Evolution in the Findings of Head-Impulse Tests During the Attacks of Menière's Disease

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Objective: To determine the vestibulo-ocular reflex (VOR) performance during the attacks of Menière's disease (MD) using video head-impulse tests (video-HITs) according to each ictal phase.

Study Design: Retrospective case series review.

Methods: We analyzed the results of video-HITs in 24 patients with unilateral definite MD during and between the attacks.

Results: The head impulse gain of the VOR was usually normal (81%, 39 of the 48 semicircular canals [SCCs] in 16 patients) in the affected ear during the irritative or recovery phase, and did not differ from that for each SCC between the attacks (horizontal [HCs], $p = 0.412$; anterior [ACs], $p = 0.920$; posterior canals [PCs], $p = 0.477$). During the paretic phase, however, the head impulse gains of the VOR were equally normal (22/42, 52%) or decreased (20/42, 48%) for the affected ear (42 SCCs in 14 patients). The gains for the HCs were lower during the paretic phase than those between the attacks in the affected ear, while those for the ACs and PCs did not differ (HCs, $p = 0.001$; ACs, $p = 0.158$, PCs, $p = 0.401$). Covert saccades were more frequently observed even in the presence of normal VOR gains during the paretic phase as well.

Conclusion: During the attacks of MD, HITs are usually normal during the irritative/recovery phases, but become positive in more than a half of the patients during the paretic phase. This evolution in the ictal findings of HITs may reflect characteristic ictal vestibular discharges in MD and should be considered in evaluating patients with MD according to each ictal phase during the attacks.

Key Words: Menière's disease—Nystagmus—Vertigo.

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Head-impulse tests (HITs) are widely applied to investigate the vestibular function in various disorders (1–4). Although patients with Menière's disease (MD) usually show diminished caloric responses (42–77%) (5–7), HITs have been reported mostly normal between the attacks (65–100%) (5–7).

During the attacks of MD, spontaneous nystagmus (SN) changes its directions over time (8). The irritative phase is characterized by SN beating toward the involved ear side. This irritative phase is followed by the paretic phase that shows SN beating toward the unaffected ear (8). After the paretic phase, restoration of inputs from the peripheral vestibular apparatus in combination with central compensation may reverse the static vestibular imbalance to favor the affected ear, resulting in recovery nystagmus that beats toward the affected side (9).

Previously, we reported that HITs are mostly normal during as well as between the attacks of MD using a magnetic search coil technique (10). However, the small number of patients did not allow comparison of the findings among the phases of MD during the attacks. This study aimed to determine the findings of video-HITs

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Study ethics: This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines of Institutional Review Board of Seoul National University Bundang Hospital (B-1906-546-102).

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during the attacks of MD according to each phase in a larger number of patients with MD.

MATERIALS AND METHODS

Patients

We reviewed the medical records of patients who had neurotologic evaluation during the attacks of vertigo and met the diagnostic criteria of definite MD from April 2015 to March 2019 according to the diagnostic criteria for MD proposed by the Barany Society in 2015 (11). The affected ear was decided with the side of auditory symptoms including hearing loss, tinnitus, and ear fullness (12). The stage of MD was determined according to the American Academy of Otolaryngology-Head and Neck Surgery hearing stage (12).

The Menière attacks were defined only when the patients suffered from vertigo that was severe enough to cause nausea/vomiting and impaired daily activities, and when abnormal SN was evident on video-oculography (10). During the attacks of unilateral MD, the irritative or recovery phase was defined by SN beating toward the involved ear, while the paretic phase was decided when SN beat toward the healthy ear (13). We could not distinguish the irritative from recovery phase since it was only possible when the nystagmus had been followed-up from the beginning of the attack. The presence of abnormal SN was determined only when SN was present even during visual fixation or the slow phase velocity of SN exceeded the values observed in normal controls ($\geq$1.1 deg/s) without visual fixation in darkness.

We reviewed the medical records of 47 patients with definite MD evaluated during an attack. After excluding 23 patients with disease duration longer than 5 years (n = 5), without video-HITs (n = 3), with a history of intratympanic gentamicin injection (n = 2), other vestibular disorders that may have affected the results of HITs (n = 2), with uncertain affected side (n = 2), or with ictal vertical nystagmus that did not allow classification of the ictal phase (n = 9), 24 patients were finally included for analyses (15 women, mean age $\pm$ standard deviation [SD] = 63 $\pm$ 12). Brain or inner ear MRIs were conducted in most patients (20/24, 83%) to exclude other causes of recurrent vestibulocochleopathy.

Head-Impulse Tests

Head and eye movements were recorded using video-based equipment (SLMED, [SLVNG, Seoul, South Korea]) for quantitative evaluation of HITs. Right eye position was recorded with a small, lightweight, high-speed digital video camera (Firefly MV, Point Grey Research Inc., Wilsonville, OR). The camera was mounted on a light plastic glasses frame with an elastic strap that locked the instrument tightly to the patient's head. The image of the eye was reflected from an infrared mirror to the camera. The eye was illuminated by two infrared light-emitting diodes. Head velocity was measured by three-axis gyroscope (L3G4200D, STMicroelectronics, Schiphol, Netherlands). Video images were analyzed online to calculate eye position using a pupil detection method based on a center-of-gravity algorithm written in C++ language. Eye velocity was obtained from the data processed by a two-point differentiator and low-pass filter (0–30-Hz bandwidth).

The patient was seated 1.2 m in front of a target. Calibration of the eye position was carried out with a red dot sequentially presented from the center by 10 degrees in vertical and horizontal directions. Then, a passive unpredictable, high-acceleration, small amplitude head rotations were delivered in the plane of the horizontal canals (HCs). After evaluation of the HCs, head-impulses for the vertical canals was delivered with the patients' head turned 30 to 40 degrees to the left or right of the fixation point eccentrically, being aligned to the plane of right anterior–left posterior and left anterior–right posterior canals. Eye and head movement data were synchronously sampled at a rate of 120 Hz. At least, 10 valid head impulses were recorded in each direction after excluding trials with blinks and outliers. Only those of the peak velocity of the head higher than 2000 deg/s were selected.

The vestibulo-ocular reflex (VOR) gains were measured for individual trials as the ratio of mean velocity of the eye divided by the mean velocity of the head during a 40-ms window centered at the time of peak head acceleration (14). Abnormal VOR gain was defined when the values were outside the mean $\pm$ 2SD obtained from the age- and sex-matched normal controls (normal gains for HCs = 0.88–1.27, for AC = 0.75–1.29, for PC = 0.77–1.13) (15). We also looked for the presence of covert and overt saccades during the examination among those with normal VOR gains. The findings observed during irritative/recovery and paretic phases were compared with those observed between the attacks in each patient.

Pure Tone Audiometry

All patients had evaluation of hearing using pure-tone audiometry. Pure-tone threshold were obtained at frequencies of 0.25, 0.5, 1, 2, 3, 4, and 8 kHz with calibrated pure-tone audiometry in a sound proof audio booth. The pure-tone average was calculated as an average of the pure-tone thresholds as measured at 0.5, 1, 2, and 3 kHz (AMA guides, 6th ed.). We only adopted the data of pure-tone audiometry performed during the attack.

Statistical Analysis

Statistical analyses were performed using SPSS (version 18.0; SPSS, Chicago, IL). The nominal/independent variables were compared using the χ^2 or Fisher's exact test, and continuous variables were compared using paired t test and repeated measures analysis of variance test with Bonferroni correction. Correlation between two variables was decided using Pearson's correlation. A significance level was set at $p < 0.05$.

RESULTS

Clinical characteristics of the patients are summarized in Table 1. The duration of disease varied from 1 month

TABLE 1. *Clinical profiles of the patients*

Age, mean $\pm$ SD	63 $\pm$ 12
Sex, women (%)	15/24 (63)
Lesion side, right (%)	12/24 (50)
Disease duration, median (IQR), years	1 (0.5–4)
MD stage (%)	
1	4 (17)
2	4 (17)
3	11 (46)
4	5 (21)
Pure tone average in affected ear, median (IQR), dB[a]	51 (38–65)
Migraine (%)	4/24 (17)
Family history (%)	
Recurrent vertigo or MD	2/24 (8)
Any autoimmune diseases	3/24 (13)

[a]The pure-tone average was calculated as an average of the pure-tone thresholds as measured at 0.5, 1, 2, and 3 kHz (AMA guides, 6th ed). In case of repetitive evaluation, those during the attack were chosen for analyses.

MD indicates Menierès disease.

TABLE 2. *Correlation analyses between disease duration, pure-tone average, and VOR gains for each semicircular canal*

	Disease Duration			Pure-Tone Average[a]		
	HC Gain	AC Gain	PC Gain	HC Gain	AC Gain	PC Gain
Irritative/recovery phase						
Affected ear	0.098	−0.064	0.031	**−0.500***	−0.160	−0.427
Unaffected ear	0.247	−0.012	−0.139	**−0.673****	−0.163	**−0.533***
Paretic phase						
Affected ear	0.112	0.487	−0.255	0.113	0.122	−0.242
Unaffected ear	0.037	−0.080	−0.009	−0.172	0.360	−0.335
Between the attacks						
Affected ear	−0.007	−0.097	0.275	−0.247	−0.198	−0.210
Unaffected ear	−0.236	−0.024	0.327	0.087	−0.195	−0.305

The values with a statistical significance ($p < 0.05$) are indicated in bold.
The values in each column indicate the Pearson's correlation coefficient.
[a]The pure-tone average was calculated as an average of the pure-tone thresholds as measured at 0.5, 1, 2, and 3 kHz (AMA guides, 6th ed).
*$p < 0.05$.
**$p < 0.01$.

to 5 years (median = 1 year, interquartile range [IQR] = 0.5–4 yr). Evaluation was performed during the irritative/recovery phase in 16 and during the paretic phase in 14 patients. Serial evaluation of HITs was available during both phases in six patients. Four patients were categorized into stage 1, four to stage 2, 11 to stage 3, and five to stage 4. During the irritative/recovery phases, the VOR gains for the HCs showed a negative correlation with pure-tone average both in the affected and unaffected ear. Meanwhile, those during the paretic phases and between the attacks did not show a correlation with the disease duration or pure tone average of the patients (Table 2).

Head Impulse Gain of the VOR During the Irritative/Recovery Phases

The head impulse VOR gains were normal for all semicircular canals (SCCs) in 10 patients (10/16, 63%) while decreased for at least one SCC in six patients (6/16, 37%; four in the affected ear and two in both ears).

Overall, the head impulse gain of the VOR was normal for 39 SCCs (39/48, 81%) in the affected ear during the irritative/recovery phase (Fig. 1A, Supplementary content 1, http://links.lww.com/MAO/A977). Covert saccades were rarely seen in the presence of normal VOR gain during stimulation of the HCs (1/11, 9%) and PCs (1/13, 8%) in the affected ear.

The gains did not differ between the sides for HCs (0.88 ± 0.17 versus 0.96 ± 0.11, $p = 0.066$), ACs (0.96 ± 0.11 versus 0.97 ± 0.11, $p = 0.832$), and PCs (0.85 ± 0.16 versus 0.91 ± 0.14, $p = 0.055$).

Head Impulse Gain of the VOR During the Paretic Phases

The head impulse VOR gains were decreased for at least one SCC in 11 patients (11/14, 79%, nine in the affected ear and two in both ears). In the affected ear, the gain was most commonly decreased for the HCs (n = 11), and then followed by PCs (n = 5) and ACs (n = 4, Fig. 1B, Supplementary content 2, http://links.lww.com/MAO/A978). In the intact ear, however, the gain was decreased for PCs (n = 1) and ACs (n = 1). Covert saccades were more frequently seen in the presence of normal VOR gain during stimulation of the HCs (2/3, 67%) and PCs (3/9, 33%) in the affected ear (Fig. 1C, Supplementary content 3, http://links.lww.com/MAO/A979).

Overall, the VOR gains were lower on the affected side than on the healthy side for the HCs and PCs, (HCs, 0.68 ± 0.19 versus 0.95 ± 0.09, $p < 0.001$; PCs, 0.78 ± 0.17 versus 0.90 ± 0.10, $p = 0.019$; 0), while those for the ACs were similar between the ears (0.88 ± 0.19 versus 0.95 ± 0.09, $p = 0.187$).

Comparison of the VOR Gains Among the Irritative/Recovery Phase, Paretic Phase, and Interictal Period

Quantitative measurements of HITs were also available in 18 patients between the attacks. The VOR gain for each SCC during the irritative/recovery phases showed no difference from that between the attacks either in the affected ($p = 0.412$; ACs, $p = 0.920$; PCs, $p = 0.477$, Fig. 2A, Supplementary content 1, http://links.lww.com/MAO/A977) or unaffected ear (HCs, $p = 0.404$; ACs, $p = 0.476$; PCs, $p = 0.982$). In contrast, the VOR gains for the HCs during the paretic phase were lower than those between the attacks in the affected ear ($p = 0.001$) while those for the ACs and PCs showed no difference (ACs, $p = 0.158$; PCs, $p = 0.401$, Fig. 2B, Supplementary content 2, http://links.lww.com/MAO/A978). By contrast, the VOR gain did not differ for each SCC in the unaffected ear (HCs, $p = 0.080$; ACs, $p = 0.984$; PCs, $p = 0.925$).

During the irritative/recovery phase, covert saccades were similarly seen during video-HITs for HCs (1/11 [9%] versus 0/11, $p \approx 1.000$), ACs (0/16 versus 0/15), and PCs (1/13 [19%] versus 1/12 [8%], $p = 0.740$) when compared with those observed between the attacks. During the paretic phase, however, covert saccades were more frequently observed during stimulation of the HCs and PCs in spite of normal VOR gains (HCs, 2/3 [66%] versus 0/11, $p = 0.033$, Fig. 1C, Supplementary content 3, http://links.lww.com/MAO/A979) while those were

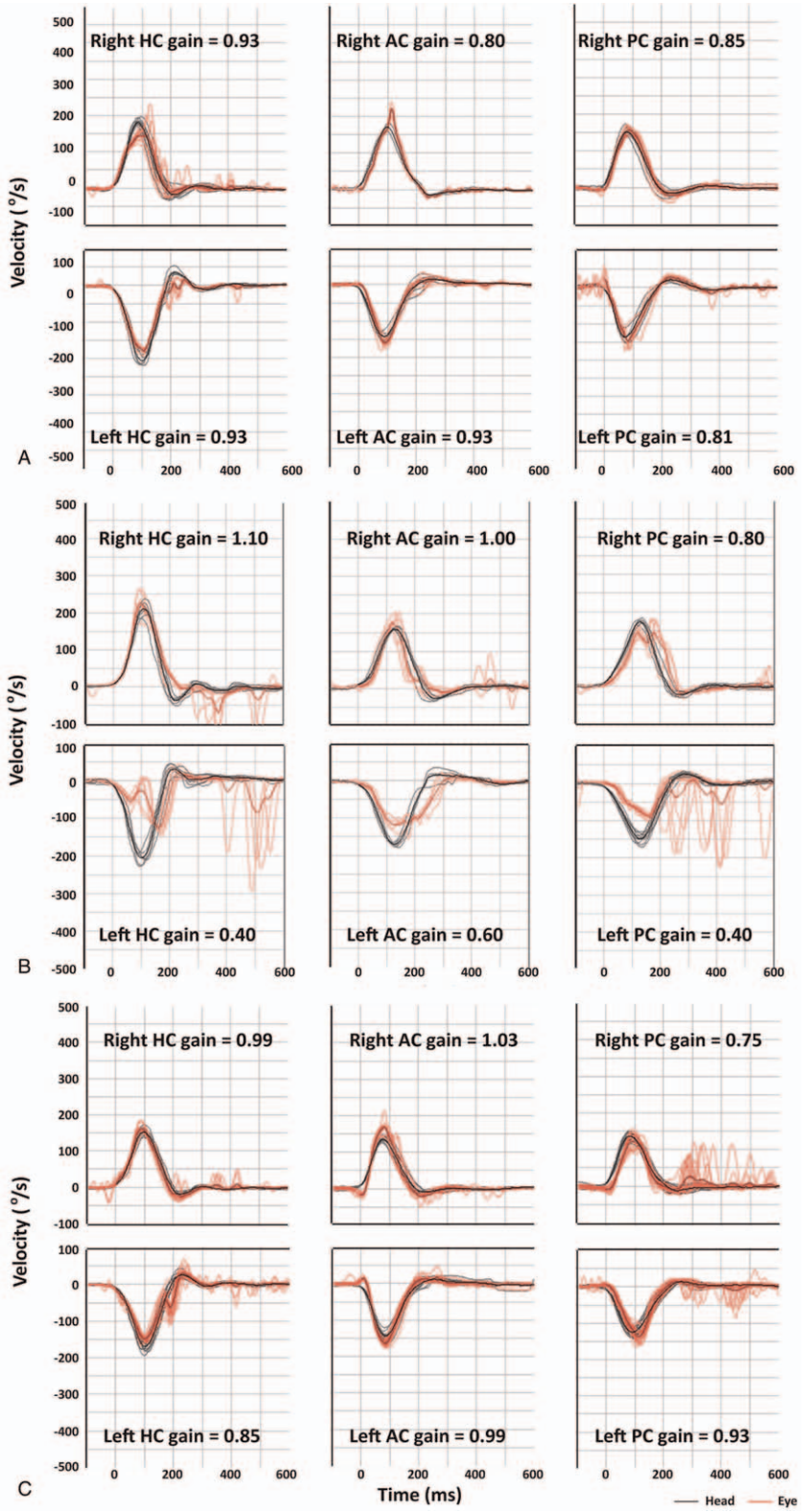

FIG. 1. *A*, Video head-impulse tests (video-HITs) in a patient during the irritative phase of Meniere's disease (MD) involving the right ear. Video-HITs show normal gain of the vestibulo-ocular reflex (VOR) for all semicircular canals. *B*, Video-HITs in a patient during the paretic phase of MD involving the left ear. Video-HITs show decreased gains of the VOR and overt saccades for all semicircular canals on the left side. *C*, Video-HITs in a patient during the paretic phase of MD involving the left ear. Video-HITs show normal gain of the VOR and covert saccades for the left HC. AC indicates anterior canal; HC, horizontal canal; PC, posterior canal.

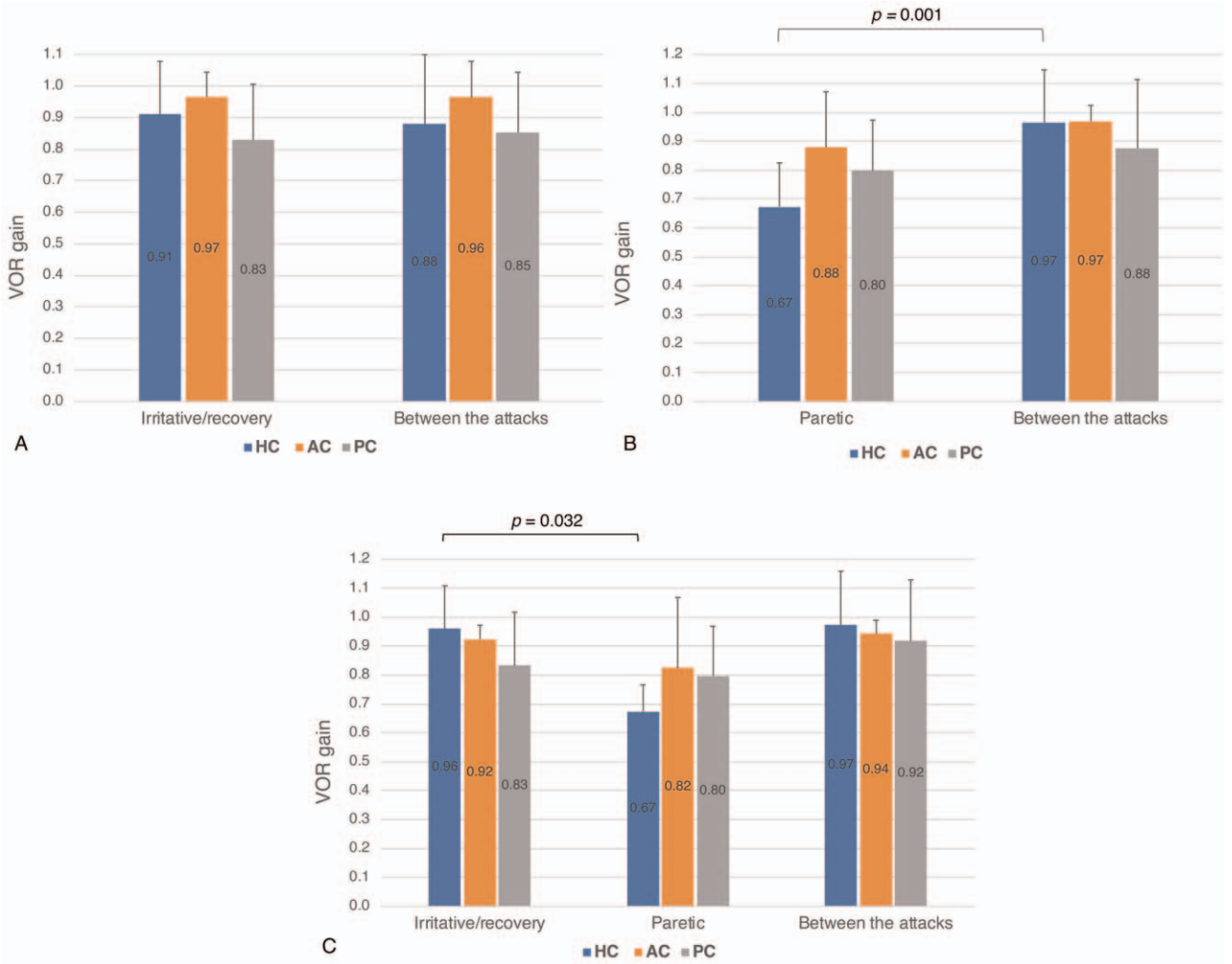

FIG. 2. *A*, The vestibulo-ocular reflex (VOR) gain for each semicircular canal during the irritative/recovery phase did not differ from that between the attacks in the affected ear. *B*, The VOR gains for the HC during the paretic phase are lower than those between the attacks in the affected ear, while those for the ACs and PCs shows no difference. *C*, In six patients with serial measurements of the VOR, the gains for the HCs during the paretic phase were lower than those during the irritative/recovery phase while those for the ACs and PCs did not differ among the phases. AC indicates anterior canal; HC, horizontal canal; PC, posterior canal.

similar for the ACs and PCs (ACs, 0/10 versus 0/15; PCs, 3/9 [33%] versus 1/12 [8%], $p = 0.272$). None of the patients with normal VOR gains during HITs showed overt saccades.

Evolution of HIT Findings

In six patients with serial measurements of the VOR, the VOR gains for the HCs during the paretic phases were lower than those during the irritative/recovery phase (mean $\pm$ SD $= 0.96 \pm 0.07$ versus 0.67 ± 0.04, $p = 0.032$) while those for the ACs and PCs did not differ among the phases (Fig. 2C, Table 3, Supplementary content 4, http://links.lww.com/MAO/A980).

Sensitivity Analysis

The details of sensitivity analyses were presented in the supplementary table, http://links.lww.com/MAO/A981.

1. Earlier stage (stage 1 and 2) versus later stage (stage 3 and 4)During the irritative/recovery phases, the VOR gains did not differ from those between the attacks, neither in the affected nor in unaffected ear irrespective of the disease stage. During the paretic phase, however, the VOR gains were decreased for the HCs of the affected ear.

DISCUSSION

Findings of this study can be summarized as follows: 1) patients with MD usually show normal head impulse VOR gains during the irritative/recovery phase and between the attacks. 2) The head impulse VOR gains are decreased during the paretic phase with frequent covert saccades even in the patients with normal gains. 3) The VOR gains are more likely to be decreased for the HCs than for ACs and PCs in the affected ear during the paretic phase.

TABLE 3. *Serial measurements of the VOR during and between the attacks.*

	Irritative/Recovery Phases			Paretic Phases			Between the Attacks		
	VOR Gain (Affected/Unaffected)			VOR Gain (Affected/Unaffected)			VOR Gain (Affected/Unaffected)		
Patients	HC	AC	PC	HC	AC	PC	HC	AC	PC
1	0.97/0.90	0.84/0.94	0.93/0.86	**0.67**/0.81	0.97/1.03	0.91/0.88	0.89/0.93	0.96/1.02	1.00/1.05
2	0.93/0.94	0.95/0.95	0.95/0.95	**0.67**/1.00	**0.72**/**0.74**	0.92/1.07	1.05/1.08	0.94/0.81	0.95/0.82
3	1.01/0.93	0.93/0.96	0.93/0.92	**0.55**/0.83	**0.44**/1.02	0.85/0.77	1.18/1.10	0.94/1.00	0.93/0.87
4	**0.74**/0.88	0.94/0.96	**0.51**/**0.62**	**0.67**/1.00	1.00/1.10	**0.50**/**0.70**	**0.70**/**0.87**	0.87/0.78	**0.57**/**0.72**
5	1.15/1.09	0.96/0.85	0.84/1.02	**0.81**/0.92	0.99/0.88	0.80/0.93	1.05/1.08	1.00/1.09	1.14/1.15
6	**0.82**/1.07	1.18/1.11	0.99/0.96	**0.58**/0.88	1.01/0.86	**0.64**/0.85	–	–	–

Abnormal values (<mean-2SD) are indicated in bold.
AC indicates anterior canal; HC, horizontal canal; PC, posterior canal; VOR, vestibulo-ocular reflex.

HITs are known mostly normal during as well as between the attacks in MD (10). However, only a few anecdotal case reports have compared the HIT findings among the phases of Menière attacks. This report, for the first time, documented the serial changes in the findings of HITs during the attacks of MD in a large number of patients.

The direction of SN may reverse during the acute stage of MD, and may reflect the vestibular asymmetry generated by excitation or paralysis of the vestibular afferents in the affected ear (8). Indeed, the VOR gains during the irritative/recovery phases are larger in the affected ear than in the healthy ear (16). This asymmetry reverses to present a larger VOR gain in the healthy ear during the paretic phase. Rotatory chair tests also showed that the increment and decrement of the VOR gain correlate with the direction of SN during the acute phases of MD (16).

Dynamic changes in the VOR during different phases may reflect the characteristic ictal vestibular physiology in MD. That is, the vestibular asymmetry may occur in favor of the affected ear during the irritative/recovery phase, which may be ascribed to overexcitation of the first-order afferent nerve fibers by mechanical distention of the membranous duct of labyrinth, leakage of the K+-rich endolymph into the perilymph, or central compensation (8,13,17). Therefore, the VOR gain of the HITs can be normal or increased during the irritative/recovery phases. Then, the vestibular asymmetry may reverse in favor of the healthy side during the paretic phase, due to depletion of ATP^{+} and blockade of action potential (8). Along with the reversal of SN (static vestibular imbalance), our study corroborates the dynamic vestibular changes during the attacks of MD.

Previously, serial evaluation of the VOR using HITs showed a rapid fluctuation of the gains in some patients with MD during the attacks (18–21). Likewise, the rapid increment of VOR gain in the affected ear just before the onset of Menière's attack also supports the dynamic changes of the VOR during the acute phases of MD (16,22). Although each ictal phase was not specified during the evaluation in those patients, we may speculate that the rapid decrease of VOR gain from the initial peak reflect an evolution from the irritative into the paretic phase. Although increased VOR gain was not recorded in our patients, it may be present only for a short period just after the onset of an attack. Indeed, some patients with MD showed an increased VOR gain during the irritative phase when measured using a magnetic search coil technique (10).

Of interest, patients frequently showed covert saccades in the presence of normal VOR gain during the paretic phases. This may reflect a small vestibular decline during the paretic phase. The presence of covert or overt saccades mostly indicates the lesion side in peripheral vestibulopathy when the VOR gains are within the reference range (23). Similarly, covert saccades in association with a normal VOR gain may be observed during the recovery after unilateral peripheral vestibulopathy (24). Indeed, compensatory covert saccades in the presence of normal VOR gains implicate that vestibular impairments may not be adequately characterized by the VOR gain only (25).

Serial follow-ups of video-HITs were available in some of our patients. In those patients, the transient VOR decrease was documented for the HCs during the paretic phase while this tendency was not observed in the vertical canals. This dissociated result among the canals may be primarily due to the small number of patients available for serial evaluation. Of note, the VOR decrement was observed for all SCCs during the paretic phase, when compared with those recorded either during the irritative/recovery phase or between the attacks in our patients. The preferential involvement of the HCs may be ascribed to distribution patterns of endolymphatic hydrops among the patients with MD. Indeed, the VOR gain reduction may not be uniform among the SCCs in MD (26,27). The endolymphatic hydrops are known to involve the vestibular organs in a rather orderly manner, mostly starting from the cochlear apex, and then saccule, utricle, and ampullae (28). However, the relative frequency of endolymphatic hydrops involving each individual SCC is still unknown. In this respect, recent advances in inner ear imaging may allow a crude estimation: The vertical canals, especially the PCs, are more frequently involved than the HCs in MD (27,29). However, these structural changes of individual SCCs do not correlate with the functional status of each SCC in our patients. Measurements of the VOR using a magnetic

search coil technique also documented a reduced gain for the HCs, but not for the vertical canals during HITs (10). This tendency was also observed in a previous study using a magnetic search coil technique (10) although the clinical implication of this result remains to be elucidated.

By convention, the diagnosis of MD mostly relies on clinical history and audiologic findings, and vestibular findings have been rarely taken into consideration for differential diagnosis. Since the clinical phenotype may vary especially during the earlier stage of MD (30,31), however, diagnoses relying solely on clinical features may not be desirable. Of interest, fluctuation of the VOR performance is not found in healthy subjects or those with other vestibular pathologies (18). Thus, the evolution in the ictal findings of HITs observed in our patients may reflect characteristic ictal vestibular discharges in MD, and would aid in diagnosis this disorder. Our study implicates that the fluctuation of VOR gain in accordance with direction reversal of SN may serve as a biomarker of MD.

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