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Ménière's disease with unremitting floating sensation is associated with canal paresis, gravity-sensitive dysfunction, mental illness, and bilaterality

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ABSTRACT

Objective: The aim of the present study was to evaluate the association of neuro-otological examination, blood tests, and scoring questionnaire data with treatment-resistant intractability of persistent dizziness in Ménière's disease.

Methods: We managed 1520 successive vertigo/dizziness patients at the Vertigo/Dizziness Center in Nara Medical University from May 2014 to April 2018. Five hundred and twenty-two patients were diagnosed with Ménière's disease (522/1520; 34.3%) according to the 2015 diagnostic guideline of the International Classification of Vestibular Disorders. Among the patients with Ménière's disease there were 102 with intractable rotatory vertigo attacks for more than 3–6 months (102/522; 19.5%), including 20 bilateral cases (20/102; 19.6%), and 88 with intractable unremitting floating sensation rather than rotatory vertigo attacks for more than 3–6 months (88/522; 16.9%), including 28 bilateral cases (28/88; 31.8%). Sixty out of 88 cases with intractable unremitting floating sensation were unilateral and were enrolled for hospitalization to undergo neuro-otological examinations including pure-tone audiometry (PTA), the caloric test (C-test), vestibular evoked cervical myogenic potentials (cVEMP), subjective visual vertical (SVV) test, glycerol test (G-test), electrocochleogram (ECoG), inner ear magnetic resonance imaging (ieMRI), blood tests including anti-diuretic hormone (ADH) and bone alkaline phosphatase (BAP), and self-rating questionnaires of depression score (SDS). Data are presented as positive (+) ratios of the number of patients with examination and questionnaire data outside of the normal range.

Results: The ratios (+) were as follows: C-test = 33.3% (20/60), cVEMP = 25.0% (15/60), SVV = 50.0% (30/60), G-test = 55.0% (33/60), ECoG = 63.3% (38/60), ieMRI = 86.7% (52/60), ADH = 35.0% (21/60), BAP = 11.7% (7/60), and SDS = 40.0% (24/60). Multivariate regression analysis revealed that the periods of persistent dizziness were significantly longer in unilateral Ménière's patients with C-test(+), SVV(+), and SDS(+) compared with those with negative findings. Additionally, the periods in bilateral cases were significantly longer than those in unilateral ones.

Abbreviations: PTA, pure-tone audiometry; SDT, speech discrimination test; C-test, caloric test; cVEMP, vestibular evoked cervical myogenic potentials; SVV, subjective visual vertical; G-test, glycerol test; ECoG, electrocochleogram; teMRI, inner ear MRI; ADH, anti-diuretic hormone; BAP, bone alkaline phosphatase; CPK, creatine phosphokinase; SDS, depression score.

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Conclusions: Although approximately 70% of patients with Ménière's disease are usually treatable through the appropriate conservative medical therapy, the presence of canal paresis, gravity-sensitive dysfunction, neurosis/depression, and bilaterality may make the persistent dizziness intractable and may thus require additional treatments.

1. Introduction

Ménière's disease (MD), characterized by recurrent vertigo attacks, fluctuating hearing loss, and tinnitus, is a common disease with an incidence of 15–50 per 100,000 population [1]. Some patients with MD are severely restricted from participating in activities of daily life and interaction with their social environment, such as work and schooling, because of frequent attacks of vertigo and more specifically with progressive sensorineural hearing loss, despite various forms of medication. This type of MD is generally called intractable MD, which to date been spotlighted as the main surgical indication [2,3].

In daily clinical experience we sometimes encounter another type of intractable MD with unremitting floating sensation that is refractory to conservative medical treatments [4,5]. This sensation in MD patients is more troublesome than attacks, because the duration of this symptom is long lasting even in the intermittent period between attacks. Currently there is no appropriate or effective treatment for such intractable cases.

In the present study, we first investigated the association of neuro-otological examination, blood testing, and scoring questionnaire data with treatment-resistant intractability in MD-related persistent dizziness. We then proposed potential effective therapeutic strategies for MD patients with intractable persistent dizziness.

2. Materials and methods

This clinical study was registered with UMIN (identification number 000018399). The use of all patients' data was approved by the Ethics Committee of Nara Medical University Hospital (identification number 0889).

2.1. Patients

We managed 1520 successive vertigo/dizziness patients at the Vertigo/Dizziness Center in Nara Medical University during the period May 2014–April 2018 (Fig. 1). Five hundred and twenty-two patients were diagnosed with MD (522/1520;

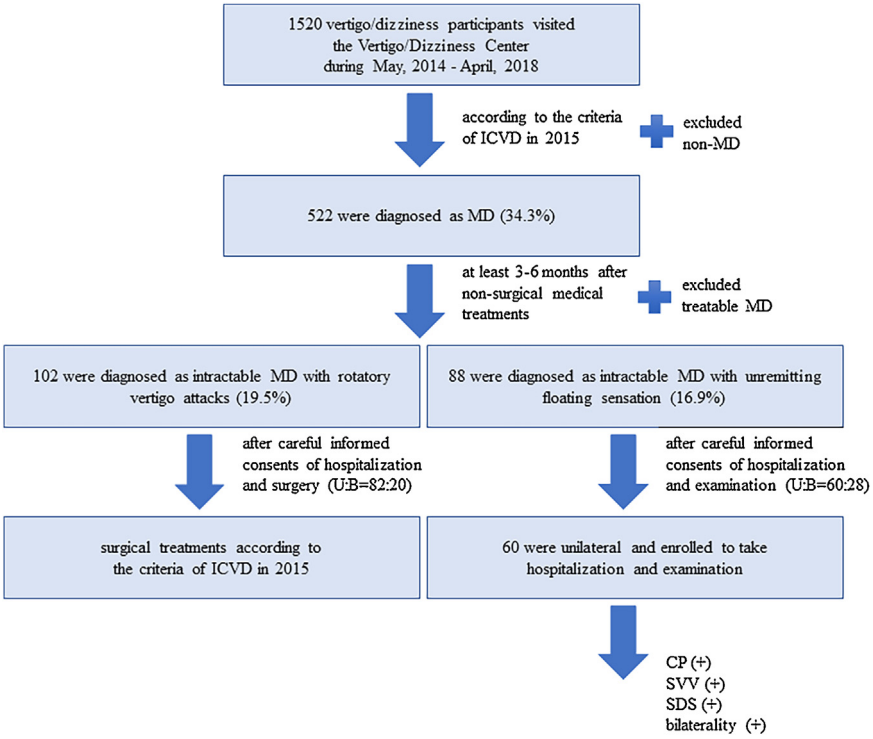

Fig. 1. Flow chart of case enrollment for the present study. We experienced 1,520 successive vertigo/dizziness patients at the Vertigo/Dizziness Center in Nara Medical University during May 2014–April 2018. Five hundred and twenty-two patients were diagnosed with Ménière's disease (MD) (522/1520; 34.3%) according to the 2015 diagnostic guideline of the International Classification of Vestibular Disorders. Among the patients with MD there were 102 with intractable rotatory vertigo attacks for more than 3–6 months (102/522; 19.5%) and 88 with intractable unremitting floating sensation rather than rotatory vertigo attacks for more than 3–6 months (88/522; 16.9%) who were refractory to conservative medical treatment. Sixty out of the latter 88 cases were unilateral and were enrolled in the present study. U, unilateral; B, bilateral.

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34.3%) in accordance with the 2015 diagnostic guideline of the International Classification of Vestibular Disorders (ICVD) [6]. These criteria can be briefly described as follows. (1) Repeated attacks of vertigo: a definitive spell is spontaneous vertigo lasting 20 min to 12 h, whereby a mixed type of spontaneous nystagmus is observed during attacks. (2) Fluctuating cochlear symptoms: the hearing test usually reveals a marked fluctuation of the threshold in the low and middle tone range. If necessary, a glycerol test or electrocochleogram is carried out to detect endolymphatic hydrops [7]. (3) Exclusion of other causes: to exclude other disorders, a thorough history is documented and neurological, neuro-otological, and magnetic resonance imaging (MRI) examinations is carried out.

Intractable MD was designated in patients for whom various forms of medical and psychological management had failed, and in whom a series of episodic vertigo attacks or unremitting floating sensation had lasted for at least 3–6 months. Medical management included diuretics, betahistine, diphenidol, dimenhydrinate, and diazepam, all of which are generally considered to be effective for the treatment of persistent symptoms in MD [8]. There were 102 patients with intractable rotatory vertigo attacks for more than 3–6 months (102/522; 19.5%), including 20 bilateral cases (20/102; 19.6%); and 88 patients with intractable floating sensation rather than rotatory vertigo attacks for more than 3–6 months (88/522; 16.9%), including 28 bilateral cases (28/88; 31.8%). In the present study we focused on the latter group of intractable unremitting floating sensation to help us propose appropriate and effective treatments, as we have already discussed thoroughly the surgical indications for the former group of intractable episodic vertigo attacks [2,3].

Sixty out of 88 cases with intractable unremitting floating sensation were unilateral and were enrolled for hospitalization to undergo neuro-otological examinations, including pure-tone audiometry (PTA), the caloric test (C-test), vestibular evoked cervical myogenic potentials (cVEMP), subjective visual vertical (SVV) test, glycerol test (G-test), electrocochleogram (ECoG), inner ear MRI (ieMRI), blood tests including antidiuretic hormone (ADH) and bone alkaline phosphatase (BAP), and self-rating questionnaires of depression score (SDS). The final 60 patients included 26 men and 34 women with a mean age of 46.2 ± 15.1 years. The average duration from the day of onset to the day of hospitalization was 48.8 ± 30.6 months.

2.2. Evaluations

2.2.1. Neuro-otological tests

Hearing function was measured by a pure-tone audiometer and was evaluated based on the four-tone average formulated by (a + b + c + d)/4 (a, b, c, and d are hearing levels at 0.25, 0.5, 1, and 2 kHz, respectively) according to the modified 2015 ICVD criteria [6]. The worst hearing level during the 6 months before examination was adopted as the hearing level, i.e., 53.3 ± 36.8 dB on the ipsilateral side, in the present 60 cases.

The C-test was used to assess the lateral semicircular canal and superior vestibular primary afferent neuron function. Cold water (20 °C; 20 mL) was injected into the external auditory meatus over 10 s by turns, and the induced nystagmus was recorded by using electronystagmography (ENG) in an open-eyes situation in darkness. Based on the maximum slow-phase eye velocity, canal paresis was judged as positive when the ENG was ≤10°/s [9].

cVEMP was used to assess saccule and inferior vestibular primary afferent neuron function. Electrodes were placed on the upper half of each sternocleidomastoid muscle, with a reference electrode placed on the lateral end of the upper sternum and a ground electrode placed on the nasion. During the recording procedure, the subjects were asked to lie in the supine position and raise their heads to contract the sternocleidomastoid muscle. Air-conducted acoustic stimuli consisting of 500-Hz and 1000-Hz short tone bursts (125 dB sound pressure level, rise/fall time = 1 ms, plateau time = 2 ms) were presented through headphones at a 5-Hz stimulation rate. The signals were amplified and bandpass filtered (20–2000 Hz), and 100 responses were averaged. The time window for the recording was from −20 ms to 80 ms. Two runs were performed for each ear to confirm data reproducibility. The first biphasic responses (p13–n23) produced by the sternocleidomastoid muscle ipsilateral to the stimulated ear were assessed. To eliminate the effects of variations in muscle activity, we calculated the mean background amplitude from the mean rectified background activity during the 20-ms prestimulus period. In the present study, the right–left or left–right ratios in the activity ≤0.5 were considered positive [10].

The SVV test was used to assess otolith organ function (i.e., the gravity sensitivity functioning test) with the bucket method. A clean, opaque, white plastic trash bucket (38 cm deep, 23 cm diameter) was converted to a test device by marking a 15-cm black line centered on the bottom inside, and placing a protractor on the bottom outside aligned with the line inside. A small weight was hung from the center of the protractor. The bucket was placed on its side on a table (29.5 × 25 cm) atop a height-adjustable tripod to stabilize the bucket in pitch and yaw. In this position, when the bucket was rolled in the clockwise and counterclockwise directions, the string and weight rotated freely so that the investigator could read the protractor. Prior to testing, the height of tripod was adjusted so that each subject's face could fit easily into the bucket. All measurements were taken by the examiner, monocularly, using the examiner's dominant eye. Two test conditions were used in random order: vertical roll from the upper end of the line, and right and left roll of 0°. Subjects were given three trials per condition. The starting point for each trial was selected randomly, and varied from 10° to 20° from the 0° line. Before each trial, the subject was instructed to state when the line was vertical while the examiner moved the bucket. In the present study, the angle gaps outside of the range between −2.0° (left) and +2.0° (right) were considered positive [11].

The G-test and ECoG were performed to detect endolymphatic hydrops (EH) [7]. The G-test was considered positive in pure-tone audiometry if there was a ≥10 dB improvement at two or more frequencies between 0.25–2.0 kHz at approximately 3 h after 1.3 mL/kg glycerol intake. ECoG was performed using tympanic recording, and was considered positive if the negative summating potential/active potential ratio was ≥0.37. It was regrettable to say that vestibular specific

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EH could not be accurately detected by way of C-test, cVEMP or VOR because of the facility limitations at our center.

2.2.2. Imaging tests

Performing ieMRI at 4 h after intravenous administration of gadolinium was previously reported to be useful for imaging of EH [12]. In the present study, all patients underwent heavily T2-weighted MRI cisternography for an anatomical reference of the total lymph fluid, heavily T2-weighted three-dimensional fluid-attenuated inversion recovery sequences with a 2250-ms inversion time for positive perilymph images, and heavily T2-weighted three-dimensional inversion recovery with a 2050-ms inversion time for positive endolymph images. After image acquisition, we obtained a hybrid image of the reversed image of the positive endolymph signal and the negative image of the positive perilymph signal after motion correction by subtracting the positive endolymph images from positive perilymph images. In this protocol, pixels with a negative value were estimated as representing EH.

Two otolaryngologists blinded to the clinical progress of the patients evaluated the ieMRI findings. If their evaluations differed, a third otolaryngologist made the final decision. The degree of EH was classified as none, mild, or significant, according to criteria reported by Nakashima et al. [13]. When evaluating cochlear EH, we used one axial slice near the modiolus. When evaluating vestibular EH, we used one axial slice that displayed the maximum extent of the vestibule, while the ampulla of the semicircular canal was excluded from evaluation.

Patients with no EH in the vestibule had a ratio of $\leq$1:3, those with mild EH had a ratio of 1:3–1:2, and those with significant EH had a ratio $>$1:2. In the present study, both mild and significant EH were defined as "positive."

2.2.3. Blood tests

Blood samples were collected between 8.00 a.m. and 10.00 a.m. during remission of vertigo to minimize the effects of circadian variation. Blood for the ADH/BAP assay was transferred into an EDTA tube and centrifuged at 4 °C, and the separated plasma was then stored at −80 °C. ADH and BAP levels were analyzed by radioimmunoassay. In our hospital, an ADH $\geq$3.0 pg/mL and a BAP $\geq$20.0 mg/L were considered positive [14,15].

2.2.4. Mental tests

The SDS questionnaire was used for this study. Patients with SDS scores $>$40 (possible range 20–80) were classified as having depression. The SDS consists of 10 positively and 10 negatively worded items that enquire about symptoms of depression. These scores were used to define categories of depression as not having significant depression ($\leq$40 points) and having significant depression ($\geq$41 points). The SDS has been translated into Japanese and the validity of the Japanese version has been previously confirmed [16].

2.3. Statistical analysis

Univariate regression analysis was used to identify statistically significant demographic variables (Table 1A). Multivariate regression analysis was used to determine which factor was the most significant contributor to duration of persistent dizziness (Table 1B). P values of $<$0.2 were considered as showing a trend toward significance for the univariate analysis, while those less than 0.05 were considered significant for the multivariate regression analysis. Chi square analysis was then performed to confirm the significance of the multivariate regression data between C-test(+), SVV(+), SDS(+), bilaterality(+) and duration of persistent dizziness in Figs. 2 and 3. $P < 0.05$ was considered statistically significant. All the statistical analyses were performed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Table 1
Univariate (A) and multivariate (B) regression analysis in results of 60 cases with intractable unremitting floating sensation.

Factors		P-value	Odds ratio	95% CI	
(A) Univariate regression analysis					
Age	(y.o.)	0.541	0.677	0.136	1.218
Sex	(m/f)	0.875	0.040	0.010	0.915
Laterality	(r/l)	0.909	0.033	0.008	0.942
Hearing	(dB)	0.267	1.005	0.730	1.272
C-test	**(+/−)**	**0.022**	**3.886**	**3.864**	**3.908**
cVEMP	(+/−)	0.825	0.058	0.008	0.883
SVV	**(+/−)**	**0.009**	**4.225**	**4.216**	**4.234**
ECoG	(+/−)	0.464	0.846	0.382	1.310
ieMRI	**(+/−)**	**0.121**	**1.025**	**0.904**	**1.146**
G-test	(+/−)	0.498	0.805	0.307	1.303
SDS	**(points)**	**0.035**	**2.440**	**2.405**	**2.475**
ADH	**(pg/mL)**	**0.086**	**1.140**	**1.054**	**1.226**
BAP	**(mg/L)**	**0.098**	**1.056**	**0.958**	**1.154**
(B) Multivariate regression analysis					
C-test	**(+/−)**	**0.026**	**3.225**	**3.199**	**3.351**
SVV	**(+/−)**	**0.010**	**4.331**	**4.311**	**4.344**
SDS	**(+/−)**	**0.048**	**1.667**	**1.418**	**1.814**

Univariate (A: $P < 0.2$) and multivariate (B: $P < 0.05$) regression analysis revealed that the periods of persistent dizziness were significantly longer in MD patients with positive caloric test (C-test+), those with positive subjective visual vertical (SVV+), and those with positive self-rating depression score (SDS+).

3. Results

All neuro-otological, imaging, blood testing, and mental test data are presented as positive (+) ratios of the number of unilateral MD patients with intractable unremitting floating sensation that were outside the normal range of examinations and questionnaires. The ratios (+) were as follows: C-test = 33.3% (20/60), cVEMP = 25.0% (15/60), SVV = 50.0% (30/60), G-test = 55.0% (33/60), ECoG = 63.3% (38/60), ieMRI = 86.7% (52/60), ADH = 35.0% (21/60), BAP = 11.7% (7/60), and SDS = 40.0% (24/60).

Subsequent multivariate regression analysis revealed that the periods of persistent dizziness were significantly longer in unilateral MD patients with C-test(+) ($P = 0.026$), SVV(+) ($P = 0.010$), and SDS(+) ($P = 0.048$) when compared with those with negative findings (Table 1). Chi-square analysis was then performed to further examine the significance of the multivariate regression data. Results showed that the presence of C-test(+) ($P = 0.018$), SVV(+) ($P = 0.006$), and SDS(+) ($P = 0.044$) was associated with persistent vertiginous sensation (Fig. 2). In addition, the periods in bilateral cases ($n = 28$:

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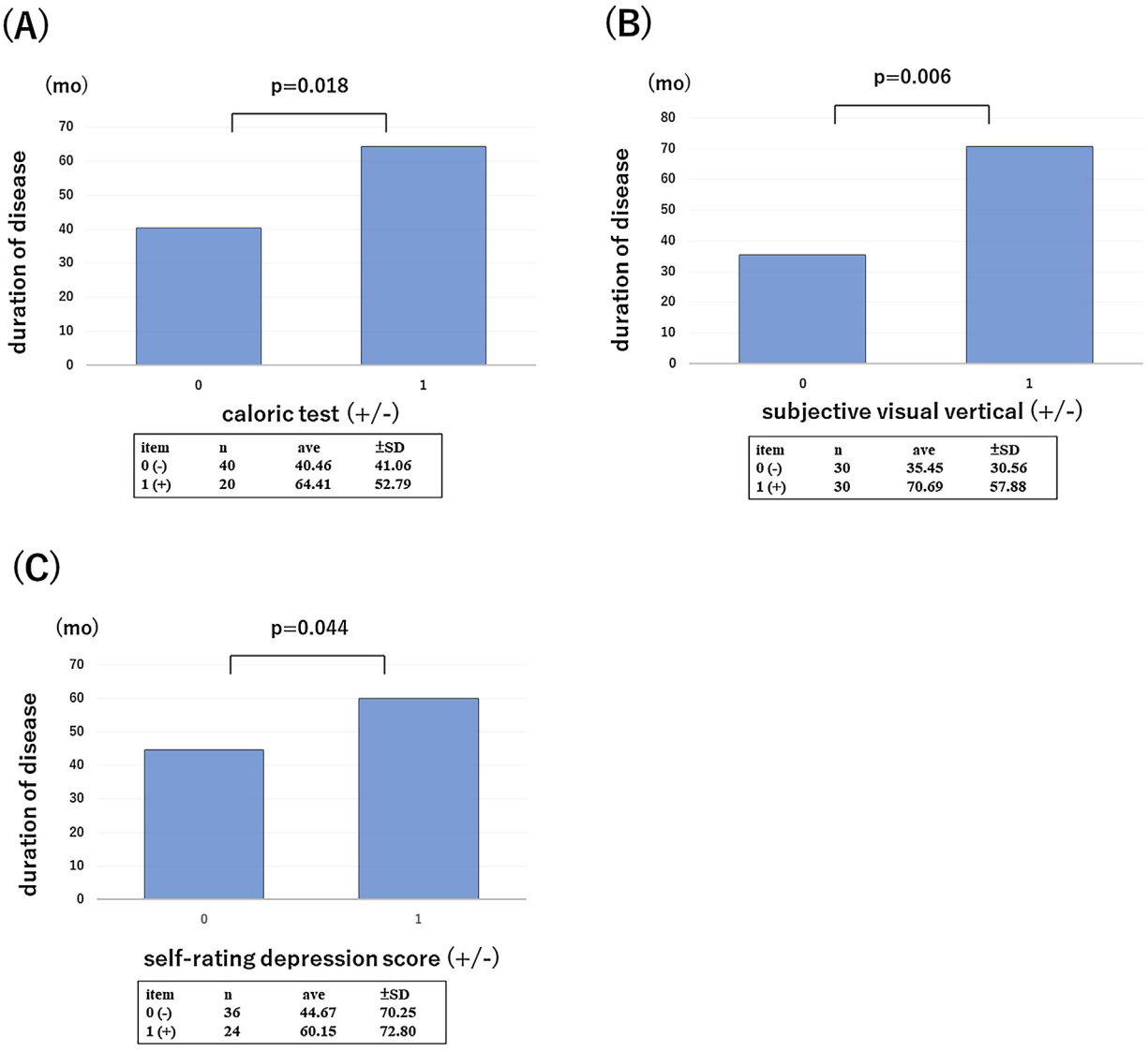

Fig. 2. Positive relationships between latent canal paresis (A), subjective visual vertical (B), and/or self-rating depression score (C) and duration of persistent symptoms of dizziness in MD. Positive caloric test (C-test+) (A), subjective visual vertical (SVV+) (B), and self-rating depression score (SDS+) (C) significantly caused persistent vertiginous sensation (chi-square analysis).

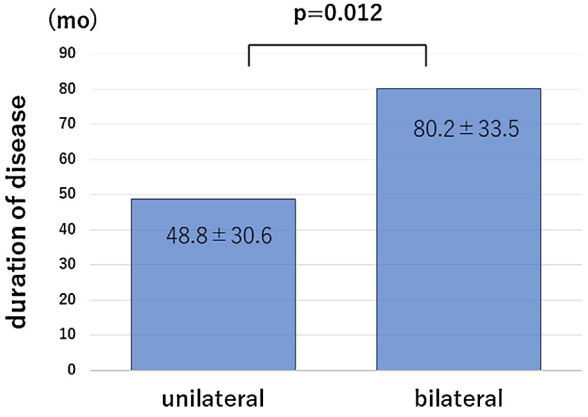

Fig. 3. Significant prolongation of periods of persistent dizziness in patients with bilateral Ménière's disease compared with unilateral cases. This figure clearly demonstrates that the periods of persistent dizziness in bilateral cases ($n = 28$) were significantly longer than those in unilateral cases ($n = 60$) (chi-square analysis).

80.2 ± 33.5 months) were significantly longer than those in unilateral ones ($n = 60$: 48.8 ± 30.6 months) ($P = 0.012$) (Fig. 3).

4. Discussion

In the present study, the ratios of the number outside the normal range of various kinds of vertigo/dizziness medical tests in unilateral MD patients with intractable floating sensation were as follows: C-test = 33.3%, cVEMP = 25.0%, SVV = 50.0%, G-test = 55.0%, ECoG = 63.3%, ieMRI = 86.7%, ADH = 35.0%, BAP = 11.7%, and SDS = 40.0%. In a previous paper we also presented the ratios of the number in idiopathic benign paroxysmal positional vertigo (BPPV) with persistent vertiginous sensation: C-test = 21.2%, cVEMP = 24.2%, SVV = 48.5%, G-test = 18.2%, ECoG = 18.2%, ieMRI = 12.1%, ADH = 9.1%, BAP = 13.6%, and SDS = 37.9% [17]. Semicircular canals deteriorated to greater extent in MD than in BPPV according to the C-test data.

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Otolith organs were as fragile in MD as in BPPV according to the results of cVEMP, SVV, and BAP, the osteoporosis-related marker of osteohomeostasis [18]. The incident ratios of EH were, as a matter of course, much higher in MD than in BPPV according to data from the G-test, ECoG, ieMRI, and ADH, the stress-related hormone with inner ear fluid homeostasis [14,15]. Psychological aspects were affected in similar manner in both MD and BPPV according to SDS data. These comparative findings suggest that the longer duration of disease could affect otolith dysfunction and that mental distress occurred to equal extent in both MD (even if not with otolith organ disease) and BPPV (even if not with mental illness). In fact it has been pointed out that 30%–40% of intractable MD coexists with BPPV [19] and 30%–40% of intractable BPPV also includes endolymphatic hydrops [17].

The present study revealed that the periods of persistent dizziness were significantly longer in unilateral MD patients with C-test(+) and SVV(+) in comparison with those with negative findings. The temporal bone study in MD reported endolymphatic hydrops mainly in otolith organs and semicircular canals [20]. Otolith dysfunction and canal paresis in MD may consist of reversible components attributable to endolymphatic hydrops and irreversible constituents related to damage to hair cells and/or neurons of the semicircular canals and otolith organs. The latter irreversible part would require vestibular rehabilitation [21] in addition to the medical treatment required for the former reversible part [8]. The discrepancy between SVV and cVEMP results is a controversial topic. SVV may have an influence both from a part of cVEMP and oVEMP. SVV may have a component other than cVEMP and oVEMP in the central vestibular system. Further studies are required about this.

The present study also revealed that the periods of persistent dizziness were significantly longer in unilateral MD patients with SDS(+) than in those with negative findings. Mental status has some influence on the stress-induced susceptibility of the inner ear and, thus, the outcomes of treatments [22]. In fact, surgical success rates of endolymphatic sac decompression have been reported as significantly worse in MD patients with neurosis/depression [23]. Although it has yet to be clarified that long-lasting MD symptoms lead to depression or that mental disease causes intractable endolymphatic hydrops, it is beyond question that MD patients with psychological distress should be treated with psychological care to improve their treatment compliance.

We set the factor of bilaterality apart from unilateral MD and into a separate analysis in the present study, because slight, but bilateral, damage in the inner ear can make dizzy symptoms much more bothersome via the jumbling phenomenon than serious, but unilateral, damage. The analysis revealed that the periods of persistent dizziness in bilateral cases were significantly longer than those in unilateral cases. In previous research, patients with a worse hearing level in the secondary affected ear (i.e., bilateral MD) had a significantly higher incidence of mental illness [23,24]. Both the psychologically susceptible condition and bilateral vestibular peripheral disorder in bilateral MD could be involved in the long-lasting motion-evoked floating sensation for the same reasons given in the foregoing discussion.

There are two major limitations to the present study. First, only unilateral MD patients with intractable persistent dizziness, who were able to be hospitalized for examination, were enrolled. Second, the duration of intractable unremitting floating sensation was determined according to the patients' history of subjective vertiginous feelings. Thus, a degree of bias could not be completely excluded. However, the aim of the study was to propose the most appropriate strategy to cure subjective vertiginous symptoms in intractable unilateral MD patients, including vestibular rehabilitation for canal paresis/otolith dysfunction and care for mental illness in addition to standard treatments for endolymphatic hydrops. Taken together, our findings indicate that MD patients with no episodic rotatory vertigo attacks but intractable persistent motion-evoked dizziness should undergo various neuro-otological, imaging, and blood tests to detect canal paresis, gravity-sensitive dysfunction, and neurosis/depression.

5. Conclusion

Although approximately 70% of patients with MD are usually treatable through the appropriate conservative medical approach, the presence of canal paresis, gravity-sensitive dysfunction, neurosis/depression, and bilaterality may make the persistent dizziness intractable and unremitting, thus creating the need for additional treatment approaches.

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Author contributions

Tadashi Kitahara: study design, data interpretation and writing. Masaharu Sakagami, Taeko Ito and Tomoyuki Shiozaki: data collection. Koichi Kitano and Akinori Yamashita: data collection and analysis. Ichiro Ota, Yoshiro Wada and Toshiaki Yamanaka: data interpretation.

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