

regulatory genes in many tissues in mammalian organogenesis including developing ear, branchial arch, and kidney. Furthermore, the interaction between *Eya1* and *Six1* is critical for the morphogenesis of the inner ear during its development [7]. So far, 9 mutations in *SIX1* have been reported from 16 unrelated BOR/BO syndrome families, and all are located on either the SIX domain or the homeodomain of *SIX1* [5,8–10]. These mutations are suggested to cause the pathology of BO syndrome through at least two different mechanisms: abolishing the formation of the SIX1–EYA complex or diminishing the ability of *SIX1* to bind DNA [5,11]. Only 4% of BOR/BO syndrome patients have *SIX1* mutations [10].

We previously reported a BO syndrome patient with a heterozygous c.386A > G (p.Y129C) mutation in *SIX1*, and suggested that *SIX1* mutation could cause enlarged vestibular aqueducts (EVA) [8]. In this study, we report the clinical course of a 9-year follow-up and audiovestibular findings in another unrelated Japanese patient with the same *SIX1* mutation.

**Material and methods**

*Patient*

This study enrolled a Japanese female who underwent a health examination at the age of 6 years and was found to have bilateral HL. She first visited our department for the further investigation of HL in January 2001 at the age of 21. She had not experienced progression of HL, tinnitus, or vertigo. The family tree obtained through the interview from the patient indicated autosomal dominant or maternally inherited HL (Figure 1A). Bilateral eardrums and external auditory canals were normal, and neither facial asymmetry nor palate abnormalities were found. Pure-tone audiometry showed bilateral moderate mixed HL with bilateral air–bone gaps at the lower frequencies (Figure 1B). The pure-tone average calculated from air-conduction thresholds at 0.5, 1, 2, and 4 kHz was 46.3 dB in the right ear and 52.5 dB in the left ear. High-resolution computed tomography (CT) and magnetic resonance imaging (MRI) of the temporal bones showed apparent EVA on the right

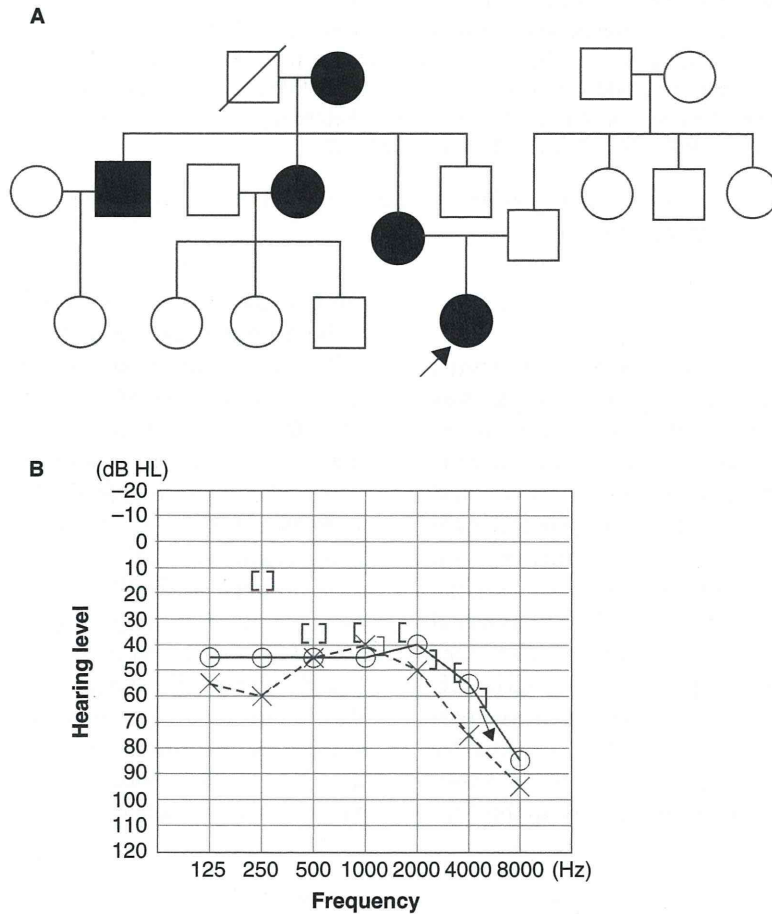


Figure 1. (A) The family tree indicates autosomal dominant or maternally inherited hearing loss (HL). (B) The audiogram shows bilateral moderate mixed HL.

side without other inner or middle ear malformations (Figure 2). Her left ear also had EVA, because the diameter of the vestibular aqueduct was wider than that of the posterior semicircular canal on 3D-MRI [12]. We had believed the patient to have nonsyndromic hereditary HL until we experienced a previous patient with a *SIX1* mutation who had similar symptoms [8]. Because of the phenotypic similarity, we searched for the presence of any branchial arch abnormalities and found a tiny preauricular pit on her left side (Figure 3). No branchial fistulae or renal anomalies were revealed by cervical and renal ultrasonic examinations. Her latest pure-tone average on July 2010 was 46.3 dB in the right ear and 53.8 dB in the left ear, indicating no apparent progression of HL during the follow-up period of 9 years.

#### Audiovestibular examination

The patient underwent audiological examinations including speech audiometry, tympanometry, acoustic reflex testing, distortion-product otoacoustic emissions (DPOAEs), and electrocochleography (ECoChG). DPOAEs were recorded and analyzed using an ILO292 analyzer (Otodynamics Ltd, Hatfield, Herts, UK). Two primary tones with a frequency ratio ( $f_2/f_1$ ) kept at 1.22 were presented at 70 dB sound pressure level. Tympanic ECoChG was performed as described previously [13]. In brief, alternating polarity clicks were used to measure summing potentials (SPs) and cochlear nerve action potentials (APs), and short tone-bursts with a frequency of 1 kHz were used to evoke cochlear microphonics (CMs). The detection thresholds of CMs and APs were deemed normal if they were less than 30 dB

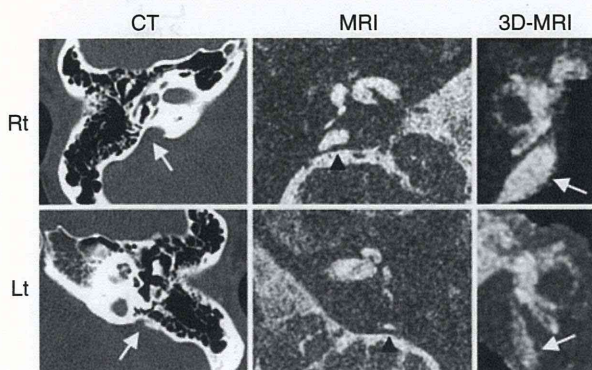


Figure 2. High-resolution computed tomography (CT) and magnetic resonance imaging (MRI) of the temporal bones. An enlarged vestibular aqueduct (arrows) and endolymphatic sac (arrowheads) are evident in the right ear. A left enlarged vestibular aqueduct is also recognized on 3D-MRI because it is wider than the posterior semicircular canal.



Figure 3. Left preauricular pit.

at a normal hearing level (nHL) (all values are the means +2 SD of 29 normal controls).

In vestibular examinations, positional, positioning, and spontaneous nystagmus tests were conducted with an infrared CCD camera. Air caloric testing was performed by electronystagmography (ENG). Caloric hypoplexia was defined as maximal slow phase velocity (MSV) less than 20°/s.

#### Mutation analysis

All protocols were approved by the Ethics Reviewing Committee of Tokyo Medical and Dental University and were carried out only after obtaining written informed consent. Genomic DNA was extracted from the peripheral blood lymphocytes of the patient. Genetic analysis for *SIX1* mutation was carried out as described previously [8]. Amplification was also conducted for the coding regions and exon-intron boundaries of *EYA1*, *SLC26A4*, *GJB2*, and mitochondrial DNA *MTRNR1* including 1555 position.

We could not perform audiovestibular examinations, imaging tests, or genetic study on the other family members, because the patient did not wish them to be involved.

## Results

#### Audiovestibular findings

The patient's speech discrimination score was 100% bilaterally. The thresholds of ipsilateral acoustic reflex in both sides ranged from 80 to 100 dB at the frequencies of 500 and 1000 Hz, indicating cochlear HL. The DPOAE amplitudes decreased to the noise levels bilaterally. The CM detection thresholds in

ECochG showed elevated values of 40 dB nHL in the right ear and 50 dB nHL in the left ear (Figure 4). The AP detection thresholds increased to 80 dB nHL in both ears, and broad AP was recognized in the left ear. The SP waveforms were obscure, and thus  $-SP/AP$  ratios could not be determined.

No gaze, positional, or positioning nystagmus was detected. The MSV of caloric testing was  $51^\circ/s$  in the right ear and  $29^\circ/s$  in the left ear, thus suggesting bilateral normal caloric responses.

#### Genetic findings

We detected a heterozygous A to G transition (c.386A>G) in exon 1 of *SIX1* that was predicted to result in a tyrosine to cysteine substitution at codon 129 (p.Y129C). No mutation was detected in *EYA1*, *SLC26A4*, *GJB2*, or *MTRNR1*.

#### Discussion

To date, a total of 9 *SIX1* mutations have been identified in 16 unrelated BOR/BO syndrome families

with various ethnic backgrounds [5,8–10]. Seven missense mutations (p.V17E, p.H73P, p.V106G, p.R110Q, p.R110W, p.R112C, and p.W122R) are located within the SIX domain, while one missense mutation (p.Y129C) and one deletion mutation (p.delE133) are located within the homeodomain. In the present study, we could not perform genetic analysis on the other family members. However, p.Y129C detected in the patient was a previously reported mutation, which was identical to the mutation identified in a large Anglo-Saxon Australian family [5,14] and our other BO syndrome patient [8]. This missense mutation was not found in 82 Japanese normal controls [8]. No mutation was identified in other deafness genes including *EYA1*. Furthermore, the findings of biological and functional studies suggested that p.Y129C contributed to the pathogenesis of BO syndrome [5,11]. Therefore, p.Y129C was deemed to be pathogenic to the present patient.

Although only a few articles have described the clinical features of patients with *SIX1* mutations [5,8–10], Kochhar et al. [10] summarized the phenotypic appearances of 27 patients including their patients, and provided a literature review. According

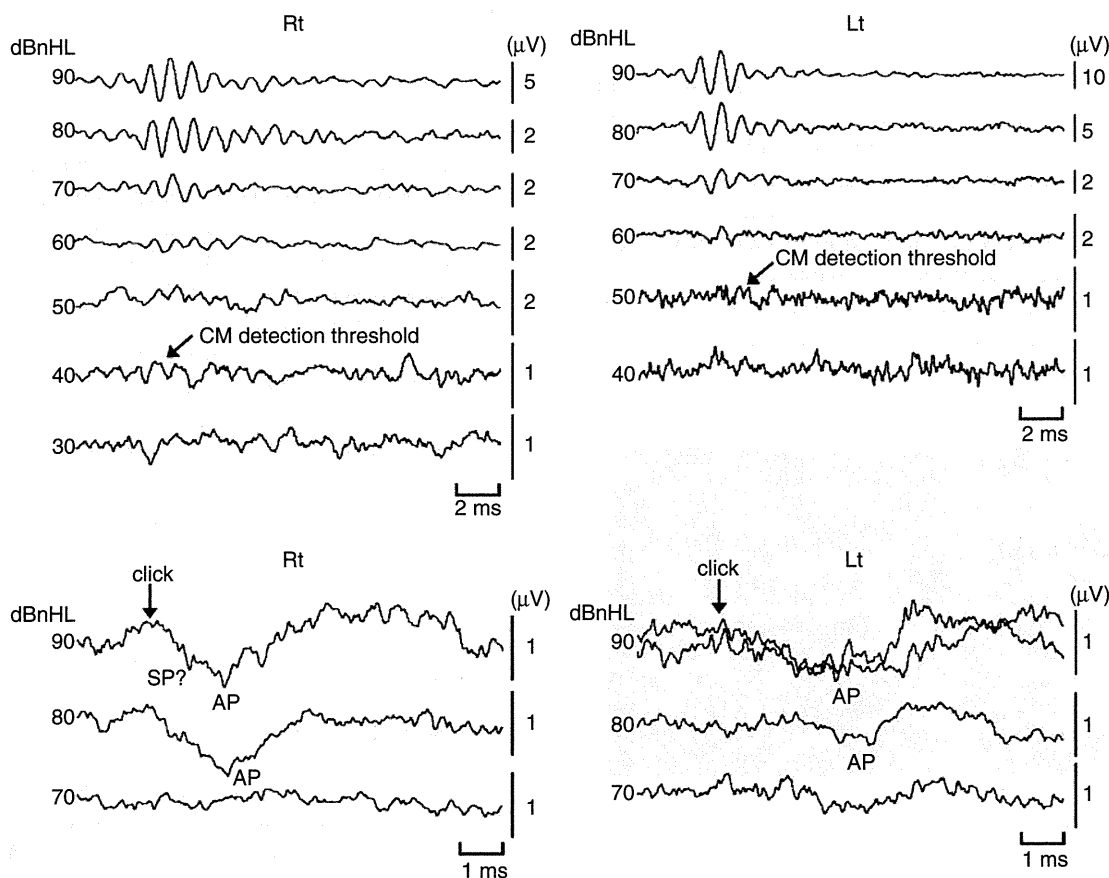


Figure 4. Waveforms of electrocochleography. The detection thresholds of cochlear microphonics and cochlear nerve action potentials are elevated, suggesting the existence of cochlear dysfunction.

to the summary, the frequencies of HL, branchial defects, preauricular pits, and renal defects were 96.2%, 68.0%, 76.0%, and 12.5%, respectively. Meanwhile, in the largest study of 40 BOR syndrome families with *EYA1* mutations, the incidence of HL, branchial defects, preauricular pits, and renal defects was 98.5%, 68.5%, 83.6%, and 38.2%, respectively [4]. These findings suggest that there is no apparent difference in frequencies of representative phenotypes of BOR/BO syndrome, other than renal defects, between patients with *SIX1* and *EYA1* mutations.

We had not expected our patient to have BO syndrome, because she lacks the characteristic phenotype of BO syndrome. The other family members of the patient might have characteristic features, such as branchial and renal defects, but we were unable to analyze these people. However, it also appears that some patients with *SIX1* mutations reported in previous literature did not necessarily meet the diagnostic criteria for BOR syndrome reported by Chang et al. [4]. The presence of HL, a preauricular pit, and a positive family history for HL showed a high incidence in patients with *SIX1* mutations [10]. Therefore, it is worth considering a *SIX1* mutation even in a patient with familial HL and a preauricular pit.

The phenotypes of BO syndrome caused by *SIX1* mutations can include outer, middle, and inner ear anomalies, lacrimal duct stenosis, facial asymmetry, hypotonia, developmental delay, and mental retardation [5,9,10,12,14,15]. With regard to HL, it ranges from mild to profound in severity [10,12,14,16]. The audiogram shows bilateral sensorineural HL with or without symmetry in most patients, but some have an additional conductive component. The present patient was thought to have no apparent middle ear anomaly according to the findings of impedance audiometry and CT. Therefore, it is possible that the bilateral air–bone gaps are associated with EVA.

Although only a few reports have previously described progressive HL in individual cases with BOR/BO syndrome [17]; nevertheless, it can occur in some patients with *SIX1* mutations [5,8,10,12,14]. A clinical study in a large BOR syndrome family who had a *SIX1* mutation suggested that a progressive sensorineural component was associated with EVA [10,12]. Our patient with EVA had showed no apparent progressive HL during the 9-year follow-up period, but it cannot be ruled out that a progression of HL may occur in the future.

The present patient showed no fluctuating HL or vertigo. Although the bilateral normal caloric responses indicate a normal vestibular function, these findings cannot necessarily interpret the nonexistence of vertigo, because nearly 50% of all patients with Meniere's disease have normal caloric responses [18].

However, fluctuating HL or vertigo have not yet been clearly reported in any patients with *SIX1* mutations. Only one BOR patient was reported to show bilateral fluctuation of HL, but a genetic analysis was not performed [17]. These findings suggest that the fluctuating HL and vertigo are rare phenotypes in patients with BOR/BO syndrome, either with or without EVA. On the other hand, the fluctuation of HL and repetitive vertigo are characteristic symptoms in EVA syndromes including DFNB4/Pendred syndrome caused by *SLC26A4* mutations [19], and type 1 distal renal acidosis caused by *ATP6V1B1* mutations [20]. In patients with *ATP6V1B1* or *SLC26A4* mutations, the disruption of the endolymph pH homeostasis may cause an exacerbation of the audiovestibular function, because the homeostasis depends on the secretion of  $\text{HCO}_3^-$  and  $\text{H}^+$ , and the products of *SLC26A4* and *ATP6V1B1* are the  $\text{HCO}_3^-$  permeable anion exchanger pendrin and the B1 subunit of  $\text{H}^+$ -ATPase, respectively [20]. However, further study is still needed to clarify the nature of fluctuating HL and repetitive vertigo recognized in EVA patients.

The findings of DPOAEs and ECoChG in our present patient suggested cochlear HL. Although the histopathology of the temporal bone in a patient with a *SIX1* mutation has not been reported, mouse mutants may provide insight into the function of the inner ear. Heterozygous *Six1*-deficient (*Six1*<sup>+/-</sup>) mice show varying degrees of HL [7]. The major cause of the HL was thought to be conductive, because middle ear abnormalities including ossicle malformations were recognized in all *Six1*<sup>+/-</sup> mice with HL but the cochlea was morphologically normal in 18 of 22 *Six1*<sup>+/-</sup> ears. It might be possible that the *Six1*<sup>+/-</sup> mice had degeneration and/or loss of inner ear cells, but unfortunately the literature did not include the information. Catweasel (*Cwe*) mice were thought to be a suitable model for BO syndrome caused by *SIX1* mutations, because the mice had a missense mutation in the *Six1* domain [21]. Heterozygous *Cwe* (*Six1*<sup>*Cwe*/+</sup>) mice exhibited mild head tossing, probably due to a posterior crista defect. Although *Six1*<sup>*Cwe*/+</sup> mice showed normal Preyer reflexes, scanning electron microscopic studies of the organ of Corti revealed an ectopic second row of the inner hair cells in all turns of the cochlea, especially in the apical turn. Homozygous *Cwe* (*Six1*<sup>*Cwe/Cwe*</sup>) mice had severe phenotypes including no Preyer reflex, and showed truncated cochlea and semicircular canals as well as loss of hair cells in the cochlea, semicircular canals, and utricle. The present patient had no apparent inner ear anomaly other than EVA, but the decrease of DPOAE amplitudes and the elevation of CM detection thresholds might be associated with cochlear hair cell loss as seen in *Cwe* mice. Further studies are

needed to determine the true nature of the inner ear dysfunction of the syndrome.

## Conclusions

A reported missense mutation in *SIX1* was detected in a patient with HL who lacked the characteristic phenotype of BO syndrome. Although the true etiology remains unknown, the findings of audiovestibular testing showed cochlear HL but no apparent vestibular impairment. Further clinical studies are therefore needed to elucidate the association between EVA itself and both fluctuating HL and repetitive vertigo.

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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

## Longitudinal study of 29 patients with Meniere's disease with follow-up of 10 years or more (In commemoration of Professor Emeritus Isamu Watanabe)

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### Abstract

**Conclusions:** A final incidence of bilateral involvement was 20.7%. Episodic spells of vertigo were completely controlled in 23 of 29 patients, while 11 of 29 patients demonstrated over 70 dB hearing loss. **Objective:** To analyze the clinical course of 29 patients with Meniere's disease during follow-up of 10 years or more. **Methods:** The subjects were 29 patients with a mean follow-up of 18.3 years. The hearing level was measured by the pure tone average (PTA) of four frequencies at the initial and the final examination, and it was classified into four categories according to the American Academy of Otolaryngology-Head and Neck Society (AAO-HNS) criteria. The control of vertigo was evaluated by the modified AAO-HNS criteria. **Results:** At enrolment two patients had bilateral involvement. In the period of follow-up, bilateral involvement emerged in four more patients. The hearing levels at the final examinations were as follows: 3 patients, <25 dB; 6 patients, 26–40 dB; 9 patients, 41–70 dB; and 11 patients, >70 dB. The control of vertigo according to the modified AAO-HNS guideline was class A in 23 patients, class B in 2 patients, and class C in 1 patient; the remaining 3 patients could not be evaluated.

**Keywords:** Vertigo, hearing loss, long-term outcome, bilateral involvement

### Introduction

Meniere's disease is not a life-threatening disease, but its major clinical symptoms such as recurrent vertiginous spells and hearing impairment significantly affect patients' quality of life. Under these circumstances, it is relevant to know the long-term clinical outcome for the treatment of patients with Meniere's disease. There have been numerous publications in which the long-term clinical course of Meniere's disease has been studied [1–12]. However, the long-term clinical course (follow-up of 10 years or more) has only been investigated in a limited number of papers [1,3,5,9].

Professor Emeritus Isamu Watanabe, Department of Otolaryngology, Tokyo Medical and Dental University, who devoted his life to the study of Meniere's

disease, passed away on September 28, 2009. He had examined many patients with Meniere's disease for a long time. In commemoration of his achievements, we retrospectively studied the longitudinal outcomes of 29 patients with Meniere's disease who had been closely examined by Professor Emeritus Watanabe and followed up for more than 10 years. The present study aimed to evaluate the long-term course of Meniere's disease with respect to the control of vertiginous spells and hearing loss, which he had intended to clarify.

### Material and methods

We performed a retrospective chart review of 29 patients with Meniere's disease whom Professor

Emeritus Watanabe had consecutively examined from February 1949 to July 1997 at the Department of Otolaryngology, Tokyo Medical and Dental University, Kudanzaka Hospital, and Soka Municipal Hospital. All of the cases accorded with the AAO-HNS criteria for a diagnosis of Meniere's disease [13], and had been followed up for periods ranging from 10 to 43 years with the mean follow-up being 18.3 years.

The patients consisted of 13 males and 16 females, and their average age at the initial examination was 49.3 years.

The control of vertiginous spells was evaluated by modifying the classification by AAO-HNS (1995). The numerical value for vertigo spells was calculated by dividing the average number of definitive vertiginous spells per month during the last 6-month period before the last examination by the average number of definitive vertiginous spells per month during the 6-month period before the initial examination. Based on this numerical value, the control of vertiginous spells was classified into six classes [13]. The hearing level was calculated by the pure tone average (PTA) of 500, 1000, 2000, and 4000 Hz instead of the four frequencies (500, 1000, 2000, 3000 Hz) proposed by AAO-HNS for reporting hearing outcomes because the hearing level at 3000 Hz has not been measured in the past in Japan [13]. The hearing level at the initial examination was evaluated by the PTA of the four frequencies of the worst audiogram during the interval of 6 months after the initial visit. The final PTA at the final examination was the worst audiogram during the interval of 6 months before and including the last visit. For the analysis of the hearing level in patients with bilateral Meniere disease we chose the worst PTA between two ears. The PTA at the initial and the final examination was classified into four categories (stage 1, <25 dB; stage 2, 26–40 dB; stage 3, 41–70 dB; stage 4, >70 dB) according to AAO-HNS criteria [13]. The clinical outcome was evaluated by the functional outcome according to the classification of vertigo spell and staging of hearing by AAO-HNS.

The initial treatment for patients with frequent episodes of vertiginous spells included both conventional dietary modification therapy and medication. Most patients received diuretic medication such as isosorbide, and/or vasodilator medication including betahistine. Surgical treatment was only performed for patients whose vertiginous spells precluded their activities of daily life in spite of the medication. Three patients received surgical treatment, which comprised labyrinthectomy, transection of the chorda tympani, and ventilation tube insertion, respectively. Because the period and combination of medication varied significantly among patients, we could not analyze

the relation between the type of medication and clinical outcome. Nevertheless, 26 (89.6%) of 29 cases were not subjected to any surgical treatment. Hence, our sample mainly indicates the progression of the disease without any surgical treatment.

All the above procedures were performed in accordance with the institute guidelines and the ethical standards of the Helsinki Declaration of 1975, as revised in 1983.

## Results

At the initial visit 27 patients had unilateral Meniere's disease and 2 patients had bilateral Meniere's disease. In the period of follow-up, bilateral involvement emerged at 11 and 31 years after onset in two patients and at undetermined periods after onset in another two. Their mean and median age at the first vertiginous attack was 51.3 and 59 years, respectively, and their mean follow-up period was 22.5 years ( $n = 6$ ). At the initial visit, cases with bilateral involvement comprised only 6.9% of the total, while they comprised 20.7% after over 10 years of follow-up.

The hearing level at the initial examinations was obtained for 24 patients; these data are shown in Table I. Most patients experienced deterioration in hearing during follow-up, with final hearing levels as follows: 3 patients, stage 1 (<25 dB); 6 patients, stage 2 (26–40 dB), 9 patients, stage 3 (41–70 dB); and 11 patients, stage 4 (>70 dB) (Table I). The hearing level in patients with bilateral disease similarly became worse over the follow-up period of more than 10 years (Table II).

The control of vertigo according to the modified AAO-HNS guidelines showed class A control in 23 patients, class B in 2 patients, and class C in 1 patient; the remaining 3 patients could not be evaluated (Table III). No patient was classified in class D, E, or F at the last examination. Vertiginous spells were also well controlled in patients with bilateral Meniere's disease: five cases were classified in class A, and one patient was in class B (Table IV).

Taken together, in 23 (79.3%) of 29 patients, including patients with bilateral disease, vertiginous spells were completely controlled at 10 or more years of follow-up, while the long-term outcome of hearing was not well preserved.

## Discussion

Meniere's disease has been well known to diminish patients' quality of life because of hearing disorder and disequilibrium. However, its pathophysiology remains uncertain, and no optimal therapy has yet been established. Further, its natural history and

Table I. Initial and final pure tone average (PTA) according to modified AAO-HNS criteria.

	Initial PTA		Final PTA			
	Number		Stage 1	Stage 2	Stage 3	Stage 4
Stage 1	5	→	3	2	0	0
Stage 2	8	→	0	3	4	1
Stage 3	9	→	0	1	3	5
Stage 4	2	→	0	0	0	2
Unknown	5	→	0	0	2	3
Total	29	→	3	6	9	11

prognosis also remain unclear. Numerous reports have been published in order to clarify the natural course and/or prognosis of Meniere's disease [1–12]; however, almost all patients with Meniere's disease have been treated by medication as well as surgical treatment, which precludes evaluation of the disease's natural course. In addition, there has been a limited number of reports in which long-term (>10 years) longitudinal analysis has been applied to cases with Meniere's disease [1,3,5,9].

Professor Emeritus Isamu Watanabe, Department of Otolaryngology, Tokyo Medical and Dental University, examined and followed many patients with Meniere's disease. His life's work was to study the long-term clinical course of Meniere's disease. We retrospectively studied the longitudinal courses of patients with Meniere's disease who had been examined by Professor Emeritus Watanabe with at least 10 years' follow-up, and by doing so, hope to commemorate his achievements. In this retrospective study, all patients have received medication during their follow-up, and three underwent surgical procedures. Many patients were apparently lost to follow-up before 10 years. Therefore, we cannot demonstrate the true natural course of Meniere's disease, and our analysis may be based on data with a selection

bias. In spite of these shortcomings, our data are worthy of evaluation because they were obtained by the distinguished researcher Professor Isamu Watanabe, who was known for his meticulous lifelong study of Meniere's disease [14–16].

Our analysis shows that the long-term outcome for the control of vertigo was complete in 79.3% of patients with Meniere's disease. Among previous studies describing at least 10 years of follow-up, Green et al. [3] reported that half of 98 cases were free from vertiginous spells at 14 or more years of follow-up. Of the 234 patients who underwent endolymphatic sac shunt surgery in the study by Telischi et al., 147 patients (62.8%) did not undergo any further surgery to control vertigo for at least 10 years (their mean follow-up was 13.5 years) [5]. Tewary et al. [9] reported that episodic vertigo was fully controlled in 26 (96.3%) of 27 cases who underwent vestibular nerve section during 10–22-year follow-up with a mean of 16 years. Several reports attempted to demonstrate the timing when the frequency of vertigo declines. Swedish researchers reported that the frequency of attacks decreased after 20 years of disease [2,17]. Green et al. [3] concluded that the point of vertiginous spell stabilization in Meniere's disease lay somewhere between onset

Table II. Initial and final pure tone average (PTA) of bilateral disease according to modified AAO-HNS criteria.

	Initial PTA		Final PTA			
	Number		Stage 1	Stage 2	Stage 3	Stage 4
Stage 1	0	→	0	0	0	0
Stage 2	2	→	0	0	2	0
Stage 3	1	→	0	0	0	1
Stage 4	2	→	0	0	0	2
Unknown	1	→	0	0	0	1
Total	6	→	0	0	2	4



Table III. Clinical outcome according to modified AAO-HNS criteria.

Vertiginous spell	Final PTA				Total
	Stage 1	Stage 2	Stage 3	Stage 4	
Class A	3	4	6	10	23
Class B	0	1	1	0	2
Class C	0	0	1	0	1
Class D, E, F	0	0	0	0	0
Not evaluated	0	1	1	1	3
Total	3	6	9	11	29

PTA, pure tone average.

and the ninth year of disease. Perez-Garrigues et al. [11] performed a prospective longitudinal study of 510 patients with Meniere's disease between January 1999 and December 2006 and found that the frequency of episodes of vertigo each year showed a rapid decline over the first 8 years. The percentage of patients who did not experience episodes of vertigo increased during the 15-year follow-up as the disease progressed. In contrast to these studies, Havia and Kentala [10] reported that in a group of 142 patients with disease durations of 5 months to 10 years, those with longer disease durations did not necessarily experience fewer incidents of vertiginous spell than those with shorter durations. Their report showed that the number of patients reporting continuous vertigo ranged from 0 to 4%, but began to grow after a duration of 10 years, reaching 21% among 17 patients who had had Meniere's disease for 20 years. However, no significant differences were observed in the mean attack frequency between different duration groups. Further, Tokumasu et al. [8] reported that the frequency of vertigo declined over the long-term follow-up, but 5 of 28 cases with a mean follow-up of 7.25 years experienced more than 10 episodes of vertigo per year 10 years after their first spell of vertigo, suggesting that the frequency of vertigo tends to decline, but that some cases continue to experience

frequent spells even more than 10 years after their first attack. When we evaluate these data, we have to consider that there were fewer patients with long-term follow-up than short-term follow-up and that the patients with persistent symptoms often sought medical treatment for a longer period than those with fewer symptoms, thereby generating a selection bias.

The present study demonstrated unfavorable results for hearing levels in patients with follow-up of  $\geq 10$  years. Twenty (69.0%) of 29 patients were classified into groups with hearing loss of more than 41 dB. Eleven of these patients (37.9%) demonstrated severe hearing loss of over 70 dB. Similar deterioration in hearing has been previously reported for cases with long disease duration. According to Stahle et al. [2] hearing deteriorated and 82% of the patients demonstrated a mean hearing loss (250–6000 Hz) of more than 50 dB after 21 years. Green et al. [3] reported a deterioration in hearing in 21% of 98 patients with follow-up periods of 14 years or more. Huang et al. [4] reported that PTA of three frequencies (500, 1000, and 2000 Hz) showed a decline from 42.1 dB to 52.3 dB over a period of 12 years from data of 809 patients with endolymphatic sac shunt surgery. Tokumasu et al. [7] reported that the worst PTA of

Table IV. Clinical outcome of bilateral Meniere's disease according to modified AAO-HNS criteria.

Vertiginous spell	Final PTA				Total
	Stage 1	Stage 2	Stage 3	Stage 4	
Class A	0	0	1	4	5
Class B	0	0	1	0	1
Class C	0	0	0	0	0
Class D, E, F	0	0	0	0	0
Total	0	0	2	4	6

four frequencies (250, 500, 1000, and 2000Hz) dropped from 35.3 dB at less than 1 year of disease duration to 51.5 dB at 15 years or more duration. Tewary et al. [9] evaluated 10–22-year follow-up data of hearing in 25 patients who underwent vestibular nerve sections, and they demonstrated an average deterioration of 15 dB at 10 years, 23 dB at 15 years, and 29 dB at 20 years. Based on their results they concluded that vestibular neurectomy did nothing to alter the course of Meniere's disease. Kotimäki et al. [18] created a multivariable model in order to clarify the factor that most influences the progression of hearing impairment. They found that hearing impairment in Meniere's disease appeared to increase linearly with the duration of the disease for patients <50 years of age, but in older subjects the effect of disease duration decreased.

In the present study, bilateral involvement increased from 6.9% to 20.7% over a 10-year follow-up. This incidence is relatively low compared with those in the previous studies. Stahle [19] reported that bilateral involvement increased with the duration of the disease. His data showed that bilateral disease occurred in 6 (8.2%) of 73 cases at the duration of 0–2 years, while it increased to 12 (20.3%) of 59 cases at the disease duration of 14 years or more. His subsequent study demonstrated that the incidence of bilateral involvement increased from 1.9% [3] of 161 initial cases to 47% of the 34 patients who were followed up for at least 20 years [2,17]. Green et al. [3] reported that bilateral disease was present initially in 13% and developed subsequently in 48% of patients by the 14-year follow-up. Tokumasu et al. [7] reported that bilateral disease was observed in 2 (12.5%) of 16 cases with less than a 1-year duration of Meniere's disease, but increased to 4 (33.3%) of 12 cases with disease duration of 15 years or more. In a more recent study, the prevalence of bilateral disease was 16% (38 of 243 cases) at the initial study and 44% among the 16 patients with more than 20 years of follow-up [10].

## Conclusion

We performed a retrospective chart review of 29 patients with Meniere's disease diagnosed by AAO-HNS criteria who had been longitudinally followed up for more than 10 years. The incidence of bilateral involvement became 20.7% (6 of 29 patients), lower than that in other studies, with bilateral involvement newly developing in four patients with a mean follow-up period of 22.5 years. Episodic spells of vertigo were completely controlled in 23 (79.3%) of these 29 patients, in accordance with the data in previous studies. At the same time, 11 (37.9%) of these 29

patients demonstrated over 70 dB hearing loss in the course of the long-term follow-up. This hearing deterioration is also consistent with data in the previous reports.

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