

Can a finding of cervical vestibular evoked myogenic potentials contribute to vestibular migraine diagnostics?

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ABSTRACT

Aim To investigate differences in vestibular evoked myogenic potentials (VEMP) results with patients suffering from vestibular migraine and healthy people, taking into consideration values of threshold and latency of occurrence of the characteristic wave complex, size of amplitude, and interaural amplitude ratio. According to the results, determine the importance and usefulness of VEMP in vestibular migraine diagnostics.

Methods A total number of 62 subjects were included in the study, 32 of them belonging to a group of patients suffering from vestibular migraine (VM), while other 30 were in a control group of healthy subjects. Information was collected during the diagnostic evaluation. General and otoneurological history of patients and bedside tests, audiological results, videonystagmography and cervical vestibular evoked myogenic potentials (cVEMP) were made.

Results There was a difference in an interaural ratio of amplitudes in the experimental and control groups, but it was not found to be clinically significant. By ToneBurst 500 Hz method, the interaural amplitude ratio higher than 35% was measured in 46.97% subjects, while the response was totally unilaterally missing in 28.8% patients.

Conclusion Even the sophisticated method as cVEMP does not give the ultimate result confirming the vestibular migraine diagnosis, and neither do other diagnostic methods. cVEMP result can contribute to the completion of full mosaic of vestibular migraine diagnostics.

Key words: vertigo, migraine, diagnosis

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INTRODUCTION

Cervical vestibular evoked myogenic potentials (cVEMP) are based on a unilateral acoustic impulse (loud clicks or sound booms, with the strength of 95-120 dB, in intervals of 200 ms and length of 7 ms) to the static stain of sacculus and irregular nerves that go from the base of hair cells type I, placed in the striola (1), which bring action potentials created in that way to the vestibular cores through the medial vestibulospinal way causing contractions of the neck muscles in the tested side. Changes in action potentials are measured by electrodes set on the sternocleidomastoid muscle. The graphical representation is biphasic and consists of two deflections which normally occur after a stimulus. The first deflection is positive after 13 ms, and the other one is negative after 23ms, named p13 and n23 wave, respectively. Sometimes, in case of inappropriate setting of electrodes, there can be a switch of polarity of the deflection, and in interpreting the results as the most significant parameters we take into consideration the size of the deflection (amplitude) and time passed until the occurrence of deflection (latency) regardless of the polarity of the wave. It must be pointed out that conductive hearing damage makes VEMP testing impossible, while sensori-neural hearing damage does not affect it. The point of making cVEMP test is to determine whether otolithic sense of sacculus and vestibular nerve with its central connections is untouched and if there is any damage manifested by their dysfunction.

Parameters used in the interpretation of VEMP results include the threshold of wave complex, p1 (p13) and n1 (n23) latency, p1 (p13) and n1 (n23) amplitude size and interneural ratio of the amplitudes expressed in percentages, and calculated according to this formula:

Interaural amplitude ratio (AR) = $100 \times (\text{higher amplitude} - \text{lower amplitude}) / (\text{higher amplitude} + \text{lower amplitude})$.

If the AR is higher or equal to 35%, it is taken as clinically significant and interpreted as a unilateral damage of the lower part of the labyrinth (2-4). As a clinically significant parameter, we take the absolute value of the amplitude which is double in size of the other one. When the values of the amplitude are lower or the same as $30\mu\text{V}$, the amplitude is absent, and when it is higher or the same as $450\mu\text{V}$, the amplitude is irregularly high.

Vestibular migraine (VM) is controversial and heterogeneous vestibular disorder is nicely explained in the article titled „Chameleon among episodic vertiginous syndromes“ (5).

Different names were used to describe this entity. Today, most authors accept the term vestibular migraine (6), which is also accepted by us, although the term migraine vertigo (7) seems better, as in the background it is a vertigo with the migraine, and not the other way around. It is the most common cause of spontaneous vertigo, and according to some authors the second most common cause of vertigo in general (8,9). The link between migraine and the vestibular sense was noted in the middle of the 19th century, when Prosper Meniere described vertigo in patients with migraine (10). Later, far greater occurrence of vertigo in patients with headaches was noted (11). Almost without exception, pair research studies, have shown the link between migraine, vertigo and dizziness (12), showing a significantly greater number of patients with migraine who have vertigo (13), compared to those who suffer from other types of headache or with healthy controls (14).

The progress in the development of molecular techniques resulted in a series of channelopathy theories about the occurrence of migraine and VM. In patients with migraine, there is channelopathy made by mutations on CACNA1A and KCNA1 genes, with disturbance of transmembrane calcium and potassium ion transport, which provokes the occurrence of familial episodic ataxia type 2 (15,16). This theory is stated to be questionable due to the lack of mutation on CACNA1A in a number of patients with familial episodic migraine with vertigo (17).

Positron emission tomography (PET) scans have made it possible to record higher activities of specific parts of the brain, such as locus coeruleus and dorsal raphe nucleus during VM attacks (18). According to their connection with vestibular nuclei in the form of noradrenergic inputs from locus coeruleus (19) and serotonergics from the dorsal raphe nucleus (20), there is a conclusion about their mutual actions during the VM attacks (21).

The aim of this prospective clinical study was to find out if there were significant differences in cVEMP results with patients suffering from VM and healthy people, taking into consideration the

values of threshold and the latency of occurrence of the characteristic wave complex, peak-to-peak amplitudes, and interaural amplitude ratio. According to the results, the aim was to determine the significance and possibilities of cVEMP in vestibular migraine diagnostics.

PATIENTS AND METHODS

Study design and examinees

This prospective clinical study was made at the Vukovar General County Hospital, the Department of Otorhinolaryngology, in the period between February, 1 and July, 31 2014. A total number of 62 subjects were included in the study, with the mean age of 43.43 (from 19 to 68 years), of which 32 made a group of patients suffering from VM according to the unique consensus criteria (22), while the other 30 made a control group of healthy subjects recruited among the blood donors from the Town Society of Red Cross Vukovar. Patients were divided into three groups depending on the age, and data were analyzed. Information was collected during the diagnostic evaluation of the patients. General and otoneurological anamnesis and bedside tests, audiologic examination, VNG and cVEMP were made. Exclusion criteria were any kind of hearing damage, unilateral weakness ($\geq 25\%$) and directional preponderance ($\geq 35\%$) in caloric test.

Methods

Testing of the patients was done after the diagnosis had been set and 3 months after the diagnosis by the same examiner.

The cVEMP was determined using Eclipse Platform (Interacoustics®, Denmark), and electromyographic (EMG) (System Otoacces, Montreal, Canada). Acoustic stimulus was made monaurally by Insert Earphones ABR 3A (Interacoustics, Assens, Denmark), with earplugs (3M Auditory Systems, Indianapolis, USA). Two different types of air conducting stimuli were used, 5,1 ms, 95 dB nHL clicks of negative polarity and 500Hz, 95 dB nHL tone bursts of negative polarity with a linear envelope (2ms rise/fall time, 1 ms plateau). Two hundred sweeps were averaged for each test.

Values that were compared were: latencies of p and n wave, peak-to-peak amplitudes and AR in

both groups of subjects, and the relation of all measured parameters between the groups.

Statistical evaluation

For the description of distribution of the frequencies of researched variables, descriptive statistical methods were used. All the variables were tested on the normality of distribution with Kolmogorov-smirnov test, and according to the results, parametric or nonparametric methods were applied. Median values of the continuous variables were presented with the arithmetical median and by standard deviation for normally distributed variable and the median for variables that are not distributed evenly. Nominal points were presented with the distribution of occurrence by groups and percentage.

For determining the differences between two independent samples, Student T-test was used, while for the determining of differences between two measurements, Student T-test for dependable samples were used (Wilcoxon test for nonparametric distribution). For determining the differences of dependent samples for the time of the measurement (3 and more) the analysis of variance for the repeated measurements (nonparametric Friedman test) was used.

ROC analysis was applied for determining the optimal borderline values, surfaces under the ROC curve, specificity, sensitivity of the tested parameters in cases of relapse. The influence of more predictors on the positive test and reoccurrence was evaluated by logical regression. The grade of connection was given by Pearson or Spearman coefficient of correlation, which depended on the normality of distribution. For determining the differences between proportions χ^2 test and Fisher exact test were used.

For the grade of significance of the results provided, the level of significance $\alpha=0.05$ was determined.

RESULTS

A total number of 62 subjects participated in this study, with a higher number females, 42 (69%), and 20 (31%) males. In the patients group there were 24 (75%) females, and eight (25%) males, while in the control group there were 18 (63%) females and 12 (37%) males.

Median age of the subjects was 45.5 (in females 45 years, and 46 in males). All three age groups were

equally represented: less than 40 years (35.5%), 40-50 years (33.9%) and more than 50 years (30.6%). During the VEMP click stimulus, there were differences in latencies p13 right, where the control group had higher results in relation to the patients group: in average the latency p13 occurred at 11.65 ms in the control group, while it occurred at 9.54 ms in the patients group. Similarly, latencies n23 right, where the latency in the control group occurred in average at 21.40 ms, while in the patients group it occurred at 17.58 ms. The latencies in the patients group were shortened in relation to the control group, for an average of 3.92 ms. There was no difference shown between the latencies of VEMP click p13 and n23 left (Figure 1).

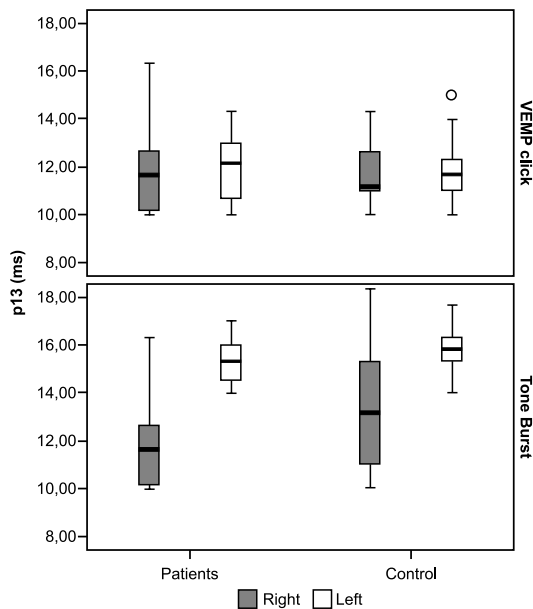


Figure 1. Latency p13 of the left and right side of the control and experimental groups during the A) acoustic stimulus VEMP click 95dB and B) Tone Burst (median, interquartile range, minimum and maximum)

During the sound boom stimulus test, with the strength of 500 Hz, there were differences in the latencies of p13 and n23, as in amplitudes cVEMP wave complex, in both sides. Latency of p13 right occurred at 15.52 ms in the control group, and in the patients group at 12.62 ms. Latency p13 left occurred at 15.88 ms in the control group, and at 13.55 ms in the patients group. Latency of n23 wave right was recorded in the control group at the average level of 25.17 ms, and in the patients group at the level of 21.98 ms, while the latency n23 left wave in the control group averaged at 22.50 ms, and in the patients group at 21.98 ms (Figure 2A).

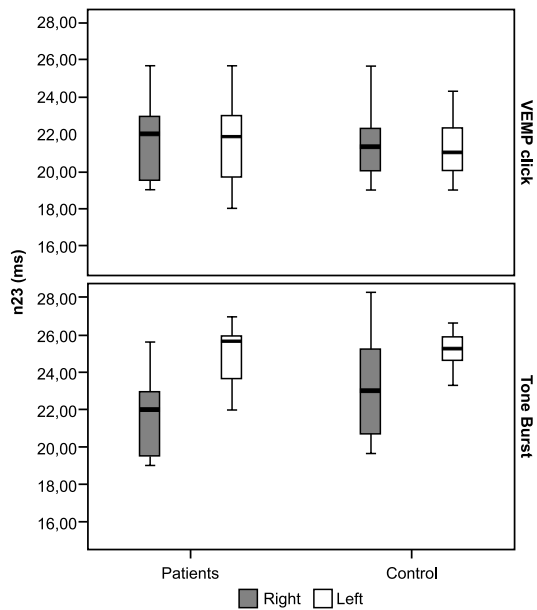


Figure 2. Latency n23 right and left side of the control and experimental group during the A) acoustic stimulus cVEMP click and B) Tone Burst

Also, there was a difference in the absolute values of amplitudes shown in μV between control and patients group, where the control group constantly showed higher values than the patients group. In variables amplitude right, control group has shown the average result of $M=61.53$ ($SD=34.912$), and the experimental group $M=37.46$ ($SD=27.407$), $t(60)=3.029$ ($p=0.004$). In variables amplitude left, control group has shown the average of $M=60.52$, ($SD=34.395$), and the experimental group $M = 41.91$ ($SD=28.452$), $t(60) = 2.328$, ($p=0.023$). (Figure 3).

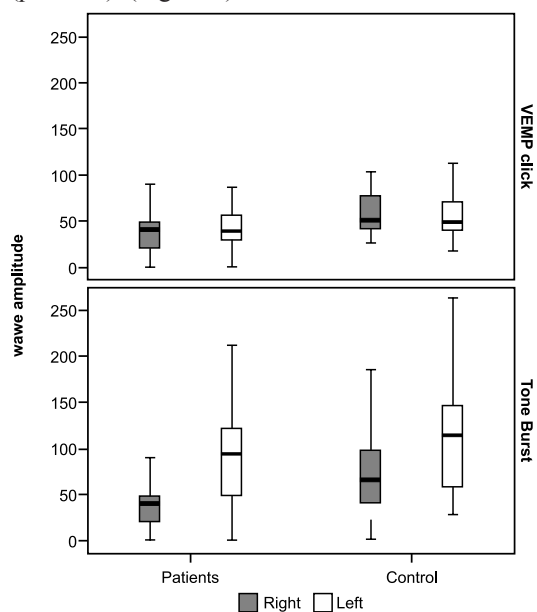


Figure 3. Amplitude of the wave of the right and left sides of control and experimental groups during the A) acoustic stimulus cVEMP click and B) Tone Burst

There was a difference in interaural ratio of amplitudes in experimental and control group: no clinically significant asymmetry of interaural amplitude ratio (AR) was found in the control group (by click stimulation averages were at 10%, and the ToneBurst method of 500 Hz averages were at 12%). In the patients group, using the method of cVEMP click a clinically significant AR discrepancy higher than 35% was found in 48,69% patients, where in 11 (34.38%) patients the wave complex was totally missing from one side; by ToneBurst 500 Hz method the discrepancy higher than 35% in 46.97% patients, while the response was totally unilaterally missing in nine (28.8%) patients (Figure 4).

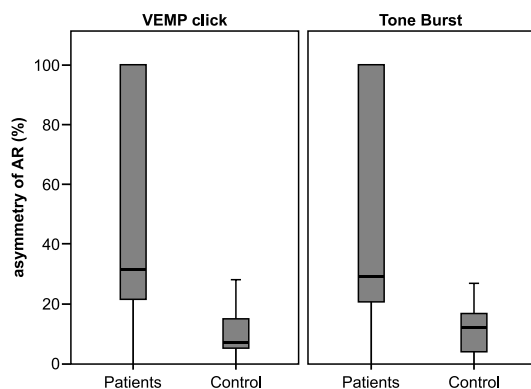


Figure 4. Representation of asymmetry ratio (AR) during the A) acoustic stimulus cVEMP click and B) Tone Burst measurement in the patients and controls

DISCUSSION

The results of this study have shown a higher VM representation in females than males in the sample as a whole, as well as in both patient and control group. Other authors have recorded similar results (23-25).

During the cVEMP click, in the patients group a significantly shortened p13 and n23 latency of the wave complex right side was found in this research, while on the left side there was no statistically significant discrepancy when compared to the control group. In the patients group the wave amplitude was in average bilaterally significantly lesser in comparison with the control group, as other authors found in their studies (26).

Vestibular diagnostic and therapy is a reflection of technological, scientific and socioeconomic trends (27). An improvement in vestibular diagnostics is characterized by the application of new tests like vestibular evoked myogenic potentials

results (VEMP), which provide additional information to those acquired by the standard battery of diagnostic tests such as videonistagmography (VNG), electronistagmography (ENG) (28).

The results of this study have shown no interaural discrepancy of the amplitude ratio in the control group, while in the patient group during the cVEMP method click and tone burst 500 HZ a discrepancy higher than 35% was found in almost half of the patients. Also, in almost a third of the patients, the wave complex was totally missing on one side, while in the control group there were no such cases. Discrepancies in the nystagmography results occur mostly in patients with migraine and they point to the lesions of central and peripheral parts of the vestibular system, but unfortunately, they are unspecific and insufficient to set the diagnosis of VM based solely on these results (29). Despite the known connection between migraine and vertigo for many years, and despite the lack of trusted biomarkers, the nature of this correlation is still not explained thoroughly. Many studies have tried to find possible specific characteristic discrepancies in laboratory test results in VM patients. Some studies have monitored the effect of saccular inhibition with the acoustic stimulus on ipsilateral contraction of SCM (30-33). In conclusion, from the literature used so far, it is suggested that VM is a heterogeneous vestibular disorder, where different pathophysiological mechanisms are included in its occurrence and progression (34). Today, the most different, more or less accepted hypotheses about the beginning of VM exists (35), and they all stem from epidemiological and empirical facts about the common etiopathogenesis of migraine and VM and the discrepancy of vestibulological research made during and in between attacks of VM (36).

A German study has shown that the prevalence of migraine in general population is about 14%, while vertigo prevalence is about 7% (37). This is probably due to accidental congruence and coexistence of migraine and vertigo in 1% of the general population, although the stated prevalence of concurrence of vertigo and migraine in the general population is 3.2% (38), suggesting the existence of linkable pathophysiological mechanism.

Although we consider migraine and VM as a consequence of brain dysfunction (39), and do-

minant vascular theory of migraine occurrence is more and more dismissed. Ear artery is considered to be a good explanation of vestibular symptoms during the VM attacks (40), as retinal vasospasm explains retinal migraine (41).

The results of this research will contribute to easier discernment of vertigo caused by peripheral lesions of vestibular apparatus and vestibular migraine. Even the sophisticated method as cVEMP does not give the ultimate result for setting the VM diagnosis, and neither do other diagnostic methods. Still, nowadays when we have the concise consensus on diagnostic criteria for VM, irregular cVEMP result in the form of lowered values of the p and n wave latencies and the amplitude values, and significant interaural amplitude discrepancies, we can consider them a small tile which, with other clinical and laboratory tests results, contributes to the making of a full mosaic in vestibular migraine diagnostics.

Despite the huge achievement in the diagnosis of vestibular disorders, we still do not have a diagnostic indicator which can definitely approve the VM diagnosis. The final diagnosis can be set only in cases of migraine and vertigo occurring at the same time, or migraine with aura (42). With great understanding of the diagnostic criteria for vestibular migraine formulated by the Committee for Classification of Vestibular Disorders of the Barany Society and the Migraine Classification Subcommittee of the International Headache Society, for VM diagnosis it is important to take full and precise history data (43,44). Clinical records of patients with VM are not characteristic and fit the records of healthy people. Sometimes, during the acute phase of the illness, we can find signs of central and peripheral damage, a spontaneous or positional, horizontal, rotatory and vertical type of nystagmus, and damage of one of the labyrinths (45).

Thanks to the similar pathophysiology and some common traits, Meniere's disease is sometimes highly similar to VM, so one must pay close atten-

tion and take an effort to diagnostically differentiate the two entities (46). Also, one should always think about the possibility of benign paroxysmal positional vertigo (BPPV), vestibular neuronitis, perilymphatic fistula and TIA in the field of vertebrobasilar circulation. Dix-Hallpike test is positive in about 25% of the cases of VM (47), but mostly subjectively, with a lack of the characteristic positional nystagmus. In recent years, a special form of positional nystagmus and vertigo has been described- migrainous positional vertigo, which occurs only in postmenopause of migrainous patients and involves only the lateral canal so it is of differential diagnostic significance in relation to lateral canal BPPV (48). Also, benign positional vertigo of children and adolescents is undoubtedly connected to migraine and VM in later years, according to numerous authors (49-51).

Although there is no unique pathognomonic test to confirm the presence of VM, all clinical and laboratory vestibular diagnostic tests aim to remove other vestibular entities as their main goal. Besides laboratory tests, there is at least double amount in discrepancy from the normal results in patients in remission period between VM attacks, and in patients who suffer exclusively from migrainous headaches (52).

The clinical usage of VEMP is still in development, but it sheds a new light on the part of the vestibular system, unavailable to the vestibular diagnostic until recently, and significant results are to be expected. For now, it can be said that it is useful in diagnostics of numerous vestibular disorders, and in some entities there is a characteristic pattern of changes in the VEMP record.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Curthoys IS, Vulovic V, Manzari L. Ocular vestibular-evoked myogenic potential (oVEMP) to test utricular function: neural and oculomotor evidence. *Acta Otorhinolaryngol Ital* 2012; 32:41-5.
2. Brantberg K, Fransson P. Symmetry measures of vestibular evoked myogenic potentials using objective detection criteria. *Scand Audiol* 2001; 30:189-96.
3. Welgampora MS, Colebatch JG. Vestibulocollic reflexes: Normal values and effect of age. *Clin Neurophysiol* 2001; 112:1971-9.
4. Myamoto A, Seo T, Node M, Hashimoto H, Sakagami M. Preliminary study on vestibular evoked myogenic potential induced by bone-conducted stimuli. *Otol Neurotol* 2006; 27:1110-4.