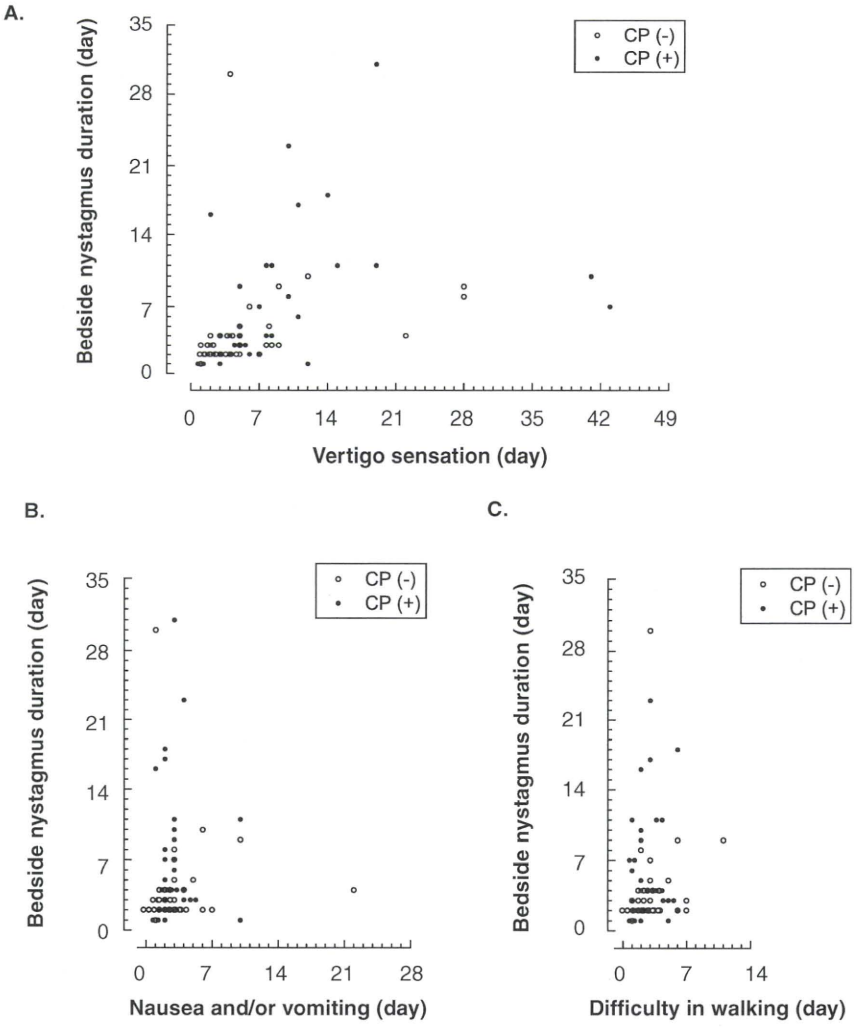

Figure 3. Relationships between resolution periods of acute symptoms and duration of bedside spontaneous nystagmus (SN). (A) Vertigo sensation. (B) Nausea and vomiting. (C) Difficulty in walking. Patients with significant canal paresis (CP) (●) and those without CP (○) are plotted separately. Longer duration of bedside SN correlated with longer resolution of vertigo sensation.

sensation varied widely among the patients (Table I and Figure 3). Correlations were observed between nausea/vomiting and the other two symptoms (correlation coefficient: vertigo sensation 0.403, $p < 0.001$; difficulty in walking 0.673, $p < 0.001$). Longer SN duration correlated with a longer resolution period of vertigo sensation (correlation coefficient 0.357, $p = 0.002$). No correlations were found between SN and the other two symptoms (correlation coefficient: nausea/vomiting −0.005, $p = 0.969$; difficulty in walking 0.110, $p = 0.390$).

Discussion

In clinical practice, a patient with a first episode of acute vertigo is often referred to a non-specialist, such as a general or an emergency physician, depending on the medical context among different countries and districts [5–7]. A large office-based survey by the National Ambulatory Medical Care reported that almost 70% of all outpatients with dizziness, who were aged 25 years and older, were initially examined by primary care physicians, such as general practitioners, family physicians, and general internists, and only 10% were examined by specialists such as otolaryngologists and neurologists [5]. Of all the patients who were referred to primary care physicians with the chief complaint of dizziness, 1.5% were hospitalized and 4.4% were referred to a specialist [5]. Vertigo/dizziness accounts for 2.5–3.5% of all the visits to the emergency departments [6,7]. Several reports have reported a clinically valid management of neurological emergencies; the focus would usually be on determining whether vertigo is related to a life-threatening condition [8–10]. Once a diagnosis of

vertigo of peripheral origin is made, it is best to estimate the evidence of vestibular hypofunction as the next step.

SN, characterized as horizontal, direction-fixed, and suppressed with fixation, in the absence of other neurological symptoms or signs reflects an imbalance in tonic neural activity in the vestibular nuclei due to sudden loss of input unilaterally from the labyrinth or the vestibular nerve. This study indicates that the resolution period of bedside SN could provide an indication of CP on a particular day. For instance, if SN presents on the fifth day after onset, the suspicion of it being CP is estimated to be approximately 70% (Figure 2B). A prospective study with 6 months follow-up showed that the degree of asymmetry of the caloric CP and age would influence balance performance and perceived symptoms after acute unilateral vestibular disorders [11]. A primary care physician may consult a specialist regarding the confirmation and degree of CP by means of a laboratory caloric test and additional treatment on the third day or later. A specific exercise improves residual imbalance and persistent dizziness [12–14]. Corticosteroids may be a treatment option because their administration in the early stage may improve the recovery of peripheral vestibular function in the long term [15] and facilitate central vestibular compensation [16,17].

Recently, Yagi et al. [18] analyzed the rotation axis of SN during the early stage of vestibular neuritis by means of an infrared charge-coupled device (CCD) camera. They determined that the rotation axis corresponds to the pathology of the superior vestibular nerve branch in all patients examined. In general, the axis initially tends to be mixed horizontal-torsional, and subsequently its orientation gradually changes during the recovery course of the early stage, as the anterior canal branch recovers faster than the horizontal canal branch, and ultimately draws closer to the horizontal [18]. This phenomenon is noticeable when the peripheral vestibular nystagmus is carefully observed using an infrared CCD camera. As mentioned in the Methods section, it is important to keep in mind that central vestibular disorder occasionally presents with a direction-fixed pure horizontal nystagmus [19,20] and, although rare, presents with a direction-fixed mixed horizontal-torsional nystagmus [21].

This study also examined symptomatic outcomes of patients who had experienced the first episode of acute isolated vertigo and direction-fixed horizontal nystagmus with symptoms severe enough to warrant hospitalization. Of the acute symptoms, nausea and/or vomiting (vestibulo-autonomic response) and gait impairment (vestibulo-spinal response) resolved relatively quickly in most patients, but the resolution period of vertigo (vestibular perception) varied widely among the patients. The duration of bedside SN (vestibulo-ocular response) was associated with the resolution of vertigo sensation, whereas it was not associated with the other two symptoms.

The presence of SN in vestibular disorders is a fundamental examination, which can be observed at the bedside in a matter of minutes without difficulty. In conclusion, observation of SN during the early stage of acute peripheral vestibular disorders provides useful information to non-specialists in predicting vestibular dysfunction, the timing of consultation, and planning of additional treatment.

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ORIGINAL ARTICLE

Long-term effects of the Meniett device in Japanese patients with Meniere's disease and delayed endolymphatic hydrops reported by the Middle Ear Pressure Treatment Research Group of Japan

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Abstract

Conclusion: The Meniett device is a minimally invasive and safe treatment that may be used to provide longer-term reduction of vestibular symptoms in patients with delayed endolymphatic hydrops (DEH) as well as those with Meniere's disease (MD). *Objective:* The effects of the Meniett device were evaluated in patients with a diagnosis of definite MD or DEH according to the 1995 AAO-HNS criteria. *Methods:* Twenty-nine ears of 28 patients with MD and 5 ears of 5 patients with DEH (ipsilateral type 4, contralateral type 1) were treated with the Meniett device by the Middle Ear Pressure Treatment Research Group of Japan. All of the patients had failed to respond to medical treatment including diuretics before the pressure treatment. *Results:* Sixteen (57%) patients with MD and all five (100%) patients with DEH remained entirely free from vertigo spells; nine (32%) patients with MD responded with a significant decrease in the frequency of vertigo spells. In regard to hearing, 25 ears (74%: MD, $n = 21$; ipsilateral DEH, $n = 4$) had stable hearing levels; only 4 ears (12%: MD, $n = 3$; contralateral DEH, $n = 1$) showed a significant hearing improvement. No complications were attributable to the Meniett device.

Keywords: *Pressure treatment, vertigo, vestibular symptoms*

Introduction

The Meniett device is a low-pressure, portable delivery system used to treat patients with Meniere's disease (MD) who suffer from recurrent episodic vertigo that is not controlled by conservative therapy. To date, in non-Japanese populations, longer-term follow-up studies [1–9] have demonstrated the long-term efficacy of the Meniett device on intractable vertigo in patients with MD. However, the results of hearing outcomes after Meniett therapy are contradictory and not conclusive. There has been no long-term follow-up study to evaluate the effect of Meniett devices on both vertigo and hearing in Japanese patients with intractable MD.

Delayed endolymphatic hydrops (DEH) is one form of secondary endolymphatic hydrops. The clinical entity of DEH was first defined by Schuknecht in 1978 [10]. It is characterized by the development of symptoms consistent with endolymphatic hydrops either ipsilateral or contralateral to an ear with a profound hearing loss. In the ipsilateral type of DEH, when recurrent episodic vertigo is not controlled by conservative therapy, labyrinthectomy and

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vestibular neurectomy on the deaf ear can be considered as a cure [11]. However, such surgical treatments are not available for recurrent episodic vertigo in contralateral DEH. In 2003, short-term effects on DEH following use of the Meniett device were first reported in Japanese patients [12]. So far, there have not been any long-term follow-up studies to evaluate the effect of this device in patients with either ipsilateral or contralateral types of intractable DEH [13].

The Meniett device has not been cleared by the Ministry of Health, Labour and Welfare of Japan; therefore, ear, nose, and throat (ENT) specialists have been required to import the devices themselves at the time of use in Japan. Under these circumstances we commenced an independent investigation in October 2001 of the short- and long-term effects of Meniett devices after approval from the institutional review board of the University of Toyama. To investigate the efficacy and safety of the Meniett device in Japanese patients with MD and DEH, the Middle Ear Pressure Treatment Research Group of Japan was convened in July 2005, and investigation of the Meniett device was started subsequently in several other institutions. The aim of our multicenter study was to investigate the long-term effects of Meniett devices in Japanese patients with medically intractable MD and DEH by use of outcome criteria devised by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology, Head and Neck Surgery in 1995 (1995 AAO-HNS criteria) [14].

Material and methods

Patients

This study comprised 28 patients with a diagnosis of definite MD, and 5 patients with DEH from 3 university hospitals, 3 general hospitals, and 1 private clinic, and whose ENT surgeons were members of the Middle Ear Pressure Treatment Research Group of Japan (Table I). MD patients were aged between 32 and 81 years (mean 57 years), and DEH patients were aged between 24 and 45 years (mean 35 years). In the MD group, 23 patients were unilateral, and 5 patients were bilateral sufferers. In the DEH group, four patients had the ipsilateral type and one patient had the contralateral type. The diagnosis was based on the history of the disease, neuro-otologic examinations, and audiometric measurements including pure-tone thresholds. The diagnostic criteria for MD defined in 1976 by the Meniere's Disease Research Committee of Japan and supported by the Ministry of Health, Labour and Welfare of Japan [15] were used. The diagnosis of definite MD was based on the coexistence of recurrent episodic vertigo (definitive spells) and fluctuating cochlear symptoms including hearing loss, tinnitus, and aural pressure. The diagnostic criteria for DEH proposed by the committee of the Japan Society for Equilibrium Research in 1987 [16] were used. The diagnosis of DEH was based on the presence of a precedent profound hearing loss (defined as a pure-tone average (PTA) of > 90 dB over the 500, 1000, and 2000 Hz frequencies) followed subsequently by the onset of recurrent episodic vertigo (ipsilateral type) and of fluctuating hearing loss in the hearing ear with or without recurrent episodic vertigo (contralateral type). As in MD, recurrent episodic vertigo in DEH occurs in definitive spells. This study was approved by the ethics committee of the University of Toyama. Informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

Table I. Characteristics of MD and DEH cases.

Characteristics	MD	DEH
No. of cases	28	5
Age (years), mean ± SD (range)	57.2 ± 16.0 (32–81)	35.88 ± 10.4 (24–45)
Female (%)	62.5	40
Affected side, one/both	23/5*	5/0
Affected ear, right/left	10/13	4/1
MD stage		
Stage 1 (≤25 dB)	1	
Stage 2 (26–40 dB)	6*	
Stage 3 (41–70 dB)	13*	
Stage 4 (>70 dB)	9	
DEH		
Ipsilateral		4
Contralateral		1

MD, Meniere's disease; DEH, delayed endolymphatic hydrops.
*In one of five patients with bilateral MD who used the Meniett device bilaterally, right and left ears were classified into stage 2 and 3, respectively.

Treatment and follow-up

All patients included in this study had previously received conservative treatment including diuretics. A ventilation tube was inserted in all patients, and a new evaluation was made about 4 weeks later, with pressure treatment commenced if the patients still presented with active vestibular symptoms.

The pressure pulses were delivered to the ear canal from an air pressure generator via a close-fitting cuff. Patients received training in how to apply pressure pulses and how to use the pressure device at home.

Three exposures were applied during the day. The patients were usually given the pressure treatment for at least 3 months (mean duration 12.8 months, SD 10.7 months). In bilateral MD patients, one of five patients used the Meniett device bilaterally, while the four remaining patients used it unilaterally. The frequency of attacks was reported during a period of 6 months before and 18–24 months after the start of treatment. We calculated numerical values and categorized each patient into one of six classes (A–F) according to the AAO-HNS guidelines published in 1995 [14].

Hearing was assessed utilizing PTA threshold at the frequencies of 500, 1000, and 2000 Hz before and after initiation of the Meniett device; 3000 Hz thresholds are rarely performed in Japan. PTA was evaluated according to the following equation: PTA = (hearing threshold of 500 Hz + 2 × (hearing threshold of 1000 Hz) + hearing threshold of 2000 Hz)/4. According to the 1995 AAO-HNS guidelines, the worst preoperative PTA for 6 months before treatment was compared with the worst postoperative PTA between 18 and 24 months after treatment. As per the guidelines, we considered a change of 10 dB or more as clinically significant. We also categorized each patient into one of four stages (stages 1–4) based on the 1995 AAO-HNS staging system [14].

The frequency of attacks, numerical values, vertigo improvement class, averaged PTA, and hearing change before and after treatment were analyzed. In regard to hearing assessment, 34 ears of 33 patients with MD or DEH treated by the Meniett device were evaluated. Only one of five patients with bilateral MD used the Meniett device bilaterally. For statistical analysis, the Wilcoxon matched-pair test and Mann-Whitney U test were performed with StatView for Windows (version 4.5, Abacus Concepts, Berkeley, CA, USA).

Results

Sixteen of 28 patients with MD and all 5 patients with DEH experienced freedom from definitive spells (class A response); 9 patients with MD responded with a significant decrease in the frequency of definitive spells (class B response); 2 patients with MD experienced limited control of definitive spells (class C response); and 1 patient with MD did not respond to pressure treatment (class D response) (Table II). Statistically, the average frequency of vertigo after treatment had significantly reduced in both MD and DEH (Table III). Regarding hearing ability, in 34 ears of 33 patients with MD or DEH treated by the Meniett device, 4 ears (unilateral MD, $n = 2$; bilateral MD, $n = 1$; contralateral DEH, $n = 1$) showed a significant hearing improvement of more than 10 dB; 25 ears (unilateral MD, $n = 17$; bilateral MD, $n = 4$; ipsilateral DEH, $n = 4$) had stable hearing levels; and 5 ears (unilateral MD, $n = 4$; bilateral MD, $n = 1$) showed significant hearing deterioration of more than 10 dB (Table IV). The hearing of one ear in the patient with unilateral MD in stage 1 was unchanged. In stage 2, the hearing of four ears (unilateral MD, $n = 2$; bilateral MD, $n = 2$) was unchanged, and in one ear of the patient with unilateral MD, hearing had deteriorated. In stage 3, the hearing of three ears (unilateral MD, $n = 2$; bilateral MD, $n = 1$) was improved; in six ears (unilateral MD, $n = 4$; bilateral MD, $n = 2$), it was unchanged; and in four ears (unilateral MD, $n = 3$; bilateral MD, $n = 1$), hearing was deteriorated. In stage 4, the hearing of 10 ears in patients with unilateral MD was unchanged. Of those with a class A response, 2 ears (unilateral MD, $n = 1$; bilateral MD, $n = 1$) were recorded with improved hearing; 13 ears (unilateral MD, $n = 10$; bilateral MD, $n = 3$) had unchanged hearing; and in 2 ears (unilateral MD,

Table II. Numerical values and vertigo improvement class of MD and DEH.

		MD		DEH	
Numerical value	Class	Unilateral	Bilateral	Ipsilateral	Contralateral
0	A	11 (48%)	5 (100%)	4 (100%)	1 (100%)
1–40	B	9 (39%)	0	0	0
41–80	C	2 (9%)	0	0	0
80–120	D	1 (4%)	0	0	0
>120	E	0	0	0	0
Secondary treatment initiated due to disability from vertigo	F	0	0	0	0
Total		23 (100%)	5 (100%)	4 (100%)	4 (100%)

MD, Meniere's disease; DEH, delayed endolymphatic hydrops.

Table III. Incidences of vertigo per month before and after treatment.

Parameter	MD (n = 28)	DEH (n = 5)
Before treatment*	2.6 (2.0) 0.2–8.3	1.7 (0.9) 0.2–2.2
After treatment*	0.4 (0.8) 0–3.3	0
p value†	<0.0001	0.043

MD, Meniere's disease; DEH, delayed endolymphatic hydrops.
*Averaged incidences of vertigo per month (SD) range of incidences of vertigo per month
†Wilcoxon signed rank test.

Table IV. Hearing changes with MD and DEH.

Hearing status	MD		DEH	
	Unilateral	Bilateral	Ipsilateral	Contralateral
Improved	2 (9%)	1 (17%)	0	1 (100%)
Unchanged	17 (74%)	4 (66%)*	4 (100%)	0
Deteriorated	4 (17%)	1 (17%)*	0	0
Total	23 (100%)	6 (100%)*	4 (100%)	1 (100%)

*In one of five patients with bilateral MD who used the Meniett device bilaterally, hearing outcome of right and left ears was classified into unchanged and deteriorated hearing, respectively.

n = 1; bilateral MD, n = 1), hearing ability had worsened. Among the nonclass A responses, the numbers of ears with unchanged or deteriorated hearing were seven (unilateral MD, n = 7) and two (unilateral MD, n = 2), respectively. There was no change in the average PTA before and after treatment in spite of the differences in the three stages (Table V) and two classes (Table VI). No complications were attributable to the Meniett device. In four ears of four patients, persistent perforation after tube insertion remained at the end of the pressure treatment. However, the patients refused tympanoplasty.

Discussion

To date, there have been four 2-year follow-up studies evaluating the effect of Meniett devices on definitive spells of MD following the class difference as defined in the 1995 AAO-HNS criteria (Table VII). Densert and Sass [1] showed that 19 of 37 Swedish patients who used the Meniett device experienced freedom from episodes of vertigo (class A response), and 15 patients reported a significant decrease in the frequency of vertigo (class B response). Gates et al. [4] reported that 26 of 58 US patients showed a class A response, and 13 patients showed a class B response. Barbara et al. [5] described that 25 of 36 Italian patients reported a class A response, and 11 showed a negative outcome. In the study by Huang et al. [8], 10 of 18 Chinese patients showed a class A response, and 8 showed a class B response. In the present study, 16 of 28 Japanese patients with MD showed a class A response, and 9 showed a class B response (Table II). The proportions of classes A and classes A and B in these studies ranged from 45% to 69% and from 69% to 100%, respectively. These findings suggest that, notwithstanding racial differences, Meniett devices may provide longer-term freedom or a reduction in definitive spells in the majority of patients with intractable MD according to the AAO-HNS criteria.

There are two longer-term studies evaluating the statistical effect of Meniett devices on the frequency of vertigo in patients with MD. In a 2-year follow-up, Densert and Sass [1] reported that the frequency of vertigo per month after treatment was significantly lower than before treatment, in spite of the difference in the stage. Dornhoffer and King in the USA [7] showed that the number of vertigo spells during the 6 months preceding the fourth anniversary post treatment was significantly lower than before treatment. In the present study, the incidence of vertigo per month

Table V. Hearing changes and levels before and after treatment of MD.

Hearing status	MD		
	Stages 1 and 2 (n = 6)*	Stage 3 (n = 13)*	Stage 4 (n = 10)
Improved	0	3 (23%)	0
Unchanged	5 (83%)	6 (46%)	10 (100%)
Deteriorated	1 (17%)	4 (31%)	0
Before treatment†	34 (5) 25–40	56 (10) 41–69	83 (13) 73–115
After treatment†	34 (18) 18–67	60 (23) 15–109	82 (14) 68–113
Wilcoxon's signed rank test	NS	NS	NS

*In one of five patients with bilateral MD who used the Meniett device bilaterally, right and left ears were classified into stage 2 and 3, respectively.
†Averaged hearing level (SD) range of hearing level (dB).

Table VI. Hearing change and levels before and after treatment of MD.

Hearing status	Class A (n = 17)*	Nonclass A (n = 12)
Improved	2 (12%)	1 (8%)
Unchanged	13 (76%)	8 (67%)
Deteriorated	2 (12%)	3 (25%)
Before treatment†	56 (16) 32–81	66 (26) 25–115
After treatment†	57 (21) 15–80	70 (31) 18–113
Wilcoxon's signed rank test	NS	NS

*In one of five patients with bilateral MD who used the Meniett device bilaterally, the numerical value was 0 (class A).
†Averaged hearing level (SD) range of hearing level (dB).

after treatment was significantly lower than before treatment in the Japanese patients with MD. Our results support those of previous studies and suggest on the basis of the statistical analysis that the Meniett device may reduce the frequency of vertigo over the longer term in patients with intractable MD.

It is clear that the Meniett device can reduce vertiginous symptoms and maintain an improvement in patients with medically intractable MD. Recently, the proportion of elderly Japanese patients with MD was quoted as 27% [17], and this could increase in the future due to the rapid aging of the population. Because vestibular compensation becomes more difficult with advancing age [18], destructive intervention is more likely to cause disequilibrium after elderly patients are treated [19]. Therefore, from a practical point of view, a Meniett device should be considered first of all as an intermediate step before surgical or chemical intervention, especially in the management of elderly MD patients [1].

There are three longer-term studies evaluating the Meniett device on hearing outcomes in patients with MD according to the 1995 AAO-HNS criteria (Table VIII). In an average 18-month follow-up, Rajan et al. [2] in Australia reported that the hearing had improved in 3 of 17 ears and remained unchanged in 14 ears. Huang et al. [8] noted that the hearing in 9 of 17 ears had improved, and it had not changed in 8 ears during a 2-year follow-up. Dornhoffer and King [7] showed that the hearing in two of six ears was unchanged, whereas after an average of 3 years of treatment, hearing had deteriorated in four ears. In the present study, 3 of 29 ears were recorded with improved hearing, 21 ears had unchanged hearing, and 5 ears showed worse hearing. The number of ears with improved, unchanged, and deteriorated hearing in these studies is thus summarized as 15 (22%), 45 (65%), and 9 (13%), respectively. These findings suggest that Meniett devices may induce insignificant changes to hearing in the majority of ears treated in patients with MD according to the AAO-HNS criteria.

In 1989, Stahle et al. [20] reported the long-term results of the natural course of Meniere's disease in a series of 161 patients followed for at least 9–12 years. After 5–10 years of the disease, the hearing loss stopped at a hearing threshold of 50–60 dB. After 20 years, 82% of their subjects still exhibited a mean hearing loss of 50 dB. With such poor levels of hearing, further deterioration is less likely, and therefore, this possibly contributes to the lack of significant changes in hearing after treatment. Similarly, where there are good levels of hearing, further improvement is hard to observe, and therefore, possibly also contributes to the lack of significant changes in hearing after treatment. Indeed, all patients with improved hearing were classified into stage 3 as in the study by Densert and Sass [1]. The Meniett device may have an advantage in the early stages of MD, before irreversible damage occurs to the inner ear sensory systems [1]. Before deciding whether this device can be offered as a reasonable treatment modality for hearing preservation, hearing results must be shown consistently to be equal to or better than results in patients undergoing other treatment, and both longer

Table VII. Vertigo improvement class according to AAO-HNS criteria in 2-year follow-up studies of MD.

	Vertigo improvement class							
Study	A	B	C	D	E	F	NonA	Total
Densert & Sass [1]	19 (51%)	15 (41%)	0	0	0	3 (8%)		37 (100%)
Gates et al. [4]	26 (45%)	13 (32%)	4 (7%)	0	1 (2%)	14 (24%)		58 (100%)
Barbara et al. [5]	25 (69%)						11 (31%)*	36 (100%)
Huang et al. [8]	10 (56%)	8 (44%)	0	0	0	0		18 (100%)
Present study	16 (57%)	9 (32%)	2 (7%)	1 (4%)	0	0		28 (100%)
Total	96	45	6	1	1	17	11	177

*Negative response.

Table VIII. Hearing outcomes according to AAO-HNS criteria in longer-term follow-up studies of MD.

	Hearing status			
Study	Improved	Unchanged	Deteriorated	Total
Rajan et al. [2]	3 (18%)	14 (82%)		17 (100%)
Dornhoffer & King [7]		2 (34%)	4 (66%)	6 (100%)
Huang et al. [8]	9 (53%)	8 (47%)		17 (100%)
Present study	3 (11%)	21 (71%)	5 (18%)	29 (100%)
Total	15 (22%)	45 (65%)	9 (13%)	69 (100%)

follow-up periods and larger numbers of patients must be examined.

In ipsilateral DEH, when recurrent episodic vertigo is not controlled by conservative therapy, labyrinthectomy and vestibular neurectomy on the deaf ear can be considered as a curative treatment [11]. However, such surgical treatments are not available for recurrent episodic vertigo in contralateral DEH due to endolymphatic hydrops occurring in only hearing ears. In the present study, four patients with ipsilateral DEH and one patient with contralateral DEH showed class A responses. In addition, the incidence of vertigo per month after treatment was significantly lower than before treatment in Japanese patients with DEH, suggesting that this device may be associated with longer-term freedom from, or reduction in, definitive spells in patients with both types of DEH. As in cases of MD, the Meniett device should be considered for elderly patients before surgery or chemical intervention because of the inefficient vestibular compensation under DEH. In contralateral DEH, this device may be worthwhile for use as an intermediate treatment between medical and surgical management in patients with endolymphatic hydrops in their only hearing ear [21]. The number of subjects in the present study was too low; therefore, further studies are necessary to elucidate the benefit of this safe, minimally invasive therapeutic device for the management of DEH.

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Original Article

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Key Words

Meniere's disease
Plasma arginine vasopressin
Plasma osmolality

Abbreviations

95% CI: 95% confidence interval
AVP: arginine vasopressin
ELP: endolymphatic pressure
PLP: perilymphatic pressure

The association of the plasma vasopressin level during attacks with a prognosis of Meniere's disease

Abstract

An elevation of the plasma arginine vasopressin (AVP) level has been frequently observed in Meniere's disease patients. However, little is known regarding the mechanism behind this elevation. The plasma AVP levels in acute phase were determined in 21 Meniere's disease patients and 16 patients with other types of vertigo. The plasma AVP levels of Meniere's disease patients in the acute phase were significantly higher than in those of other vertigo patients ($p<0.01$). In Meniere's disease patients with abnormally high levels of AVP (more than 3.5 pg/ml) in the acute phase, 36% of patients were resistant to conservative treatments for frequent vertigo attacks for the follow-up period of at least 2years. A significant correlation was observed between the plasma AVP in the acute phase and the highest hearing threshold level at a frequency of 1kHz for the follow-up period of at least 1 year ($r=0.45$, $p<0.05$). These results suggest that the elevation in plasma AVP level in the acute phase is associated with the prognosis of Meniere's disease.

Sumario

La elevación del nivel plasmático de vasopresina arginina (AVP) ha sido frecuentemente observado en los pacientes con enfermedad de Meniere. Sin embargo, se sabe poco de los mecanismos detrás de esta elevación. Se determinaron los niveles plasmáticos de AVP durante la fase aguda en 21 paciente con enfermedad de Meniere y en 16 pacientes con otro tipo de vértigo. Los niveles plasmáticos de AVP en los pacientes en la fase aguda de la enfermedad de Meniere fueron significativamente más elevados que aquellos con otro tipo de vértigo ($p<0.01$). De los pacientes con enfermedad de Meniere y niveles anormalmente elevados de AVP (más de 5.5 pg/ml) durante la fase aguda, 36% de ellos fueron resistentes al tratamiento conservador para los ataques frecuentes de vértigo en un periodo de seguimiento de hasta 2 años. Se observó una correlación significativa entre el nivel plasmático de AVP en la fase aguda y el umbral más elevado en la frecuencia de 1kHz durante el periodo de seguimiento de un año ($r=0.45$, $p<0.05$). Estos resultados sugieren que la elevación plasmática de AVP en la fase aguda está asociada con el pronóstico de la enfermedad de Meniere.

The episodic symptoms of Meniere's disease are related to the fluctuating volume/pressure changes within a closed fluid system. Normally, endolymph moves from the cochlea to the endolymphatic sac where it is absorbed. The volume/pressure in the labyrinth is maintained by a variety of subtle regulatory mechanisms under normal conditions (Juhn et al, 1981). Any disturbance in this process can result in the accumulation of fluid within the membranous labyrinth and cochlea. The resulting endolymphatic hydrops distorts the cochlear duct and produces various hearing symptoms. Vertigo also results from endolymphatic pressure (ELP) changes in the labyrinth and/or from changes in the chemical composition of the endolymph fluid that affects neural transmission (Andrew & Strelioff, 1995).

Although there is an interindividual variation in the values of the ELP and perilymphatic pressure (PLP) in the inner ear of normal animals, the ratio of ELP to PLP is approximately 1, and this ratio normally remains constant for individuals in a prone position. The ratio of ELP to PLP in animals with endolymphatic hydrops is significantly higher than that in normal animals in a prone position (Andrew et al, 1991). A non-adapted imbalance between the ELP and PLP subsequently may cause an alteration in the micromechanism of the inner ear or a change in the microvascular blood flow, however it remains unclear how such altered intralabyrinthine pressure may affect the inner-ear function.

It has been reported that the plasma arginine vasopressin (AVP) level decreases after compression of the ELP, followed by decompression induced by an increase in the plasma AVP in animal study. These changes occur without any changes in the plasma osmolality and plasma sodium level (Bartoli et al, 1989, Podda et al, 1999). In addition, AVP may decrease fluid reabsorption in the endolymphatic sac, thereby inducing endolymphatic hydrops in guinea pigs (Kumagami et al, 1998). These results indicate that plasma AVP release may be partially controlled by inner-ear osmoregulatory mechanisms.

AVP receptors are present in the inner ear, and AVP in the inner ear reduces endolymphatic water reabsorption in the endolymphatic sac. In addition, AVP in the endolymphatic sac of the inner ear has the opposite effect to its normal action by reducing aquaporin translocation (Kumagami et al, 1998). The chronic administration of excess levels of AVP in guinea pigs is associated with the development of endolymphatic hydrops (Takeda et al, 2000). In a clinical study, elevated plasma AVP concentrations were observed in patients with Meniere's disease, and the level is significantly higher in the acute phase in comparison to the remission phase (Takeda et al 1995, Aoki et al, 2005). These findings lead us to the possibility that repeated attacks with the elevation of AVP in acute phase of Meniere's disease as observed in our previous study may thus result in the development of endolymphatic hydrops. However, Meniere's disease patients showed no elevation in the plasma AVP levels during the remission period, and no elevation in the serum AVP, even in the acute phase of Meniere's disease, was observed in another study (Lim et al, 2003). Therefore, the clinical significance of AVP in patients with Meniere's disease remains unclear.

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Table 1. Summary of reporting guideline.

Numerical value	*Class*
0	A (complete control)
1–40	B (Substantial control)
41–80	C (limited control)
81–120	D (insignificant control)
>120	E (poorer control)
secondary treatment initiated	F

Numerical value=(X/Y)×100, rounded to the nearest whole number, where X is the average number of definite spells per month for the 6–24 months after therapy, and Y is the average number of definite spells per month for the six months before therapy.

Methods

Subjects and study design

In order to study the plasma AVP level during the acute period in Meniere's disease patients and other cases of vertigo, the clinical data of patients who required admission for severe vertigo attacks were retrospectively analyzed using the AAO-HNS guideline (Table 1). We showed this study to all participants and obtained their informed consent, according to the guidelines of the Ethics Committee. This study population consisted of 21 unilateral Meniere's disease patients, as defined by the 1995 guidelines from American Academy of Otolaryngology—Head and Neck Surgery; AAO-HNS (AAO, 1995), and 16 patients with other causes of vertigo due to peripheral origins (Vestibular neuritis, n=5; sudden deafness with vertigo, n=3; idiopathic labyrinth dysfunction, n=8).

Their plasma AVP levels, plasma osmolality, and plasma sodium levels were obtained during the morning between 8:00–10:00 AM in acute phase of vertigo. The blood samples were also collected during the morning between 8:00–10:00 AM from 16 of the 21 Meniere's disease patients and the 16 patients with other causes of vertigo mentioned above in the remission phase, which was defined by tl absence of vertigo attacks within one month before and after collecti the blood samples. Meniere's disease patients were classified by stagi based on the four-tone average of the pure tone thresholds at 0.5, 1, and 4 kHz, according to the AAO-HNS guidelines (results with audi metric outcome data may be modified by the use of 4 kHz instead 3 kHz) as shown in Table 2. Four patients were classified as stage 4 patients as stage 2, 11 patients as stage 3, and 2 patient as stage The 16 Meniere's disease patients were followed up for at least 2 ye after collection of their blood for measurement of AVP during th vertigo attacks and of the frequency of vertigo attacks. Among the Meniere's disease patients described in our previous study (Aoki et 2007), 13 patients could be followed up for at least two years, howev the other five patients could not be followed up for two years f various reasons. Therefore, we added three new patients (50M, 54 and 72M in Table 3) to this study population.

Table 2. Staging of Meniere's disease. Staging is based on the four-to average of the pure tone thresholds at 0.5, 1, 2, and 4 kHz of the wor audiogram during the six months before treatment.

Stage	*Four-tone average (d*
1	≤25
2	26–40
3	41–70
4	>70

In the 16 Meniere's disease patients, we observed the results of t treatment for Meniere's disease according to the AAO-HNS guid lines, based on a numerical value calculated by the frequency definitive vertigo attacks after treatment for two years in compari to that for a period of 6 months before conservative treatment we assessed (Table 1). In addition, we investigated the correlati

Table 3. Duration of Meniere's disease, four-tone average of audiogram, and plasma AVP levels at admission in our hospital. The reportin result of treatment in 16 Meniere's disease patients who could be followed up for at least two years.

age	*sex*	*Duration of disease (year)*	*Fourtone average (dB)*	*pAVP (pg/ml)*	*Class after treatme*
28	F	3	20	2.4	A
31	F	2	11	4.1	B
33	M	3	45	7.2	D, F (M,G)
35	F	1	16	3.7	A
45	F	1	34	3.1	A
46	F	2	14	2.9	A
46	M	4	61	7.9	C
50	M	1	61	3.8	D, F (G)
52	F	2	29	4.8	B
53	F	1	61	5.7	B
54	M	3	45	2.7	B
54	M	2	55	8.4	D, F (M)
59	F	3	45	4.6	B
65	F	3	55	2.3	A
72	M	2	75	9.7	D, F (M)
84	F	5	59	3.8	A

F: female, M: male, duration of disease; duration of Meniere's disease before collecting their blood in the acute phase, Four-tone average: average of 0.5, 1, and 4kHz in pure tone audiogram, F (M); Meniett device was used as secondary treatment initiated due to disability from vertigo, F (M, G); intratympar injection of gentamicin was performed because the vertiginous symptoms did not improve after treatment with the Meniett device.

between the plasma AVP in acute phase and the highest hearing threshold levels in pure tone audiograms for the follow-up period of at least one year in the 21 Meniere's disease patients. They included five Meniere's disease patients reported in previous study, who could not be followed up for two years in this study.

Measurement of plasma vasopressin

The blood for a plasma AVP assay was transferred into an EDTA tube and then i centrifuged at 4°C and the separated plasma stored at −80°C. The plasma AVP was determined by an RIA (Arginine vasopressin RIA kit; Mitsubishi Yuka, Japan). The normal range of the plasma AVP level was 0.3–3.5 pg/ml (average 1.2 pg/ml) based on the data acquired from blood samples collected at 8:00–10:00 AM from 105 healthy subjects (male: 61, female 44; with informed consent) with no history of vestibular or cochlear disease. In addition, the plasma sodium concentration and the plasma osmolality were also measured.

Statistical analysis

The statistical significance of the differences between the groups of patients was determined by the use of a two-tailed unpaired t-test, and correlations among the plasma sodium and the plasma osmolality were analyzed using Spearman's correlation test. The correlations of the plasma AVP levels in acute phase and age with hearing threshold levels at each frequency in pure tone audiogram were also analyzed using Spearman's correlation test. Values of $p<0.05$ were considered to be significant. The illustrated values are presented as the mean and 95% confidence interval (95% CI).

Results

Vasopressin and osmolality analysis

There was no significant difference in the mean age between the Meniere's disease group (n= 16, mean: 46 years old, 95%CI; 49–52) and the other vertigo groups (n=16, mean: 52 years old, 95%CI; 46–57, p=0.12). The blood samples from the Meniere's disease patients were obtained at 1.2 days (95% CI; 0.7–1.6 days) and that of other vertigo patients at 1.9 days (95% CI; 1.1–2.7 days) after the onset of a vertigo attack. No significant difference in the sampling days after the onset of vertigo attacks was observed between either group (p=0.15). According to the clinical data, 56% of Meniere's disease patients and 75% of other vertigo patients experienced nausea or emesis in collecting their blood.

The plasma AVP levels of Meniere's disease patients in the acute phase (n=16, 4.8 pg/ml, 95% CI; 3.7–5.9 pg/ml, Figure 1) was significantly higher than that of the other vertigo patients (n=16, 1.9 pg/ml, 95% CI; 1.5–2.4 pg/ml; p<0.01, Figure 1). The average plasma AVP level of the 16 Meniere's disease patients in the remission phase (2.0 pg/ml, 95% CI; 1.5–2.5 pg/ml) was significantly lower than that of the Meniere's disease patients in the acute phase (p<0.01, Figure 1). No significant difference was observed in the plasma AVP levels between the Meniere's disease patients in the remission phase and other vertigo patients in the acute phase (p=0.79). The average plasma osmolality of the Meniere's disease group in the acute phase was 293 mOsm/kg H_2O, (n=16, 95% CI; 289-296 mOsm/kg H_2O), which was not significantly different from that of the other vertigo patient group in the acute phase (n=16, 291 mOsm/kg H_2O, 95% CI; 288–294 mOsm/kg H_2O; p=0.61, Figure 1). The average concentration of the plasma sodium of the 16 Meniere's disease patients in the acute phase was 140 mEq/l (95% CI; 139–142 mEq/l), while that of the 16 patients with other vertigo in the acute phase was 141 mEq/l (95% CI; 140–141 mEq/l, Figure 1). There was no significant difference in the concentration of plasma sodium between the two groups (p=0.67, Figure 1). In addition, a significant positive correlation was observed between the plasma sodium level and the plasma osmolality in both groups in the acute phase (p<0.01, Figure 1).

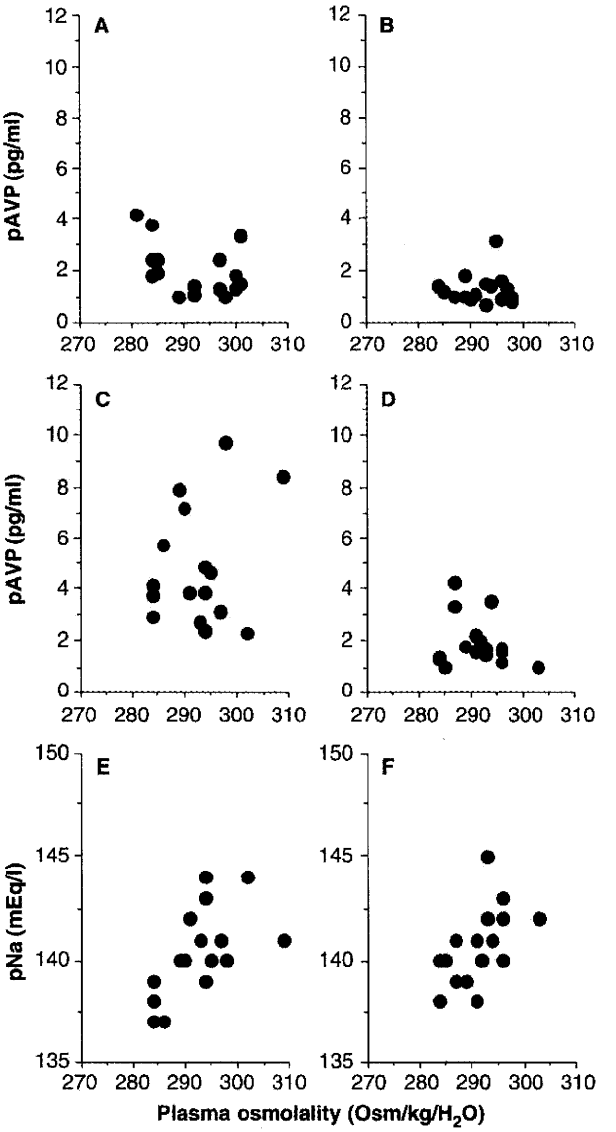

Figure 1. Plasma AVP vs. Plasma osmolality for individual Meniere' disease patients (n=16) and other vertigo patients (n=16) during the remission phase and the acute phase. The plots indicate the actual individual values of plasma AVP of Meniere's disease patients (a) other vertigo patients (b) in the remission phase, Meniere's disease patients (c), and other vertigo patients (d) in the acute phase. The correlation between the plasma sodium and plasma osmolality for Meniere's disease patients (e) and other vertigo patients (f) in the acute phase. A dotted line shows the normal level of plasma AVP (3.5 pg/ml)

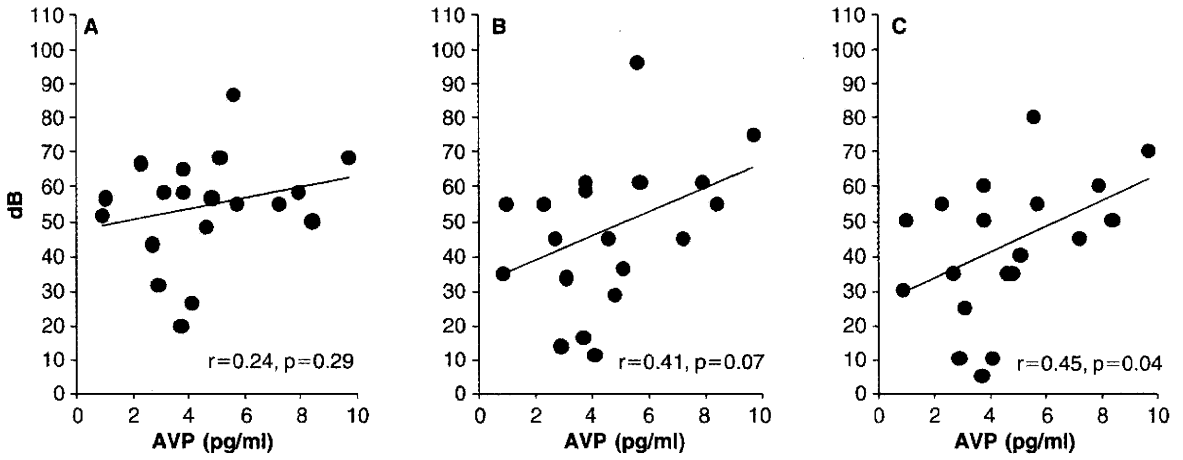

Figure 2. The correlation between the plasma AVP level in acute phase and the hearing thresholds in 21 Meniere's disease patients. A: averag of the highest hearing threshold level at low frequencies (0.125, 0.25 and 0.5 kHz), B: average of the highest hearing threshold level at fou tone frequencies (0.5, 1, 2, and 4kHz), C: the highest hearing threshold level at 1kHz for the follow-up period of at least one year.

Association of the plasma AVP with a prognosis of Meniere's disease

There was a significant correlation between the plasma AVP in acute phase and the highest hearing threshold levels at a frequency of 1kHz for the follow-up period of at least one year in 21 Meniere's disease patients (r=0.45, p=0.04, Figure 2C, Table 4). The plasma AVP levels in acute phase also showed weak correlations with the four-tone average of the highest hearing threshold levels at 0.5, 1, 2, and 4 kHz for follow-up period (r=0.41, p=0.07, Figure 2B, Table 4) and the highest hearing threshold levels at 2kHz for the follow-up period (r=0.43, p=0.06, Table 4). However, there was no significant correlation between the plasma AVP levels in acute phase and the average of the highest hearing thresholds levels at low frequencies of 0.125, 0.25, and 0.5 kHz for the follow-up period (r=0.24, p=0.29, Figure 2A). The plasma AVP level was not correlated with age, however, the hearing threshold level increased with age except for threshold in 8 kHz (Table 4).

Among 16 Meniere's disease patients who could be followed up for at least two years, four patients had been distressed by frequent vertigo attacks resistant to conservative treatments, such as a low-salt diet and diuretic drugs (Table 3). The frequent vertigo attacks in three of those patients (33M, 54M, and 72M in Table 3) were managed by the Meniett Low-Pressure Pulse Generator, which restored the balance in the hydrodynamic system of the inner ear by applying low-pressure pulses to the middle ear (Gates et al, 2004) In addition, two patients (33M and 50M in Table 3) underwent a intratympanic injection of gentamicin for the chemical ablation o the vestibular system (Minor et al, 2004) because the vertiginou symptoms did not improve after treatment with the Meniett devic alone. The plasma AVP levels of the four Meniere's disease patient in acute phase were more than the normal upper level (3.5 pg/ml) whereas all of the Meniere's patients with normal AVP levels i acute phase (less than 3.5 pg/ml) could be managed with conserva tive treatments (Table 3).

Discussion

The elevation of AVP during Meniere's attacks never seemed t accompany a change of plasma sodium and osmolality, whereas proportional relationship between the plasma sodium and plasm osmolality was preserved in patients with Meniere's disease in th acute phase as well as in patients with other types of periphera vertigo in this study. This result may indicate that such patients hav functions to maintain the fluid balance normally. Although severa factors that induce elevated AVP release have been identifie including nausea and emesis (Rowe et al, 1979), there was n

Table 4. The correlations among the plasma AVP in acute phase, age, and the highest hearing threshold levels in pure-tone audiograms for th follow-up period of at least one year.

				Frequency in pure tone audiogram (kHz)						
		AVP	*age*	*0.125*	*0.25*	*0.5*	*1*	*2*	*4*	*8*
AVP	*r*	1	0.11321	0.18846	0.17989	0.32511	0.45042	0.43117	0.28182	0.0814
	p-value	–	0.63463	0.42621	0.4479	0.16191	*0.04627*	0.05769	0.22868	0.73297
age	r	0.11321	1	0.45172	0.52147	0.56368	0.5644	0.63021	0.65376	0.39514
	p-value	0.63463	–	*0.04556*	*0.01837*	*0.00964*	*0.00953*	*0.0029*	*0.00177*	0.08465

r: correlation coefficient.

significant difference in occurrence of nausea and emesis during vertigo attack between Meniere's disease and other vertigo patients in this study. The release of AVP has been reported to be associated with overactivation of the major stress regulation system by psychosocial stress (Scott et al, 1988). We previously reported that the life-change unit (LCU) score to identify the life events that they recognized as stressful in the Meniere's disease group was not significantly higher than that in the other vertigo group. Our results did not support the hypothesis that the elevation in the plasma vasopressin level in Meniere's attacks is caused by the stress status (Aoki et al, 2007). It therefore remains unclear how the elevation of the plasma AVP in Meniere's disease patients may be associated with the vertigo attacks.

The AVP secretion is mainly controlled by cardiovascular volume receptors, whereas the extra-vascular volume receptors in the inner ear may play a role in controlling the water balance not only in the ear but also partially in the whole body (Bartoli et al, 1989). The system in the inner ear may be associated with the release of AVP, which may represent a finer bias of homeostatic control, especially when plasma osmolality is stable. In an animal study, electrical vestibular stimulation and caloric stimulation also increased plasma AVP levels, suggesting that imbalance of intervestibular activity induced by vestibular activation or inhibition may increase plasma AVP levels in animals (Horii et al, 2004). However we could not find the elevation of plasma AVP levels in other peripheral vertigo patients in acute phase. Kitahara et al showed an overexpression and hyperactivity of vasopressin-2 receptors (V2R) in the endolymphatic sac in intractable Meniere's disease patients, thus speculating that susceptibility of the V2R-overexpressed endolymphatic sac to elevation of plasma AVP may be essential for the pathogenesis of Meniere's disease attack (Kitahara et al, 2008). In order to evaluate the precise mechanism for the elevation of the plasma AVP in Meniere's disease patients, further clinical basic studies may be needed. However, our study and other reports may support the possibility that testing of plasma AVP levels may provide helpful information for distinguishing between Meniere's disease and various other inner-ear diseases.

The abnormal elevation of AVP in some patients with Meniere's disease in acute phase may cause inner-ear disorders. This possibility may be supported by the findings of an animal study that demonstrated that AVP produces endolymphatic hydrops, resulting in hearing loss due to a decrease in the endolymphatic potential in an endolymphatic hydrops ear (Lohuis et al, 1999). Takeda et al demonstrated that high levels of plasma AVP ($>$ 5.0 pg/ml) were often observed in patients between 6 and 19 years of age with the early onset of profound hearing loss. Moreover, persistent elevations of plasma AVP were frequently observed in patients with clinical signs of the development of the delayed endolymphatic hydrops (Takeda et al, 2008). In this study, 36% of Meniere's disease patients with abnormally high levels of the AVP ($>$ 3.5 pg/ml) in the acute phase were resistant to symptomatic control of vertigo by conservative treatment. In contrast, all Meniere's disease patients with normal levels of the AVP in acute phase could be managed by conservative treatments. Although, because of the small number of cases, we need further study before making any definitive conclusions, we speculate that the elevation of the AVP may be associated with the Meniere's attack, resulting in irreversible formation of the endolymphatic hydrops.

On the other hand, there was a significant correlation between plasma AVP in acute phase and the highest hearing threshold le at a frequency of 1 kHz for the follow-up period of at least one y It is highly possible that an elevation of the AVP levels during Menie attacks may influence a prognosis of hearing threshold level. Howe there are still numerous controversial statements regarding pathop iology and management of Meniere's disease, and additionally t is no means of predicting how the hearing loss may progress. Evalua the association between plasma AVP and prognosis of Meniere's dise may therefore provide helpful information for understand Meniere's disease patients.

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ORIGINAL ARTICLE

Semi-quantitative evaluation of endolymphatic hydrops by bilateral intratympanic gadolinium-based contrast agent (GBCA) administration with MRI for Meniere's disease

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Abstract

Conclusion: Bilateral intratympanic administration of a gadolinium-based contrast agent (GBCA) in MRI was successfully performed and proved to be beneficial in the semi-quantitative evaluation of endolymphatic hydrops. Such image-based diagnosis will lead to re-revaluation and reclassification of the diagnostic criteria for Meniere's disease (MD). *Objective:* To visualize endolymphatic hydrops semi-quantitatively in patients with MD, by using bilateral intratympanic GBCA administration with MRI. *Patients and methods:* A total of 13 patients were evaluated, including 12 with MD and one with acute low-tone sensorineural hearing loss. Diluted gadodiamide (a kind of GBCA) was administered to the bilateral tympanic cavity by injection through the tympanic membrane. After 24 h, the endolymphatic hydrops was evaluated with a 3.0 T MR scanner. The areas enhanced by gadodiamide were measured semi-quantitatively. *Results:* Three-dimensional, fluid-attenuated inversion recovery (3D-FLAIR) MRI showed that the gadodiamide successfully penetrated the round window membrane, entering the perilymphatic space and delineating the gadodiamide-enhanced perilymphatic and gadodiamide-negative endolymphatic spaces of the inner ear. All the patients with MD showed a reduced gadodiamide-enhanced area representing the perilymphatic space, and the quantitative ratio was 0.15 to 0.85. Furthermore, endolymphatic hydrops was also demonstrated in the patient with atypical MD who had fluctuating low frequency sensorineural hearing loss without vertigo.

Keywords: *Endolymphatic hydrops, Meniere's disease, semi-quantitative analysis, gadolinium, gadolinium-based contrast agent (GBCA), MRI*

Introduction

Meniere's disease (MD) is an idiopathic disorder of the inner ear characterized by fluctuating sensorineural hearing loss (SNHL), tinnitus and aural fullness, and recurrent spontaneous episodic rotational vertigo (see Sajjadi and Paparella for review [1]). MD has been thought to be attributable to endolymphatic hydrops, but this has only been confirmed histopathologically after death. Therefore, MD has been diagnosed on the basis of clinical symptoms and is classified into typical MD with all cochlear and vestibular symptoms, and atypical MD with either cochlear symptoms (e.g. hearing loss, tinnitus, aural pressure) or vestibular symptoms (e.g. vertigo alone with aural pressure) [2]. Typical MD can further be classified into certain, definite, probable, and possible MD according to the nature of the hearing loss, tinnitus, aural fullness, and vertigo [2]. In addition, clinical diagnosis has sometimes been hampered by other conditions that closely resemble MD, such as acute low tone sensorineural hearing loss (ALSNHL) [3]. Therefore, along with clinical symptoms, clinical tests suggestive for endolymphatic hydrops are usually used for diagnosis. Functional

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testing including electrocochleography (EcochG) or glycerol test has been used to estimate endolymphatic hydrops [1]. However, even if functional testing is performed, the results are still indirect proof.

Recent advances in imaging by three-dimensional, fluid-attenuated inversion recovery (3D-FLAIR) of magnetic resonance imaging (MRI), in association with enhancement by gadolinium-based contrast agents (GBCAs), enables visualization of endolymphatic hydrops in patients with MD [4–6]. In the present study, involving patients with typical MD, atypical MD, and ALSNHL, we evaluated endolymphatic hydrops in a semi-quantitative manner, through comparison of bilateral perilymphatic spaces enhanced by a GBCA.

Patients and methods

Subjects

Ten patients with 'definite' MD and one with 'possible' MD who met the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria, one patient with atypical MD (who had fluctuated low frequency sensorineural hearing loss without vertigo), and one patient with acute low-tone sensorineural hearing loss (ALSNHL) participated in this study.

MRI

Gadodiamide (Omniscan, Daiichi Pharmaceutical Co. Ltd, Tokyo) was diluted eightfold with saline, and 0.4–0.6 ml of the diluted gadodiamide was administered to the bilateral tympanic cavity by injection through the tympanic membrane using a 23 G needle. The injection was carried out under a microscope. The patient then lay down in the supine position for 60 min. After 24 h, the endolymphatic hydrops was evaluated by MRI. We used a 3.0 T MR scanner (Trio, Siemens, Erlangen, Germany) with a receive-only eight-channel phased-array coil. It can perform T1-weighted three-dimensional (3D) magnetization prepared rapid gradient echo (MP-RAGE). The parameters for MP-RAGE were: TR 1500 ms, TE 3 ms, matrix size of 320 × 290 × 320; 72 axial 0.8 mm thick slice, 0.8 mm × 0.8 mm × 0.8 mm isotropic voxels, heavily T2-weighted 3D-TSE sequence, and 3D fluid-attenuated inversion recovery (FLAIR) with variable flip angle echo train (SPACE). The parameters for heavily T2-weighted SPACE were: TR 1350 ms, TE 199 ms, echo train length (ETL) 93, matrix size of 320 × 288 × 278, 56 axial 0.8 mm thick slice, and voxel size of 0.6 × 0.4 × 0.8 mm. In addition to the methods described previously, we used 3D-FLAIR with higher in-plane spatial resolution. The scan parameters for the 3D-FLAIR sequence were as follows: repetition time of 10 000 ms, echo time of 666 ms, inversion time of 2500 ms, single slab 3D turbo spin echo with variable flip angle distribution, echo train length of 173, matrix size of 320 × 320, 52 axial 0.8 mm thick slices to cover the labyrinth with a 20 cm square field of view, acceleration factor of two using the parallel imaging technique, and generalized autocalibrating partially parallel acquisitions. Voxel size was 0.7 × 0.8 × 0.8 mm. The number of excitations was one and the scan time was 9 min.

The multi-planar reconstruction (MPR) image was created from 3D-FLAIR images by imaging analysis software (Aquarius Net Viewer). The areas enhanced by gadodiamide in the cochlea and vestibule were traced and measured on the image in the plane perpendicular to the modiolus. Then, the affected side/contralateral side ratios were calculated (Figure 1). Semi-quantitative comparison of endolymphatic space in the vestibule was also calculated using Dicom Viewer software (EV Insite).

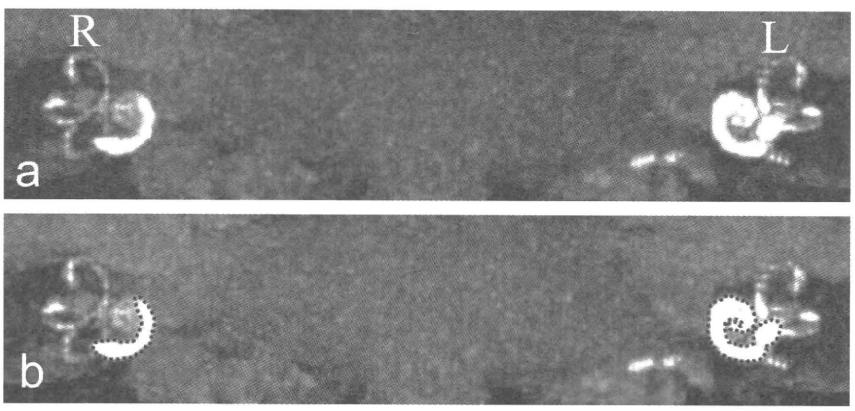

Figure 1. The areas enhanced by gadodiamide in cochlea and vestibule were measured using multi-planar reconstruction (MPR) image by imaging analysis software (dotted lines), and the affected side/unaffected side ratios were calculated.

Clinical testing

Pure tone audiometry (PTA) was performed before and after the experiment. The average of 0.5, 1, 2, and 4 Hz is shown in Table I. For vestibular testing, caloric testing and vestibular-evoked myogenic potential (VEMP) testing were performed. In caloric testing, maximum slow eye velocity was measured by cold water irrigation (20°C, 5 ml, 20 s). In VEMP testing, the electrographic signal from the stimulated side was amplified and averaged using a Neuropack evoked potential recorder (Nihon Kohden Co. Ltd, Tokyo, Japan). Clicks lasting for 0.1 ms at 105 dBnHL were presented through a headphone. The stimulation rate was 5 Hz, the band-pass filter intensity was 20–2000 Hz, and analysis time was 50 ms. The responses to 200 stimuli were averaged twice.

The Ethics Review Committee of Shinshu University School of Medicine approved the protocol of the study and all patients gave their informed consent to participation.

Results

In this study, 3D-FLAIR MRI clearly showed that the gadodiamide successfully penetrated the round window membrane, entered the perilymphatic space, and delineated the gadodiamide-enhanced perilymphatic and gadodiamide-negative endolymphatic spaces of the inner ear. The endolymphatic space is comparatively small and difficult to identify as a vacant area in the normal side. In contrast, the endolymphatic space in an ear with endolymphatic hydrops is partially or entirely expanded, making identification of the endolymphatic space easier (Figures 2 and 3).

Gadodiamide distribution patterns within the inner ear were variable and differed individually. In patient no. 3, who had definite MD, after 24 h the intratympanic gadodiamide moved toward the perilymphatic space, and the endolymphatic hydrops could be detected as a black area surrounded by the perilymphatic space filled with the gadodiamide in the basal turn of the left cochlea (Figure 2). In the unaffected side, the endolymphatic space (which was significantly small) may have been masked by the strong enhancement of perilymphatic space. In patient no. 6, who also had definite MD, the endolymphatic space in the vestibule on the affected side was significantly larger than that on the normal side (Figure 3). In this patient, in association with the imaging, VEMP was absent, but the caloric test showed normal response.

Table I summarizes imaging results and clinical data obtained for each patient. In the cases such as no. 3 or 6 mentioned above, endolymphatic hydrops could be easily identified qualitatively. However, in some cases, it was difficult to obtain supportive imaging for endolymphatic hydrops. Therefore, the present study tried to perform semi-quantitative analysis by using the MPR image, created from 3D-FLAIR images. Based on the semi-quantitative analysis, the gadodiamide-enhanced area representing the perilymphatic space ratio was 0.14 to 3.86 (Table II). In 9 of 10 patients with definite MD the ratio was reduced, and the quantitative ratio was 0.15 to 0.85 (Table II). In the exception, patient no. 4, gadodiamide was not introduced in the perilymphatic space even on the normal side, probably due to technical failure.

Table I. Summary of bilateral intratympanic gadolinium administration.

Patient no.	Age/sex	Diagnosis	Side	Caloric test CP%	VEMP	PTA-pre (dB)		PTA-post (dB)	
						Affected side	Unaffected side	Affected side	Unaffected side
1	51/M	MD	R	7.2	Depressed	38.8	15.0	38.8	15.0
2	41/F	MD	R	51.2	–	37.5	11.3	32.5	11.3
3	42/M	MD	L	41.3	Depressed	50.0	12.5	53.8	12.5
4	42/F	MD	L	19.9	ND	33.8	12.5	32.5	10.0
5	76/F	MD	L	39	ND	46.5	30.0	40.0	27.5
6	51/F	MD	R	11.9	Absent	22.5	13.8	28.8	12.5
7	53/M	ATMD	R	–	–	58.8	13.8	47.5	13.8
8	38/M	MD	R	22.6	Depressed	20.0	6.3	28.8	5.0
9	76/M	ALSNHL	R	–	–	17.5	46.3	13.8	43.8
10	67/F	MD	L	6.9	ND	55.0	28.8	52.5	26.3
11	52/F	MD	L	6.8	ND	65.0	12.5	62.5	13.8
12	53/F	MD	L	42.3	Depressed	53.8	22.5	47.5	20.0
13	33/M	pMD	R	50.6	Normal	12.5	6.3	6.3	6.3

ALSNHL, acute low tone sensorineural hearing loss; ATMD, atypical Meniere's disease; F, female; L, left; M, male; MD, 'definite' Meniere's disease; ND, not detectable; pMD, 'possible' Meniere's disease; PTA, pure-tone audiometry; R, right.

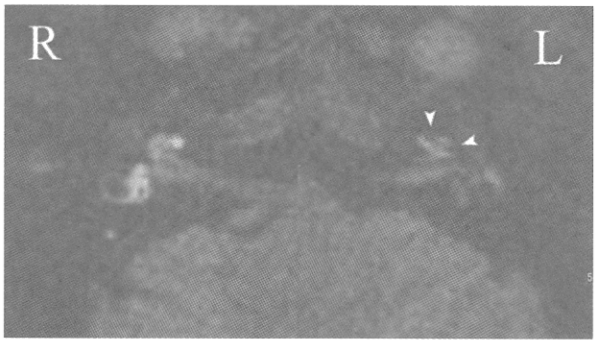

Figure 2. MRI imaging in patient no. 3 (definite Meniere's disease). The endolymphatic hydrops is detectable as a black area (arrowheads) inside the perilymphatic space filled with the gadodiamide in the basal turn of the left cochlea. In the normal side, the endolymphatic space (a significantly small area) is not detectable, probably due to strong signal intensity in the perilymphatic space.

We measured the saccular endolymphatic space by bilateral comparison. Eleven of 13 patients, including 8 with definite MD, 1 with possible MD, 1 with atypical MD, and 1 with ALSNHL, showed differences in endolymphatic space in the saccules. Significant differences (Student's *t* test) in patient nos 6, 8, 10, and 11 were noted (Figure 4)

Concerning vestibular functional testing, caloric testing was performed in all but two patients (nos 7 and 9), and showed decreased response in five cases. VEMP testing was performed in all patients, except nos 2, 7, and 9. In 6 of the 10 patients who underwent the testing, VEMP was either absent on the affected side or depressed compared with the healthy side. VEMP amplitude could not be obtained because of low muscle contraction in patient nos 4, 5, and 10.

No adverse effects, such as vertigo, hearing deterioration, or tinnitus due to the intratympanic injection of gadodiamide were observed and there were no changes in hearing level (Table I).

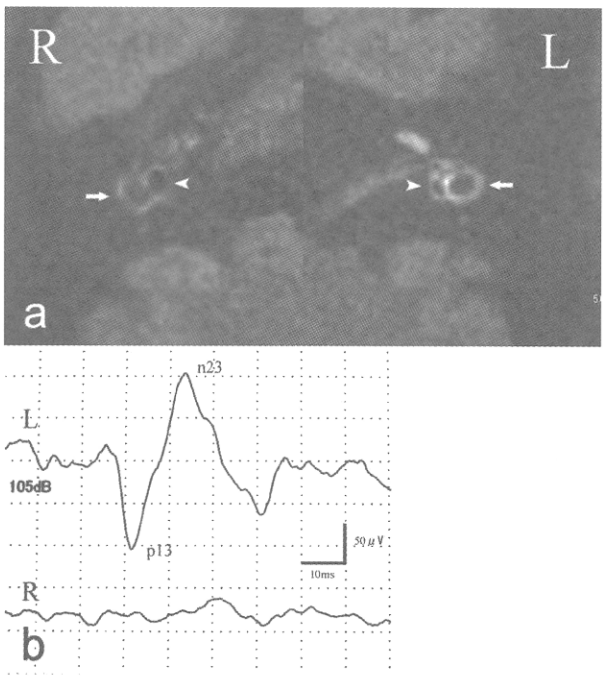

Figure 3. MRI imaging in patient no. 6 (definite Meniere's disease). The endolymphatic space in the saccules is detectable as a black area inside the perilymphatic space filled with gadodiamide in the vestibule (arrowheads). In the normal side (L), the endolymphatic space in the saccules is also detectable in the unaffected side, but is smaller than in the affected area. Arrows indicate lateral semicircular canals. In the affected side (R), enhancement by gadodiamide was weaker than in the unaffected side, indicating that endolymphatic hydrops may be present in the canal. VEMP testing showed no response in the affected side.

Discussion

The hallmark of MD diagnosis is to prove endolymphatic hydrops, but this has been achieved only in temporal bone histopathology after death. Initial attempts to identify endolymphatic hydrops involved visualization of the Reissner membrane, and it was successfully visualized in animals [7] and human cadavers [8]. The subsequent attempts to identify endolymphatic hydrops used intratympanic GBCA administration with 1.5 T MRI to visualize the

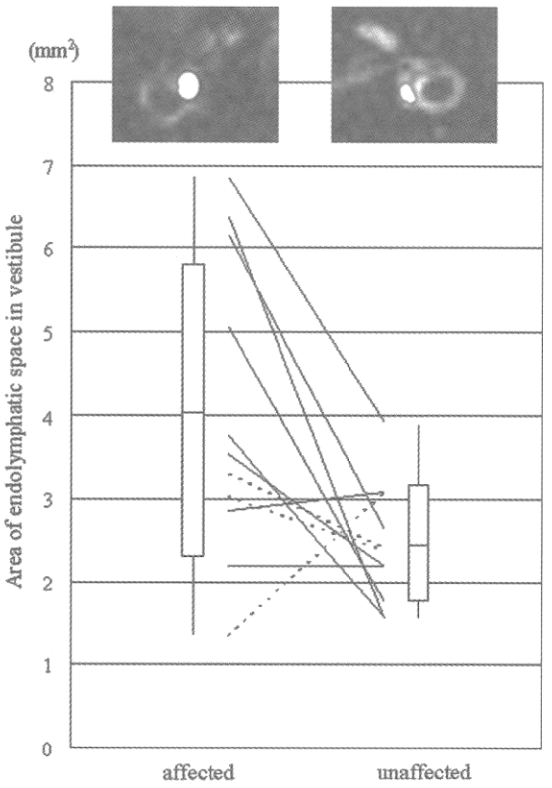

Figure 4. Semi-quantitative analysis of bilateral endolymphatic space in the sacculus.