Correlation between cVEMP and ABR for the Evaluation of Vestibular Migraine

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OBJECTIVE: Vestibular migraine (VM) is a clinical condition characterized by temporal overlap between vestibular symptoms and migraine. In this study, we aimed to determine the changes in vestibular myogenic potential (cVEMP) and auditory brainstem response (ABR) in patients with VM and migraine.

MATERIALS and METHODS: A total of 86 participants with no hearing loss or additional disease between the ages of 18 and 45 were enrolled in three different groups: group 1, VM; group 2, migraine without aura; and group 3, healthy controls. cVEMP and ABR were performed for all participants during attacks and attack-free periods. The differences between the right and left sides were calculated.

RESULTS: There was no significant difference in cVEMP p13-n23 latencies between any of the groups. There were statistically significant differences related to cVEMP p13-n23 amplitudes between groups 1, 2, and 3. This significant difference originated from group 1 when compared with the other groups (p<0.05). When we compared the cVEMP results of patients with VM during attack and attack-free periods, a statistically significant decrease was determined in the p13-n23 amplitude values during the attack period (p<0.01). Additionally, when we compared group 1 and group 3, the wave V peak latencies in ABR were significantly prolonged in group 1 (p<0.05).

CONCLUSION: cVEMP and ABR can be used as diagnostic criteria for patients with VM during attacks. Further studies with larger groups are needed to verify our findings.

KEYWORDS: Vestibular migraine, vestibular evoked myogenic potential, auditory brainstem response

INTRODUCTION

Cervical vestibular evoked myogenic potential (cVEMP) was first described by Colebatch et al. [1] and Colebatch and Halmagyi [2]. cVEMP is a non-invasive and relatively quick test that provides information about the function and integrity of the ipsilateral saccule and ipsilateral inferior vestibular nerve. cVEMP is an inhibitory myogenic response that can be measured at the tonically contracted sternocleidomastoid muscle (SCM) in response to acoustic stimuli [1]. Findings of recent studies emphasize the potential role of cVEMP in the diagnosis of several peripheral vestibular disorders, including Meniere's disease, benign paroxysmal positional vertigo, vestibular neuritis, idiopathic vestibulopathy, acoustic neuromas, and dehiscence of the superior semicircular canal [3-8].

Auditory brainstem response (ABR) consists of a sequence of volume-conducted waves recorded at the scalp following a click stimulus to the ear. The seven most common waveforms are designated I–VII; wave I probably represents activation of the acoustic nerve, wave III represents the cochlear nuclei, wave IV represents the lateral lemniscus tracts and nuclei, and wave V represents the inferior colliculi [9]. Decline and prolongation of the latency of wave V may indicate physiological dysfunction in the auditory system up to the brainstem level.

Migraine has long been described as a clinical condition related to various vestibular syndromes [10-13]. In recent years, many studies have been published regarding cVEMP responses in migraine; although some studies describe normal cVEMP responses and decreased amplitudes [14-17], others report delayed or nonexistent cVEMP responses [18-21]. Vestibular migraine (VM) is known as migrainous vertigo/dizziness, migraine-related vestibulopathy, and migraine-associated dizziness or vertigo. VM is a disabling neurological disorder characterized by vestibular symptoms, such as vertigo, dizziness, or imbalance. It should be noted that the headache does not necessarily occur at the same time as the vertigo symptoms. When the literature is examined, studies which examine the relationship between migraine and cVEMP can be found; however, there are no studies examining the relationship between VM, cVEMP, and ABR.

In this study, we aimed to determine the characteristics of the cVEMP and ABR responses of patients with VM and migraine in contrast to healthy controls. In this study, cVEMP and ABR changes during the VM attack period were compared with the cVEMP and ABR.
ABR responses of participants with migraine and healthy controls. In addition, the cVEMP and ABR responses of the patients with VM were compared with the responses during the attack-free period. To our knowledge, this is the first clinical study to compare cVEMP and ABR findings in vestibular migraine and migraine.

MATERIALS and METHODS

This study was conducted in both the neurology and otorhinolaryngology departments. Informed consent was obtained from the patients.

All participants in the study were between the ages of 18 and 45. None of the study participants had auditory symptoms or any other chronic disease history. Pure tone audiometric examination and MRI scanning was performed for each participant to confirm that the participants had no hearing loss or other diseases. Cases with hearing loss or additional disease were excluded from the study. ABR and cVEMP were performed on all participants. All tests were performed during headache and/or vertigo-free periods and during vertigo attacks.

The participants of the study were divided into three groups. Group 1 included 32 patients with definite VM (28 female and 4 male, mean age 33.2±10.2) as defined by the International Headache Society (2013) (Table 1). Patients with VM suffer attacks of vertigo that often occur in isolation from headache attacks; the vertigo is mostly spontaneous or positional, lasting seconds to days. Motion intolerance during attacks was the most common complaint (25 patients, 78% of the group). Six patients had vertigo attacks after headache, 11 patients had vertigo attacks preceding headache, and 15 patients had simultaneous headache and vertigo. None of the patients had auditory symptoms accompanying vestibiginous symptoms. Twenty-four patients had hemicranial headache, and 8 patients had holocranial headache. Neurological examination findings of the patients were normal. Group 2 included 27 patients with migraine without aura (22 female and 5 male, mean age 31.2±9 years) fulfilling the criteria of the International Classification of Headache Disorders, 3rd ed. (ICHD-II 2013) (Headache Classification Subcommittee, 2013). Severe pulsatile headache attacks were usually hemicranial in 20 patients and at the vertex in 7 patients. All of the patients had nausea and/or vomiting complaints. Patients with vestibular history or existing symptoms and hearing loss were excluded from the study. Group 3 (control) included 27 healthy volunteers of comparable age and gender distribution (20 female, 7 male, mean age 33.4±9.8 years) who did not have any vestibular symptoms or migraine. Audiometric tests were normal in all of the groups.

Table 1. Demographic data of all groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>27</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>33.20</td>
<td>31.20</td>
<td>33.40</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>10.20</td>
<td>9.00</td>
<td>9.80</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>28</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>4</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Onset of disease (years)</td>
<td>Mean</td>
<td>3.80</td>
<td>3.90</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>1.41</td>
<td>1.61</td>
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</table>

Auditory brainstem response (ABR) of the patients was recorded using a Vivosonic device (Vivosonic Inc., Toronto, ON, Canada). ABR was elicited with an alternating rarefaction and condensation click stimulus delivered via an unshielded headphone (Vivosonic; Vivosonic Inc., Toronto, ON, Canada), with 0.1 ms clicks at a rate of 37.7 clicks/s. Each trial was performed at an intensity of 70 dB nHL. White-noise masking (40 dB nHL) was performed in the contralateral ear. Before the ABR test was performed, all the patients were subjected to pre-cleaning of the skin and attachment of disposable electrodes in the frontopolar region (Fpz) and right and left mastoids (M1 and M2), in accordance with the norms of the International Electrode System (IES 10-20). The electrode impedance was <5 kΩ. The filter bandwidth used for recording was 100–3000 Hz. Totals of 1000–2000 responses were averaged. Each test was conducted two or three times to ensure that the results were reproducible. The results were recorded both ipsilateral and contralateral to the stimulation.

Cervical vestibular evoked myogenic potentials (cVEMP) were recorded using a Vivosonic device (Vivosonic Inc., Toronto, ON, Canada). The active electrode was placed on the center point of the same side sternocleidomastoid (SCM) muscle, the reference electrode was placed on the upper 2/3 portion of the SCM, and the ground electrode was placed in the middle of the forehead to record superficial EMG activity. Patients were placed in the supine position in a sound-isolated room; when the stimulus was given, they responded by straightening and turned to the contralateral side of the stimulus that provided the contraction of the SCM muscle. The contraction of the SCM muscle was monitored with a manometer. The stimulus was given in the order of the right and left ears, and the electromyographic activity of the sternocleidomastoid muscle was recorded from the ipsilateral direction. The electrode impedance was <5 kΩ. The acoustic stimuli were clicks at an intensity of 100 dBnHL (normal hearing level) with a duration of 0.1 ms, delivered at a frequency of 5 Hz through a headphone unilaterally to each ear. The EMG signal was bandpass-filtered from 10 to 1000 Hz and averaged during a 100 ms interval. The totals of 200 responses were averaged. P13 and n23 were the peak waves with positive/negative polarity concerning their latencies. The latencies of peaks p13 and n23 and the peak-to-peak amplitude of p13-n23 were evaluated. To achieve independence from the level of background activation, the amplitude of the cVEMP was expressed as the ratio of the peak to peak amplitude separated by a mean pre-stimulus rectified EMG measured during the recording.

The Statistical Package for the Social Sciences Version 20 program (SPSS, IBM Corporation; Armonk, NY, USA) was used for the statistical analysis. In addition to standard descriptive statistical calculations (mean, median, and standard deviation), qualitative parameters showing normal distribution were compared with the independent sample t-test, and parameters showing abnormal distribution were compared with the Mann-Whitney U test. One-way ANOVA was used to compare the quantitative data between ≥3 groups showing normal distribution, and Tamhane's test and Tukey's HSD test were used to determine the group responsible for the difference. The Kruskal-Wallis test was used to compare the data of quantitative parameters showing abnormal distribution between ≥3 groups. The paired sample test and the Wilcoxon signed-rank test were used to evaluate parameters in the groups. The Fisher-Freeman-Halton test was used to evaluate qualitative data comparisons. The statistical significance...
levels were established at p<0.01 and p<0.05. Power analysis was conducted to determine the necessary patient population for obtaining reliable latencies and amplitudes of cVEMP and ABR values.

RESULTS

Cervical vestibular evoked myogenic potential (cVEMP) latencies and the p13-n23 amplitudes of patients with VM, migraine without aura, and healthy controls (group 1, group 2, and group 3, respectively) were obtained (Table 2). In the control group (group 3), the average latency of p13 on the right side was 15.53 ms (min: 14 ms, max: 17 ms), and that on the left side was 15.26 ms (min: 14 ms, max: 17 ms). Also, in the control group, the average latency of n23 on the right side was 23.43 ms (min: 15 ms, max: 25 ms), and that on the left side was 23.25 ms (min: 14 ms, max: 26 ms). There was no significant difference between the groups in terms of right and left p13 latencies (p=0.541; p=0.256; p>0.05). Additionally, the differences in the right and left n23 latencies were not statistically significant (p=0.606; p=0.189; p>0.05).

In group 1 (VM), the average cVEMP p13-n23 amplitudes during the attack period were 1.65 µv (SD: 1.26) on the right side and 1.62 µv (SD: 1.29) on the left side. Additionally, in group 2 (migraine), the average cVEMP p13-n23 amplitudes were 2.41 µv (SD: 1.25) on the right side and 2.42 µv (SD: 1.02) on the left side. In group 3 (healthy controls), the average p13-n23 amplitudes were 2.32 µv (SD: 0.56) on the right side and 2.26 µv (SD: 0.55) on the left side. When we compared the average cVEMP p13-n23 amplitudes, we found statistically significant differences between all the groups. The cVEMP p13-n23 amplitudes in group 1 (VM) were significantly lower than in the other groups (right side p<0.05, left side p<0.05). There was no significant difference in the cVEMP p13-n23 amplitudes between group 2 and group 3 (right side p>0.05, left side p>0.05) (Figures 1, 2).

In group 1 (VM), during cVEMP evaluation, bilateral non-response was recorded in six patients, left side non-response was recorded in three patients, and right side non-response was recorded in three patients. The cVEMP responses were in normal ranges for all patients during the attack-free period. When the cVEMP p13-n23 amplitudes of group 1 patients during the attack and attack-free periods were compared, there were statistically significant differences between the two periods (p<0.01 and p<0.01) (Figure 3).

In group 1, the average peak latency value of wave V in ABR was 5.27 ms (SD: 0.31) on the right side and 5.33 ms (SD: 0.29) on the left side. Additionally, in group 2, the average peak latency value of wave V in ABR was 5.34 ms (SD: 0.17) on the right side and 5.29 ms (SD: 0.26) on the left side. In group 3 (healthy controls), the average peak latency value of wave V in ABR was 5.42 ms (SD: 0.24) on the right side and 5.46 ms (SD: 0.28) on the left side (Table 3). There were no statistically significant differences in any of the groups between the right and left peak latency differences of wave V in ABR (right side p>0.05, left side p>0.05) (Figures 4, 5). However, the average wave V peak latency was
6.05 (min: 5.5 ms, max: 6.5 ms) on the right side and 5.95 ms (min: 5 ms, max: 6.5 ms) on the left side in 12 (37%) patients in group 1 (VM) who had bilaterally or unilaterally absent cVEMP responses. In these patients, the wave V peak latency was prolonged significantly compared to the control group (p<0.05).

DISCUSSION

cVEMP is an indication of vestibulo-colic reflex resulting from the activation of the inferior branch of the vestibular nerve, the vestibular nucleus, the vestibular tract, the accessorial nucleus, the accessorial nerve, and the sternocleidomastoid muscle. In clinical practice, cVEMP is used in the diagnosis of various peripheral and central vestibular diseases. Although a delay in reflex is the major pathological sign, a decrease in amplitude and the absence of amplitude reflexes are also accepted as pathological [24, 25].

There are many studies in the literature regarding migraine. Boldingh et al. [21] applied acoustic stimuli tone bursts to patients with migraine-associated vertigo and Meniere’s disease; they calculated a decreased slope of 500–1000 Hz in the cVEMP responses of these patients. Their findings may be due to shared pathophysiology. Additionally, 36% of patients with migraine-associated vertigo had prolonged p13 latencies; these patients may have brainstem lesions, showing differences in the etiology of VM [21].

Baier et al. [16] reported reduced cVEMP amplitudes in patients with VM. Three of 63 patients with VM (5%) had no waveforms bilateral-

Table 3. Right and left average wave V peak latencies in all groups (p>0.05, p>0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>Right (ms)</th>
<th>Left (ms)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Vestibular migraine)</td>
<td>Mean 5.27</td>
<td>5.33</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation 0.31</td>
<td>0.29</td>
<td></td>
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<tr>
<td>Group 2 (Migraine)</td>
<td>Mean 5.34</td>
<td>5.29</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation 0.17</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Group 3 (Healthy control)</td>
<td>Mean 5.42</td>
<td>5.46</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation 0.24</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Mean 5.34</td>
<td>5.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Std. Deviation 0.26</td>
<td>0.29</td>
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</table>

Figure 3. cVEMP p13-n23 amplitudes of vestibular migraine patients during attack and attack-free periods (right side p<0.01, left side p<0.01). VM: vestibular migraine

Figure 4. Mean latency values of right side wave V for all groups

Figure 5. Mean latency values of left side wave V for all groups
ly, and one patient had no waveform unilaterally (on the right side). Baier et al. reported no abnormality in p13 or n23 latencies and cVEMP asymmetry in patients with migraine vertigo. Bilaterally absent cVEMPs were only observed in the patient group, suggesting lesions in the sacculocollic pathway. Boldingh et al. indicated unilaterally or bilaterally absent cVEMP response in 44% of patients with VM and in 25% of patients with migraine, compared to 3% of the healthy controls. Taylor et al. reported no significant differences in cVEMP amplitudes or symmetry between control patients and those with VM. No caloric test abnormalities were observed in these patient groups. In 2009, Baier and Dieterich reported a high range of test abnormalities, which was attributed to the narrow normal range used; the authors concluded that peripheral vestibular function is usually protected in VM and that central mechanisms must be the cause of vertigo.

Several different reports on VM patients show peripheral vestibular dysfunction as the underlying mechanism of cVEMP abnormalities. Taylor et al. reported that the caloric profile of the VM patients was normal. Contrastingly, some studies reported caloric abnormalities in 20%–25% of migraine patients with vertigo. However, there was no correlation between abnormalities in the cVEMP and caloric tests.

Boldingh et al. also found that 44% of patients with VM had bilaterally or unilaterally absent cVEMP responses. In one of the most recent studies, performed by Hong et al., bilaterally absent cVEMPs were reported in 41.9% of controls and 60% of patients with migrainous vertigo. Similarly, in our study, we recorded unilaterally or bilaterally absent cVEMP responses in 37% (n=12) patients in group 1 (VM). Responses were absent on the right side in three patients, on the left side in three different patients, and bilaterally in six patients. In these patients, the ABR and cVEMP responses were recorded simultaneously. When the findings were compared with those of the controls, a 0.5 ms delay in the wave V peak latency was found between the two sides; this finding is compatible with the cVEMP results. Bilateral ABR responses were >6 ms in patients with bilaterally absent cVEMP responses. The sacculocollic pathway is located very close to the brainstem, and cVEMP abnormalities are believed to be concurrent with dysfunction of brainstem mechanisms. When the cVEMP p13-n23 amplitudes of group 1 (VM) during the attack and attack-free periods were examined, there was a statistically significant decrease during the attack period (right side p<0.01 and left side p<0.01).

In our study, when we examined the cVEMP p13-n23 amplitude values during the attack period, there were statistically significant differences between all groups. When the groups were examined in pairs, the cVEMP and p13-n23 amplitude values of group 1 (VM) were significantly lower than those of other groups (right side p<0.05 and left side p<0.05). However, there were no significant differences in the cVEMP responses and the p13 and n23 latency scores. When we compared the wave V latency duration of ABR, there were statistically significant differences. The wave V peak latency in group 1 was significantly prolonged in contrast to the control group (p<0.05).

**CONCLUSION**

To date, no report has been published that simultaneously studies cVEMP and ABR responses in attack and attack-free periods of VM patients to understand the pathophysiology of the disease. In our study, cVEMP responses were bilaterally or unilaterally negative in 37% of VM patients; in accordance with the cVEMP responses, wave V peak latency was prolonged significantly when compared to the control group. When we evaluated the cVEMP and ABR values of the VM patients during attack and attack-free periods, there were statistically significant differences between the periods. When cVEMP and ABR were analyzed together, statistically significant changes were observed for VM patients during attack and attack-free periods. We believe that the cVEMP and ABR examination records of patients with VM during attack and attack-free periods may be used as diagnostic criteria.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Health of Sciences University, Umranli Training and Research Hospital.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - M.S.; Design - M.S.; Supervision - C.O.; Resources - İ.D.; Materials - S.O.; Data Collection and/or Processing - S.O.; Analysis and/or Interpretation - A.D.Y.; Literature Search - İ.D.; Writing Manuscript - R.S.; Critical Review - M.S.; Other - M.S.

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