8 mg/mL dexamethasone sodium phosphate (Orgadrone injection [1.9 mg]; MSD, Inc., Tokyo, Japan) that was injected into the middle ear through the tympanic membrane. In the literature [9-15], a variety of regimens for intratympanic injections of corticosteroids have been used. Considering practical use in common clinical settings, we chose four doses. Injections were performed over 4 consecutive days in principle. Within at least 7 days, four injections were administered. Patients were placed in the supine position with the affected ear slightly raised and remained in this position for 30 min after the injection. For 16 weeks after treatment, the patients were examined at the outpatient clinics of the participating sites. The PTA was measured on the day of enrolment, and then at 1, 2, 4, 8, 12, and 16 weeks after treatment. During the observation period, which totaled 16 weeks, all adverse events were recorded.

Outcomes

The primary outcome measure was the proportion of patients showing hearing improvement of 10 dB or greater in the mean hearing level. Hearing improvement was based on PTA at five tested frequencies and was defined as better than slight recovery, based on the criteria for hearing improvement determined by the Sudden Deafness Research Committee of the Japanese Ministry of Health, Labor and Welfare in 1984 (Table 1) at 8 weeks after treatment. Briefly, the complete recovery includes patients showing recovery of a hearing level within 20 dB SPL or to the similar level to the opposite side, the marked recovery is more than 30 dB recovery, and the no recovery is less recovery than 10 dB. Secondary outcome measures included the change in the pure-tone average hearing thresholds over time (i.e., from the first audiogram to the 16-week follow-up audiogram), the proportion of patients showing hearing improvement at 12 and 16 weeks after treatment, and the incidence of adverse events during the observation period. In addition to checking vital signs in the physical examination at each visit, laboratory studies were performed at registration, and then at 1 week, 8 weeks, and 16 weeks after treatment.

Table 1 Criteria for hearing improvement determined by Sudden Deafness Research Committee of the Japanese Ministry of Health, Labour and Welfare in 1984

Complete recovery	Recovery of a hearing level within 20 decibels (dB) at all five frequencies tested (0.25, 0.5, 1.0, 2.0 and 4.0 kHz) or recovery to the same level as the opposite side in pure-tone auditometry
Marked recovery	30 dB and over recovery in the mean hearing level at the five frequencies tested
Slight recovery	Recovery of better than 10 dB and less than 30 dB in the mean hearing level at the five frequencies tested
No response	Less recovery than 10 dB in the mean hearing level at the five frequencies tested

Statistical analysis

The null hypothesis was that the effect of topical IGF-1 treatment on the proportion of patients showing hearing improvement would not be superior to intratympanic injection of Dex. The sample size was determined based on our previous findings and on published papers. In our previous clinical trial of topical IGF-1 therapy, no patient that had been enrolled later than 26 days after sudden hearing loss recovered their hearing [23]. The proportion of patients with hearing improvement after topical IGF-1 treatment was 62.5% (10 of 16 patients) at 12 weeks and 68.8% (11 of 16 patients) at 24 weeks, using the eligibility criteria of patients with SSHL within 25 days after onset of sudden hearing loss. Based on these findings, we hypothesized that the expected proportion of patients showing hearing improvement with topical IGF-1 therapy would be 65%. To determine the expected proportion of patients showing hearing improvement for intratympanic Dex therapy, we referred to the information in several publications [9-15] that were available in October 2010 and used the following criteria: i) the sample size had more than 10 participants and ii) intratympanic Dex therapy was a salvage treatment (Table 2). In these previous reports, the mean proportion of patients showing hearing improvement was 39% (range, 21–58%). Therefore, the proportion of patients who would show hearing improvement with intratympanic Dex therapy was expected to be approximately 40%. The sample size was based on the continuity-adjusted arcsine test with a one-sided significance level of 0.05 and a power of 0.80. The required sample size was 120 participants, assuming that 5% of the patients would be excluded from the analysis.

All statistical analyses were performed on an intention-to-treat basis. The safety analyses were conducted on all patients who underwent randomization and received at least one dose of the study drugs. Efficacy was analyzed in all patients except those who had been excluded from the

Table 2 Previous studies of intratympanic dexamethasone therapy as a salvage treatment

	No. of patients	PTA recovery	Dexamethasone concentration	Doses	Proportion of recovery (%)
Ho et al. [9]	15	28 dB	4 mg/mL	3 doses, once a week	53%
Choung et al. [10]	34	9 dB	5 mg/mL	4 doses, twice a week	39%
Roebuck et al. [11]	31	12 dB	24 mg/mL	Single	29%
Haynes et al. [12]	40	5 dB	24 mg/mL	Single	27.5%
Plontke et al. [13]	11	14 dB	4 mg/mL	Pump for 14 days	45%
Kakehata et al. [14]	24	17 dB	4 mg/mL	15 doses	58%
Lee et al. [15]	34	NA	4 mg/mL	6 doses for 14 days	21%
Mean (95% CI)	27 (21–33)				39% (30%–48%)

PTA, Pure-tone audiometry; NA, Not available; CI, Confidential interval.

safety analyses due to eligibility violations. The differences between treatments in the proportion of patients showing hearing improvement at 8, 12, and 16 weeks after treatment were evaluated with Fisher's exact test at a one-sided significance of 0.05. The difference between treatments in changes in pure-tone average hearing thresholds over time was investigated with repeated measures linear mixed model containing terms for treatment, time, and treatment-by-time interaction with an unstructured covariance structure [25]. The effect of treatment-by-treatment interaction was analyzed with the *t*-test at a one-sided significance of 0.05. The differences between treatments in the incidence of adverse events and in the baseline characteristics were analyzed with either Fisher's exact test or the *t*-test at a two-sided significance of 0.05. Statistical analyses were performed by using SAS version 9.3 software (SAS Institute, Inc., Cary, NC, USA).

Results

Study overview

Patients from nine participating sites were enrolled between March 2011 and October 2013. The recruitment and enrollment period was originally planned to close in February 2013, but it was extended to meet the recruitment targets. There were 120 patients who consented to participate (Figure 1). All patients were randomized to either the IGF-1 group or the Dex group; 118 patients were included in the safety analysis (60 IGF-1, 58 Dex) because 2 patients from the IGF-1 group withdrew consent. Of the 118 patients who were included, 4 patients completed the treatments, but missed the 8-week follow-up (2 IGF-1, 2 Dex) and 1 patient was excluded owing to examiner error (1 IGF-1).

Baseline characteristics were comparable between the two treatment groups (Table 3). Between the IGF-1 and Dex groups, no significant baseline differences in demographics, physical characteristics, ear examination, or PTA thresholds were found except the proportion of patients presenting with aural fullness (Table 3). The mean age of all participants was 49.3 years, and 45.8% of the participants were male. The mean PTA thresholds in the affected and unaffected ears were 85.2 dB SPL (95% confidence interval [CI], 81.3–89.1) and 18.1 dB SPL (95% CI, 14.9–21.3), respectively. The mean number of days

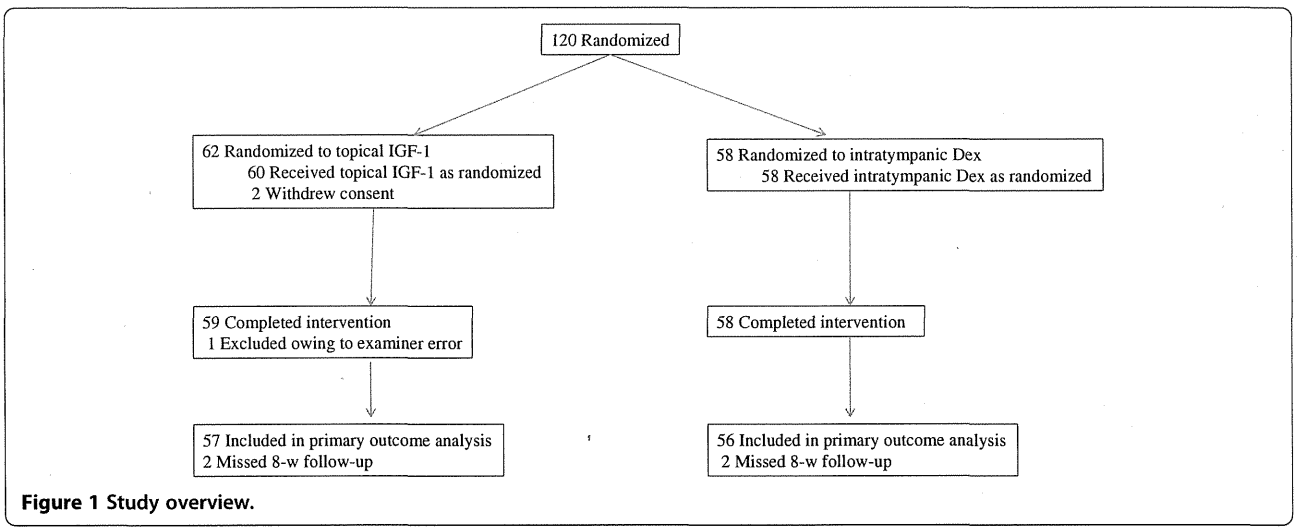

Figure 1 Study overview.

Table 3 Baseline characteristics of patients

Characteristics	Intratympanic Dex (n = 58)	Topical IGF-1 (n = 60)	*P* value
Age-yr, mean ± SD	50.1 ± 13.0	48.6 ± 14.0	0.557
Male sex-no. (%)	26 (44.8)	28 (46.7)	0.855
No. of days for study entry from onset, mean (95% CI)	16.3 (15.1–17.5)	15.8 (14.6–17.0)	0.574
Hearing improvement by pre-treatment-no. (%)			
>10 dB, <30 dB	13 (22.4)	17 (28.3)	0.528
<10 dB	45 (77.6)	43 (71.7)	
Hearing-dB pure-tone average, mean (95% CI)			
Affected ear	84.8 (79.1–90.4)	85.6 (80.0–91.2)	0.835
Unaffected ear	15.8 (12.4–19.2)	20.4 (15.0–25.7)	0.160
Other symptoms-no. (%)			
Dizziness/Vertigo	23 (39.7)	31 (51.7)	0.202
Tinnitus	49 (84.5)	51 (85)	>0.999
Aural fullness	44 (75.9)	32 (53.3)	0.013*

An asterisk indicates statistical significance with Fisher's exact test. Dex: dexamethasone.

from symptom onset to study entry was 16.0 days (95% CI, 15.2–16.9). At enrolment, dizziness or vertigo was present in 45.8% of the patients, tinnitus was present in 84.8% of the patients, and aural fullness was present 64.4% of the patients.

Primary outcome

The primary outcome was the proportion of patients showing hearing improvement (10 dB or greater in pure-tone average hearing thresholds) at 8 weeks after treatment. In the Dex group, 53.6% (95% CI, 39.7–67.0%) of patients showed hearing improvement at 8 weeks after treatment, whereas in the IGF-1 group, 66.7% (95% CI, 52.9–78.6%) of patients showed hearing improvement (Table 4). The null hypothesis for the primary outcome was not rejected ($P = 0.109$). However, a trend was observed in the higher proportion of patients in the IGF-1 group showing complete or marked recovery (30 dB or greater in pure-tone average hearing thresholds) over that in the Dex group (Table 2).

Secondary outcomes

The changes in the pure-tone average hearing thresholds occurring over time in both treatments are shown in Figure 2. The difference in the changes in the pure-tone average hearing thresholds over time between the treatments was statistically significant with repeated measures linear mixed model containing terms for treatment, time, and treatment-by-time interaction with an unstructured covariance structure (the effect for the interaction term [standard error]: −0.28 [0.10], $P = 0.003$). This demonstrated that pure-tone average hearing thresholds of the IGF-1 group significantly reduced over time, if changes in pure-tone average hearing thresholds over time in the Dex group were set to zero.

The proportions of patients showing hearing improvement (i.e., 10 dB or greater) at 12 weeks and 16 weeks after treatment were estimated as the secondary outcomes (Table 4). The null hypothesis for the proportions of patients showing hearing improvement at 12 weeks or 16 weeks after treatment was not rejected ($P = 0.066$ for 12 weeks; $P = 0.116$ for 16 weeks). At 12 and 16 weeks after treatment, there was a trend in the IGF-1 group showing a larger number of patients with complete and marked recovery when compared to the Dex group (Table 4).

Adverse events

No serious adverse events were observed in either treatment group. During the observation period, moderate adverse events occurred in 43.1% (95% CI, 30.2–56.8) of the patients in the Dex group and in 35.0% (95% CI, 23.1–48.4) of the patients in the IGF-1 group (Table 4). No significant difference in the incidence of adverse events was found between treatments ($P = 0.452$). Most adverse events, such as otitis media, otitis externa, tinnitus, and nausea or vomiting disappeared during the observation period. However, tympanic membrane perforation persisted in 15.5% (95% CI, 7.3–27.4%) of the patients in the Dex group at the end of the observation period. On the other hand, no patient in the IGF-1 group showed residual perforation in the tympanic membrane. The difference in the incidence of tympanic membrane perforation was statistically significant ($P = 0.001$).

Discussion

This is the first randomized controlled clinical trial to test the efficacy of a growth factor for the treatment of sensorineural hearing loss. In the current study, we locally applied IGF-1 to patients with SSHL refractory to

Table 4 Primary and secondary outcomes

	Intratympanic Dex	Topical IGF-1	*P* value
Primary outcome			
Proportion of patients showing hearing recovery at 8 weeks	53.6% (30/56)	66.7% (38/57)	0.109
	[95% CI: 39.7–67.0]	[95% CI: 52.9–8.6]	
Complete recovery	0.0% (0/56)	3.5% (2/57)	
Marked recovery	16.1% (9/56)	24.6% (14/57)	
Slight recovery	37.5% (21/56)	38.6% (22/57)	
No recovery	46.4% (26/56)	33.3% (19/57)	
Secondary outcomes			
Proportion of patients showing hearing recovery at 12 weeks	55.4% (31/56)	70.7% (41/58)	0.066
	[95% CI: 41.5–68.7]	[95% CI: 57.3–81.9]	
Complete recovery	0.0% (0/56)	5.2% (3/58)	
Marked recovery	21.4% (12/56)	31.0% (18/58)	
Slight recovery	33.9% (19/56)	34.5% (20/58)	
No recovery	44.6% (25/56)	29.3% (17/58)	
Proportion of patients showing hearing recovery at 16 weeks	54.7% (29/53)	67.9% (36/53)	0.116
	[95% CI: 40.4–68.4]	[95% CI: 53.7–80.1]	
Complete recovery	0.0% (0/53)	5.7% (3/53)	
Marked recovery	22.6% (12/53)	24.5% (13/53)	
Slight recovery	32.1% (17/53)	37.7% (20/53)	
No recovery	45.3% (24/53)	32.1% (17/53)	
Adverse events			
Serious	0.0% (0/58)	0.0% (0/59)	>0.999
Non-serious	43.1% (25/58)	35.0% (21/59)	0.452
Tympanic membrane perforation	15.5% (9/58)	0.0% (0/59)	0.001*
Otitis media	1.7% (1/58)	6.8% (4/59)	0.364
Otitis externa	0.0% (0/58)	1.7% (1/59)	>0.999
Tinnitus	8.6% (5/58)	0.0% (0/59)	0.027*
Nausea/Vomit	3.4% (2/58)	3.4% (2/59)	>0.999
Others	24.1% (14/58)	30.5% (18/59)	0.535

Asterisks indicate statistical significance with Fisher's exact test.

systemic steroids. The null hypothesis of the primary outcome was that the proportion of patients showing hearing improvement after topical IGF-1 therapy would not be better than that after intratympanic Dex therapy. The null hypothesis was not rejected in the present study. The major reason for this is an unexpectedly high proportion of patients showing hearing improvement after intratympanic Dex therapy. The proportion of patients showing hearing improvement after topical IGF-1 therapy was 66.7 to 70.7%, which was nearly identical to our hypothesized value of 65%, whereas the proportion of patients showing hearing improvement after intratympanic Dex therapy (range, 53.6– 55.4%) was higher than our hypothesized value of 40%.

Although the null hypothesis for the primary outcome was not rejected, this randomized controlled trial showed significantly better recovery of pure-tone average thresholds over time in the IGF-1 group, compared to the Dex group. In addition, a trend that the proportion of patients in the IGF-1 group who showed complete or marked recovery was higher than that in the Dex group was observed at 8, 12, or 16 weeks after treatment. Complete recovery of hearing was observed only in the IGF-1 group. These findings strongly suggest the superior efficacy of topical IGF-1 therapy over intratympanic Dex therapy.

In the current study, we used intratympanic corticosteroid therapy as a control treatment because it has widely been accepted as a salvage treatment for SSHL refractory to systemic corticosteroids [9-15]. The current randomized study also provided evidence for the safety and efficacy of intratympanic Dex therapy for SSHL refractory to systemic corticosteroids. Similar to the results

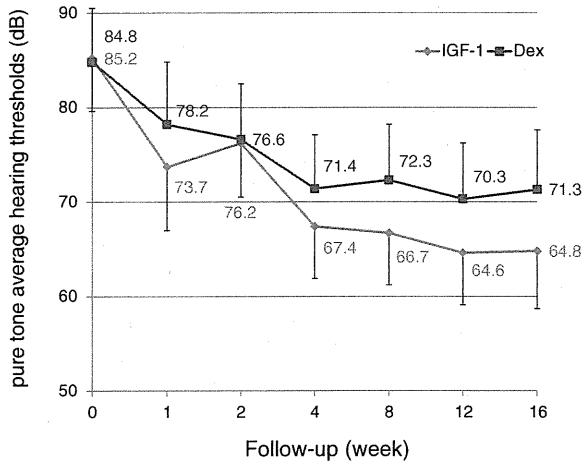

Figure 2 Changes in pure-tone average hearing thresholds over time. The difference between IGF-1 and dexamethasone (Dex) treatments in changes in pure-tone average hearing thresholds over time was statistically significant. Captions in the graph show mean values. Bars represent 95% confidence intervals.

of previous studies [9-15], no serious adverse events occurred in the Dex patient group. However, tympanic membrane perforation persisted in 15.5% of these patients, while tympanic membrane perforation was absent in the IGF-1 patient group. The incidence of tympanic membrane perforation in the Dex group in the present study was higher than the 3.9% incidence in a previous randomized trial of intratympanic corticosteroid therapy as the initial treatment [8]. This may be because of a difference in either the application regimen or the influence of the preceding systemic corticosteroid treatment. It is important to note that intratympanic injection of corticosteroids causes tympanic membrane perforation in a certain proportion of treated patients, while both our previous [23] and present results demonstrated no occurrence of residual perforation in tympanic membranes of patients treated with topical IGF-1 therapy. This indicated the superior safety of topical IGF-1 therapy over intratympanic Dex therapy. On the other hand, the high incidence of tympanic membrane perforation in the Dex group might affect hearing recovery outcomes in the Dex group.

The present findings indicate the efficacy and safety of topical IGF-1 therapy for SSHL. However, topical IGF-1 therapy requires surgical procedures and causes uncomfortable symptoms associated with the local application. In addition, spontaneous recovery of hearing occurs in 30 to 60% of patients with SSHL [5,26-28]. Therefore, with the need for balancing the harmful side effects and the benefits, SSHL patients showing insufficient hearing improvement after the administration of oral corticosteroids or after strict observation for 7 days may be good candidates for topical IGF-1 therapy. On the other hand, IGF-1 is a promoter of cell proliferation in some cellular contents. Therefore, a long-term follow-up of patients may be required. Of note, in our previous clinical trial, we locally applied IGF-1 in the middle ear of 25 patients with refractory SSHL [23]; in the 5-year follow-up, no tumor formation was identified in those patients.

Conclusions

We performed a randomized, controlled clinical trial of topical IGF-1 therapy in patients with SSHL refractory to systemic corticosteroids and compared this treatment to intratympanic corticosteroid therapy. Present results suggest the possibility that IGF-1 is superior to intratympanic Dex therapy, but the current study design failed to confirm this possibility. The positive effect of topical IGF-1 application on hearing levels and its favorable safety profile suggest utility for topical IGF-1 therapy as a salvage treatment for SSHL.

Abbreviations

CI: Confidence interval; dB: Decibels; Dex: Dexamethasone; IGF-1: Insulin-like growth factor-1; PTA: Pure-tone audiometry; SSHL: Sudden sensorineural hearing loss.

Competing interests

All authors declare that they have no competing of interests.

Authors' contributions

TN obtained funding. TN, ST, HT, TI-I, TI, ASh, AY, YT, and JI contributed to the research design. AY and YT designed and prepared gelatin hydrogels. HT and ASh undertook and monitored study conduct with supervision from TN. JI, TN, KK, SU, NH, KT, MT, KF, ASa, SK, TS, HH, and NY recruited patients and undertook patient treatments. HT performed data cleaning and preparations for analysis. MY performed statistical analyses and wrote the statistical sections. TN and MY interpreted data. TN wrote the first draft of the manuscript. All authors contributed to the revised draft versions. All authors approved the final version.

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Role of the funding source

This work was initiated by the investigators and was conducted independently of any commercial entities. The drugs were purchased commercially.

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ORIGINAL ARTICLE

One-third of vertiginous episodes during the follow-up period are caused by benign paroxysmal positional vertigo in patients with Meniere's disease

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Abstract

Conclusion: In the present study, about one-third of patients with Meniere's disease developed benign paroxysmal positional vertigo (BPPV)-like attacks. Additionally, more than one-third of all vertigo attacks were BPPV-like attacks. Thus, vertigo attacks in patients with Meniere's disease must be carefully treated because the therapy for such vertigo attacks is totally different from the therapy for BPPV. *Objective:* Physicians sometimes encounter patients with previously diagnosed Meniere's disease who develop BPPV attacks during the course of clinical follow-up. In this study, we explored the frequency with which BPPV was involved in all vertiginous episodes among patients with Meniere's disease. *Methods:* This retrospective study involved 296 patients with Meniere's disease who visited Kyoto University Hospital. The diagnosis of Meniere's disease was based on the guidelines for the diagnosis of Meniere's disease proposed by the Committee on Hearing and Equilibrium. We judged the cause of vertigo as one of the following five types: (1) definite Meniere's disease attack, (2) suspicious Meniere's disease attack, (3) definite BPPV attack, (4) suspicious BPPV attack, or (5) unknown. *Results:* In all, 96 patients (32.8%) developed BPPV-like attacks, and 187 vertiginous episodes (37.9%) were caused by BPPV. The lateral semicircular canal was the most frequently involved canal.

Keywords: *Vertigo attack, Meniere's disease, Kyoto University Hospital*

Introduction

The epidemiology of vertigo is of interest to many ear, nose, and throat (ENT) doctors and neurologists because vertigo is 1 of the top 10 reasons for emergency room consultations. Benign paroxysmal positional vertigo (BPPV) is the most frequently encountered cause of vertigo [1], and a relationship between BPPV and Meniere's disease has been reported in several publications [2-4]. Previous studies have shown that 0.5–31.0% of patients with BPPV also have Meniere's disease [5] and that the recurrence rate of BPPV in patients with Meniere's disease is higher than that of idiopathic BPPV [2]. The period of recovery from vertigo is longer in patients with BPPV that is associated with inner ear disease [4]. Moreover, BPPV associated with Meniere's disease is reportedly intractable [5-7].

The above-mentioned reports mostly focused on whether BPPV was accompanied by other ear diseases and the affected patients' clinical features. We took a different approach in the present study; i.e. we focused on the vertiginous episodes encountered during the follow-up period in patients with Meniere's disease and determined how frequently vertigo due to BPPV was involved in these episodes. We found that more than one-third of vertiginous episodes in patients with Meniere's disease were caused by BPPV. Because the treatment for BPPV differs greatly from that for Meniere's attacks, this considerably high

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probability of BPPV in patients with Meniere's disease cannot be overemphasized.

Material and methods

Patients with Meniere's disease who visited the ENT outpatient department at Kyoto University Hospital from January 2008 to December 2012 were retrospectively recruited and followed for more than 6 months. The following variables were evaluated: the type of vertigo attack, time required for recovery, treatment, and duration of consultation. The diagnosis of Meniere's disease was based on the Committee on Hearing and Equilibrium guidelines for the diagnosis of Meniere's disease [8]. In short, vertigo attacks that are accompanied by cochlear symptoms, such as fluctuating low-frequency sensorineural hearing loss or tinnitus, are diagnosed as Meniere's disease. Spontaneous, gaze, positional, and positioning nystagmus were observed using an infrared eye camera (IRN-2; J. Morita Co., Tokyo, Japan). Pure-tone audiometry was performed in most patients at the first visit and was repeated as necessary during the course of follow-up. We classified the attacks into five categories using the following criteria. (1) Definite Meniere's disease attack: the patient had either transient low-pitch hearing threshold elevation or aural fullness in one ear, and the vertigo continued for >20 min with accompanying unidirectional nystagmus. (2) Suspicious Meniere's disease attack: the patient experienced vertigo for >20 min with cochlear symptoms (this is based on the report of patients). (3) Definite BPPV attack: positional nystagmus typical for BPPV was observed in the clinic, with a short vertigo duration and without accompanying cochlear symptoms. (4) Suspicious BPPV attack: the patient experienced short-term positional vertigo without cochlear symptoms (this is based on the report of patients). (5) Unknown: the episodes met none of the above criteria.

In definite BPPV attacks, we further explored which canal was involved by assessing the patient's eye movements. We judged the affected side of BPPV by the directional change of nystagmus. In posterior semicircular canal (PSCC) type, the direction of tortional nystagmus at Dix–Hallpike position was adapted as the affected side. In lateral semicircular canal (LSCC) type, the side with which stronger nystagmus was observed in the supine position was adapted as the affected side. In cupulolithiasis LSCC type, the affected side was judged by the null position of nystagmus. However, in some cases it was difficult to decide the affected side. So we excluded those cases from the discussion of affected sides.

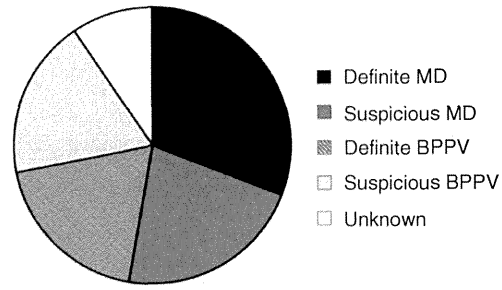

Figure 1. Details of vertigo attacks in patients with Meniere's disease (MD). The total number of vertigo attacks was 494. The most frequent diagnoses were definite Meniere's disease attacks (n = 153, 30.9%), suspicious Meniere's disease attacks (n = 108, 21.9%), definite benign paroxysmal positional vertigo (BPPV) attacks (n = 95, 19.2%), and suspicious BPPV attacks (n = 92, 18.6%).

The time of improvement was investigated from the disappearance of patients' subjective symptoms. Episodes with unclear or incomplete descriptions of the recovery period in the clinical record were discarded from further analysis of the time course of improvement (see Figure 3). Quantitative differences were evaluated by Fisher's analysis and Welch's test. Statistical significance was considered to be present at $p < 0.05$.

Results

A total of 296 patients with Meniere's disease consulted Kyoto University Hospital within the 30-month study period. The mean age of the patients was 59 ± 17 years (mean ± standard deviation, SD). Female and male patients comprised 66.6% and 33.4% of the patients, respectively. The affected sides were as follows: right, 36.5%; left, 41.2%; and both, 22.3%.

Of all 296 patients, 96 (32.8%) developed BPPV-like vertiginous episodes (definite BPPV and suspicious BPPV) during the study period. The mean age of patients with BPPV-like attacks was 62 ± 14 years, and the mean age of patients without BPPV-like

Table I. Number of benign paroxysmal positional vertigo (BPPV)-like attacks.

No. of BPPV-like attacks	No. of cases
1	41
2	29
3	20
4	4
>5	2
Total	96

Fifty-five of 96 patients (57.3%) exhibited more than one attack. The mean observation period was 28.8 ± 18.0 (SD) months.

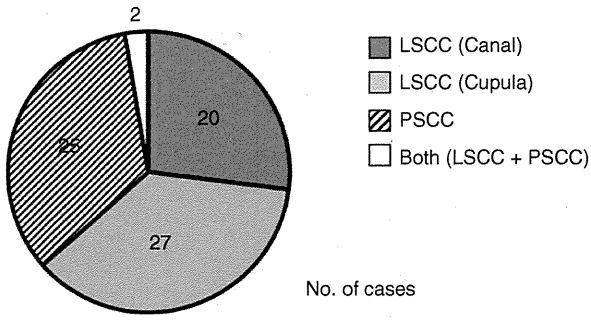

Figure 2. Canal involvement in benign paroxysmal positional vertigo (BPPV)-like attacks. In 47 patients (63.5%), vertigo was provoked during the supine roll test, implying involvement of the lateral semicircular canal (LSCC). In 20 patients, the observed nystagmus was geotrophic (canalolithiasis), and in 27 patients (36.5%), the nystagmus was persistent apogeotrophic (cupulolothiasis). The LSCC type affected 63.5% of patients. In 25 patients (33.8%), vertigo was provoked unilaterally during the Dix–Hallpike test.

attacks was 58 ± 18 years. The mean age of patients with BPPV was significantly higher than that of patients without BPPV (p = 0.03). Female patients represented 69.8% and 64.9% of all patients with and without BPPV-like attacks, respectively. The affected sides were as follows: right, 36.5%; left, 37.5%; and both, 27% in patients with BPPV-like attacks, and right, 37.2%; left, 42.8%; and both, 19.9% in patients without BPPV-like attacks. There were no significant differences between patients with and without BPPV regarding sex (p = 0.41) or affected side (p = 0.38). In patients with unilateral Meniere's disease, the side of the canal presumed to be involved in BPPV corresponded to the side of the Meniere's disease in 67.6% of patients.

Details of the vertigo attacks are shown in Figure 1. The total number of vertigo attacks was 494. The numbers of attacks in each category were as follows: definite Meniere's disease attacks, n = 153 (30.9%); suspicious Meniere's disease attacks, n = 108 (21.9%); definite BPPV attacks, n = 95 (19.2%); suspicious BPPV attacks, n = 92 (18.6%); and others, n = 46 (9.3%).

The numbers of recurrent BPPV attacks are shown in Table I. In total, 55 of the 96 affected patients (57.3%) experienced more than 1 attack. The mean observation period was 28.8 ± 18.0 months. There was no temporal relationship between Meniere's disease and BPPV attacks, because almost all BPPV attacks were observed between Meniere's disease attacks. Also, there was no significant correlation between the number of Meniere's disease attacks and that of BPPV attacks (correlation coefficient was 0.18).

The canals involved in the BPPV attacks are shown in Figure 2. In 47 patients (63.5%), horizontal nystagmus was provoked during the supine roll test, implying involvement of the LSCC. In 20 patients (27%), the observed nystagmus was geotrophic (canalolithiasis), and in 27 patients (36.5%), the nystagmus was persistently apogeotrophic (cupulolothiasis). LSCC involvement affected a total of 63.5% of patients. In 25 patients (33.8%), vertical and/or torsional nystagmus was provoked unilaterally and the changes of direction were observed during the Dix–Hallpike test.

The time course of the improvement in vertigo symptoms is shown in Figure 3. More than 2 days were required in patients with Meniere's vertigo attacks. In contrast, most vertigo symptoms in patients with BPPV attacks disappeared within 1 day. However, the rate of definite BPPV was lower in patients who exhibited rapid improvement.

The treatments required for vertigo attacks are shown in Figure 4. For most of the vertigo attacks

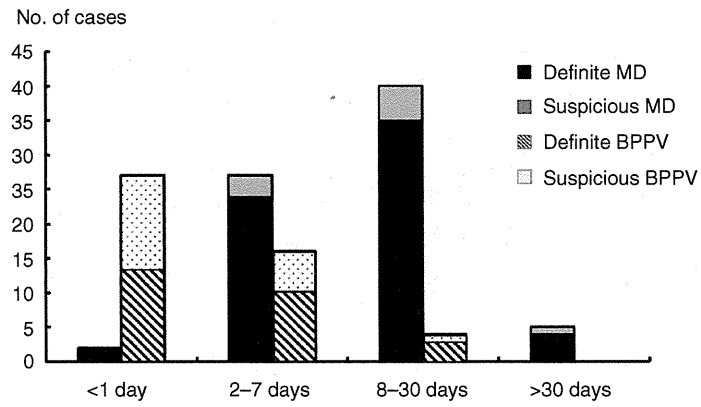

Figure 3. Time course of improvement. More than 2 days were required for improvement of Meniere's disease attacks. However, in patients with benign paroxysmal positional vertigo (BPPV) attacks, most vertigo symptoms improved within 1 day; although the rate of improvement in definite BPPV was lower in the rapid improvement group (patients who improved within 1 day).

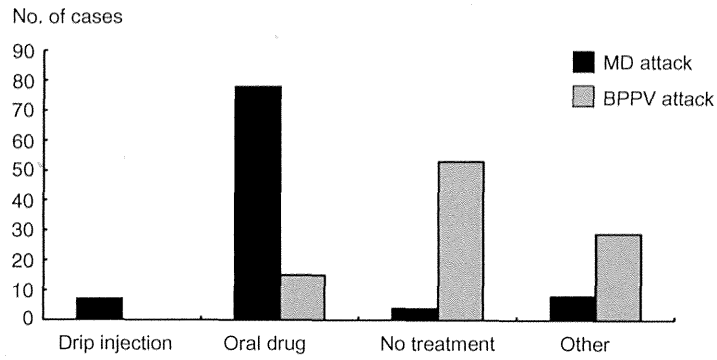

Figure 4. Additional treatment. For most vertigo attacks due to Meniere's disease (MD), anti-vertigo drip injections or oral drugs were given. However, for most benign paroxysmal positional vertigo (BPPV)-like vertigo attacks, no treatment other than positional maneuvering was performed.

induced by Meniere's disease (n = 261), anti-vertigo injection and/or administration of additional drugs such as sodium bicarbonate or betahistine mesilate was necessary. However, for most of the BPPV attacks (n = 187), no treatments other than positional maneuvers were required.

Discussion

Meniere's disease is well known to cause recurrent vertigo attacks. However, vertigo attacks in patients with Meniere's disease are not always caused by Meniere's disease. Meniere's disease is sometimes accompanied by BPPV [2-4]. In such patients, BPPV is reportedly secondary to Meniere's disease [7]. In the present study, however, BPPV was also observed during the follow-up period in patients previously diagnosed with Meniere's disease, and these BPPV attacks were not intractable in most cases.

The total number of vertigo attacks counted in this study was 494. Among these vertigo attacks, 187 (37.8%) were BPPV attacks. This might be higher than generally expected.

In this study of patients with Meniere's disease, the mean age was 59 years, and women comprised 66.6% of the patients, similar to a previous report [9]. Sex differences have been previously reported as well, with a female to male ratio of 1.7–2.0 to 1.0 as described by Sekine et al. [10]. Of the present patients with Meniere's disease, 96 (32.8%) exhibited BPPV-like attacks during the follow-up course. The mean age of patients with BPPV was higher than that of patients without BPPV. The prevalence of BPPV in patients with Meniere's disease was thus much higher than that in the normal population (10.7–64.0 per 100 000 population [11]). Hughes and Proctor also reported that 31% of patients with BPPV had an associated diagnosis of Meniere's disease [3]. One possible explanation for this high prevalence of BPPV in patients with Meniere's disease is that the endolymphatic hydrops secondarily damages the otolith organ, leading to detachment of the otoconia and subsequent BPPV. Takeda et al. reported that the utricular function is deranged in patients with BPPV [12], suggesting that floating debris from the damaged otolith causes BPPV. Another possibility is that the membranous labyrinth becomes distended by endolymphatic hydrops and loses its resilience, leading to adherence of the otolith to the membranous labyrinth and partial obstruction of the otolith [13,14]. The mean age difference between the patients with and without BPPV in the present study might have been due to degeneration of the otoconia in elderly patients and the ease of otolith detachment.

The cause of Meniere's disease remains controversial. Paparella and Yamane et al. reported that free-floating otoliths could induce endolymphatic hydrops by obstructing the endolymphatic flow [14,15]. A relationship between Meniere's disease and otoliths may exist; the frequency of patients with concomitant BPPV is higher than that of other vestibular disorders [12]. Improperly performed canal repositioning treatment could also cause obstruction within the membranous duct of the canal [13]. It is easy to imagine that these BPPV episodes might be relatively difficult to resolve. Alternatively, another possible reason is that complete cure is difficult to achieve in patients with Meniere's disease and that patients may suffer from BPPV during the long treatment process.

In previous papers, BPPV associated with Meniere's disease was reported to be secondary or symptomatic [7]; it was also reported to be intractable [5,6]. However, in the present study, most BPPV episodes observed during the follow-up period in patients with Meniere's disease were not intractable (Figure 3). This clear discrepancy between previous

studies and ours might be associated with the difference in the data collection methods. We focused on the vertiginous episodes encountered during the follow-up course in patients with Meniere's disease and not whether Meniere's disease was simultaneously active with BPPV. However, most previous studies evaluated BPPV accompanied by other inner ear diseases.

The canal primarily involved in the BPPV attacks was the LSCC (47/74 patients, 63.5%). The primarily involved canal in patients with idiopathic BPPV was the PSCC (49.8%) [16]. This high involvement of the LSCC in BPPV associated with Meniere's disease is also compatible with a previous report [2]. However, there is still no clear explanation for the LSCC predilection. Buckingham argued that loose otoliths could more easily slide onto the LSCC cupula when a supine patient turns to one side or the other because of the adjacent location of the ampulla of the LSCC [17]. Other authors argued that anatomic factors predominate over gravitational factors in Meniere's-associated BPPV and are responsible for the predilection for involvement of the PSCC in idiopathic BPPV [16,18].

The time course for the improvement in vertigo symptoms is quite different between Meniere's attacks and BPPV attacks. In our patients with Meniere's attacks, improvement required more than 2 days in almost all cases. However, in patients with BPPV attacks, a large proportion of vertiginous episodes improved within 1 day. Conversely, the rate of improvement of definite BPPV attacks was lower. This result might have been due to the long interval of consultation at Kyoto University Hospital. Patients at our hospital usually come to the outpatient clinic once every few months. Thus, even when patients experience a BPPV attack, the vertigo symptoms disappear soon. This might be one reason for our inability to detect the patients' nystagmus. We considered these attacks to be suspicious BPPV attacks. There is a possibility that these suspicious BPPV attacks might have been of the PSCC type because the LSCC type generally requires more time to improve than does the PSCC type [4]. That is, PSCC-type BPPV is easy to treat, and we could not detect patients' typical nystagmus. Therefore, we can speculate that the BPPV in our study was not intractable because of the existence of suspicious (underlying) PSCC type, despite the fact that the LSCC type comprised 63.5% of definite BPPV episodes.

Additional therapies for each vertigo attack were therefore different between Meniere's disease attacks and BPPV attacks. For most patients with vertigo attacks due to Meniere's disease, anti-vertigo injections and/or additional administration of drugs were required. In contrast, for most BPPV-like vertigo attacks, no treatments with the exception of positional maneuvers were performed. Thus, most of the BPPV attacks encountered during the follow-up of patients with Meniere's disease were not intractable. This is different from previous papers [19]. However, Ganança et al. reported that BPPV attacks associated with Meniere's disease were eliminated within three Epley maneuvers [20]. Selection bias may be one reason for this difference in improvement. Previous studies of intractable BPPV associated with Meniere's disease focused on BPPV and compared BPPV with idiopathic BPPV, but they did not mention the time relationship between BPPV attacks and the Meniere's disease status. This difference in improvement might also have been be related to the stage of Meniere's disease, definition of BPPV, and so on.

In summary, we have reported the epidemiological features of vertigo attacks in patients with Meniere's disease treated at Kyoto University Hospital. Of 296 patients with Meniere's disease, 96 (32.8%) developed BPPV-like attacks. Among these, 187 vertigo attacks (37.8%) were BPPV attacks. These BPPV attacks were not intractable in most cases. Thus, vertigo attacks encountered during the follow-up period in patients with Meniere's disease must be carefully diagnosed to prevent unnecessary treatment.

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The Laryngoscope

Does Endolymphatic Sac Decompression Surgery Prevent Bilateral Development of Unilateral Ménière Disease?

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Objectives/Hypothesis: The aim of the study was to elucidate whether endolymphatic sac decompression surgery (ESDS) has the potential to prevent unilateral Ménière disease (MD) from becoming bilateral.

Study Design: Prospective case–control study at tertiary referral center.

Methods: Between 1996 and 2008, we performed a glycerol test (G-test) and electrocochleography (ECoG) on 237 patients with intractable unilateral MD. We performed ESDS on 179 patients (144 with no endolymphatic hydrops and 35 with silent endolymphatic hydrops in the contralateral ear). The other 58 patients (40 without endolymphatic hydrops and 18 with silent endolymphatic hydrops in the contralateral ear) were given available medical treatments. All underwent regular follow-up for at least 5 years.

Results: Altogether, 22.4% (53 of 237) of patients with clinically diagnosed unilateral intractable MD had silent endolymphatic hydrops in the contralateral ear using G-test and ECoG. In the nonsurgical group, six of 40 patients with unilateral MD with no endolymphatic hydrops in the contralateral ear developed bilateral disease, whereas in the surgical group 12 of 144 patients did so ($P = .231$, Fisher test). In the nonsurgical group, nine of 18 patients with unilateral MD and silent endolymphatic hydrops developed the disease in the contralateral ear, whereas in the surgical group six of 35 patients developed bilateral disease ($P = .022$, Fisher test).

Conclusions: The present findings suggest that ESDS may decrease the incidence of developing MD in silent endolymphatic hydronic contralateral ears diagnosed with G-test and ECoG within the first 5 postoperative years.

Key Words: Symptomatic endolymphatic hydrops, asymptomatic endolymphatic hydrops, glycerol test, electrocochleography, endolymphatic sac drainage, bilateral Ménière disease.

Level of Evidence: 3b

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INTRODUCTION

Ménière disease (MD), characterized by recurrent vertigo, fluctuating hearing loss, and persistent tinnitus, is a common disease, with an incidence of 15 to 50 per 100,000.[1] If MD were a unilateral vertigo disease, even intractable cases could be cured simply by vestibular ablative surgery. However, 10% to 40% of MD cases gradually develop from unilateral to bilateral disease.[2–4] The bilateral disease is associated with the development of bilateral sensorineural hearing loss that gradually becomes the focus of the patient's problems instead of vertigo.[3] It is for this reason that MD was designated a specific disease by Japan's Ministry of Health, Labor, and Welfare in 1957.[5] Despite its importance, there have been few well-designed clinical studies concerned with preventing bilateral MD that have included control groups or long-term observation.

The aim of the present study was to determine whether endolymphatic sac decompression surgery (ESDS)[6–8] has the potential to prevent unilateral MD from becoming bilateral.

MATERIALS AND METHODS

The Ethics Committee of Osaka University Hospital approved the present study (certificate number 0421). It was registered with ClinicalTrials.gov of the US Food and Drug Administration (certificate number NCT00500474). All the patients included in the present study received informed consent and signed permission to join in this study.

Patients and Treatments

Between April 1996 and March 2008, 5,838 successive patients with MD-like symptoms aged at least 20 years were sent by home doctors and prescreened for eligibility in the vertigo and dizziness departments of Osaka University Hospitals to determine whether they had received a clinical diagnosis of unilateral (n = 1,492) or bilateral (n = 398) definite MD according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria.[9] A total of 3,948 patients with diseases other than MD that cause vertigo and dizziness were excluded. A total of 373 intractable cases of MD

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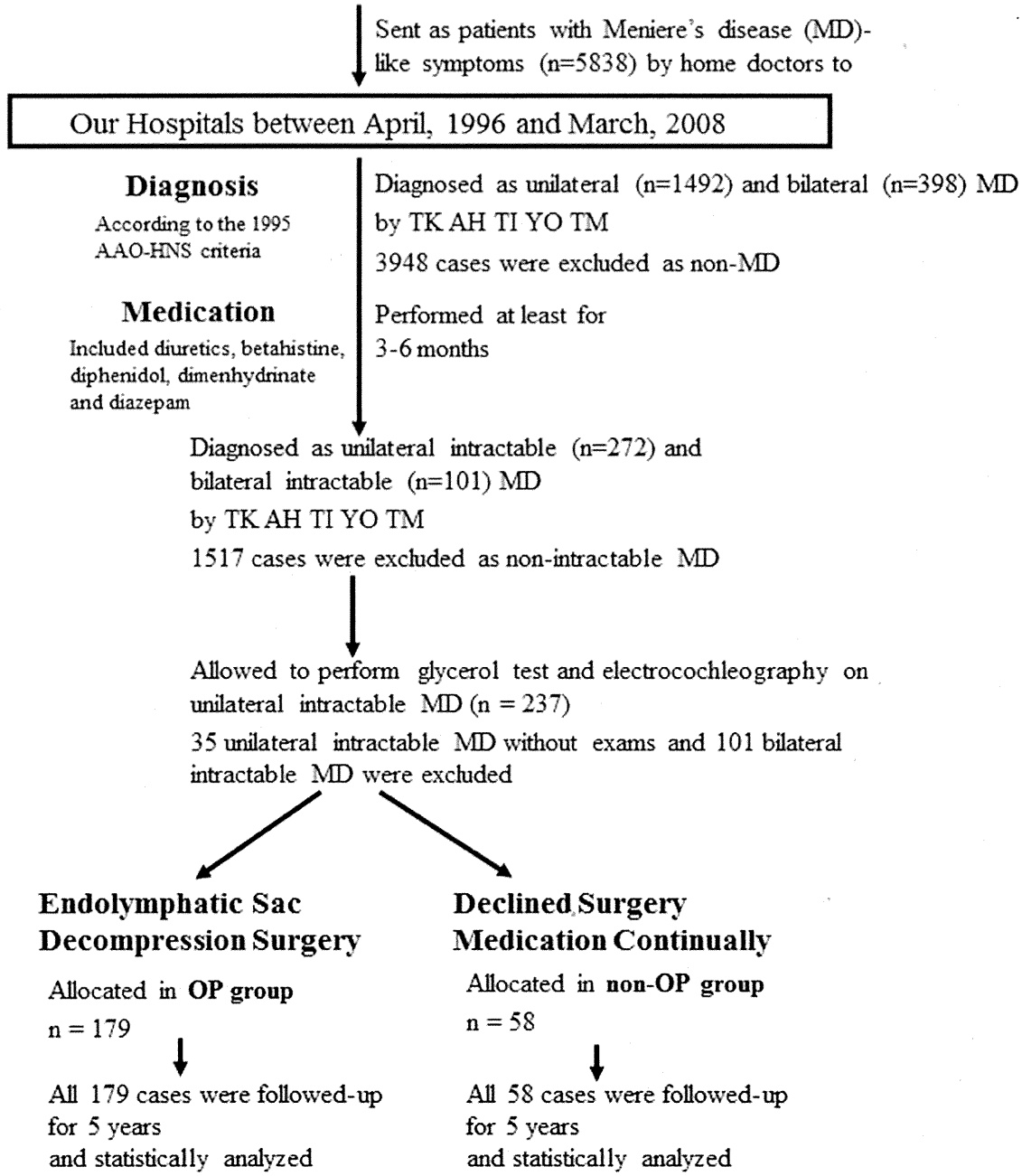

Fig. 1. A flowchart of subjects in the present study. Patients were eligible for enrollment if they had received a clinical diagnosis of unilateral and bilateral definite Ménière disease (MD) according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria. Between April 1996 and March 2008, we offered endolymphatic sac decompression surgery (ESDS) for 237 patients with unilateral intractable MD and performed ESDS on 179 of these patients (OP group). We treated the remaining 58 patients, who declined ESDS, with the best available medicines (non-OP group). All the patients were followed up regularly until March 2013 for at least 5 years.

(unilateral, 272; bilateral, 101) were clinically diagnosed in patients who had undergone various forms of medical and psychological management for at least 3 to 6 months for their symptoms, it having failed according to the Lancet Seminar.[10] Patients with either bilateral MD or MD not intractable were also excluded from the study.

Our study protocol for prevention from MD bilateralization in the present study is shown in Figure 1. This protocol was originally demonstrated as surgical results of ESDS in a previous article.[7] There were some points modified from the original as follows. Because of strict long-term follow-up systems in Osaka, Japan, we excluded cases in Kyoto, Japan and treated additional unilateral intractable ones at our hospitals in Osaka. We were allowed to perform a glycerol test (G-test) and electrocochleography (ECoG) on 237 of 272 patients with unilateral intractable MD and evaluated endolymphatic hydrops in the contralateral ear before treatment.[11] We then offered ESDS for all the patients and actually performed ESDS on 179 of these patients[6–8]: 144 without endolymphatic

TABLE I.
Patients' Backgrounds in Four Groups.

Group	contraEH, +/−	Age, yr	Sex, M/F	Dur, mo	Vf, a/mo	wHL, dB	pAVP, pg/ml
OP, n = 144	−	47.2 ± 4.5	71/73	45.5 ± 16.8	3.0 ± 1.2	52.2 ± 18.0	3.0 ± 1.8
OP, n = 35	+	49.6 ± 6.6	15/20	47.2 ± 24.5	3.2 ± 2.1	60.8 ± 12.6	3.8 ± 3.0
non-OP, n = 40	−	50.3 ± 7.2	21/19	50.2 ± 18.2	2.8 ± 2.0	47.5 ± 20.2	3.2 ± 2.2
non-OP, n = 18	+	54.8 ± 6.3	9/9	51.0 ± 28.6	2.6 ± 1.7	56.3 ± 15.8	3.5 ± 3.2

In the surgical group (OP), nonendolymphatic hydrops was found in 144 cases (contraEH[−]) and silent endolymphatic hydrops was found in 35 cases (contraEH[+]) in the contralateral ear. In the nonsurgical group, nonendolymphatic hydrops was found in 40 cases and silent endolymphatic hydrops was found in 18 cases in the contralateral ear. There were no significant differences in patients' backgrounds between OP and non-OP groups.

a = attacks; Dur = duration of disease; F = female; M = male; pAVP = plasma vasopressin level; Vf = vertigo frequency; wHL = preoperative worst hearing level.

hydrops and 35 with silent endolymphatic hydrops in the contralateral ear. These patients formed the OP group. We treated the remaining 58 patients, who declined ESDS, with the best available medicines.[12] Among them, 40 had no endolymphatic hydrops, and 18 had silent endolymphatic hydrops in the contralateral ear. These patients formed the non-OP group. All the patients were followed up regularly until March 2013 for at least 5 years. ESDS is a very common strategy for patients with intractable MD, as seen in the Lancet Seminar.[10] It would thus be difficult not to apply this surgery to some patients for a perfect randomized controlled trial. The patients' backgrounds in both groups are shown in Table I. The best available medicines used for 179 cases in the OP group and 58 cases in the non-OP group during the study period are listed in Table II.

Examinations for Inner Ear Hydrops

To detect endolymphatic hydrops not only in the ipsilateral ear but also in the contralateral ear, we carried out a G-test and ECoG before treatment.[11] The G-test is considered positive in pure tone audiometry (PTA) if there is a ≥10-dB improvement at two or more frequencies between 0.25 and 2.0 kHz. ECoG is considered positive if the negative summating potential/active potential ratio is ≥0.40. We diagnosed endolymphatic hydrops if there was at least one positive result for the two examinations (G-test and ECoG).

Surgical Procedures

The technical details of ESDS are as follows.[6–8] 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. It was opened with an L-shaped incision made along the posterior and distal margins of the lateral wall. It was then filled with 20 mg of prednisolone. While it was dissolving, we prepared a bundle of absorbable gelatin film with fan- and stick-shaped ends. These films were tied to each other with biochemical adhesive at the stick-shaped end. The fan-shaped end was then inserted into the sac. 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 expanded with the bundle. The dexamethasone-containing sponges placed outside the sac were coated with the adhesive so that dexamethasone was slowly delivered into the sac over a long period of time. 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 remained expanded for as long as possible. The mastoid cavity was filled with relatively large pieces of absorbable gelatin sponge dipped in a steroid–antibiotic solution (ofloxacin etc., harmless to the inner ear), after which the wound was closed with skin sutures.

Diagnosis of Bilateralization

Contralateral MD is clinically diagnosed based on recurrent vertigo attacks originating from the contralateral ear or if hearing fluctuates in the contralateral ear. A definitive spell of vertigo (lasting >20 minutes) accompanied by contralateral ear cochlear symptoms (tinnitus, hearing loss, ear fullness) is regarded as having its origin in the contralateral ear. Hearing fluctuation is evaluated by PTA based on the four-tone average formulated by (a + b + c + d)/4 (a, b, c, and d are hearing levels at 0.5, 1.0, 2.0, and 4.0 kHz, respectively). Changes in hearing levels of >10 dB in the contralateral ear were regarded as hearing fluctuation. Finally, at the 5th postoperative year, we calculated the ratio of the number of patients transitioning from unilateral to bilateral in both groups.

Statistical Analysis

The data were shown as the ratio of the total number of cases to those treated. They were analyzed statistically using SPSS version 14.0 software (SPSS, Chicago, IL). These data were analyzed with a 2 × 2 contingency table method. Each correlation was assessed using the χ^2 test or Fisher test. All reported probability values were two-sided, with $P < .05$ as the accepted level of significance.

All the statistical analyses in the present study were conducted by Dr. Michiko Shuto, a registered statistician independent from our organization.

RESULTS

A total of 237 patients were clinically diagnosed as having unilateral intractable definite MD. Among them,

TABLE II.
The Best Available Medicines for 237 Cases During the Study Period.

Group	contraEH, +/−	Adenosine Triphosphate/ Betahistine/Chinese Diuretics /Diazepam/Dimenhydrinate/ Osmotic Diuretics*
OP, n = 144	−	88/85/16/76/57/88
OP, n = 35	+	28/30/4/25/20/24
non-OP, n = 40	−	34/35/5/25/24/34
non-OP, n = 18	+	15/16/4/12/12/16

The best available medicines used for 179 cases in the surgical group (OP) group and 58 cases in the non-OP group during the study period are listed here. There were no significant differences in these medicines between the OP and non-OP groups.

*Number of cases.

contraEH(−) = nonendolymphatic hydrops in the contralateral ear; contraEH(+) = silent endolymphatic hydrops in the contralateral ear.

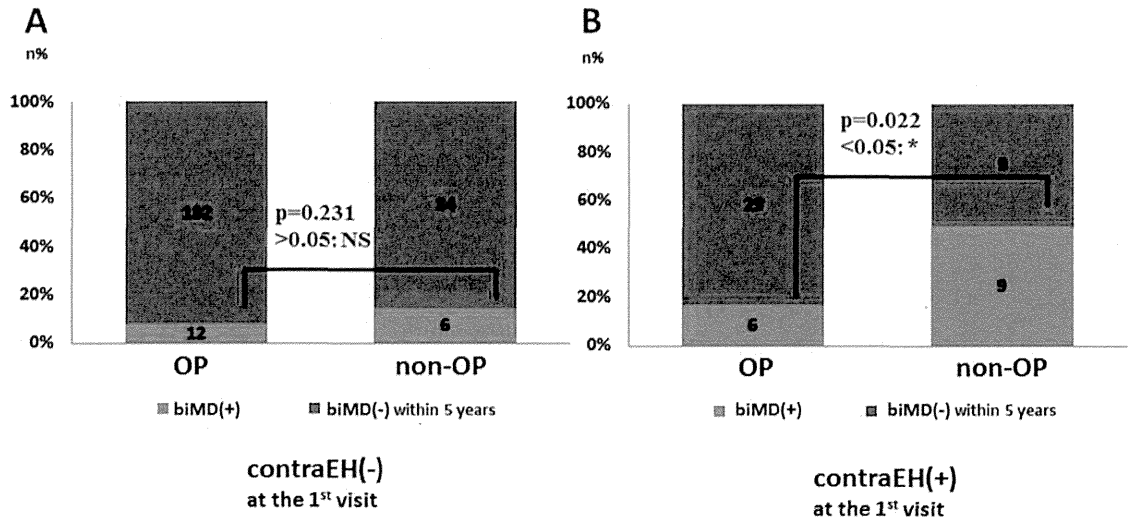

Fig. 2. The ratio of bilaterality after surgical and nonsurgical treatments. (A) During 5-year post-therapeutic observation, there were 6 bilaterally developed cases (biMD[+]) of 40 with unilateral Ménière disease with nonendolymphatic hydrops in the contralateral ear in the nonsurgical group (contraEH[−] in non-OP), whereas there were 12 bilaterally developed cases of 144 in the surgical group. (B) There were 9 bilaterally developed cases of 18 with unilateral Ménière disease with silent endolymphatic hydrops in the contralateral ear (contraEH[+]) in the nonsurgical group, whereas there were six bilaterally developed cases of 35 in the surgical group. NS = nonsignificant. *Significant difference. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

161 patients had positive signs in the ipsilateral ear (161 of 237, 67.9%) and 53 patients had also positive signs in the contralateral ear (53 of 237, 22.4%) using G-test and ECoG. There were no significant differences in patients' backgrounds between OP and non-OP groups (Table I).

Among 40 patients treated medically (non-OP group) who had unilateral MD without endolymphatic hydrops in the contralateral ear, six developed bilateral MD during the 5-year follow-up. During the same time period, 12 of 144 patients in the OP group developed bilateral MD ($P = .231$, Fisher test; Fig. 2A). Among 18 patients in the non-OP group who had unilateral MD with silent endolymphatic hydrops in the contralateral ear, nine developed bilateral disease. In the OP group, six of 35 patients developed bilateral disease ($P = .022$, Fisher test; Fig. 2B).

DISCUSSION

Yamakawa in Osaka, Japan[13] and Hallpike in London, United Kingdom[14] almost simultaneously revealed that the otopathology of MD was endolymphatic hydrops. Their conclusions were based on the results of temporal bone studies they had conducted. Several similar studies thereafter indicated that approximately 30% of patients with MD had endolymphatic hydrops in bilateral ears.[15] Based on clinical observations alone, the ratio of bilateral cases approximated 30%.[2–4] Also, neuro-otologic examinations showed that the ratio of unilateral MD with silent endolymphatic hydrops in the contralateral ear was 10% to 35%,[16,17] similar to the 22.4% reported in the present study.

We neuro-otologists cannot ignore these ratios because bilateralization is one of the most important pivotal factors in changing simple MD into an intractable form. We earlier proposed a modified ESDS technique with the application of steroids to the intraendolymphatic sac in patients with intractable MD.[6–8] The aim of the present study was to determine whether ESDS has the potential to prevent unilateral MD from becoming bilateral. Our 5-year findings suggest that ESDS can prevent the onset of MD in patients with silent endolymphatic hydrops in the contralateral ear. It did not prevent it, however, in patients who did not have endolymphatic hydrops in the contralateral ear.

The mechanisms by which bilateralization of MD was prevented by ESDS in the present study deserve discussion. Although it has not been established that Reissner's membrane rupture theory is true,[18] ESDS significantly suppressed progression of endolymphatic hydrops to the onset of Ménière symptoms in patients with silent endolymphatic hydrops in the contralateral ear. Previous clinical studies[19,20] and basic studies[21,22] demonstrated that a high level of plasma vasopressin was a possible cause of endolymphatic hydrops in MD patients. ESDS was shown to decrease the plasma vasopressin level in MD patients in advance of good surgical results.[23] These findings led to the possibility that ESDS—in addition to its decompression effects in the ipsilateral ear—could lessen the severity of endolymphatic hydrops in the contralateral ear by reducing the systemic plasma vasopressin level. In another recent study, we showed that abundant water intake, tympanic ventilation tubes, and sleeping in darkness could manage vasopressin secretion in Ménière patients with good results (Kitahara et al., unpublished observations). Therefore, regardless of the treatment strategy, reducing the plasma vasopressin level might ameliorate the severity of endolymphatic hydrops and suppress bilateralization of MD.

Conversely, ESDS did not significantly suppress hydrops generation or the onset of MD in the contralateral ear that did not have endolymphatic hydrops. One possibility for these results is that a follow-up of >5 years is needed to determine whether ESDS can suppress hydrops generation or MD onset in the contralateral ear in the absence of endolymphatic hydrops.[2–4] Another possibility is that the duration of MD before treatment in our study was around 4 to 5 years in both the OP and non-OP groups. The absence of endolymphatic hydrops in the contralateral ear at that time may indicate that the ear would be free of endolymphatic hydrops in the future regardless of the treatment applied.[2–4]

It was previously reported that, compared with nonsurgical treatment, surgery prevented clinically diagnosed unilateral MD from becoming bilateral.[24] There were a few problems in that report, however. First, the surgeries included both conservative and ablative operations. Second, the patients excluded from the surgical arm of the study were subjected to stricter criteria than those in the nonsurgical group. In the present study, ESDS was the only surgical treatment. Also, endolymphatic hydrops in the contralateral ear was detected by means of the G-test and ECoG in both the OP and non-OP groups. We are planning a randomized controlled study for the future.

In the present study, both unilateral and bilateral definite MD was diagnosed based on clinical symptoms according to the 1995 AAO-HNS criteria.[9] At that time, neuro-otologic examinations looking for signs of endolymphatic hydrops were not necessarily included in the criteria. This limitation may have caused the diagnosis of definite MD to be confused with nonendolymphatic hydrops. Conversely, in the present study, both unilateral and bilateral endolymphatic hydrops was diagnosed by neuro-otologic examinations such as the G-test and ECoG. Each of these tests has approximately 60% sensitivity at most.[11,25] In recent reports, including those from our group, endolymphatic hydrops was demonstrated using gadolinium-enhanced inner ear magnetic resonance imaging (MRI).[25–27] The sensitivity of this imaging analysis for endolymphatic hydrops was >90%—better than that of neuro-otologic examinations. Further studies including gadolinium-enhanced inner ear MRI could evaluate the effects of treatment for MD on the suppression of bilateralization.

CONCLUSION

Among our patients, 22.4% with clinically diagnosed unilateral intractable definite MD had silent endolymphatic hydrops in the contralateral ear using G-test and ECoG. ESDS prevented MD onset in these patients but did not prevent it in those without endolymphatic hydrops in the contralateral ear using G-test and ECoG within the first 5 postoperative years.

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Effects of Endolymphatic Sac Decompression Surgery on Vertigo and Hearing in Patients With Bilateral Ménière's Disease

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Objective: The aim of the present study, which involved a 2-year observation period and a nonsurgical control group, was to determine whether endolymphatic sac decompression surgery (ESDS) has the potential to prevent the progression of vertigo and hearing loss in patients with intractable bilateral Ménière's disease (MD).
Study Design: Prospective case-control study.
Setting: Tertiary referral center.
Methods: Between 1996 and 2008, we subjected 67 patients with intractable bilateral MD to ESDS and local corticosteroid treatment. Another 34 patients with intractable bilateral MD who declined ESDS were treated with the best available medical therapies. All of the patients underwent regular follow-up examinations for at least 2 years.
Results: Vertigo was resolved in 22 of 34 patients in the non-ESDS group and 60 of 67 patients in the ESDS group ($p = 0.055$, Fisher's exact test). Of the 24 patients in the non-ESDS group and 55 patients in the ESDS group in whom the ipsilateral ear (the treated ear) exhibited worse hearing function than the contralateral ear, the hearing level of the former ear was preserved in 13 and 52 patients, respectively ($p = 0.007$, Fisher's exact test). Of the 10 patients in the nonsurgical group and 12 patients in the surgical group in whom the ipsilateral ear exhibited better hearing function than the contralateral ear, the hearing level of the former ear was preserved in 2 and 11 patients, respectively ($p = 0.035$, Fisher's exact test).
Conclusion: The present findings suggest that ESDS combined with local corticosteroid treatment can control progressive hearing loss in both ears in patients with bilateral MD at least during the first 2 postoperative years. **Key Words:** Bilateral Ménière's disease—Endolymphatic sac drainage—Local steroid treatment—Surgical effects.
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Ménière's disease (MD) is a common inner ear disease characterized by vertigo, hearing loss, and tinnitus. It occurs at an incidence of 15 to 50 per 100,000 individuals (1). In cases of unilateral MD, in which only the periphery of the inner ear is affected, even intractable cases can be cured with vestibular ablative surgery alone. However, approximately 10% to 40% of cases of unilateral MD gradually become bilateral (2–4). Bilateral disease is associated with the development of profound bilateral sensorineural hearing loss, the severity of which gradually surpasses that of the associated vertigo (3). For this reason, MD was designated as a specific disease by Japan's Ministry of Health, Labour, and Welfare in 1957 (5). Despite the importance of bilateral MD, there have been few well-designed clinical studies, that is, studies involving control groups or long-term observation, of the suppression of frequent vertigo attacks and progressive hearing loss in patients with bilateral MD.

The aim of the present study, which involved a 2-year observation period and a nonsurgical control group, was to determine whether endolymphatic sac decompression surgery (ESDS) (6–8) has the potential to prevent progressive symptoms in patients with intractable bilateral MD.

MATERIALS AND METHODS

The ethics committee of Osaka University Hospital approved the present study (certificate no. 0421), which was registered at the ClinicalTrials.gov registry run by the U.S. Food and Drug Administration (certificate no. NCT00500474). All of the patients included in the present study signed informed consent forms before participating.

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The authors disclose no conflicts of interest.