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Evaluation of Cervical Vestibular Evoked Myogenic Potentials in Patients with Migraine

Migrenli Hastalarda Servikal Vestibüler Uyarılmış Miyojenik Potansiyellerin Değerlendirilmesi

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Summary

Objective: Recent studies have indicated that the brain stem may contribute in the pathogenesis of migraine through different mechanisms. In addition to being used mainly in otologic diseases, vestibular evoked myogenic potentials (VEMP) testing is also used in neurological diseases affecting the brain stem such as stroke and multipl sclerosis in the literature. Studies involving VEMP testing in patients with migraine are novel and few in number. The purpose of this study was to evaluate whether VEMP values in patients with migraine provide additional information regarding the pathogenesis.

Methods: This study included 52 patients with migraine and 52 control subjects. In both patients and controls, VEMP examination was performed using click stimuli, and all responses were recorded for both portions of the sternocleidomastoid muscle. Latency, amplitude and threshold values of the P1–N1 wave were compared between the two groups.

Results: The amplitude of the left p1 was 4.47±3.52 μv in patients and 6.15±4.79 μv in the controls, and the difference was statistically significant. On the left, the average difference in the P1–N1 amplitude was 9.04±6.13 μv in patients and 12.03±7.79 μv in the controls; this difference was also statistically significant.

Conclusion: The available studies on the pathophysiology of migraine show that the brain stem is particularly affected at the upper part. However, VEMP testing is mainly used for the assessment of the neuronal pathway starting from the saccula-macula and finishing at the sternocleidomastoid muscle in the lower brain stem. In this study, the only significant differences in amplitude were found in left-P1 and P1-N1. The results of our study show that in patients with migraine, neuroanatomical structures in the lower brain stem can be asymmetrically affected. *(Turkish Journal of Neurology 2013; 19:134-138)*

Key Words: Migraine, cervical vestibular evoked myogenic potentials, pathogenesis, brain stem

Özet

Amaç: Tarihsel olarak yeni çalışmalar, migren patogenezinde beyin sapının farklı mekanizmalarla rolü olabileceğine dikkat çekmektedir. Vestibüler Uyarılmış Miyojenik Potansiyeller (VEMP) başlıca otolojik hastalıklarda kullanılmış olmakla birlikte özellikle inme ve multipl skleroz gibi beyin sapını etkileyen nörolojik hastalıklarda da yapılmış çalışmalar literatürde mevcuttur. Migrenli hastalarda VEMP'le ilgili çalışmalar oldukça yeni tarihli ve az sayıdadır. Bu çalışmada migrenli hastalarda VEMP incelemesi yapılarak VEMP değerlerinin bu hastalarda patogenezle ilgili ek bir bilgi sağlayıp sağlamayacağının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 52 migren hastası ve 52 kontrol alındı. Migrenli hastalarda ve kontrollerin hepsinde klik uyarı ile yapılan VEMP incelemesinde her iki sternokleidomastoid kasından yanıtlar kaydedildi. P1-N1 dalgasının latans, amplitüd ve eşik değerleri ayrıca taraflar arasındaki farklar kaydedildi.

Bulgular: Migrenli hastalarda sol P1 amplitüdü 4,47±3,52 μv, kontrol grubunda ise 6,15±4,79 μv idi ve aradaki fark istatistiksel olarak anlamlıydı. Ayrıca migrenli olgularda solda P1-N1 amplitüd farkı ortalama 9,04±6,13 μv iken kontrol grubunda 12,03±7,79 μv idi. Bu değer yönünden gruplar karşılaştırıldığında aradaki farkın istatistiksel olarak anlamlı olduğu görüldü.

Sonuç: Migren patofizyolojisiyle ilgili çalışmalar bütün halinde gözden geçirildiğinde eldeki bulgular bu hastalarda özellikle üst beyin sapının etkilendiğini göstermektedir. Buna karşılık VEMP, sakkula-makuladan başlayıp, sternokleidomastoid kasında sonlanan nöronal bir yolun çalışmasını, yani nöroanatomik olarak başlıca alt beyin sapını değerlendirmektedir. Bu çalışmada sadece sol P1 ve P1-N1 amplitüd farkındaki düşüklüğün anlamlı olduğu saptandı. Çalışmamızın sonuçları migrenli hastalarda alt beyin sapındaki nöroanatomik yapıların da asimetrik bir şekilde etkilenebileceğini düşündürtmektedir. *(Türk Nöroloji Dergisi 2013; 19:134-138)*

Anahtar Kelimeler: Migren, vestibüler uyarılmış myojenik potansiyeller, patogenez, beyin sapı

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Introduction

A number of theories related to the vascular and neural mechanisms in the pathophysiology of the migraine have been proposed in the studies to date. However, not a single unifying hypothesis capable of explaining the pathophysiology of migraine or interpreting the current evidence in a pathophysiological context has emerged. Recent studies argued that the neuroanatomical structures or the neurotransmitter mechanisms in the brainstem that are activated during the onset and offset of the migraine attack might be playing a role in the pathogenesis (1-3). Vestibular evoked myogenic potentials (VEMP) is a non-invasive, easy to administer electrophysiological test that engages the inferior-vestibular, brain stem and central neural connections starting from saccular macula (4-8). While VEMPs are often used in otological disorders, there are studies in the literature on their use in cerebrovascular disorders affecting brainstem and neurological disorders such as multiple sclerosis (5-15). Studies looking at VEMP in migraine patients have recently started gaining interest and are few in numbers (16-20).

It is important to uncover the factors related to pathogenesis and develop an appropriate course of treatment in patients with migraine. Objective measures of evaluating the relationship between the pathogenesis-related anatomical structures and mechanisms, and the clinical properties of the disease, its course and treatment are still not being employed to their fullest extent.

In this study, we compared patients diagnosed with migraine according to International Headache Society (IHS) criteria with healthy controls using VEMP test and investigated whether the VEMP results in this population can provide additional information on the pathogenesis of the disease.

Materials and Methods

Study organization: Fifty two patients who visited our clinic between January 2010 and March 2010 who were diagnosed with migraine according to IHS criteria by two neurologists were included in the study. Fifty two volunteers from an age and sex distribution similar to our study group were randomly selected as the control group. In the selection of control group, only the individuals who were not previously diagnosed with headache according to IHS criteria and who scored between 1 and 0 in the Visual Analog Scale (VAS) evaluation were included.

The study was approved by the university's ethical committee (2009/213). The study was conducted in accordance with Helsinki Decleration. All patients and the control group were informed extensively about the procedures of the study and gave their informed consents.

The inclusion criteria were: 1. The patients were between 18 and 60 years old, 2. Having at least one attack per month but no attacks within the past 15 days, 3. diagnosis with migraine, 4. being in the attack-free period, 5. not having a chronic neurological, systemic or inner ear/auditory condition indicating an otological disorder that would affect the results of VEMP analysis or a past cervical trauma. Both with and without aura migraine patients were included in this study. Different subtypes of migraine such as chronic migraine or probable migraine were not included in the study.

Data acquisition from patient and control groups and evaluation: The patient and control groups filled detailed evaluation forms prepared in consideration of their demographic information, medical history and IHS criteria. All of the cases included in the study were diagnosed for migraine according to IHS criteria separately by two different neurologists following interviews and medical examinations (21). Individuals who scored between 0 and 1 were included in the study as the control group.

The patient and the control groups were included in the study after an otorhinolaryngology specialist confirmed the absence of an otological pathology or hearing loss that could potentially confound VEMP analysis.

Electrophysiological measurements: All electrophysiological recordings were conducted in a ventilated, dimly lit room at 25°C (77° F) temperature using Medtronic electromyography device (v4.3.505.0-Model 190B6), by recording VEMP from right and left sternocleidomastoid muscles (SCM).

Vestibular evoked myogenic potentials protocol: VEMP relies on the principle that intense stimulation to the ears evokes strong responses in the neck muscles such as the SCM and this activity would be visible from the surface. Cervical VEMP involves the acquisition of the response to high-intensity audiotry stimulation from the surface of the skin above the tensed SCM. Vestibular evoked myogenic potentials occur as a positive-negative peaking waveform. The ipsilateral muscle response occurs after 13 ms following the auditory stimulation in the positive direction and 23 ms in the negative direction, named as P13 and N23 (or P1-N1) respectively (4,5).

The participants were asked to keep their eyes open and fixate on a static point while they were monitored to ensure their awakeness and comfort. A click sound was delivered to the ear through the earphones in the VEMP recordings. During the procedure, the subject was put in a supine position and EMG was recorded with a conventional surface electrode on the SCM (1/3rd upper part) as the head was held in a flexed position. The participants were asked to keep their head unsupported and flexed upwards. The reference electrode was placed on the sternum and a ground electrode was placed underneath. The monoaural click stimulation was delivered through the headphone. The bilateral VEMP recordings were repeated for both sides at least twice. VEMP 3 Hz frequency was recorded after a 0.1 ms stimulation. The high intensity (115 dB) click sound was repeatedly delivered to each ear for 200 ms. Electrode impedance was set to be smaller than 5 Ohms. The frequency of the stimulation was set to 10 Hz. Myogenic potentials were amplified. The filtering was between 10 Hz and 3 kHz. The waves were averaged over 250 trials. Each ear was recorded over at least two successive stimulations. The latency, amplitude and threshold values as well as the contralateral differences were recorded for the P1-N1 wave. Since the recording levels were high, headphone placement was controlled throughout the recording session. The first reflexive response (P1-N1) was the positive-negative wave approximately about 13 ms latency. The latencies of potentials were indicated at their beginning by using the marker. The absolute amplitude of the P1-N1 component was measured.

Statistical Analyses

The data was analyzed with SPSS 11.5 (Statistical Package for the Social Sciences) package program. The means for both groups were compared with a t-test. Chi-square test was used for the comparison of non-parametric tests. The data was treated as means and standart deviation (SD). The threshold for statistical significance was determined as $p<0.05$.

Table 1. Clinical Information of the Migraine Group

		Patient (n=52) n (%)
Pain location	right-unilateral	19 (36.5)
	left-unilateral	24 (46.2)
	bilateral	9 (17.3)
Pain type	throbbing	52 (100)
	tightness/pressure	
Nausea		52 (100)
Vomiting		24 (46.2)
Phonophobia		47 (90.4)
Photophobia		41 (78.8)
Increase with activity		52 (100)
Aura		21 (40.4)
Family history		35 (67.3)
Attack frequency (month/attack) (min-max)		3.83 (1-10)
Attack duration (hour)		27
Attack intensity		medium 8 (15.4)
		high 44 (84.6)

Results

Sociodemographic properties: Migraine group consisted of 52 (40 female, 12 male) patients with a mean age of 34.7±7.5. The healthy control group consisted of 52 healthy volunteers (39 female, 13 male). The mean age of the control group was 34.0±7.3. There were no statistically significant differences found between the patient and the control groups in terms of sex and age distribution.

Clinical properties of migraine patients: The mean duration for the disorder was 8 years. Nineteen (36.5%) of the patients reported right-unilateral, 24 (46.2%) left-unilateral, 9 (17.3%) reported bilateral localization for the headache. The pain in all patients was of throbbing character. In addition, headache was modulated by physical activities and almost all patients complained that their daily activities were affected by the headache. Nausea was a symptom in all patients. Twenty four patients (46.2%) reported vomiting accompanying the headache, 41 (78.8%) reported photophobia, 47 (90.4%) reported phonophobia. Twenty one (40.4%) of the patients described aura-like symptoms. Thirty five (67.3%) patients mentioned a family history.

The mean attack count for the migraine patients was 3.83 and the attack duration was 27 hours. Eight patients included in the study (15.4%) rated the intensity of the headaches as medium, and 44 (%84.6) rated theirs as high. The clinical properties of the patients are summarized in Table 1.

Comparison of migraine group and control group VEMP findings: There were no significant differences between the groups when the mean latencies of the P1 in either side were compared between the groups. Similarly, a comparison between the groups in terms of N1 latency also did not show and statistically significant difference.

Other comparisons that did not show statistically insignificant differences between the groups were the right P1 amplitude, right and left N1 amplitude, right and left P1-N1 latency difference, and right-left ear N1 latency difference. However, left P1 amplitude was 4.47±3.52 µV in migraine patients and 6,15±4,79 µV in control group and the difference was statistically significant (p=0.03). The comparison of VEMP values between the groups is summarized in Table 2.

Discussion

In this study, we compared 52 patients with migraine with 52 healthy control groups using VEMP. There were statistically significant differences between the migraine and the control group in terms of left P1 amplitude and left P1-N1 amplitude difference. Even though there are different hypotheses on the pathophysiology of migraine, the brain structures that are responsible for triggering migraine attacks are still unknown. ,It is suggested , however, that the brainstem and the hypothalamic generators may be triggering migraine attacks (1-3).

During a migraine attack, the blood flow between audiovisually responsive areas such as cingulate cortex and the dorso-lateral region of the brainstem increases and remain high even after the attack. This led to the naming of this region as "migraine generator" in the brainstem (1,3). In addition, even though the application of Sumatriptan alleviates migraine symptoms and diminishes the cortical activity, the localized increase in mesencephalon blood flow was still observed (1,3). For this reason, the activity seen in the side contralateral to the pain is argued to be the first sighting of a migraine center (1,3). Moreover, it was also argued that this region is not responsible for the emergence of the pain but it possibly plays a role in the central pain

Table 2. VEMP Values of Patient and Control Groups

	Patient (n=52)	Control (n=52)	p
Right N1 latency (ms)	16.18±2.73	17.24±3.37	0.082
Left N1 latency (ms)	16.86±2.62	17.61±2.44	0.134
Right P1 latency (ms)	12.23±1.63	12.59±1.88	0.291
Left P1 latency (ms)	12.14±1.62	12.55±1.72	0.214
Right N1 amplitude (µV)	4.29±4.20	4.38±4.15	0.919
Left N1 amplitude (µV)	4.57±3.98	5.87±4.72	0.133
Right P1 amplitude (µV)	5.17±3.62	4.67±4.02	0.506
Left P1 amplitude (µV)	4.47±3.52	6.15±4.79	0.044*
Right P1-N1 amplitude difference (µV)	9.47±6.68	9.05±6.53	0.748
Left P1-N1 amplitude difference (µV)	9.04±6.13	12.03±7.79	0.032*

regulation or at least it can lead to pain because of a general or area-specific sensitivity. Studies on brain stem's generative role in migraine point out to a potential role of serotonin (1,3). The dense presence of the seratonergic neurons are responsible for arterial vasodilation or vasoconstriction mechanisms in the brain stem (especially dorsal raphe); the precipitation of recurrent migraine attacks after stereotaxic lesioning dorsal raphe and periaqueductal gray matter; the fact that certain antimigraine drugs bind to locations in the midbrain support the role of this structure in the pathophysiology of the migraine. Welch et al.'s 2001 functional magnetic resonance study showed consequent activation of nucleus ruber, substantia nigra and occipital cortex during the migraine attacks triggered by visual stimulation paradigm (22).

Vesibular evoked myogenic potentials is a relatively novel technique and it tests the saccular macula, inferior-vestibular nerve, brain stem and central connections, and sacculocollic reflex arch (4, 5). This test is primarily used in otological disorders such as superior canal dehiscence syndrome, vestibular nerve disorders, acoustic tumor, benign paroximal positional vertigo, central vestibular disorders, Ménière's disease and hearing impairment (4-8,11-13). In addition to those there have been a small number of studies with VEMP on neurological diseases affecting the brain stem such as multiple sclerosis, cerebrovascular diseases (brain stem involvement) and migraine (9, 10, 14-20). In a VEMP study conducted on 20 basilar migraine patients by Lih-Jen et al., evoked potentials could not be recorded in 7 patients, two patients showed delayed responses bilaterally and one patient showed no response on one side and delayed response on the other. The remaining 10 (50%) patients showed normal bilateral responses. In summary, half of the basilar migraine patient group showed either unilateral or bilateral VEMP abnormalities. The abnormal state of VEMP in half of this basilar migraine patient group was found to be caused by lower brain stem hypoperfusion during the attack and reportedly returned to normal states in the VEMP recordings following treatment (18).

In the VEMP study by Baier et al. using 63 vestibular migraine and 63 healthy controls, bilateral VEMP amplitudes were found to be lower in the vestibular migraine group. Based on this finding, the researchers argued that inner ear structures including saccula may be affected in vestibular migraine in addition to brain stem pathology, and that this can lead to symptoms such as vertigo (16). In another VEMP study made by Baier et al. on vestibular migraine and Ménière patients, they suggested that these two disorders may originate from a common cause which is the peripheral vestibular dysfunction. They investigated the electrophysiological aspects of similarity by using VEMP. Sixty three vestibular migraine patients and 16 Ménière disease patients were compared to a matching healthy control group. They found significantly reduced bilateral P1-N1 in both groups as compared to healthy controls. There were, however, no statistically significant differences between the two patient groups in the same variable. There were also no statistically significant differences between the three groups for P1 and N1 latency values. The researchers concluded that saccula is affected in both of these disorders and suggested a pathological condition associated with the labyrinth in the pathogenesis of these disorders (17).

A survey of VEMP studies on otolithic function reveals that the delay in P1 and N1 latencies is the primary finding and this delay has a particular importance for these types of patients. However, in a limited number of studies on migraine P1-N1 latencies were found to be normal but their amplitude was significantly reduced compared to normal levels (16-19). An important point to note in these studies is that the study groups consisted of basilar or vestibular migraine patients as opposed to classical migraine. Furthermore, the amplitude decreases in these studies are both bilateral and affecting both P1 and N1. Therefore the left unilateral decrease in the P1 amplitude and the P1-N1 amplitude difference raises question of whether these findings are meaningful in explaining the pathophysiology of migraine.

To our knowledge, there is only one recent study on turkish patients with classical migraine. This study, conducted by Kandemir et al., compared 20 migraine cases without aura, 20 tension-type headache and 24 vestibular migraine patients to 30 healthy controls. They reported no statistically significant difference in any of the VEMP-related measurements (20).

Studies on migraine pathology converge on the idea that especially the upper brain stem is affected in patients with migraine. On the other hand, VEMP targets the neural pathway starting from saccula, going through inferior vestibular nerve, vestibular nucleus, medial vestibulospinal bundle, accessory nucleus, 11th cranial nerve and terminating at the SCM, which is neuroanatomically more relevant for the lower brain stem. It is known that the hypofusion/reversible

ischemia in the basilar artery and its branches supplying blood to the brain stem play a role in the migraine pathophysiology. Therefore

In this study, the only meaningful differences between the patient and the control groups were the unilateral left P1 amplitude and P1-N1 amplitude difference. In addition to this, 46.2% of the patients expressed that the attacks are located on the left unilateral parts. The results of our study motivate further investigation in that the lower brain stem structures can be affected asymmetrically and considering the "generally unilateral" clinical manifestations of migraine, this finding can easily point a relationship with the pathogenesis. Additional studies with larger experimental groups are required on this subject and it is shown that VEMP test and/or other neurophysiological/neuroradiological assessment methods are useful in such investigations. These future studies may potentially provide additional information in regard to the hypothesis that the lower brain stem is the generator of attacks in the pathogenesis of migraine.

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