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石津, 和幸

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Diagnosis and following up of Ménière's disease using multifrequency tympanometry—Cutoff values and temporal changes in measurements

Kazuyuki Ishizu [a], Akihiro Tamae [b,*], Kazuhiko Kubo [c], Takamasa Yoshida [d], Nozomu Matsumoto [d], Tetsurou Yasui [d], Takashi Nakagawa [d]

[a] Otorhinolaryngology ISHIZU Clinic, Ooazaharugami 1778-2 Shingu-tyo Kasuya-gun, Fukuoka, Japan
[b] Department of Otorhinolaryngology, Hamanomachi Hospital, Nagahama 3-3-1 Chuo-ku, Fukuoka 810-8539, Japan
[c] Department of Otorhinolaryngology, Chidoribashi General Hospital, Chiyo 5-18-1, Hakata-ku, Fukuoka, Japan
[d] Department of Otorhinolaryngology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi Higashi-ku, Fukuoka, Japan

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ABSTRACT

Objective: This study aimed to verify cutoff values for G width (the width of bimodal peaks for the waveform obtained when measuring conductance at 2000 Hz) in Japanese individuals diagnosed with Ménière's disease (MD) using multifrequency tympanometry (MFT) and to determine the relationship between the G width and ability to hear low-pitched sounds using measurements over time.

Methods: The study included 51 patients with clinically diagnosed MD, who had not undergone endolymphatic sac surgery, but had no other known ear disease (57 ears in patients aged 22–80 years were affected, and 45 ears in patients aged 18–83 years were unaffected; mean age: 53.3 ± 16.9 years). We also enlisted 80 healthy controls with no prior history of ear disease (160 ears, aged 22–76 years, mean age: 40.8 ± 15.7 years). MFT was used to measure the bimodal peak width of the waveform obtained when measuring conductance at resonance frequency of 2000 Hz. For patients who had G width measured several times over multiple outpatient visits, we used initial test data to analyze cutoff values. In nine cases with four or more measurements over time, we evaluated a possible correlation between G width and the sum of the hearing threshold for three low-pitched frequencies (125 Hz, 250 Hz, and 500 Hz). We used Student's t-test to determine significance.

Results: The both ears in the MD patients had a G width wider than the distribution in the control group. There was a significant difference between G width in the control group and in affected ears with MD ($p = 0.00026$) and there was also a significant difference between G width in the control group and in unaffected ears of MD patients ($p = 0.0056$). The cutoff value set with a specificity of 95% was 200 daPa, with a sensitivity of 35.1% and specificity of 95.6%. The cutoff value set with a sensitivity of 50% was 140 daPa, with sensitivity of 50.9% and specificity of 78.8%. There was no significant difference between resonance frequency of ears in the control group and ears with MD ($p = 0.41$). In nine cases with four or more measurements over time, a case showed a statistically significant positive correlation between the G width and hearing ability threshold for low-pitched sounds (125 Hz, 250 Hz, and 500 Hz) ($p = 0.03$), while an another case showed a tendency toward a

* Corresponding author. Fax: +81 92 714 3262.
E-mail addresses: kazu7250jp@gmail.com (K. Ishizu), tamae-a@hamanomachi.jp (A. Tamae), kubokazu@qent.med.kyushu-u.ac.jp (K. Kubo), yoshitak@qent.med.kyushu-u.ac.jp (T. Yoshida), kubokazu@qent.med.kyushu-u.ac.jp (K. Kubo), yasui@scb.med.kyushu-u.ac.jp (T. Yasui), nakataka@med.kyushu-u.ac.jp (T. Nakagawa).

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positive correlation, which was not statistically significant (p = 0.08). Further, there were cases that did not show significant differences in the present study, but might have shown a negative correlation if the number of measurements had been increased.
Conclusion: Measurement of G width using MFT may have accuracy as the traditional endolymphatic hydrops test. MFT is non-invasive, causes little discomfort for patients, requires little time to perform, and can be performed by paramedics. MFT was shown to be useful in screening for MD and it is effective in diagnosing MD to measure the change over time of G width using MFT.

1. Introduction

Ménière's disease (MD) is characterized by recurrent dizziness that is accompanied by auditory symptoms such as hearing loss, tinnitus, and aural fullness; it is accepted that endolymphatic hydrops (EH) is the cause of MD. In order to differentiate MD from recurrent dizziness caused by other conditions, the EH test is recommended [1,2]; however, the EH test as presently used is uncomfortable for patients, and is hard to be used in the same patient multiple times. Thus, a less invasive and easier diagnostic method of the EH is desirable.

Multifrequency tympanometry (MFT) is able to measure eardrum impedance by changing the frequency of the sound wave used for measurement; thus, resonance frequency and conductance can be measured for the middle ear. In prior studies, MFT was mainly used for analysis of middle ear conductive hearing system parameters such as resonance frequency. Darrouzet et al., recently reported that measurement of G width (the width of bimodal peaks for the waveform obtained when measuring conductance at 2000 Hz) with MFT can be used to determine endolymphatic pressure [3]. In addition, Franco-Vidal et al. in a French study, reported that measurement of G width with MFT can be used to diagnose MD [4]. If more widely adopted, MFT would be useful as a noninvasive and easy test for the diagnosis of MD. In addition to a study by Franco-Vidal et al., a study by Sugasawa et al. recently evaluated the cut-off value for G width [4,5]. Since, to date, clinical studies on G width are few, there is currently no consensus on the cut-off value for establishing a diagnosis of Ménière's disease. To generalize the diagnosis of MD by this test method, a consensus on the cut-off value for the diagnosis of MD must be reached. Therefore, we have performed a similar trial previously conducted by Franco-Vidal et al. and Sugasawa et al. to evaluate the cut-off value for MD diagnosis [4,5]. With regard to resonance frequency, Franco-Vidal et al. reported no significant difference between the MD group and the control group [4]. On the other hand, Sugasawa et al. reported a significantly lower resonance frequency for the MD group compared to the control group [5]. Thus, it is controversial whether measurement of resonance frequency is useful in the diagnosis of MD or not. Therefore, in this study, we evaluated the usefulness of measurement of resonance frequency for diagnosing MD. The study by Franco-Vidal et al. and Sugasawa et al. were limited to a single measurements, and there was no discussion of changes over time. In order to understand the relationship between G width and MD, we evaluated a possible correlation between G width and the hearing ability threshold for low-pitched sounds in patients for whom four or more tests were conducted over time.

2. Patients

The participants were 51 patients with diagnosed MD who had not undergone endolymphatic sac surgery at Chidoribashi Hospital, Fukuoka City, Japan, but had no other known ear disease (57 ears in patients aged 22–80 years were affected, and 45 ears in patients aged 18–83 years were unaffected; mean age: 53.3 ± 16.9 years). Measurements could not be performed in patients with distorted ear canals preventing use of earplugs; these patients were excluded from the study. We also enlisted 80 healthy controls with no prior history of ear disease (160 ears, aged 22–76 years, mean age: 40.8 ± 15.7 years). When examining the reproducibility of G width, we enlisted 4 healthy controls with no prior history of ear disease (7 ears, aged 23–24 years) separately from the examination of the cutoff value. One of the eight ears had poor ear condition and was not suitable for measurement.

3. Method

MFT was performed using Tympstar (Grason-Stadler, 10395 W 70th St., Eden Prairie, MN 55344, USA). We calibrated the instrument each day prior to measurement. Fukuoka City is at 0 m sea level; therefore, a pressure adjustment was not made. We measured G widths (the width of bimodal peaks for the waveform obtained when measuring conductance at 2000 Hz, Fig. 1) for MD patients and the control group using MFT in the 5 daPa step. For those patients in whom G width was measured several times over multiple visits, we used the initial test data for the analysis of cutoff values. When examining the reproducibility of G width, 4 controls (7 ears) were measured five consecutive times. Between the measurement and the next measurement the earplug was removed once and inserted again. In nine cases with four or more measurements over time, we evaluated a possible correlation between G width and the sum of hearing threshold for three low-pitched frequencies (125 Hz, 250 Hz, and 500 Hz). We used Pearson's product-moment coefficient to analyze the correlation. To test significance, we used Student's t-test; $p < 0.05$ was considered significant. This clinical study was approved by the ethics committee at Chidoribashi General Hospital (CH-2016-03) and was performed in accordance with the Declaration of Helsinki.

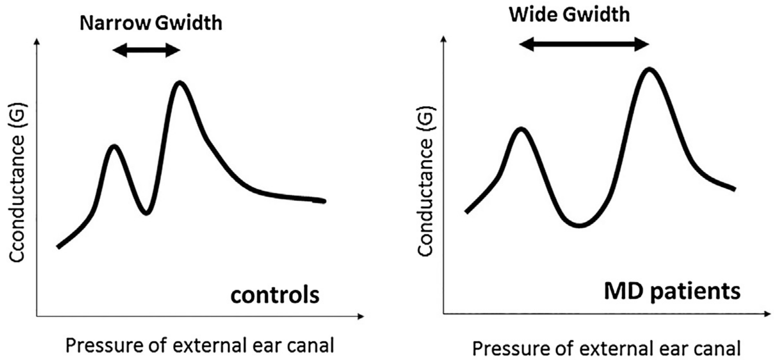

Fig. 1. The traces of conductance (G) tympanograms at 2 kHz in controls and MD patients. G width is the width of bimodal peaks for the waveform obtained when measuring conductance at 2000 Hz.

4. Results

The maximum value for G width in the control group was 305 daPa, the minimum was 20 daPa, and the mean was 97.0 daPa (Table 1). In the control group, there was no difference in G width between the sexes ($p = 0.21$) and between the right and left ears ($p = 0.18$).

The maximum value for G width in ears with MD was 490 daPa, the minimum value was 10 daPa, and the mean was 166.0 daPa (Table 1). Fig. 2(1) shows the G width of affected ears in interictal MD patients over the distribution of the G width for the control group; the horizontal axis shows the G width and the vertical axis shows the number of ears. The G width of the control group peaked at 60–75 daPa, while the both

Table 1
G width and resonance frequency for the control group, the affected side in MD patients, and the unaffected side in MD patients.

	N (ears)	Gwidth Ave.±SD (daPa)	Gwidth Distribution (daPa)	RF Ave±SD (Hz)	RF Distribution (Hz)
Control	160	97.0 ±52.0	20～305	955.0 ±241.7	200～1600
Affected ear	57	166.0 ±130.9 *	10～490	992.1 ±310.4	250～1850
Unaffected ear	45	135.9 ±86.1 *	20～390	994.3 ±283.5	450～1600

*$p < 0.05$.

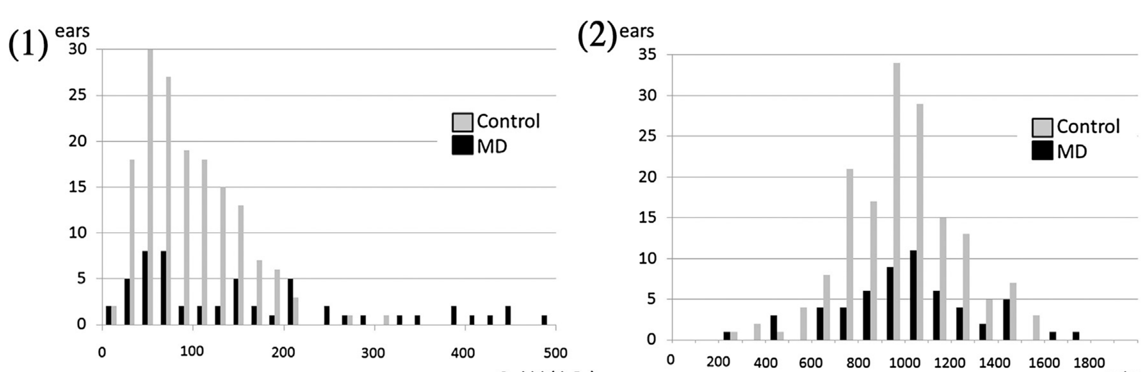

Fig. 2. (1) Distribution of G width for the control group and the affected side in MD patients.
(2) Distribution of resonance frequency for the control group and the affected side in MD patients.

Table 2
Relationship between the cutoff value, sensitivity, and specificity.

Cut-off (daPa)	Sensitivity	Specificity
130	52.60%	75.00%
140	50.90%	78.80%
150	45.60%	81.30%
160	40.40%	88.10%
170	40.40%	91.30%
180	38.60%	92.50%
190	35.10%	94.40%
200	35.10%	95.60%
210	35.10%	96.90%
220	29.80%	97.50%
235	22.80%	98.80%

Table 3
Four controls (7?ears) were measured five consecutive times. The standard deviations were 2.2–11.2 daPa.

G width(daPa)							
		1st	2nd	3rd	4th	5th	S.D.
Control 1	rt.	215	210	225	220	225	6.5
Control 2	rt.	70	75	75	75	80	3.5
	lt.	75	80	80	85	85	4.2
Control 3	rt.	55	55	50	55	55	2.2
	lt.	45	50	50	55	55	4.2
Control 4	rt.	20	50	45	45	45	11.9
	lt.	30	35	40	35	35	3.5

ears in the MD group had a G width wider than the distribution in the control group (Fig. 2(1)). There was a significant difference between G width in the control group and in affected ears with MD ($p = 0.00026$) and there was also a significant difference between G width in the control group and in unaffected ears of MD patients($p = 0.0056$). Distribution of resonance frequency in the control group and the MD group is shown in Table 1 and Fig. 2(2). In both groups, peaks were observed at 800–1100 Hz, with a nearly identical distribution. There was no statistically significant difference ($p = 0.41$).

On the basis of the above results, we examined the cutoff values using G widths (the conductance widths at 2 kHz) for diagnosis of MD (Table 2 and Fig. 3). In the report by Franco-Vidal et al., if 235 daPa was used as the cutoff value, sensitivity was 56.5% and specificity was 96.7%; however, when the same cutoff value (235 daPa) was used in this study, sensitivity was 22.8% and specificity was 98.8%. The cutoff value set with the specificity of 95% was 200 daPa, with a sensitivity of 35.1% and specificity of 95.6%. When the cutoff value was set for higher sensitivity, the cutoff value became 140 daPa with sensitivity of 50.9% and specificity of 78.8%. The cutoff value set with a sensitivity of 50% was 140 daPa, with sensitivity of 50.9% and specificity of 78.8%.

The results of the study of the reproducibility of G width are shown (Table 3). The standard deviations were 2.2–11.2 daPa.

We show the results for G width and the sum of the hearing threshold for three low-pitched frequencies (125 Hz, 250 Hz, and 500 Hz) for nine cases with four or more measurements over time. Cases 1, 2, 3, and 4 showed a correlation coefficient of 0.4 or higher between G width and hearing ability threshold for low-pitched sounds (Fig. 4(1)), while the correlation coefficient for Cases 5, 6, and 7 was between −0.4 and 0.4 (Fig. 4(2)). The coefficient was −0.4 or less for Cases 8 and 9 (Fig. 4(3)). Case 2 showed a statistically significant positive correlation between the G width and hearing ability threshold for low-pitched sounds ($p = 0.03$), while Case 1 showed a tendency toward a positive correlation, which was not statistically significant ($p = 0.08$). Although there were cases showing a positive correlation between MD and G width in the present study, there were cases that did not show statistically significant differences, but may have shown a negative correlation if the number of measurements had increased. Therefore, the results did not show a definite relationship.

5. Discussion

MFT performs measurements by continuously changing frequencies, and is able to measure conductance, susceptance, and admittance (reciprocal of impedance). When the frequency is increased, conductance shows bimodal peak beyond resonance frequency, unlike susceptance and admittance (Fig. 5). Resonance frequency measured by MFT is approximately 750–1100 in this stuby and prior studies [4–6], and conductance clearly presents bimodal peaks around 2000 Hz.

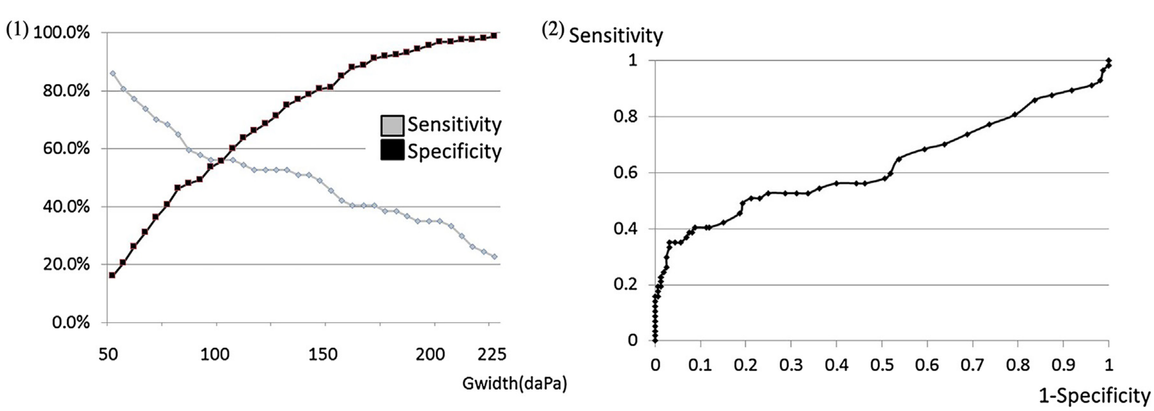

Fig. 3. (1) Relationship between the cutoff value, sensitivity, and specificity. (2) Relationship between sensitivity and specificity.

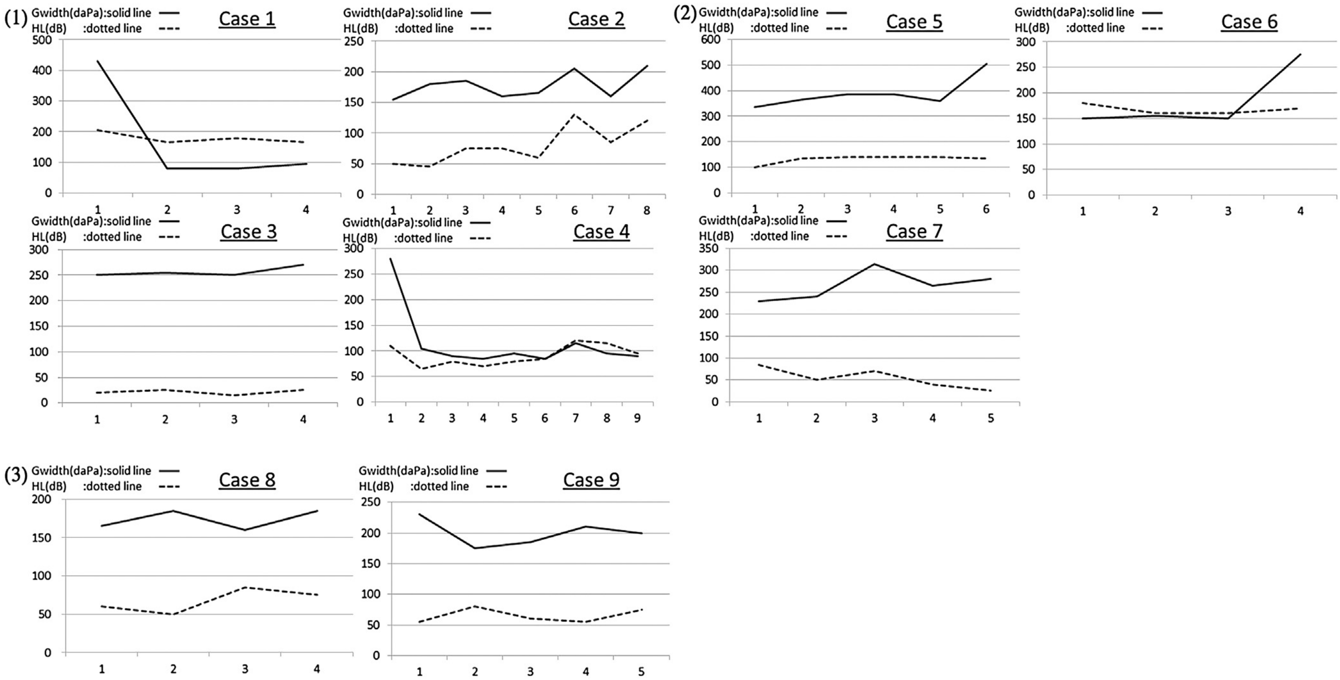

Fig. 4. The course of G width and the sum of hearing threshold for three low-pitched frequencies (125 Hz, 250 Hz, and 500 Hz) in nine cases with four or more measurements over time.
(1) Four cases with a correlation coefficient of 0.4 or higher (Case 1 at the top left, Case 2 at the top right, Case 3 at the bottom left, and Case 4 at the bottom right).
(2) Three cases with correlation coefficient between −0.4 and 0.4 (Case 5 at the top left, Case 6 at the top right, and Case 7 at the bottom left).
(3) Two cases with correlation coefficient of −0.4 or lower (Case 8 on the left and Case 9 on the right).

Darrouzet et al. reported that the width of bimodal peaks (G width) reflected endolymphatic pressure in a study using guinea pigs [3]. In addition, Franco-Vidal et al. reported that the G width was greater in patients with MD [4]. Recently, a study by Kato et al. that compared the contrast-enhanced MRI scans and measurement of G width reported that G width reflects EH [6]. Sugasawa et al. also reported that MFT is useful in the diagnosis of MD [5]. Based on the above studies, a concept that G width of MFT reflects EH can be established. Similar to the reports by Franco-Vidal et al. and Sugasawa et al., the present study observed increased G width in patients with Ménière's disease. In addition to the affected ear of MD patients, the G width of the unaffected ear was also wider than that of the controls. In MD patients, there is a possibility that there is a potential EH in the unaffected side, although there is no symptom. With regard to resonance frequency, Franco-Vidal et al. reported no significant difference between the MD group and the control group [4]. On the other hand, Sugasawa et al. reported a significantly lower resonance frequency for the MD group compared to the control group [5]. Thus, it is a matter of debate whether measurement of resonance frequency is useful in the diagnosis of MD or not. In this study, there was no significant difference in resonance frequency between the control group and the MD group, which is similar to the results reported by Franco-Vidal et al.

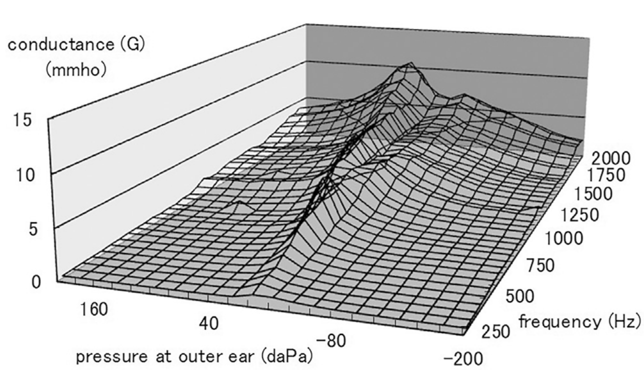

Fig. 5. Relationship between ear canal pressure, measurement frequency, and conductance.

Franco-Vidal et al. reported a specificity of approximately 95% when the cut-off value for G width for diagnosing Ménière's disease was set at 235 daPa [4]. Sugasawa et al. reported a sensitivity of 47.3% and specificity of 86.8% when the cut-off value for G width was set at 237.5 daPa [5]. Similarly, in the present study, when the cut-off value was set at 235 daPa, the sensitivity was 22.8% and the specificity was 98.8%. At a specificity of approximately 95%, the cut-off value for G width was 200 daPa. Based on the results of the present study, the appropriate cut-off value is likely lower than those observed in the two reports cited above. But since an appropriate cut-off value is depend on the prevalence of the disease and the ratio of MD among patients varies depending on the medical institution, it is necessary to set a cutoff value taking the ratio of MD patients in each facility into consideration.

EH tests have used glycerol, furosemide, glycerol load vestibular evoked myogenic potential (VEMP), electrocochleogram, and Gd-contrast MRI [7–13]. However, the glycerol test, furosemide test, and glycerol load VEMP are invasive, and require much effort, since multiple measurements are required for each test [7–9,11]. In addition to being invasive, as it involves placing an electrode in the eardrum, an electrocochleogram is not easy to perform [10,11]. Gd-contrast MRI has greater sensitivity than other tests, and is thought to be useful [11], but instilling Gd through the eardrum is invasive and even intravenous administration requires a higher dose of Gd than usual [11,12]. Moreover, safety is an issue, measurement takes time, and the cost is high; thus, it is not a safe and easy test. Therefore, except in facilities that specialize in dizziness evaluation, EH testing is difficult to perform, and a simple, less invasive EH test is needed. This study suggests that 140–200 daPa may be appropriate as the cutoff value for G width for diagnosis of MD. Sensitivity and specificity based on this cutoff value would be 50.9–35.1% and 78.8–95.6%, respectively. A cutoff value set with a specificity of 95% would be 200 daPa, with sensitivity of 35.1% and specificity of 95.6%. A cutoff value set for greater sensitivity becomes 140 daPa, with sensitivity of 50.9% and specificity of 78.8%. Sensitivity was similar or worse compared to the results in a prior report that did not use MRI [7–10]. However, considering that MFT is a simple test, the measurement of G width using MFT is clinically useful. MFT causes little discomfort for patients, requires little time to perform, and can be performed by paramedics. Thus, MFT could be a simple EH screening test. If used in patients with recurrent dizziness, the cutoff value should be 140 daPa, and invasive tests to confirm the diagnosis should only be used in positive cases.

In order to make clinically significant measurement of G width over time, it is necessary to clarify the reproducibility of measurement of G width. The measurement error of G width was as shown in Table 3. The error was limited, and it was thought that it was enough to follow the clinical course for each case. In addition, as the patient burden is low and measurements can be performed during outpatient visits, it is easy to follow the clinical course for each case. The study by Franco-Vidal et al. and Sugasawa et al. were limited to a single measurement in interictal patients, and changes over time were not discussed. In contrast, this is the first report to evaluate data over time. In examination of nine cases in which four or more measurements were taken, some showed a positive correlation between MD and G width.

Suga et al. [14] examined 20 ears using MRI, EH improved in two of three ears in which also showed improved symptoms with 1 year of conservative treatment, however, EH improved in only one of 17 ears that showed no symptom improvement. A relationship between reduction in EH and improvement in symptoms has been noted [14]. If MD were simply due to increased endolymphatic pressure, the more severe the MD, the greater would be the hearing ability threshold with increasing G width; further, with improvement in MD, G width would decrease and the hearing ability threshold would also decrease. Therefore, the mechanism is easy to understand for cases in which the hearing ability threshold for low-pitched sound and G width show a positive correlation. However, there were cases in the present study that did not show significance with MFT, but which might have shown a negative correlation if the number of measurements had increased. What would happen if the hearing ability threshold for low-pitched sound and G width showed an inverse correlation? Although such a mechanism cannot be derived from this study, Schuknecht's hypothesis for Reissner's membrane rupture [15] may provide a clue for elucidating this phenomenon. This hypothesis states that when the endolymph pressure increases, part of the membrane ruptures, and potassium ions leak from the endolymphatic space to the perilymphatic space, causing dizziness and hearing loss. If a small rupture persists, the endolymphatic pressure does not decrease even when there is leakage of endolymph, and the increased pressure results in more leakage, which causes deterioration in hearing ability for low-pitched sound. Cases in which membrane rupture or closure occurs easily may indicate that when endolymphatic pressure increases and the membrane

Table 4
The course of G width and the sum of hearing threshold for three low-pitched frequencies (125 Hz, 250 Hz, and 500 Hz) in nine cases with four or more measurements over time.

No.		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	Correlation function
1	G width (daPa)	430	80	80	95						0.92*
	LT-HL (dB)	205	165	180	165						(*p < 0.1)
2	G width (daPa)	50	45	75	75	60	130	85	120		0.76**
	LT-HL (dB)	155	180	185	160	165	205	160	210		(*p < 0.05)
3	G width (daPa)	20	25	15	25						0.69
	LT-HL (dB)	250	255	250	270						
4	G width (daPa)	280	105	90	85	95	85	115	95	90	0.41
	LT-HL (dB)	110	65	80	70	80	85	120	115	95	
5	G width (daPa)	335	365	385	385	360	505				0.36
	LT-HL (dB)	100	135	140	140	140	135				
6	G width (daPa)	150	155	150	275						0.16
	LT-HL (dB)	180	160	160	170						
7	G width (daPa)	230	240	315	265	280					−0.19
	LT-HL (dB)	85	50	70	40	25					
8	G width (daPa)	60	50	85	75						−0.47
	LT-HL (dB)	165	185	160	185						
9	G width (daPa)	55	80	60	55	75					−0.69
	LT-HL (dB)	230	175	185	210	200					

ruptures, the pressure decreases, causing hearing ability for low-pitched sound to deteriorate. As the membrane is subsequently repaired, the attack will subside, and the endolymphatic pressure increases. In addition, if a large membrane rupture cannot close for some reason, even if the endolymphatic pressure is low, inflow of potassium ions occurs intermittently, resulting in ongoing intermittent dizziness. There are many MD cases in which G width does not increase (Fig. 2(1)), and there are MD patients in whom EH is not detected with high sensitivity on contrast MRI. Therefore, multiple mechanisms may be involved in the deterioration of MD. There was a considerable overlap in the distribution of G width between MD group and control group (Fig. 2(1)). And the relationship between G width and low-frequency hearing was not substantial (Fig. 4(1–3), and Table 4). Also, the width of G width is also affected by the middle ear, clinical significance of G width is only one indicator to assist MD diagnosis at the moment. But MD is thought to have various pathologies, no single clinical test has been found to diagnose MD with high accuracy. G width is thought to be worthwhile to diagnose some type of MD. In order to investigate under what conditions the G width will be expanded, it is necessary to compare the clinical findings and the examination results of the case where the G width is expanded and the case where it is not expanded. Theoretically, the glycerol test, furosemide test, and glycerol load VEMP evaluate the function of the cochlea and vestibule, while MRI evaluates EH, and the measurement of G width using MFT evaluates perilymphatic pressure. G width theoretically reflects the perilymphatic pressure, but considering that the G width is wide in patients with EH, it is speculated that G width also reflects the endolymphatic pressure via perilymphatic pressure. Additional measurements over time using MFT at each outpatient visit, combined with traditional EH testing, will further clarify the status of MD.

6. Conclusion

The both ears in the MD patients had a G width wider than the distribution in the control group. There was a significant difference between G width in the control group and in affected ears with MD ($p = 0.00026$) and there was also a significant difference between G width in the control group and in unaffected ears of MD patients ($p = 0.0056$). The cutoff value set with a specificity of 95% was 200 daPa, with a sensitivity of 35.1% and specificity of 95.6%. The cutoff value set with a sensitivity of 50% was 140 daPa, with sensitivity of 50.9% and specificity of 78.8%. There was no significant difference between resonance frequency of ears in the control group and ears with MD ($p = 0.41$). In addition, in nine cases with four or more measurements over time, a case showed a statistically significant positive correlation between the G width and hearing ability threshold for low-pitched sounds (125 Hz, 250 Hz, and 500 Hz) ($p = 0.03$), while an another case showed a tendency toward a positive correlation, which was not statistically significant ($p = 0.08$).

Measurement of G width using MFT may have accuracy as the traditional endolymphatic hydrops test. MFT is non-invasive, causes little discomfort for patients, requires little time to perform, and can be performed by paramedics. MFT was shown to be useful in screening for MD and measurement of change in G width over time might be effective in clarifying the status of MD.

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