

ORIGINAL ARTICLE

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Assessment of cervical and ocular vestibular evoked myogenic potentials in migraine patients

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Abstract

Background: Patients suffering from vestibular migraine (VM) are known to have various vestibular test abnormalities interictally and ictally. Recently, vestibular evoked myogenic potentials (VEMPs) have become accepted as a valid method for otolith function assessment. Many studies have identified various vestibular symptoms and laboratory abnormalities in migraineurs. Since migraineurs with no accompanying vestibular symptoms might exhibit subclinical vestibular dysfunction, we investigated vestibular function using ocular and cervical VEMPs in migraine patients. The aim was to study cervical VEMP and ocular VEMP in migraineurs with and without vestibular symptoms interictally.

Results: Migraine and VM patients showed significantly longer P₁₃ latency of cVEMP compared to controls. A statistically significant cVEMP interaural P₁₃ latency difference was found in VM compared to healthy controls. Cervical VEMP N₂₃ latency, peak-to-peak amplitude, interaural N₂₃ latency, and amplitude asymmetric ratio did not show any significant difference in migraine and VM patients compared to healthy controls as well as no significant difference across the three groups regarding oVEMP parameters.

Conclusions: Abnormal interictal cVEMP results in migraineurs might indicate subclinical vestibulo-collic pathway dysfunction.

Keywords: Vestibular evoked myogenic potential (VEMP), Ocular VEMP, Cervical VEMP, Migraine

Background

Migraine is a multiphasic disorder. Understanding of its pathophysiology starts with acknowledging that migraine is not simply a disease of intermittently occurring pain, but that it involves processes that affect the brain over-time. Patients with migraine frequently have vestibular complaints, such as dizziness, unsteadiness, or head motion intolerance. Approximately, 10% of the population has migraine headaches [1], and one third of these patients experience dizziness [2]. Vertigo is regularly associated with headache in 25 to 50% of migraine patients [3, 4]. Vestibular migraine (VM) has a strong female

predominance of up to 5 to 1 [5]. Patients with migraine frequently have vestibular complaints, such as spontaneous vertigo, positional vertigo, visually induced vertigo, head motion-induced vertigo, and head motion-induced dizziness with nausea [6]. Vertigo can arise in the context of a headache attack (preceding, occurring with, or even after) [3] or between attacks. It is extremely variable [7]. Temporal pattern, presenting as aura, occurs only in approximately 10% of cases [8]. Temporal association between dizziness and headache was found in 66% of patients [3]. VM patients could also have cochlear symptoms such as aural fullness and tinnitus [9]. Tinnitus, ear fullness, and hearing loss are reported by about 48% of migraine patients, causing difficulty in the differential diagnosis [10].

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Both peripheral and central vestibular deficits have been observed in patients with VM, although the pathophysiology is not clear. One theory supporting the peripheral pathophysiology suggests vascular changes in the internal auditory artery may lead to ischemic damage to labyrinthine structures [11]. The vasospasm-induced ischemia of the labyrinth and plasma extravasation during migraine attacks may result in permanent damage of the cochlea and vestibule [12]. The inner ear blood supply is devoid of collaterals, and hence, it is highly vulnerable to ischemic effects.

Otolith end organs/otolith reflex pathways might be affected by abnormal neurotransmitter modulation originating in the brainstem [13]. Neuropeptides (i.e., substance P, neurokinin A, and CGRP), serotonin, adrenaline, and dopamine are known to play a neuromodulatory role in both peripheral and central vestibular systems [14]. They are released into the dural circulation resulting in reduction of cerebral blood flow in the areas of spreading depression.

Many studies have identified various vestibular symptoms and laboratory abnormalities in migraineurs. Although the vestibular tests may be abnormal, the changes may exist without vestibular symptoms. To date, vestibular evoked myogenic potential (VEMP) has been the easiest, simplest, and non-invasive test for measuring the otolith organ function in the clinical practice.

Cervical VEMP (cVEMP) represents an uncrossed vestibulo-collic reflex, which assesses the saccular function, the inferior vestibular nerve, and vestibular nuclei serving a pathway through the lower brainstem to the motor neurons of the sternocleidomastoid muscle [15]. The more recently described ocular VEMP (oVEMP), is a manifestation of crossed vestibulo-ocular pathway, reflects predominantly utricular function and involves the medial longitudinal fasciculus, oculomotor nuclei and nerves, and extraocular muscles following activation of the superior vestibular nerve and nucleus [15, 16]. Thus, the combined measurement of cVEMP and oVEMP provides complementary information of the descending and ascending vestibular pathway respectively.

Since migraineurs who do not complain from vestibular symptoms might exhibit subclinical vestibular dysfunction, the aim was to investigate vestibular function using ocular and cervical VEMPs in migraine patients interictally and assessment of the interaural difference as a possible indication of lateralized vestibular signs in migraine.

Methods

The study was carried out on 30 adult subjects (60 ears) attending the Audio-Vestibular Medicine Unit or were referred from the neurology clinic. They were divided

into 3 groups: the control group consisted of 10 healthy adult subjects' age and gender-matched to the patients' group.

The second group consisted of 10 migraine patients based on the criteria of the ICHD-3 β [7]. Exclusion criteria included any vestibular symptoms: known otologic disease, known neurologic disease-causing headache, peripheral hearing loss, and known disease affecting cervical vertebrae or spinal cord.

The third group consisted of 10 VM patients based on the jointly formulated diagnostic criteria of the classification of Vestibular Disorders of the Bárány Society and the Migraine Classification Subcommittee of the IHS [6]. Only patients complaining of spontaneous vertigo including either internal vertigo, a false sensation of self-motion, or external vertigo, a false sensation that the visual surround is spinning or flowing, were included. Exclusion criteria included known otologic disease, known neurologic disease-causing headache, peripheral hearing loss, and known disease affecting cervical vertebrae or spinal cord.

An informed consent was obtained from each participant in the study. All subjects were subjected to complete history taking to rule out the exclusion criteria. Evaluation of the peripheral auditory system was done using tympanometry and acoustic reflexes to check middle ear status using Interacoustics AT235 Impedance-meter (Interacoustics, Denmark). Pure tone audiometry for air and bone-conduction thresholds' assessment at frequencies from 250 to 8000 Hz for air conduction and from 250 to 4000 Hz for bone conduction using MADSEN Itera II (GN otometrics, Denmark) was done.

Patients with headache underwent VEMP testing on headache-free days using the GSI Audera evoked system (Grason-Stadler, USA). One channel recordings were obtained. The order of testing, whether to start with cVEMP/ oVEMP or right/left ear, was randomly determined for each subject. Individual random 500 Hz tone burst air conducted sound (ACS) of condensation polarity was monaurally delivered to the tested ear at an intensity of 95 dB nHL via supra-aural TDH-39 headphone. Stimuli were Blackman gated with 2 cycles rise/fall and 1 cycle plateau. The stimulation rate was 5 Hz.

Cervical VEMP test

The active electrode was placed on the upper one third of the sternocleidomastoid muscle, ipsilateral to the sound stimulation. The reference electrode was placed on the sternoclavicular joint, while the ground electrode was placed on the forehead (Fpz) [17].

The patients' neck, forehead, and supra-sternal skin were cleaned with alcohol and rubbed with rough gauze

prior to surface electrode placement to obtain acceptable electrode impedances that were below 5000 Ohms.

All subjects were tested in sitting position with the head rotated away from the side of stimulation. Myogenic variability was minimized by standardized seating orientation and using target markers on the examination room walls. They were asked to maintain focus on these markers during VEMP recordings and to return to these markers during subsequent recordings.

The sternocleidomastoid muscle ipsilateral to the tested ear was selected to record the cVEMP. At least 2 runs were performed, and 150 sweeps were averaged for each run with an analysis window of 50 ms. The electromyography signals were amplified and band-pass filtered between 5 and 750 Hz and monitored to maintain background muscle activity. An artifact rejection system was used.

Cervical VEMP was defined as bi-phasic response; the first positive peak P13 and the first negative peak N23, the mean peak latency of P13 latency and N23 latency (in ms), and the mean P13-N23 amplitude (in μv) were measured. Absence of the bi-phasic response was defined as absent cVEMP. The interaural difference (IAD) in reflex amplitude can be expressed as an asymmetry ratio (AR) using the following formula:

$$\text{AR}\% = 100 \times (\text{Al} - \text{As}) / (\text{Al} + \text{As}),$$
 where Al and As are the larger and smaller amplitudes, respectively, obtained from stimulating each ear [18].

For computing the interaural latency difference, we subtracted the right and left values for all parameters in all participants and then compared the mean of this difference among the three studied groups [19].

Ocular VEMP test

Active electrode was placed over the contra-lateral inferior oblique muscle, approximately 3 mm below the eye and centered beneath the pupil. Reference electrode was placed 2 cm below the recording electrode, while the ground electrode was placed on the forehead (Fpz). This electrode montage was similar to what was reported by Chihara et al. [20]. The electrode sites were cleaned with alcohol and rubbed with rough gauze prior to surface electrode placement to obtain acceptable electrode impedances that was below 5000 Ohms.

The subjects were tested in a seated position. They were instructed to maintain an upward gaze at a fixed mark in the ceiling, all through oVEMP stimulation. The targeted sealing mark was mounted at 30° from the neutral gaze point. To prevent extraocular muscle fatigue, 1-min rest period was allowed before testing the other ear, additionally 30 s rest intervals were allowed between the runs.

The same recording parameters were utilized. oVEMP was defined as bi-phasic response: the first negative peak

N10 (N1) and the first positive peak P15 (P1). The latencies of N10 and P15 (in ms) and the mean N10-P15 amplitude (in μv) were measured. IAD of peak-to-peak amplitude and latency was calculated using the same method as that mentioned in cVEMP.

Statistical analysis of the data

Statistical evaluation was carried out using the IBM SPSS software package version 20.0. Qualitative data were described using number and percentage. The Kolmogorov-Smirnov test was used for verification of the normality of distribution. For quantitative data description, the range (minimum and maximum), mean, standard deviation, and median were used.

For demographic data analysis, the chi-square test was used to compare categorical variables between different groups. Fisher's Exact or Monte Carlo correction was used for chi-square correction when more than 20% of the cells had expected count less than 5.

For comparing VEMP finding in the three groups, *F* test (ANOVA) was used for normally distributed quantitative variables. Post hoc test for pairwise comparisons and Kruskal-Wallis test for abnormally distributed quantitative variables. For comparing VEMP finding in migraine and migraine-associated vertigo (MAV) groups, Mann-Whitney test was used for abnormally distributed quantitative variables analysis. The mean \pm 2 standard deviation (SD) of healthy controls was used to define the normal range for each parameter. Significance of the obtained results was judged at the 5% level. *P* values \leq 0.05 were considered statistically significant. Latencies and amplitudes for absent responses were excluded from analysis.

Results

Demographic data

Each studied group consisted of 10 subjects. In the control group, there were 2 males and 8 females. The migraine group had 1 male and 9 females, while in the MAV group, there were 2 males and 8 females. Age of the healthy controls ranged from 19 to 38 years with mean age 28.35 ± 6.71 years. Migraine patients' age ranged from 22 to 47 years with mean age 33.30 ± 7.93 years. MAV group's age ranged from 19 to 54 years with mean age 34.30 ± 10.93 years. No significant age difference was found between the three groups.

Migraine laterality, type, and duration

In the migraine group, 5 patients suffered from right headache, 3 from left headache, and 2 had bilateral headache, while in the MAV group, 4 patients suffered from right headache, 5 from bilateral headache, and only 1 had alternating headache. In the migraine group, 9 cases suffered from common migraine, and 1 had a

classic type of migraine. While in the MAV group, 6 patients suffered from common migraine ((without aura) and 4 from a classic type of migraine (with aura). No statistically significant difference was found between the two groups.

In the migraine group, 60% of the patients suffered from headache for less than 2 years, 20% for 2–10 years, and 20% of migraine patients had headache for more than 10 years. While in the MAV group, 20% of the patients suffered from migraine headache for 2–10 years and 80% for more than 10 years. The duration of migraine was significantly longer in the MAV group (mean = 5.20 ± 4.76 years) compared to the migraine group (3 ± 3.74 years).

Cervical VEMP results

There was a statistically significant delay in P_{13} latency in the migraine group (mean = 15.92 ± 0.85 ms) and MAV group (mean = 16.13 ± 1.0 ms) compared to the

control group (mean = 14.69 ± 1.18 ms). There was no statistical significant difference found across the 3 studied groups as regarding N_{23} latency or the peak-to-peak amplitude (Table 1).

The MAV group had a statistically significant increased P_{13} latency IAD (mean = 0.82 ± 0.57 ms) compared to controls ($p = 0.016$). There was no statistical difference in P_{13} IAD in migraine compared to the MAV group and controls. Additionally, there were no statistical significant difference of IAD of N_{23} latency and the P_{13} - N_{23} amplitude across the three studied groups.

The migraine group did not show abnormal prolongation of P_{13} latency nor N_{23} latency on the other hand, and 20% of ears showed abnormally large P_{13} - N_{23} amplitude. In MAV patients, 15% of ears showed abnormally increased P_{13} latency and no abnormality of N_{23} latency, while 20% had abnormally large P_{13} - N_{23} amplitude.

The migraine group did not show abnormal IAD of P_{13} or N_{23} latency, while 10% of ears had abnormal

Table 1 Cervical VEMP P_{13} , N_{23} latencies (in ms), P_{13} - N_{23} amplitude (in μ V), and IAD in the three studied groups

	Control	Migraine	MAV	H	p
Cervical VEMP					
P_{13} latency	(n = 20)	(n = 20)	(n = 20)		
Min.–max.	12.84–17.01	14.34–16.97	14.51–18.17	8.735	0.004*
Mean \pm SD.	14.69 \pm 1.18	15.92 \pm 0.85	16.13 \pm 1.0		
Median	14.42	15.97	16.09		
Sig. bet. groups.	$p_1 = 0.001^*$, $p_2 = 0.000^*$, $p_3 = 0.483$				
N_{23} Latency	(n = 20)	(n = 20)	(n = 20)		
Min.–max.	19.34–28.84	20.72–26.34	20.51–28.67	2.586	0.205
Mean \pm SD.	24.64 \pm 2.65	23.71 \pm 1.29	24.0 \pm 1.90		
Median	24.84	23.76	23.67		
P_{13}-N_{23} amplitude	(n = 20)	(n = 20)	(n = 20)		
Min.–max.	46.48–242.4	49.57–349.5	46.86–279.1	1.583	0.453
Mean \pm SD.	106.4 \pm 45.01	120.5 \pm 71.11	137.7 \pm 72.38		
Median	106.0	108.0	116.5		
Interaural difference					
P_{13} latency	(n* = 10)	(n* = 10)	(n* = 10)	8.212	0.017*
Min.–max.	0.00–0.70	0.17–3.67	0.16–2.15		
Mean \pm SD.	0.31 \pm 0.24	0.91 \pm 1.0	0.82 \pm 0.57		
Median	0.25	0.66	0.80		
Sig. bet. groups.	$p_1 = 0.083$, $p_2 = 0.016^*$, $p_3 = 0.834$				
N_{23} latency	(n* = 10)	(n* = 10)	(n* = 10)	2.121	0.787
Min.–max.	0.00–5.01	0.17–3.29	0.0–5.50		
Mean \pm SD.	1.42 \pm 1.52	0.93 \pm 0.92	1.4 \pm 1.62		
Median	1.09	0.67	0.92		
P_{13}-N_{23} amplitude	(n* = 10)	(n* = 10)	(n* = 10)	1.897	0.849
Min.–max.	1.87–36.91	4.34–42.47	5.57–49.22		
Mean \pm SD.	18.4 \pm 10.70	20.92 \pm 10.97	22.01 \pm 12.81		
Median	19.74	19.52	20.31		

n number of ears, n* number of cases

H, p: H and p values for Kruskal-Wallis test, Sig. bet. groups was done using post hoc test (Dunn's multiple comparisons test)

p_1 : p value for comparing between group control and Migraine

p_2 : p value for comparing between group control and MAV

p_3 : p value for comparing between group MIG and MAV

*Statistically significant at $p \leq 0.05$

interaural P₁₃-N₂₃ amplitude difference. In MAV patients, 10% of ears showed abnormal IAD of P₁₃ and N₂₃ latency and P₁₃-N₂₃ amplitude difference.

Ocular VEMP results

Ocular VEMP could not be recorded from the left ear of a 40-year-old female complaining of MAV for 2 years. She was excluded from the analysis of IAD of oVEMP parameters. There was no statistically significant difference between the three studied groups regarding N₁₀ and P₁₅ latencies and N₁₀-P₁₅ amplitude.

No significant difference was found between groups regarding the IAD of N₁₀ and P₁₅ latency and N₁₀-P₁₅ amplitude of oVEMP (Table 2).

Five percent of migraine patients showed abnormally prolonged N₁₀ and P₁₅ latency and increased N₁₀-P₁₅ amplitude. In the MAV group, 5.26% of ears had

abnormally prolonged N₁₀ and P₁₅ latencies, while 10.52% showed increased N₁₀-P₁₅ amplitude.

None of the migraine patients had abnormal oVEMP IAD, while MAV patients are presented with abnormal IAD oVEMP parameters in 11.11% of ears.

Discussion

Cervical VEMP was successfully recorded from 100% of controls. This agrees with Rosengren et al. [15] and Welgampola and Colebatch [21] who reported presence of cVEMP response in all normal subjects under the age of 60. Additionally, cVEMP was recorded from all migraine and VM patients. The results in the present study are in line with Moallemi et al. [19] and Bremova et al. [22] who studied patients with migraine and VM patients, respectively. They reported 100% prevalence of cVEMP using tone burst stimuli.

Table 2 Ocular VEMP N₁₀, P₁₅ latencies (in ms), N₁₀-P₁₅ amplitude (in μ V), and IAD in the three studied groups

		Control	Migraine	MAV	H	p
Ocular VEMP	P₁₅ latency	(n = 20)	(n = 20)	(n = 19)		
	Min.-max.	13.67–17.84	13.34–17.67	14.34–22.17	0.062	0.969
	Mean \pm SD.	16.13 \pm 1.12	16.01 \pm 1.13	16.43 \pm 1.90		
	Median	16.34	16.34	15.84		
	N₁₀ latency	(n = 20)	(n = 20)	(n = 19)		
	Min.-max.	10.0–12.84	9.17–14.0	10.17–18.51	2.723	0.256
	Mean \pm SD.	11.17 \pm 1.01	11.61 \pm 1.05	11.98 \pm 2.17		
	Median	10.75	11.67	11.67		
	N₁₀-P₁₅ amplitude	(n = 20)	(n = 20)	(n = 19)		
	Min.-max.	2.56–7.87	2.11–9.06	1.59–13.34	0.295	0.863
	Mean \pm SD.	4.20 \pm 1.72	4.40 \pm 1.64	4.87 \pm 2.91		
	Median	3.54	3.90	4.11		
Ocular VEMP	IAD	Control (n* = 10)	Migraine (n* = 10)	MAV (n* = 9)	H	P
	N₁₀ latency					
	Min.-max.	0.17–2.33	0.16–2.33	0.16–1.67	1.658	0.437
	Mean \pm SD.	1.30 \pm 0.74	0.85 \pm 0.70	0.83 \pm 0.64		
	Median	1.34	0.58	1.0		
	P₁₅ latency					
	Min.-Max.	14.66–17.51	13.34–17.67	15.0–20.34	0.305	0.859
	Mean \pm SD.	16.14 \pm 0.97	15.96 \pm 1.37	16.38 \pm 1.61		
	Median	16.17	16.34	15.84		
	N₁₀-P₁₅ amplitude					
	Min.-Max.	0.25–42.35	0.54–36.65	1.27–53.85	4.338	0.114
	Mean \pm SD.	10.88 \pm 14.7	16.36 \pm 12.47	24.76 \pm 18.25		
Median	5.10	12.87	27.68			

n number of ears, n* number of cases

H, p: H and p values for Kruskal-Wallis test. Sig. bet. groups was done using post hoc test (Dunn's multiple comparisons test)

p₁: p value for comparing between group control and migraine

p₂: p value for comparing between group control and MAV

p₃: p value for comparing between group migraine and MAV

*Statistically significant at p \leq 0.05

However, other studies have reported absent cVEMP waveform in migraine and VM patients using tone burst stimuli based on different diagnostic criteria for migraine [23–26]. Other researchers reported absent cVEMP responses in both migrainous [27] and migrainous vertigo patients [28, 29] using click stimuli which may contribute to the discrepancies of the results compared to the present study.

In the present study, there was a statistical significant delay in P13 latency in migraine group and VM group compared to controls, while N23 showed no significant prolongation among the three studied groups. Murofushi et al. [30] have suggested that P13 latency is superior to N23 latency in evaluating the prolonged latencies of VEMP since N23 latency has a larger standard deviation of normal values than P13 [30].

Delayed VEMPs indicate brainstem lesion, especially in the vestibulo-spinal tract as assumed by Murofushi et al. [30], Allena et al. [13], Koo et al. [31], and Liao et al. [32]. Prolonged latency is an indication of a retro-labyrinthine lesion, such as vestibular nerve or brainstem lesions [33]. Abnormal cVEMP results in migraine patients, who do not have vestibular symptoms, may indicate subclinical vestibular affection.

A statistically significant delay of P₁₃ latency in migraine and VM patients has been reported without significant difference in N₂₃ latency compared to controls by Moallemi et al. [34] and Lotfi et al. [26] as well. Other authors reported insignificantly different cVEMP latencies in the patients' group compared to that of healthy controls [24, 35–38]. They diagnosed migraine and migrainous vertigo patients based on the International Headache Society (IHS) 2004 criteria [39] and the ICHD-2nd ed. [40] and the criteria of Neuhauser and colleagues [3, 41].

It is to be noted that the Neuhauser and ICHD-2nd ed. criteria indicated that at least one migrainous symptom must occur in at least two vertiginous attacks. On the other hand, migraine and migrainous vertigo cases included in the present study were diagnosed based on the more recent and more strict criteria of the ICHD-3β [7] and the jointly formulated diagnostic criteria of the classification of Vestibular Disorders of the Bárány Society and the Migraine Classification Subcommittee of the IHS [6], respectively. They state that one or more migrainous features must occur with at least 50% of the vestibular episodes.

Conversely, one study reported significantly reduced cVEMP latencies in VM [22]. They proposed an increased vestibular sensitivity due to abnormal central integration of canal and otolith signals in VM as an interpretation for their findings.

The present study did not reveal a statistically significant difference in P13-N23 amplitude across the three

studied groups. Reviewing the literature, similar consistent results have been found in the studies of Murofushi et al. [42] ($n = 11$), Khalil et al. [43], Inoue et al. [44], and Bremova et al. [22] investigated VM patients using tone burst-cVEMPs. Taylor et al. [45] and Kandemir et al. [37] reported insignificant difference of P13-N23 amplitudes' mean in VM and migraine patients compared to normal subjects using click- cVEMPs.

In contrast, Moallemi et al. [34] and Lotfi et al. [26] reported significantly lower cVEMP amplitudes in migraine and migrainous vertigo patients, respectively, compared to controls. The former study recruited their patients according to the IHS-1988 [46] criteria for migraine patients' diagnosis. Both studies presented 500 Hz tone burst stimulus without plateau, which may account for the difference since VEMPs amplitudes were shown to increase with increasing tone burst duration (rise and fall time and plateau) [47, 48].

Additionally, Baier et al. [23, 24] reported reduced cVEMP amplitudes in 68% of patients with VM. However, we defined our normal range in terms of the mean ± 2 SD since 95% confidence interval revealed query results, whereas Baier et al. used the 95% confidence interval for the population mean. This narrower normal range may have resulted in a higher proportion of "abnormal" results in their study than in ours. The variability in amplitude results between studies can be explained by the wide range of absolute amplitude measurements which depends greatly on the EMG level of sternocleidomastoid muscle contraction [49, 50].

In the current study, there was a statistically significant interaural cVEMP P13 latency difference in VM group versus controls. This difference might indicate asymmetric central involvement of the vestibular system in these patients. However, no difference was found in interaural N23 latency nor P13-N23 amplitude IAD among the three studied groups.

Reviewing the literature reveals consistent results regarding insignificant difference of cVEMP amplitude asymmetry in migraine patients as a whole versus healthy controls [26, 35, 37, 45]. Lotfi et al. [26], Taylor et al. [45], and Hong et al. [35] found insignificant interaural amplitude difference in VM patients compared to healthy controls. The same results have been reported by Kandemir et al. [37] as well. On the contrary, Inoue et al. [44] reported a significantly larger amplitude IAD for cVEMPs in VM than in controls. They justified the discrepancies among their results and the previous work as differences in the stimulation used to evoke cVEMPs or in the profiles of the chosen VM patients.

Moallemi et al. [19] reported no significant differences between migraine patients and normal control groups in either the IAD of either peak-to-peak amplitude or latency values. They concluded that the diagnostic value

of VEMP asymmetry measurements in migraine patients is not high because there is no meaningful difference between migraine patients compared to a healthy group in the VEMP asymmetry measures in their study. They considered the lack of consistency regarding the location of the headache as a possible reason that amplitude ratio and side difference values were not statistically different between the migraine and control groups.

Regarding the oVEMP results, all controls had intact waveforms bilaterally. Piker et al. [51] reported oVEMP response rate that was 100% in healthy subjects less than 50 years, whereas only 77% of subjects 50 years or older generated repeatable oVEMP responses. In the patients' groups of the current study, oVEMP waves could be recorded successfully from all migraineurs in both ears. One case in the MAV group did not show oVEMP waveforms in the left ear. She was 40 years old and had common migraine since 2 years while the rest of the group showed 100% prevalence of the oVEMP response bilaterally. Reviewing the literature, the absence of oVEMP wave form has been frequently reported in both groups [25, 43, 45, 52].

Taylor et al. [45] reported that oVEMP reflexes were absent in 3% of VM patients depending on the Neuhauser et al. [3] criteria. Gozke et al. [52] reported absent oVEMP in 18.6% of migraine cases compared to none of the controls. However, they diagnosed migraine cases based on the ICHD2nd [39]. They concluded that sub-clinical vestibular dysfunction can be elicited using oVEMP in migraine patients without vestibular complaints. Both authors used click stimuli, while tone bursts have proved to be superior to clicks in producing both cVEMPs and oVEMPs [20, 53].

Zaleski et al. [25] reported significantly higher rate of bilaterally absent oVEMPs in the VM group (28%) compared to none of the controls. Khalil et al. [43] found absent response in 20% of VM patients. Both authors used tone burst stimuli with 0 ms plateau. The latter study selected their patients according to the Neuhauser criteria [41]. Moreover, Talaat and Talaat [54] reported absent oVEMP in 32% of VM patients depending on the ICHD2nd [39] for vestibular migraine diagnosis. Inoue et al. [44] reported bilaterally absent oVEMP responses in 39% of VM patients compared to 21% of the controls using tone bursts, with no mention of the time of the VEMP testing in relation to the last migraine attack.

There was no significant difference in N10 and P15 latencies among the three studied groups. Consistent results have been reported in VM patients compared to healthy controls by Inoue et al. [44], Taylor et al. [45], Zaleski et al. [25], Bremova et al. [22], and Zuniga et al [38]. In contrast to Gozke et al. [52] and Khalil et al.'s [43] study, they reported statistically significant prolongation of N10 and P15 mean latencies in migraine

and VM patients, respectively, compared to healthy controls depending on ICHD2nd [39] and Neuhauser criteria [41] for cases diagnosis, respectively. Moreover, Talaat and Talaat [54] reported delayed N10 latency of oVEMP in 16% of VM patients' ears depending on the ICHD-II [39] criteria for VM diagnosis. The different diagnostic criteria may account for the discrepancies between the results as well as the different stimuli used. Moreover, Gozke et al. [52] used 120 dB click stimuli and Khalil et al. [43] included VM patients with longer mean duration of migraine in (6 ± 2.6 years) in their study.

No statistically significant difference was found regarding N10-P15 amplitude across the three studied groups. Khalil et al. [43], Inoue et al. [44], Bremova et al. [22], and Taylor et al. [45] reported that oVEMPs' amplitude in VM did not differ significantly from healthy controls. Zuniga et al. [38] found that VM patients had reduced oVEMP amplitudes relative to controls using click stimuli relying on the ICHD2nd [39] criteria for VM diagnosis. However, they reported insignificant differences using 500 Hz tone burst stimuli.

There was no significant difference in N10 or P15 latencies or amplitude IAD among the three groups. Taylor et al. [45] reported insignificant differences in amplitude symmetry between controls and VM as well. Zaleski et al. [25] reported insignificant IAD of N10 or P15 latency between sides while IAD of peak-to-peak amplitudes was significantly higher in VM group compared to the controls. They included patients who were typically symptomatic the same day of testing, which may be the cause of higher incidence of VEMP abnormalities within their study group. Inoue et al. [44] reported significant differences in oVEMP amplitude IAD in VM patients compared to controls using 135 dB SPL tone burst. They did not mention the last attack/VEMP testing-time relationship.

Overall, abnormal cVEMP responses in the present study were more frequent in the MAV group (35%) compared to the migraine group (10%). The main abnormality was prolonged latency, while oVEMP abnormalities were 15% and 21.04% in the migraine and MAV groups, respectively, regarding latencies prolongation. Additionally, one ear in MAV patient had absent response. Oh et al. [55] reported 21.7% and 34.8% of 23 VM patients that had abnormalities in cervical and ocular VEMPs, respectively, and most patients did not generate VEMP responses or had markedly reduced amplitudes. They recruited their patients depending on the Neuhauser criteria [41]. In contrast to Baier et al. [23] who reported cVEMP abnormalities in 68% of their entire VM group, Taylor et al. [45] reported only 3% of VM participants that had abnormal ACs cVEMPs. Regarding the oVEMP Zaleski et al. [25] reported

abnormalities (absent or asymmetric) in 61% of VM group and they suggested a greater vulnerability of the ascending utricular pathway in VM patients.

The inconsistency in the retrieved results from the literature may be due to the differences in the patients participating in the studies regarding the time elapsed since the onset of the disease, severity of attacks, the time of last attack, and the different diagnostic criteria for patients' pick up. Other parameters (stimulus used, subjects, response recording method, and response recording criteria) can influence the test results as well. Additionally, there are several factors jeopardizing the interpretation of VEMP outcome, such as the stimulus intensity, muscle anatomy and contraction, subcutaneous fat layer [56] skin impedance, and location of active surface electrode [57, 58].

Subclinical vestibular dysfunction might be an integral part of migraine pathology in general and not solely in VM. The hypothesis of exclusive involvement of peripheral structures is questionable, and the possibility of the involvement of the brainstem due to either abnormal serotonergic regulation or the impact of ischemia caused by reduced blood flow on the vestibular nucleus should be taken into consideration [24]. The more frequent abnormalities in VEMP test were in the cervical type, making it a more reliable measure than oVEMP to assess the vestibular function in migraineurs, although both tests are complementary to each other. The shorter oVEMP pathway in the brainstem is rendering it less vulnerable than cVEMP to the effect of migraine disease pathophysiology.

Conclusions

Migraine and MAV patients did not show significant differences compared to each other regarding cVEMP and oVEMP suggesting that vestibular insult is an integral part in the migraine pathophysiology. Migraine and MAV patients, who had abnormally delayed P₁₃ latency compared to healthy controls, are suggested to have subclinical vestibular dysfunction in the vestibulo-collic pathway. MAV patients who have abnormal interaural P₁₃ latency difference compared to healthy controls are postulated to have a central lateralizing vestibular insult. Cervical VEMP is more reliable than oVEMP in assessing vestibular dysfunction in migraineurs.

Recommendations

Further separate studies are needed for investigating the pathophysiology of migrainous vertigo on a larger and more homogenous group of patients in terms of frequency of attacks per month, time of last attack and duration of affection, and the clinical utility of VEMP in diagnosing it. We recommend complete vestibular test battery including both cVEMPs and oVEMPs in

evaluation of dizzy migraine patients to widen the scope of migraine analysis and to correlate of its findings with the MRI findings.

Abbreviations

VM: Vestibular migraine; MAV: Migraine associated vertigo; VEMP: Vestibular evoked myogenic potential; cVEMP: Cervical vestibular evoked myogenic potential; oVEMP: Ocular vestibular evoked myogenic potential; IHS: International Headache Society; ICHD-3β: International Classification of Headache Disorders-3 beta version; ACS: Air conducted sound; Fpz: Forehead; ms: Milliseconds; μV: Microvolt; Hz: Hertz; TDH: Telephonic dynamic headphones; dB: Decibel; nHL: Normal hearing level; IAD: Interaural difference; SPL: Sound pressure level; SD: Standard deviation

Acknowledgements

Not applicable.

Authors' contributions

DM, HK and JM done the Definition of intellectual content and design. DM, JM and DG done the Data analysis. DM and DG done the Clinical studies. DM, HK and DG done the Statistical analysis. DM and HK done the Manuscript review. HK done the Concepts. DG done the Literature search, Data acquisition and Manuscript preparation. DM done the Manuscript editing. All authors have read and approved the manuscript.

Funding

No funding.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by Faculty of Medicine, Alexandria University ethics committee on 21/1/2016. An informed consent was obtained from each participant in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 11 April 2020 Accepted: 11 June 2020

Published online: 09 September 2020

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