

Vestibulo-ocular reflex tests may reflect unilateral Ménière disease progression

A cross-sectional study

Renhong Zhou, MS, Yangming Leng, MD, Bo Liu, MD* 

Abstract

Vestibular disorders can manifest several patterns of horizontal vestibulo-ocular reflex (VOR) impairment, which can be detected by caloric test and video head impulse test (vHIT). Several studies have examined the patterns of caloric-vHIT response in Ménière disease (MD). The purpose of this study was to investigate the diversity of caloric-vHIT response and its related factors in unilateral MD patients. We also explore the possibility of assessing the progression of unilateral MD by using the horizontal VOR tests.

Ninety-eight patients with unilateral MD were enrolled and underwent a battery of audio-vestibular evaluations, including the pure tone audiogram, caloric test, and horizontal vHIT. Some patients received the electrocochleography and glycerol test. The combined results of caloric test and horizontal vHIT were categorized qualitatively into 4 patterns: Pattern I: normal caloric and vHIT responses; Pattern II: abnormal caloric and normal vHIT responses; Pattern III: normal caloric and abnormal vHIT response; and Pattern IV: abnormal caloric and vHIT responses. The abnormal caloric results were semi-quantitatively subdivided into sub-patterns as mild, moderate, and severe abnormality. The associations between these patterns/sub-patterns and related factors were analyzed.

Pattern I was found in 35 cases (35.7%), Pattern II in 57 (58.2%), and Pattern IV in 6 (6.1%). No patient had Pattern III. No significant differences were found between the patterns/sub-pattern distribution and age, electrocochleography, and glycerol test results. Disease duration was not associated with the pattern distribution, while remained a relation with sub-pattern distribution. The pattern/sub-pattern distribution varied significantly across MD stages. The proportion of pattern II or pattern IV increased with the stage of unilateral MD.

MD can manifest several patterns of horizontal VOR impairment, of which the impaired caloric response with normal vHIT is the most common pattern. With the progression of unilateral MD, the caloric-vHIT pattern tends to shift, which may reflect the deterioration of endolymphatic hydrops and vestibular hair cells impairments.

Abbreviations: AAO-HNS = American Academy of Otolaryngology Head and Neck Surgery, AP = action potential, CP = canal paresis, cVEMPs = cervical VEMPs, ECoChG = electrocochleography, ELH = endolymphatic hydrops, MD = Ménière's disease, MRI = magnetic resonance imaging, oVEMPs = ocular VEMPs, PTA = pure tone average, SCC = semicircular canal, SD = standard deviation, SNHL = sensorineural hearing loss, SP = summing potential, SPVmax = maximum slow phase velocity, VEMPs = vestibular evoked myogenic potentials, vHIT = video head impulse test, VOR = vestibulo-ocular reflex.

Keywords: caloric test, electrocochleogram, endolymphatic hydrops, glycerol test, Ménière disease, vestibulo-ocular reflex, video head impulse tests

Editor: Muhammad Tarek Abdel Ghafar.

RZ and YL are joint first authors.

This work was supported by the National Natural Science Foundation of China (NSFC No. 81670930), Natural Science Foundation of Hubei Province, China (No. 2016CFB645), and Fundamental Research Funds for the Central Universities, China (No. 2016YXMS240).

This study was approved by the ethical committee of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, and conducted in strict accordance with the tenets of the Declaration of Helsinki.

The authors have stated explicitly that there are no conflicts of interest associated with this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Zhou R, Leng Y, Liu B. Vestibulo-ocular reflex tests may reflect unilateral Ménière disease progression: A cross-sectional study. *Medicine* 2020;99:52(e23706).

Received: 24 February 2020 / Received in final form: 14 September 2020 / Accepted: 17 November 2020

<http://dx.doi.org/10.1097/MD.00000000000023706>

1. Introduction

Ménière disease (MD) represents an idiopathic inner ear disorder characterized by episodic vertigo, fluctuant sensorineural hearing loss (SNHL), tinnitus, and aural fullness. It affects both auditory and vestibular end organs, and is hallmarked histopathologically by endolymphatic hydrops (ELH).^[1] The clinical diagnosis depends on the symptoms, audiometry, and exclusion of other vertiginous disorders as recommended by the published criteria or guidelines^[2,3]; therefore, some tests are needed to definitively diagnose the condition.^[4] These auxiliary methods include the electrocochleography (EcochG), glycerol test, vestibular testing, and magnetic resonance imaging (MRI).^[5–7] Up to now, the severity or progression of MD has been quantified mainly on the basis of hearing level, which was proposed by the Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 1995.^[2] Although MD patients invariably exhibit vestibular symptoms, no generally accepted criteria exist to quantify the severity or progression of MD by using vestibular tests.

The assessment of the vestibular function is important in the management of MD, as it can facilitate differential diagnosis, quantitatively estimate the severity of vestibular damage, monitor the functional vestibular status.^[6] Clinically, the available instrumental vestibular tests included the caloric test, rotation test, vestibular evoked myogenic potentials (VEMPs), and video head impulse test (vHIT), etc.^[8] Among these tests, the cervical and ocular VEMPs (cVEMPs and oVEMPs) address the functions of the saccule (inferior vestibular nerve) and utricle (superior vestibular nerve) respectively, while the caloric, rotation test and vHIT assess the vestibulo-ocular reflex (VOR) function of semicircular canal (SCC). Furthermore, the caloric test evaluates the horizontal VOR function in low-frequency range (0.002–0.004 Hz), and vHIT measures the VOR of 6 SCCs in high-frequency domain (5–7 Hz).^[9–11] In most cases, caloric test and vHIT yield concordant results but may produce discordant results in some pathological conditions.^[12] Recently, many studies have demonstrated that the abnormal caloric reflex with preserved vHIT was common in patients with MD.^[13–16] Nevertheless, the incidence of this caloric-horizontal vHIT dissociation in MD varies greatly in the literatures.^[13,17,18] This variation may be explained by study population, instrument and procedure of vestibular tests. Until now, to our knowledge, no study has investigated the related factors regarding to the concordant and dissociated response of caloric-horizontal vHIT in patients with MD.

In this study, we retrospectively examined the audio-vestibular results of patients with unilateral MD. The aim of this study was to explore the diversity of caloric-vHIT response and its related factors in unilateral MD patients; and to investigate the potential application of vestibular tests of horizontal VOR function in assessing the progression of unilateral MD.

2. Materials and methods

2.1. Study populations

This study was approved by the ethical committee of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, and conducted in strict accordance with the tenets of the Declaration of Helsinki. All patients signed an informed consent form.

From July 2017 to June 2019, subjects who visited Department of Otorhinolaryngology, Union Hospital with a chief complaint

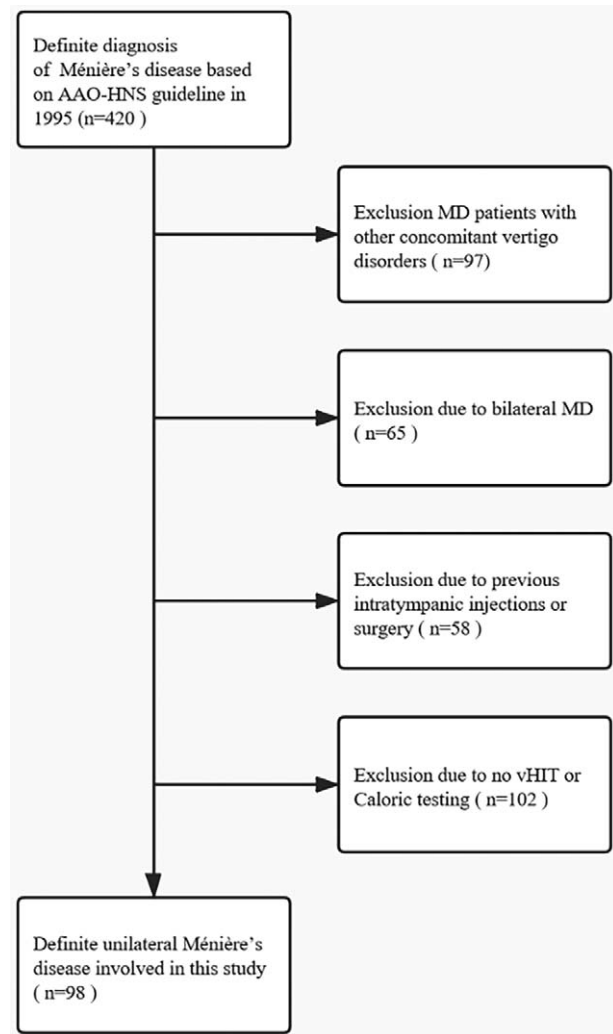


Figure 1. Flowchart for patient inclusion.

of vertigo or dizziness were included against the following criteria: definite diagnosis of MD based on AAO-HNS guideline (1995)^[2]; no symptoms or signs suggestive of central nervous system or other vertigo disorders, such as vestibular migraine, benign paroxysmal positional vertigo, persistent postural perceptual dizziness, etc; and no retro-cochlear space-occupying lesion confirmed by MRI. The exclusion criteria included bilateral MD, the patients with previous intratympanic injections (steroids or gentamycin) or surgery, concurrent middle or inner ear anomaly, and systemic diseases that could affect vestibular system. A flowchart of patient enrollment is presented in Figure 1.

2.2. Methods

The audio-vestibular evaluations were performed for all subjects during the interictal period, including the pure tone audiometry, caloric test, and horizontal vHIT. Furthermore, some patients also underwent the EcochG and glycerol test. The audio-vestibular tests were performed within an interval of 3 days.

2.3. Audio-vestibular evaluations

2.3.1. Pure-tone audiometry. Pure-tone audiometry was conducted in a soundproof room, at 0.125, 0.25, 0.5, 1.0, 2.0, 4.0,

and 8.0 kHz. Pure tone average (PTA; simple arithmetic mean of 0.5, 1.0, and 2.0 kHz pure tone threshold) was used to determine the stage of MD, which was classified as Stage I, a PTA of < 26 dB HL; Stage II, a PTA of 26 to 40 dB HL; Stage III, a PTA of 41 to 70 dB HL; and Stage IV, a PTA of > 70 dB HL.^[2]

2.3.2. Caloric test. The bithermal caloric test was performed on an infrared video-oculographic system (Visual Eyes VNG, Micromedical Technologies, Chatham, IL). The subject lay supine with their head and upper trunk elevated at 30°. Each ear was irrigated alternately with constant flow of air at temperatures of 24°C and 50°C for 60 seconds. The maximum slow phase velocity (SPV_{max}) of caloric nystagmus was measured following each irrigation, and the canal paresis (CP) was calculated according to the traditional Jongkees' formula. An interaural difference of caloric nystagmus of ≥25% is considered as significant CP, indicating an abnormal caloric response. According to the published criteria,^[19] if the summated SPV_{max} of the nystagmus was less than 20°/s under 4 stimulation conditions, the caloric response is indicative of bilateral vestibular hypofunction. In this case, ice water irrigation (4°C, 1.0 mL) would be used to confirm the caloric unresponsiveness.

2.3.3. Horizontal video head impulse test. The horizontal semicircular canals vHIT was administered by using an ICS Impulse system (GN Otometrics, Denmark) in accordance with the manufacturer's instructions by experienced technicians. Each patient wore a pair of lightweight, tightly fitting goggles with a small video oculography camera to record and analyze the eye movement. Patient was seated upright facing the wall 1.0 m away and was instructed to fixate a static target on the wall. The patient's head was passively and randomly rotated to the left and right with a low amplitude (5°~15°) and at a high peak velocity (150~250°/s) in an abrupt, brief and unpredictable manner. At least 20 head impulses were delivered in each direction. Refixation saccades were categorized, in terms of their appearance, as covert or overt. If the velocity of the saccade exceeded 50°/s, they were deemed positive. In the present study, it was taken as abnormal if the horizontal vHIT gain < 0.8 and refixation saccades appeared.

2.3.4. EcochG and Glycerol test. The methods of EcochG and glycerol pure-tone audiometry have been described in detail in our previous study.^[5] Summating potential (SP) and action potential (AP) were recorded. SP/AP ratio greater than 0.4 indicated the presence of ELH, and was defined as positive results, while the SP/AP ratio < 0.4 was deemed negative. The result of glycerol test was considered positive when the pure-tone hearing threshold was decreased by at least 10 dB at any 3 or more frequencies or at least 15 dB at one frequency at any time point after glycerol intake.

2.4. Classification of caloric-vHIT results

In the present study, the combinations of the caloric test and vHIT findings were qualitatively classified into 4 types: Pattern I: both caloric and vHIT responses were normal; Pattern II: caloric test yielded abnormal results but vHIT responses was normal; Pattern III: caloric response was normal while vHIT response abnormal; and Pattern IV: both caloric and vHIT responses were abnormal. Furthermore, the abnormal CP value was subdivided semi-quantitatively as follows: sub-pattern A: 26% to 50% (mild abnormality); sub-pattern B: 51% to 75% (moderate abnormality); sub-pattern C: 76% to 100% (severe abnormality). In this

study, the sub-pattern of A, B, and C was combined with Pattern II and IV to evaluate the severity of abnormal caloric response.

2.5. Statistical analyses

Statistical analysis was performed by employing the SAS software package, version 9.4. Quantitative variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR 25th to 75th percentiles) after verification of normal distribution. Qualitative variables were expressed as absolute values and percentages. Kruskal–Wallis H tests were used, respectively, to assess the effect of age and disease duration on the patterns/sub-pattern of caloric-vHIT results. When the pattern II and pattern IV were pooled together, the Mann–Whitney test was used to analyze the effect of age and disease duration on the combination patterns. Spearman rank correlation test was used to analyze the relationship between the Ménière stage and patterns or sub-patterns. Fisher exact test was utilized for analyzing the effect of results of EcochG and glycerol test on the combination patterns. In this study, *P* value < .05 was considered as statistically significant.

3. Results

3.1. Demographic data of the patients

This study included 98 patients with unilateral definite MD, of whom 50 (51%) were male and 48 (49%) were female. The mean age was 49.6 ± 12.9 years. The median course of unilateral MD was 1.0 (0.5–3.0) years.

In this series, caloric test yielded abnormal results in 63 cases (64.3%) and vHIT in 6 (6.1%). In terms of combinations of caloric and vHIT results, 35 cases (35.7%) were categorized as pattern I, 57 as Pattern II (58.2%), and 6 (6.1%) as Pattern IV. No patient had Pattern III. Thirty-five cases (35.7%) were categorized as Pattern II-A, 16 as Pattern II-B (16.3%), 6 as Pattern II-C (6.1%), 2 as Pattern IV-A (2.0%), and 4 as Pattern IV-C (4.1%).

3.2. Related factors of caloric-vHIT patterns and sub-patterns

3.2.1. Age. The age distribution among Pattern I, II, and IV was not significantly different ($H=0.746$, $P=.689$). When pooling the Pattern II and IV together, age was not significantly different between the patients of Pattern I and Pattern II+IV ($Z=-0.853$, $P=.394$). Furthermore, there was no significant difference of age distribution among sub-pattern I, II-A, II-B, II-C, IV-A, and IV-C ($H=3.308$, $P=.653$).

3.2.2. Course duration. The disease duration of Pattern I, II, and IV did not show significant difference ($H=2.691$, $P=.260$). When pooling the Pattern II and IV together, there was no significant difference in disease duration between the patients of Pattern I and Pattern II+IV ($Z=-0.802$, $P=.423$). However, the course duration was significantly different between sub-pattern I, II-A, II-B, II-C, IV-A, and IV-C ($H=17.27$, $P=.004$).

3.2.3. Stage of MD. According to AAO-HNS criteria in 1995,^[2] 13 patients were (13.3%) in stage I, 20 patients (20.4%) in stage II, 53 patients (54.1%) in stage III, and 12 patients (12.2%) in stage IV. Ménière stage was associated with caloric-vHIT pattern ($r=0.239$, $P=.018$, as shown in Figure 2) and sub-pattern ($r=0.246$, $P=.015$, as summarized in Table 1), respectively. The

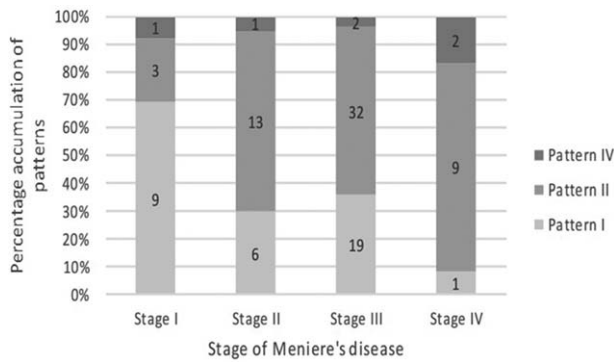


Figure 2. Percentage accumulation bar chart of pattern classifications in patients with unilateral MD at various stages. The number shown in the bar represents the case number.

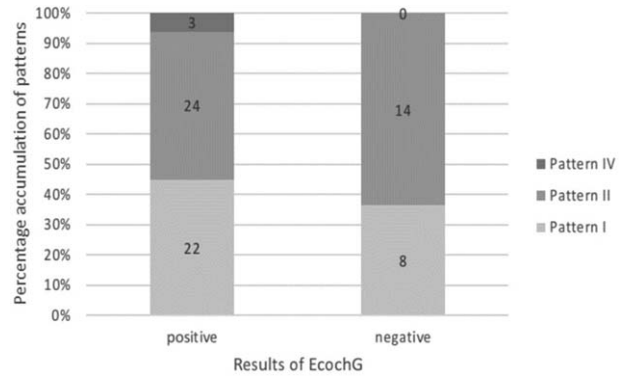


Figure 3. Percentage accumulation of patterns in unilateral MD disease patients with different SP/AP results in EcochG. The number shown in the bar represents the case number. EcochG, electrocochleography.

proportion of Pattern II or Pattern IV increases with the MD progression ($\chi^2 = 10.564, P = .013$).

3.2.4. EcochG. Eighty MD patients also underwent EcochG, and the clear wave forms of SP and AP peaks were obtained in 71 patients. Of these 71 patients, 49 had positive results and 22 negative results. The distribution of pattern or sub-pattern was not significantly different between patients with positive EcochG results and those with negative ones ($P = .453$ and $P = .862$, respectively, as shown in Figure 3 and Table 2).

3.2.5. Glycerol test. Thirty-four MD patients also received glycerol tests, with positive result in 16 cases and negative in 18. Neither pattern nor sub-pattern distribution was significantly different between patients with positive and negative results ($P = .884$ and $P > .999$, as shown in Figure 4 and Table 3, respectively).

4. Discussion

4.1. Patterns of caloric-vHIT response in unilateral MD patients and its related factors

In this study, Pattern II (ipsilateral attenuated caloric response as well as normal vHIT result) was most common (58.2%) in the patients with unilateral MD during the interictal period. The prevalence of Pattern II in our study was higher than that reported by Lee et al (18.1%)^[12] and Hennigan et al (5.9%)^[16] in unselected patients with vertigo or dizziness. This high prevalence of caloric-vHIT dissociation in MD patients may be explained by the following 2 hypotheses. The first is the hydrostatic temperature

dissipation hypothesis that attributed the caloric-vHIT dissociation to the different test mechanisms between caloric test and vHIT.^[13] The expansion of membranous duct of the horizontal SCC may allow a local convective flow of endolymph, thus the thermally induced pressure gradient across the cupula was reduced, leading to less deflection of the cupula and consequently diminished caloric response. In support of this assumption, Choi et al^[6] observed an association between the caloric response and the severity of vestibular hydrops (as demonstrated by gadolinium-enhanced MRI of the inner-ear) in MD patients with normal vHIT results. The second is the dual frequency hypothesis. In this hypothesis, the caloric-vHIT dissociation might result from differential activation of vestibular hair cells by stimuli with different frequencies.^[20] It is believed that vHIT and the caloric test operate at different frequency ranges, with vHIT being of the high-frequency domain and caloric test low-frequency domain and stimulates type I and type II vestibular hair cell populations, respectively. Previous postmortem histological studies of archival human temporal bones showed that in MD type II hair cell populations decreased more obviously than type I hair cell populations.^[20] However, the dual frequency hypothesis was challenged by the recent histological evidence using fresh inner ears tissue from the living human MD patients, which found that both the type I and II hair cells are equally affected in MD.^[21] In addition, vestibular compensation may be at play. As rapid angular head movement is common in everyday activities, the high-frequency VOR may recover more readily from the vestibular hypofunction.^[22] Our results were consistent with previous studies, confirming such discrepancy in MD patients, which may be a new diagnostic marker for MD.^[4,6,9,15,16]

Table 1
Distribution of sub-patterns in patients with unilateral MD stratified by Meniere stage.

	Sub-pattern classifications						Total	Correlation coefficient	P
	I	II-A	II-B	II-C	IV-A	IV-C			
Stage I	9	2	1	0	1	0	13	$r = 0.246$.015
Stage II	6	11	0	2	0	1	20		
Stage III	19	15	14	3	1	1	53		
Stage IV	1	7	1	1	0	2	12		
Total	35	35	16	6	2	4	98		

MD = Meniere disease.

Table 2
Correlation between results of EcochG and sub-pattern in patients with unilateral MD.

Results of EcochG	Sub-pattern						P
	I	II-A	II-B	II-C	IV-A	IV-C	
Positive	22	13	8	3	1	2	.884
Negative	8	8	4	2	0	0	

EcochG = electrocochleography, MD = Meniere disease.

Besides the dissociated caloric-vHIT response, 2 concordant patterns were observed in this group. Pattern I occurred in 35 patients (35.7%) with unilateral MD. Although the pattern II was most commonly associated with MD,^[16] some MD patients still exhibited normal caloric test and vHIT response. Previous studies had demonstrated that the prevalence of normal caloric responses ranged from 23% to 58% in MD patients.^[10,23] According to the 2 aforementioned hypotheses, pattern I response, which was mainly found in early-stage of unilateral MD in this study, might indicate less expansion of membranous duct of the horizontal SCC or less impairment of vestibular hair cell. Six patients (6.1%) were categorized into Pattern IV (concordant abnormal caloric-vHIT results). The pathological low vHIT gain values were rarely observed although the refixation saccades can occur very frequently in MD patients.^[14] In this study, the prevalence of pathologic vHIT, low VOR gain as well as refixation saccades, was lower than that of previous studies.^[17,18] This may be explained by the lower proportion (12.2%) of patients in Ménière stage IV in this study, as abnormal vHIT results occurred in higher stage of MD.^[24,25] Another possible explanation was the effect of course duration.^[18] The average disease duration in this study was shorter than that of previous studies.^[18,25] Thus,

concordant caloric-horizontal vHIT response was common in patients with MD.

In current study, no patient displayed Pattern III response. In agreement with our findings, Hannigan et al^[16] also reported an absence of Pattern III in an unselected cohort of vertiginous patients. Furthermore, several studies reported that the abnormal horizontal vHIT with preserved caloric response occurred mainly in central lesions.^[26,27] Recently, other studies reported the Pattern III can also be found in MD patients.^[12,17] The exact mechanism is unknown and might be ascribed to the selective damage of vestibular hair cells. The clinical significance of Pattern III in MD patients requires further investigations.

We found no correlation between age and pattern of caloric-vHIT response, which was consistent with previous studies.^[9,14] Blödown et al^[9] demonstrated that abnormal caloric or vHIT response did not depend on a patient's age. Also, Jerin et al^[14] did not find a correlation between age and vHIT gain or refixation saccades. However, age-related vestibular dysfunction can be observed clinically and histopathologically. Using head thrust dynamic visual acuity testing, Agrawal et al^[28] demonstrated that the SCC dysfunction is highly prevalent in the elderly ≥70 years older. The mean age of our cohort was about 50 years, thus the aging effect might be insignificant.

The present study found no correlations between the pattern of caloric-vHIT response and results of EcochG or glycerol test. It is generally accepted that the SP/AP ratio and positive glycerol results are the audiologic indicators for ELH in diagnosis of MD. The lack of correlation between the pattern of caloric-vHIT response and the conventional audiologic ELH indicators may be ascribed to the different testing mechanisms, that is, the caloric and vHIT target the functions of SCC, while the EcochG and glycerol test assess the cochlear function. In addition, it has been shown that cochlea ELH and vestibular ELH may progress nonsimultaneously in MD progression.^[29] Furthermore, by using inner-ear MRI with gadolinium injection in MD patients, Gurkov et al^[30] demonstrated some association between the radiological ELH with weaker caloric response, and failed to show any correlation between these ELH and the SP/AP ratio. Therefore, these indicators, such as the SP/AP ratio, results of glycerol testing and caloric-vHIT pattern, may have complementary clinical significance and should be used in combination in MD patients.

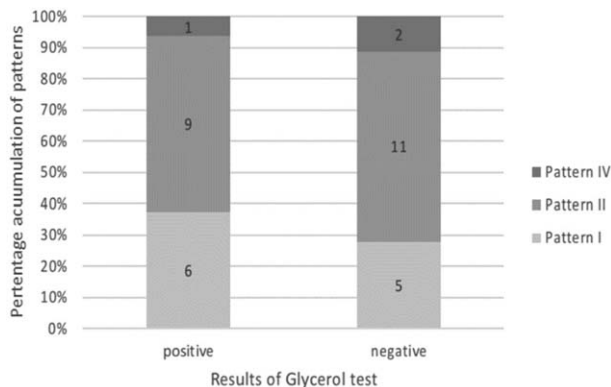


Figure 4. Percentage accumulation of patterns between the caloric test and vHIT in unilateral MD patients with positive and negative results of glycerol test. The number shown in the bar represents the case number.

Table 3
Correlation between results of glycerol test and sub-pattern in patients with unilateral MD.

Results of glycerol test	Sub-Pattern						P
	I	II-A	II-B	II-C	IV-A	IV-C	
Positive	6	6	2	1	0	1	>.999
Negative	5	6	3	2	0	2	

MD = Meniere disease.

4.2. Horizontal VOR tests may reflect MD progression

Our results demonstrated an association between the patterns of caloric-vHIT response and the MD stages based solely on hearing level. With the progression of disease, the caloric-vHIT pattern in unilateral MD patients tended to shift from Pattern I to Pattern II or Pattern IV.

Caloric test has long been in clinical use as measures of the horizontal SCC function. Compared with the caloric test, vHIT is a low-sensitivity, high-specificity test for detecting horizontal VOR pathology.^[17] Recent studies have found that in MD patients, the reduced caloric response, rather than vHIT response, is correlated with the severity of ELH (as demonstrated by gadolinium-enhanced MRI of the inner-ear).^[6,31] Because of the fluctuating nature of MD, the vestibular hair cell population driving the response could vary depending on the condition of the disease and the type of hair cell involved.^[18] On the basis of these findings, we suggest combination use of caloric test and horizontal vHIT in MD patients, as these tests allow for an integrated and comprehensive evaluation of the horizontal VOR function. Furthermore, the shift of caloric-vHIT pattern across MD stages may reflect the progression of ELH and impairments of vestibular hair cells involved, which indicated the possibility that caloric-vHIT pattern may serve as an ancillary indicator for assessing the progression of unilateral MD.

In the current study, the disease duration did not affect the distribution of caloric-vHIT pattern but was correlated with the caloric-vHIT sub-pattern. This finding may be due to the classification methodology, that is, the pattern of caloric-vHIT results were classified qualitatively and sub-pattern classification was classified semi-quantitatively. As the prevalence of vHIT abnormality was lower than that of caloric test in our series, the classification of pattern and sub-pattern mainly depended on the caloric results. McMullen et al^[32] found a correlation between abnormal caloric results and increasing duration of MD. Furthermore, the duration of MD correlated positively with ELH in vivo detected by MRI, and the higher rate of abnormal caloric response in severe ELH was observed.^[33] Thus, with the advancement of MD, the disease duration may affect the severity of ELH and sub-pattern of caloric-vHIT response subsequently.

The conventional staging system of MD was based on the arithmetic mean of the pure-tone thresholds,^[2] which is still used to assess the progression of MD. Until now, no staging criteria on the basis of vestibular function have been established yet for MD patients.^[2,3] Previous researchers have investigated the relationship between the MD stages and the vestibular function from the perspective of localization of vestibular impairment. Young et al^[34] found an association in the results of cVEMPs and MD stages. Moreover, Sobhy et al^[35] suggested that with the advancement in the stage of MD, the prevalence of abnormal cVEMPs, oVEMPs, caloric test, and vHIT responses was in agreement with the histopathological evidence of progression of the disease from the saccule up to the semicircular canals. Alternatively, by measuring the severity of horizontal VOR deficit, we observed a shift of pattern of caloric-vHIT results with the advancement of MD stage.

This study had some limitations. In this study, few patients with stage IV were enrolled. Besides, no patients showed Pattern III regarding with caloric-vHIT response. Compared with the dissociation Pattern II, Pattern III is more frequently encountered in central vestibulopathies. The diversity of caloric-vHIT pattern in MD should be investigated in future studies with larger sample size. Furthermore, to elucidate the change of caloric-vHIT

response during the progression of MD, longitudinal studies are warranted to better understand what role VOR plays in the development of MD.

5. Conclusion

Vestibular disorders can manifest several patterns of horizontal VOR impairment. Impaired caloric response with normal vHIT is most prevalent in patients with unilateral MD, but other combination patterns of these 2 tests are possible. With the progression of unilateral MD, the caloric-vHIT pattern tends to shift, which may reflect the deterioration of ELH and vestibular hair cells impairments.

Acknowledgment

We appreciate Pro. Meixia Lu for statistical consultation and analysis.

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