Cervical VEMP Tuning Changes by Meniere’s Disease Stages

**Objective:** To determine if changes in cervical vestibular-evoked myogenic potential (cVEMP) testing reflect the different stages of cochlea-saccular hydrops in Meniere’s disease (MD).

**Methods:** This is a case-control retrospective series. Forty-seven patients with unilateral MD by American Academy of Otolaryngology-Head and Neck Surgery diagnostic and staging criteria, and 30 with non-MD vertigo as control. Meniere patients were further classified based on symptoms at the time of testing as active or stable. Subsequently, patients underwent cVEMP testing by tone-burst stimuli at 500 and 1,000 Hz. The main outcome measure was to compare the cVEMP 1,000 and 500 Hz amplitude ratio in ears with MD and non-MD vertigo, and in active versus stable MD.

**Results:** The cVEMP 1,000/500 Hz amplitude ratio was higher in Meniere’s ears (mean = 1.14 μV, SD = 0.25) than in non-Meniere’s ears (mean = 0.96 μV, SD = 0.2) (Student’s t test, P = .001), and higher in active (mean = 1.22 μV, SD = 0.25) than in stable MD (mean = 1.00 μV, SD = 0.18) (P = .0035). The diagnostic value of cVEMP 1,000/500 Hz amplitude ratio to differentiate MD versus non-MD vertigo was evaluated with a receiver-operating characteristics (ROC) curve and the area under the curve (AUC) was 0.716 (95% confidence interval [CI] [0.591, 0.829]). The ideal cutoff point was 0.9435 with sensitivity and specificity values of 83% and 53%, respectively. The sensitivity and specificity values for this test to differentiate active versus stable MD were 68% and 81%, respectively, with AUC 0.746 (95% CI [0.607, 0.885]) and cutoff value of 1.048. In all ears, the 1,000/500 Hz amplitude ratio increased by a decrease of the 500 Hz amplitude with increasing age.

**Conclusion:** The cVEMP 1,000/500 Hz amplitude ratio is elevated in ears with MD but not in those with non-MD vertigo. After corrected by age, this ratio is higher in active but not in stable MD, probably reflecting dynamic changes in saccular membrane motion mechanics in hydrops, and may be a useful marker of disease progression and the effect of therapy.

**Key Words:** cVEMP, Meniere’s, dizziness, hydrops.

**Level of Evidence:** IV

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**INTRODUCTION**

Meniere’s disease (MD) is a chronic inner ear disorder characterized by episodic vertigo, ear fullness, fluctuating hearing loss, and tinnitus. The diagnosis of MD is largely based on symptoms and supported by audiometric findings of sensorineural hearing loss.\(^1\) There is significant variability in the clinical presentation of MD and this creates a diagnostic dilemma in patients with atypical presentations. Temporal bone studies of MD have shown variable occurrence of endolymphatic hydrops in the different inner ear receptors, and that endolymphatic hydrops is more common in the cochlea and saccule than in the utricle and in the semicircular canals in probable and definite MD.\(^2\) Furthermore, since the AAOHNS criteria rely on the audiological threshold level,\(^3\) and considering that saccular hydrops might coexist with cochlear hydrops, we wanted to evaluate the usefulness of a test of saccular function,\(^4\) the cervical vestibular evoked-myogenic potential test (cVEMP).

The function of the saccule is measured by cVEMP.\(^3\) Loud auditory stimuli (clicks or tone bursts) applied to the saccule result in an electrical signal that is carried by the inferior vestibular nerve resulting in a large, short-latency, inhibitory potential in the contracted ipsilateral sternocleidomastoid muscle. Several groups recommend 500 Hz tone-bursts as the stimulus that more often yields the largest response amplitude and lowest threshold in young normal adults.\(^5,6\) Others, in contrast, have suggested that in MD, the best stimulus frequency shifts to 1,000 Hz.\(^7,8\) This frequency shift likely explains the reported conflicting findings in studies of cVEMP in MD.\(^7,12\) Young et al\(^11\) studied cVEMP in unilateral MD using 500 Hz tone-burst stimuli and reported a greater proportion of decreased amplitude or absent responses in later MD stages, and a positive correlation between interaural amplitude difference and MD stages. In contrast, Rauch et al\(^1\) have shown that tone-burst cVEMP amplitude responses (ie, decreased or absent waveform) do not correlate with ipsilateral audiometric thresholds, and also that cVEMP threshold and tuning may be abnormal in the unaffected ears of patients with unilateral MD, raising questions about the validity of interaural cVEMP amplitude comparisons. Consequently, we focused on another feature of cVEMP, the 1,000 to 500 Hz amplitude ratio, also known as the cVEMP tuning. cVEMP “tuning” is the amplitude difference between p13 and n23 at 1,000 Hz divided by the amplitude difference of the same peaks at 500 Hz within the same ear. The cVEMP 1,000/500 Hz amplitude ratio has been...
reported to be abnormal in MD and used in the differential diagnosis of non-MD vertigo.9,12 These reports, however, have not taken into account the fact that cVEMP responses and tuning vary with age. Piker et al13 have shown that the best frequency for evoking a VEMP increases with age. Accordingly, for older patients, 500 Hz may not be the ideal frequency to elicit VEMPs. In fact, they showed that for some older subjects, VEMP responses were only present in response to tone-burst stimuli of 750 and 1,000 Hz.

Multifrequency testing of VEMP subverts problems that derive from interaural comparisons when only using 500 Hz tone-bursts, as the best possible response for the patient will be obtained. Similarly, since it has been reported that cVEMP responses are absent at 500 Hz more often in later MD stages,11 multifrequency testing may still identify responses at higher stimulation frequencies allowing cVEMP to be of value in these later stages. Furthermore, it is hypothesized that the observed shift in VEMP frequency-dependent responses reflects changes in the mechanical properties or the electrical resonance of the hair cells in the saccule, and as such cVEMP tuning changes may be a valuable means of assessing disease progression in MD. Consequently, we sought to compare the cVEMP 1,000/500 Hz amplitude ratio in patients with definite MD and patients with non-MD vertigo, and among patients with MD at different stages of the disease.

MATERIAL AND METHODS

This study is a retrospective review of cases involving patients who presented with vertigo to our Neurotology clinic from January 2013 to December 2014, and approved by the University of Miami institutional review board (IRB# 20140154). We reviewed 440 records and the inclusion criteria were the following: 1) age 18 years or older; 2) recurrent spontaneous vertigo episodes as main complaint; 3) complete history and physical examination; and 4) audiovestibular testing. Cases of benign paroxysmal positional vertigo, superior semicircular canal dehiscence, bilateral MD, central vertigo, previous otologic surgery, retrocochlear lesions, and gentamicin therapy were excluded. After exclusions, patients with episodic spontaneous vertigo were classified into two groups: non-Meniere vertigo (non-MD), and Meniere disease (MD), based on the 2015 Diagnostic Criteria for Meniere’s disease formulated by the Classification Committee of the Bárány Society and adopted by several International Otolaryngology Societies.1 Meniere patients were further classified based on symptoms at the time of testing as (1) active MD (at least one definite MD vertigo attack and documented hearing change within the preceding 1 month) and (2) stable MD if patients had no vertigo episodes and stable hearing levels within 1 month before cVEMP testing.

Audiometry was done according to accepted standards (ISO 8253-1, 1989) and consisted of measurement of air and bone conduction pure-tone thresholds at 500, 1,000, 2,000, and 4,000 Hz. The bone conduction four-frequency pure-tone average (PTA) was calculated. In patients with MD, the worst audiogram before testing was used to calculate the PTA. The PTA was then used to classify patients into the four AAOHNS stages: stage I less than 26 dB, stage II 26–40 dB, stage III 41–70 dB, and stage IV greater than 70 dB.

Saccular function was assessed using cVEMP as previously described.14,15 Briefly, VEMP recordings were performed with the Navigator-PRO system (Bio-Logic Systems Corp., Mundelein, IL) using 500 Hz tone-burst air-conducted stimuli of 95 dB normal hearing level (nHL), 200 msec intervals, delivered via an earphone in the test ear. Surface electrodes were placed at the middle third of the ipsilateral sternocleidomastoid muscle (recording), low forehead (ground), and high forehead (reference). Subjects were in a semi-recumbent position with head turned to the contralateral side and slightly flexed, so that adequate level of tonic neck activation is maintained during the recording. Electromyography (EMG) feedback was used to maintain muscle tone at around 60 μV. The EMG was amplified (60 dB) and band-pass filtered (5–1,000 Hz). The test was performed at least twice to ensure reproducibility, and cVEMP responses were normalized by dividing raw amplitudes by background EMG activity. Both the left and right ears were tested separately. The amplitude values of the first biphasic responses (p13-n23) were analyzed. Responses were considered abnormal if absent, or decreased in the tested ear if the interaural amplitude difference was greater than 47%.1 To test the hypothesis that the frequency tuning of cVEMP is abnormal in MD,7,12 air-conducted 1,000 Hz tone-bursts stimuli cVEMP testing, following the same methodology as for 500 Hz testing, was performed for each separate ear. The 1,000/500 Hz amplitude ratio was calculated using the following formula:

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\text{cVEMP tuning} = \frac{\text{Amplitude difference (p13-n23) at 1,000 Hz}}{\text{Amplitude difference (p13-n23) at 500 Hz}}
\]

cVEMP 1,000/500 Hz amplitude ratio is referred to as cVEMP tuning interchangeably throughout the text.

MD patients underwent additional testing, including videonystagmography (VNG) and electrocochleography (ECOG). VNG included bi-thermal caloric testing and an interaural difference >30% was considered abnormal.14 ECOG was performed using the Navigator PRO system, Version 6.2 (Bio-Logic Systems Corp., Mundelein, IL) using a tympanic membrane recording electrode (Lilly TM-Wick; Intelligent Hearing Systems; Miami, FL) and stimulating with alternating click stimuli of 100 μsec at 90 dB nHL presented at a rate of 7.1 stimuli/sec. Based on the manufacturer’s data, summatting potential (SP)/action potential (AP) greater than 0.45 was considered positive.

In comparisons between the MD and non-MD vertigo groups, only the affected ear of MD cases was included for analyses. In non-Meniere cases, the test was reported abnormal if at least one ear was affected. Only one ear per patient was included in the analyses, and when both ears had abnormal results, one side was selected randomly. Descriptive statistics were used for prevalence estimates. Associations between diagnostic categories, MD stages, and the test outcomes were explored with contingency table and Fisher’s exact test. To discern whether the 1,000/500 Hz amplitude ratio can distinguish between active and stable MD, we employed univariate analyses. The diagnostic value of the 1,000/500 Hz amplitude ratio was also characterized by using a ROC curve. When a significant cutoff value was observed, sensitivity, specificity, and positive predictive value were presented. Furthermore, to
control for the effect of age on the cVEMP amplitude responses, a logistic regression using the disease status (active versus stable) as the outcome and age and the ratio as covariates was performed. All statistical analyses were performed using JMP Pro 14 (SAS Institute, Cary, NC) assuming a type I error rate of 0.05, except for the ROC calculations which were performed with R Studio software, version 1.1.456 (R-Tools Technology, Inc., Richmond Hill, Canada).

RESULTS
The initial review of records identified 81 suitable cases, of these 50 patients had a diagnosis of MD and 31 had non-MD vertigo. We were unable to record replicable cVEMP responses in the affected ear of three MD patients and in both ears of one patient with non-MD vertigo, and these four patients were excluded, rendering a total of 47 MD and 30 non-MD patients (77 patients). The study cohort’s age range was 23–89 years (mean = 53.7; SD = 16.2) and with equal gender distribution (male:female = 1:0.8). Diagnoses included in the non-MD group were labyrinthitis, vestibular neuritis, vestibular migraine, and recurrent vertigo of unknown origin. Table I shows demographic and testing data. There were no differences in terms of age and gender. MD patients were more likely to have unilateral hearing loss (60% vs. 21%, P = .045) and a shorter disease duration at the time of VEMP testing than non-MD patients (10.4 months vs. 16.2 months, P < .0001).

cVEMP and MD Versus Non-MD Groups
There were no significant differences in the mean cVEMP amplitude of the 500 Hz responses in the affected ear between the groups. The mean amplitude of the 1,000 Hz, however, was higher in the MD group. Similarly, the mean cVEMP 1,000/500 Hz amplitude ratio was significantly higher in MD than in non-MD patients (1.14 vs. 0.96, P = .0013). (Table I).

The diagnostic value of cVEMP 1,000/500 Hz amplitude ratio to differentiate MD versus non-MD vertigo was evaluated with a ROC curve (Fig. 1A). The diagnostic value of cVEMP 1,000/500 Hz amplitude ratio was fair with an area under the curve (AUC) of 0.716 (95% CI [0.591, 0.829]). The ideal cutoff point was 0.9435 with sensitivity and specificity values of 82.97% and 53.33%, respectively (Fig. 1A).

When comparing the proportion of abnormal cVEMP amplitude (ie, either absent response or decreased response) to 500 and 1,000 Hz stimulation of the affected ear, either absent or decreased, cVEMP had a modest diagnostic use with sensitivity of 76.92%, specificity of 57.58%, and positive predictive value of 68.18%.

Stages of MD
Despite a tendency for a greater proportion of patients with stable MD than with active MD to be in the late stages of MD, a Student’s t test did not show a significant difference in terms of age and the ratio of active versus stable disease status (P = .183). Active MD disease was associated with a mean duration of 23–89 years (mean = 53.7; SD = 16.2) and was more likely to have unilateral hearing loss (60% vs. 21%, P = .045) and a shorter disease duration at the time of VEMP testing than non-MD patients (10.4 months vs. 16.2 months, P < .0001).

| TABLE I. Distribution of 47 Meniere Patients in Disease Stages. |
|-------------------|-------------------|-------------------|-------------------|-------------------|
| Meniere Disease | Non-Meniere Vertigo | P |
|-----------------|-------------------|-------------------|-------------------|-------------------|
| N | 47 | 30 | .94 |
| Age (yr, mean [SD]) | 50.9 [17.9] | 52.3 [15.2] | .628 |
| Gender (M:F) | 25:22 | 15:15 | .815 |
| Disease duration (mo, mean [SD]) | 10.4 [2–22] | 16.2 [2–120] | <.0001* |
| Affected ear 500 Hz (amplitude [SD] [μV]) | 346.1 [130] | 347.4 [105.6] | .963 |
| Affected ear 1,000 Hz (amplitude [SD] [μV]) | 391.2 [157] | 316.6 [71.9] | .0172* |
| Affected ear 1,000 to 500 Hz ratio (mean [SD]) | 1.14 [0.25] | 0.96 [0.2] | .0013* |
| Nonaffected ear 500 Hz (amplitude mean [μV]) | 352 [129.8] | 338.9 [113.3] | .643 |
| Nonaffected ear 1,000 Hz (amplitude mean [μV]) | 289.04 [94.7] | 299.33 [83.8] | .643 |
| Nonaffected ear 1,000 to 500 Hz ratio (mean [SD]) | 0.85 [0.2] | 0.92 [0.2] | .127 |

*Significant difference at .05.

Stages of MD

| TABLE III. Mean 1,000/500 Hz Amplitude Ratio and Meniere’s Disease Stages. |
|-------------------|-------------------|-------------------|-------------------|-------------------|
| Stage | N | Mean (μV) | SD | P Value |
|-----------------|-------------------|-------------------|-------------------|-------------------|
| I | 6 | 1.09 | 0.2 | .643 |
| II | 22 | 1.18 | 0.3 | .628 |
| III | 14 | 1.1 | 0.2 | .6108* |
| IV | 5 | 1.09 | 0.2 | .547 |

*Analysis of variance (ANOVA) with post hoc Tukey-Kramer test.

**Student’s t test.**
stages III and IV (69% vs. 26%), the difference was not statistically significant. Interstage comparison of mean of 1,000/500 Hz amplitude ratio showed no significant difference (analysis of variance [ANOVA] with post hoc Tukey-Kramer test, $P = .818$). We further classified patients into two groups, “early” MD (stages I and II) and “late” MD (stages III and IV), and found no significant difference in the mean of the 1,000/500 Hz amplitude ratio between these two groups (Tables II and III).

Active Versus Stable MD
Among 47 MD patients, 31 were staged with “active” disease and 16 with “stable” disease. There were no significant intergroup differences in age and gender, but patients with “stable” disease had a longer disease duration, that is, the period from their reported onset of symptoms to the time of testing (14.7 months vs. 7.7 months, $P < .0001$) (Table IV). There were no significant intergroup differences in PTA, caloric testing, and ECOG results. Patients with active disease had a greater 1,000/500 Hz amplitude ratio in the affected ear than those with stable disease (1.22 vs. 1.00, $P = .0035$).

The sensitivity, specificity, and positive predictive value for the cVEMP 1,000/500 Hz amplitude ratio to differentiate active versus stable MD were 68%, 81%, and 88%, respectively, with an AUC 0.746 (95% CI [0.607, 0.885]) and a cutoff value of 1.048 (Fig. 1B; Table V).

### TABLE IV.
Demographic, Clinical, and cVEMP Test Results of 47 Meniere Patients by Disease Status: Active Versus Stable Disease.

|                      | Active Meniere | Stable Meniere | $P$  |
|----------------------|----------------|----------------|------|
| N                    | 31             | 16             |      |
| Age (yr, mean [SD])  | 50.6 [3.2]     | 51.4 [4.5]     | .891 |
| Gender (M:F)         | 18:13          | 7:9            | .375 |
| Disease duration (mo, mean [range]) | 7.7 [2–22] | 14.7 [11–19] | <.0001* |
| PTA (500–4,000 Hz, dB, mean [SD]) | 44.2 [22] | 42.2 [24.6] | .867 |
| Canal paresis (>30%) by caloric test | 13/31 (42%) | 8/16 (50%) | .758 |
| ECOG (SP/AP > 45%)   | 15/31 (48%)    | 8/16 (50%)     | 1.0  |
| Absent or reduced cVEMP response† | 23/31 (74%) | 8/16 (50%) | .371 |
| Abnormal 1,000/500 Hz ratio of affected ear (>1.04) | 21/31 (68%) | 3/16 (19%) | .002† |
| Affected ear 500 Hz (amplitude (mean [SD]) (μV) | 323.0 [125.2] | 390.8 [131.7] | .091 |
| Affected ear 1,000 Hz (amplitude (mean [SD]) (μV) | 395.9 [175.1] | 382.1 [119.9] | .779 |
| Affected ear 1,000/500 Hz ratio (mean [SD]) | 1.22 [0.25] | 1.0 [0.18] | .0035† |
| Nonaffected ear 500 Hz (amplitude mean [SD]) (μV) | 336.9 [135.7] | 382.1 [115.9] | .263 |
| Nonaffected ear 1,000 Hz (amplitude mean [SD]) (μV) | 275.8 [101.7] | 314.6 [75.6] | .186 |
| Nonaffected ear 1,000/500 Hz ratio (mean [SD]) | 0.86 [0.03] | 0.84 [0.04] | .971 |

* Student’s t test, two-tailed.
† Fisher’s exact test, two-tailed.
‡ Interaural amplitude difference (affected-nonaffected ear) > 47%.

AP = action potential; cVEMP = cervical vestibular-evoked myogenic potentials by tone-bursts using 500 and 1,000 Hz stimuli; ECOG = electrocochleography; M:F = male-female counts; PTA = pure-tone average; SP = summating potential.

### TABLE V.
Sensitivity, Specificity, and Positive Predictive Value of Diagnostic Tests in Differentiating Active Versus Stable Meniere’s Disease.

|                      | Caloric Paresis >30% | ECOG SP/AP >45% | Absent or >47% Reduced cVEMP at 500 Hz | 1,000/500 Hz ratio >1.04 |
|----------------------|----------------------|-----------------|--------------------------------------|--------------------------|
| Sensitivity (95% CI) | 41.9% (24.5–60.9)    | 65.22% (42.73–83.6) | 74.2% (55.4–88.1) | 67.8% (57.7–88.9) |
| Specificity (95% CI) | 50% (24.6–75.3)      | 33.33% (15.6–55.3) | 50 (24.6–75.4) | 81.2% (35.4–84.1) |
| Positive predictive value (95% CI) | 61.9% (46.1–75.5) | 48.4% (34–64) | 74.2 (62.8–83.1) | 87.5% (68.3–88.9) |

AP = action potential; cVEMP = cervical vestibular-evoked myogenic potentials by tone-bursts using 500 and 1,000 Hz stimuli; ECOG = electrocochleography; SP = summating potential.
There were no significant intergroup differences in PTA, caloric testing, and ECOG results. The sensitivity, specificity, and positive predictive values of the VNG caloric test were 41.9% (95% CI [24.5, 60.9]), 50% (95% CI [24.6, 75.3]), and 61.9% (95% CI [46.1, 75.5]), respectively. The sensitivity, specificity, and positive predictive values of ECOG were 65.2% (95% CI [42.7, 83.6]), 33.3% (95% CI [15.6, 55.3]), and 48.4% (95% CI [34.1, 64.1]), respectively. When using a cVEMP 1,000/500 Hz amplitude ratio value of 1.048 or greater, this test had greater sensitivity, specificity, and positive predictive value than ECOG and VNG (Table V).

**Effect of Age on cVEMP**

In active and stable MD patients, a decrease of the cVEMP amplitude at 500 Hz with increasing age was noted (Fig. 2). In all ears, the 1,000/500 Hz amplitude ratio increased by a decrease of the 500 Hz amplitude with increasing age, noticeably after age 54 years. A logistic regression using the disease status (active vs. stable) as the outcome and age and the ratio as covariates was performed (Table VI). The association between cVEMP 1,000/500 Hz amplitude ratio and disease status is still significant ($P = 0.0084$), though it should be noted that the relatively small sample size has led to a wide confidence interval. This means that, after correcting by age, the cVEMP $1,000/500$ Hz amplitude ratio is still able to discern between active and passive patients.

**DISCUSSION**

The diagnosis of MD is mostly based on historical information and the results of the audiogram. Although vestibular tests have been used for many years, audiometry remains the most useful test to support the diagnosis of MD in patients presenting with episodic vertigo. More recently, VEMP has been introduced as diagnostic tools for superior semicircular canal dehiscence and for macular vestibulopathies. However, the diagnostic value of VEMP in MD has not been fully determined. Our study aimed to assess the value of cVEMP for the diagnosis of MD, particularly the 1,000/500 Hz amplitude ratio. It has been reported that in healthy individuals, the stimulating frequencies that resulted in the highest amplitude responses are found at 250–500 Hz, and that in healthy individuals the cVEMP 1,000/500 Hz amplitude ratio should be <1.7,10,16 Our data suggest that patients with MD have a higher ratio than those presenting with non-Meniere’s vertigo, reflecting a tuning shift to a higher stimulation frequency in MD. Our results are consistent with others.12,16,17 Sandhu et al12 consistently noted that MD patients had decreased cVEMP amplitude at 500 Hz when compared to healthy individuals and better responses at higher frequencies (ie, a tuning shift). These authors found these changes to be more prominent in ocular VEMP testing. Salviz et al16 also reported increases of the 1,000/500 Hz amplitude ratio of both cVEMP and ocular VEMP in MD. These authors reported that this test had a fair diagnostic value (AUC of 0.731) and sensitivity and specificity values of 75% and 75%, respectively, when a cutoff value was set at 0.86. Our results showed that the tuning shift in MD patients was present in cVEMP as well. As in the study by Salviz et al, we found that the 1,000/500 Hz amplitude ratio had a fair diagnostic value for differentiating MD versus non-MD vertigo. However, we showed a higher ideal cutoff value than the one reported by these authors at 0.943. Perhaps this difference in cutoff value can be explained by the fact that the mean age of our cohort was higher than in the study by Salviz et al (53.7 vs. 44.5 years). In our study, cVEMP amplitude, and consequently the 1,000/500 Hz amplitude ratio, increased markedly in both MD and non-MD cases after age 54 years. Although Salviz et al also observed a modest positive relationship between this ratio and age, it is possible that in their relative younger cohort, the ratio was less influenced by age than in our cohort.

Zhang et al17 reported on the association between VEMP and MD stages, perhaps related to the fact that cVEMP amplitude decreases with the decrease in hearing in advancing stages. These authors performed a meta-analysis combining several studies that reported either absence or decreased amplitude in interaural comparisons of patients with unilateral MD. In contrast, other investigators have also reported on the lack of association between VEMP and AAOHNS disease stages as defined by the hearing level.17,18 In some cases of late stage MD with severe hearing loss, the saccular function may remain intact while some patients with minimal hearing loss may have saccular hydrops3,17,19 Since cVEMP assesses saccular function, the VEMP results may not correlate with ipsilateral audiometric thresholds. VEMP responses were also reported frequently absent in AAOHNS stages III and IV, and this probably affected comparisons. Therefore, tests of the vestibular function such as VEMP could potentially complement audiometry as a diagnostic and staging tool in MD diagnosis. In our study, we found no association between the cVEMP 1,000/500 Hz amplitude ratio and the AAOHNS MD stages.

Manzari et al20 measured cVEMP in MD patients during an acute attack and between attacks. They showed that the response amplitudes of cVEMP to 500 Hz tone-bursts were higher during the vertigo attack than between the attacks. Consequently, we wanted to assess changes in 1,000/500 Hz amplitude ratio during periods of MD activity and classified our MD patients into active and stable disease, based on whether a patient had suffered a classic MD attack.

| Covariate | Coefficient | Exp Coefficient | Exp 95% CI | $P$ Value |
|-----------|-------------|----------------|------------|-----------|
| Intersect | -4.526458   | 0.01081893     | (0.00009833982, 0.6238613) | .03923    |
| Age       | 0.006761    | 1.00678403     | (0.9685890, 1.0479593)    | .73170    |
| Ratio     | 4.379965    | 79.83526518    | (4.124792, 3.330,7463319) | .00844    |

*Table VI. Logistic Regression Analysis of 47 Patients With Meniere Disease (31 Had Active Disease While 16 Were in the Passive State).*
within 1 month of testing. The analysis of cVEMP amplitude at 500 Hz failed to differentiate active versus stable MD, and it was necessary to evaluate the 1,000/500 Hz amplitude ratio to demonstrate a difference between active and stable cases. In “active” ears, the mean 1,000/500 Hz amplitude ratio was higher than in “stable” cases (1.22 vs. 1.0; \( P = .0035 \)). We also identified the ideal cutoff value that provided the greatest sensitivity and specificity at 1.0481, and found a greater proportion of patients with an elevated 1,000/500 Hz amplitude ratio (ie, value equal or greater than 1.0481) in active ears than in stable cases (81\% vs. 38\%; \( P = .004 \)). However, when controlling for age, even when the association between 1,000/500 Hz amplitude ratio and activity status was still significant (\( P = .0084 \)), the wider 95\% CI diminishes the diagnostic value of this test. A larger sample size and narrower confidence intervals are needed to determine a more precise cutoff value when controlling for age.

It has been speculated that changes in cVEMP tuning observed in patients with MD follow physical changes in the membranous saccule in response to endolymphatic hydrops. Todd et al\(^ {15} \) proposed the mass stiffness theory to explain this observation. They argue that endolymphatic hydrops causes distention of the membranous saccule and this limits low frequency responses. It could be argued that the degree of membrane distention and membrane electrical resonance can vary with the severity of hydrops, and that cVEMP tuning changes may follow the severity of saccular hydrops. Our finding that cVEMP 1,000/500 Hz amplitude ratio was higher in active MD ears than in stable MD cases perhaps reflects a temporal association with disease activity. Normalization of the cVEMP tuning could be explained by a neurophysiological compensatory mechanism in patients with stable MD disease where cVEMP amplitude responses progressively return to baseline. Other authors have highlighted the utility of cVEMP tuning in differentiating MD from non-MD,\(^ {12,16,20} \) but none has characterized its diagnostic value as an indicator of disease activity in MD. In our cohort of patients with unilateral MD, the cVEMP 1,000/500 Hz amplitude ratio was helpful in differentiation active and stable ears and showed greater positive predictive value than the caloric test, ECOG, and the interaural cVEMP amplitude comparisons (Table V).

We recognize important limitations. Given the retrospective nature of this study, it would be impossible to avoid ascertainment bias. Second, we were unable to record VEMP responses in the affected ears of 3 of 50 MD patients and had to exclude them from the analyses. Third, although there were no differences in terms of age and gender, the comparison groups were of relatively small and different sizes. In particular, the regression analyses used to control for age were affected by the small sample size. Prospective studies of larger and matched groups are needed to reach definitive conclusions regarding the precise cutoff point of the cVEMP 1,000/500 Hz amplitude ratio and the association of cVEMP tuning and MD stages. Our future studies are focusing on the assessment of cVEMP tuning by performing longitudinal evaluations of patients at different stages of their disease. Last, the methodology used to record VEMP is variable among institutions, therefore, the findings of the present study are possibly dependent on the author’s specific methodology and may not be generalizable to sites using a different VEMP methodology (eg, those that do not normalize the data or do not correct for age) and, consequently, not suitable to compare with other studies since the wide variability of the methodology use can act as a confounding leading to inadequate conclusions.

The recently accepted diagnostic criteria of definite MD require the simultaneous occurrence of vertigo and unilateral hearing loss.\(^ {1} \) However, a diagnostic challenge exists when MD patients have atypical presentation, such as in cases of vertigo presenting without hearing loss. This is not a rare clinical situation as it has been reported that in 20\% of MD patients it can take more than 5 years before cochlear and vestibular symptoms occur simultaneously,\(^ {21–23} \) There is recent interest in the development of diagnostic strategies to refine the diagnosis of MD by imaging alone or in combination with vestibular tests.\(^ {21–23} \) Existing vestibular tests allow for topo-diagnosis of the vestibular dysfunction and may be helpful in characterizing the variable clinical phenotype of MD. Our study showed that an abnormal cVEMP tuning is superior to the VNG caloric test and ECOG to differentiate active versus stable MD. The cVEMP 1,000/500 Hz amplitude ratio was shown to have greater sensitivity, specificity, and positive predictive value than those traditional tests (Table V). The observation that abnormal cVEMP tuning is more prevalent in active MD than in stable MD opens an opportunity to have a marker of disease activity. This could be of tremendous clinical value to monitor the evolution of the disease and effectiveness of treatment.

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