Air Conducted Cervical and Ocular Vestibular Evoked Myogenic Potentials in Peudotumor Cerebri Patients

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Abstract: *Objective*: Pseudotumor cerebri is a disorder of unknown etiology that results in raised intracranial pressure (ICP) and characterized by attendant signs and symptoms of increased ICP in an alert and oriented patient but without localizing neurologic findings. Vestibular evoked myogenic potentials (VEMPs) are short latency reflex responses produced by stimulation of the vestibular apparatus. The purpose of this study was to determine whether group of pseudotumor cerebri patients have abnormal changes in VEMPs (cervical and ocular) and to analyze the results and compare them with matched group of normal subjects.

Design: Ocular and cervical VEMPs were performed to the entire study groups. The responses were obtained from thirteen pseudotumor cerebri patients and compared to fifteen age matched normal subjects. All participants were subjected to audiological assessments that include pure tone audiometry, tympanometry and acoustic reflexes.

Results: Ocular and cervical VEMPs amplitudes were reduced in response in pseudotumor cerebri patients than normal but still of non-statistical significant difference $p>0.05$.

Discussion and Conclusion: The results of this study suggest that patients with pseudotumor cerebri do not have statistically significant changes in comparison with the normal control as regard ocular and cervical VEMPs testing. Hence, asserting a query whether there is affection of VEMPs in pseudotumor cerebri patients.

Keywords: Vestibular evoked myogenic potentials, pseudotumor cerebri, idiopathic intracranial hypertension, oVEMPs, cVEMPs, vertigo, dizziness.

INTRODUCTION

Pseudotumor cerebri, also called idiopathic intracranial hypertension (IIH), is a disorder of unknown etiology that results in raised intracranial pressure. The disorder is characterized by attendant signs and symptoms of increased intracranial pressure in an alert and oriented patient but without localizing neurologic findings [1]. It is a disorder without any evidence of infection, vascular abnormality, and space occupying lesion, hydrocephalus or alteration of consciousness [2]. In adults, there is an established association between gender, females and obesity and pseudotumor cerebri [3]. The disease is characteristically diagnosed in obese women of reproductive age [4].

The classic symptoms of pseudotumor cerebri include headache, nausea, and vomiting, the patients may also complain of blurred vision, double vision due to cranial nerve palsies, and stiff neck [1]. The disease characterized by normal neuroimaging studies and elevated opening pressure on lumber puncture with normal cerebrospinal fluid composition [5]. The pathogenesis is unknown, although, brain edema, increased cerebral blood volume, and increased CSF secretion have been postulated as mechanisms [6]. The elevated intracranial venous pressure is also suggested to be a universal mechanism of the disease in adults and children [7, 8].

Vestibular evoked myogenic potentials (VEMPs) are short latency reflex responses produced by stimulation of the vestibular apparatus. Stimuli used to evoke these vestibular dependent responses include air-conducted sounds and bone-conducted vibration. The otolith organs appear to be the main vestibular receptors excited by these stimuli [9]. They are usually elicited by a train of short duration tone bursts and click stimuli [10, 11]. It is used to assess otolithic function in cases of vestibular neuritis, endolymphatic hydrops, superior canal dehiscence syndrome, acoustic neuroma, auditory neuropathy and some neurodegenerative diseases [12]. Cervical VEMP (cVEMPs) recorded from the sternocliedomastoid muscles originate from the saccule [13]. The responses are characterized by biphasic waves which often labeled p13–n23 [14].

On the other hand, ocular VEMPs (oVEMPs) are a short-latency negative-going evoked myogenic potential from surface electrodes placed beneath the eyes in response to acoustic stimulation [15]. The peripheral generator of oVEMP to acoustical stimulation is mainly utricular in origin, but it could be both saccular and utricular [9]. It can be recorded

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bilaterally to unilateral stimulation though the contralateral response predominates. The inferior oblique is the muscle of origin for at least the contra-lateral response [16].

Both cVEMP and oVEMP are defined by broadly tuned frequency response curves. Their tuning is similar, but not identical [17]. There is a general agreement that frequency response and threshold of the oVEMP are consistent with the normal response properties of the cVEMP. Also it seems to be a general agreement that the oVEMP response represents a modulation of EMG activity in extraocular muscles [15], and shows the greatest amplitude when recorded from beneath the contralateral eye when gaze is upward and stimuli are high-intensity 500 Hz tone bursts [16]. In air conducted stimuli, the largest amplitude and lowest threshold for VEMPs recording have been shown to be produced by tone bursts in the range of 200 to 1000 Hz [18-20] and the most common optimal frequency to elicit the cVEMP is 500 Hz [17].

As the Pseudotumor cerebri patients complain of dizziness which can mimic other vestibular disorders. Thus, for differential diagnosis, VEMPs may prove valuable, since increased CSF secretions have been postulated as a mechanism for pseudotumor cerebri. We can assume that, it can also affect the vestibular system with the possibility of dysfunction in the sacular and utricular parts in those patients. The objectives of this study were to measure and analyze the results of VEMPs (ocular and cervical) to air conducted tone bursts in patients with pseudotumor cerebri and to compare the responses as regards its latencies and amplitudes with normal gender and age matched group.

MATERIALS AND METHODS

Participants

Thirteen patients ranged in age from 20 to 50 years participated in this study. All participants were women in the child bearing period. The audiological evaluations were conducted at audiology clinic in our hospital. They were compared to fifteen age matched normal women as a control group. The modified Dandy criteria for idiopathic intracranial hypertension were used and patients that fulfill these criteria are diagnosed as having the disease. The criteria include signs and symptoms of increased intracranial pressure, absence of localizing findings on neurologic examination in awake and alert patient with no other causes of present increased intracranial pressure. The patients as well show absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neuro-diagnostic studies, except for increased cerebrospinal fluid pressure (> 250 mm of water in obese patients) [8]. The study was approved by the ethics and research committee of the hospital and informed written consents were obtained from all enrolled participants.

All participants had normal hearing sensitivity thresholds in both ears for air and bone conduction on behavioral hearing assessment with normal tympanometry to ensure that the middle ear functions were normal. They underwent VEMPs testing (ocular and cervical) in both ears; hence, data were collected from (26) ears of the study and (30) ears of the control groups.

Apparatus and Procedures

To evaluate the hearing sensitivity, a calibrated two channel clinical audiometer AC 40 audiometer (Interacoustics, DK-5610, Assens, Denmark) were used to determine the air and bone conduction thresholds. Middle-ear functions were analyzed using a middle ear analyzer AT 235 Impedance Audiometer (Interacoustics, DK-5610, Assens, Denmark). Vestibular evoked myogenic potentials were recorded using an ICS Medical version 3.00 CHARTR, USA, coupled with a preamplifier (ICS medical CHARTR preamplifier PA-800), output amplifier, computer and insert earphones (ICS medical, IL, USA).

Firstly, pure tone thresholds were obtained at octave intervals between 250 and 8000 Hz for air conduction and between 500 and 4000 Hz for bone conduction. Secondly, tympanometry was conducted with a probe tone frequency of 226 Hz. Ipsi-lateral and contra-lateral acoustic reflexes thresholds were measured for 500, 1000, 2000 and 4000 Hz tones.

Cervical VEMPs

The cervical VEMPs were recorder using the following parameters; stimuli consisted of 500 Hz tone bursts (rise/fall time =1 ms, plateau = 2 ms), presented at a rate of 5 Hz through insert earphones of 200 averaged sweeps. It was evoked by stimulus delivered monaurally to the tested ear. The stimulus intensity was 95 dBnHL. VEMPs signals were recorded from surface electrodes which were applied overlying the upper half of the sternum laterally and the upper third

of the sternocliedomastoid muscle. Ground electrode was placed over the forehead. The skin at the site of the surface electrodes placement was cleaned with abrasive to obtain acceptable electrode impedance. Impedances were maintained below 5kΩ. The analysis time was set to 60 ms post-stimulus interval with 20 ms pre-stimulus epoch. The signal was band pass-filtered from 20 Hz to 2500 Hz. The myogenic signal was amplified by 5,000 and digitized at a sample rate of 5 kHz and then signal averaged. The recording was achieved twice for reproducibility of the response.

During the test, each participant was positioned supine on an examination bed with the upper half of the bed elevated 30°. The participant was instructed to rotate her head so that the test ear was up before each average was obtained. She was instructed to lift the head one inch off the bed to achieve an isolated contraction of the ipsi-lateral sternocliedomastoid muscle. Thus, the vestibular evoked myogenic potential results recorded were presumably due to the acoustic stimuli supplied rather than to changes in sternocliedomastoid muscle contraction. The p13 and n23 waveform latencies were determined for all participants and the amplitude of p13–n23 was evaluated.

Ocular VEMPs

The oVEMPs were recorded using the following stimulating and recording parameters to obtain the response activity. A 500 Hz tone bursts (rise/fall time =1 ms, plateau = 2 ms) were presented *via* the standard foam insert earphones. The stimulus was presented at 95 dBnHL for all participants and was replicated to confirm the presence of the responses. 5 Hz stimulation rate was delivered. One hundred sweeps of electromyogenic activity were recorded on the side contra-lateral to acoustic stimulation. The responses were collected, amplified (100,000×) and filtered between 5 and 1000 Hz. The analysis time was 50 milliseconds pos-stimulus interval with 10 ms pre-stimulus epoch. The ground electrode was place on the high forehead, the active electrode was placed approximately one centimeter inferior to the contra-lateral lower eyelids and the reference electrode was placed immediately inferior to it. Impedances were maintained below 5kΩ. The skin of the face at the site of the surface electrodes placement was cleaned with abrasive to obtain acceptable electrode impedance.

Contra-lateral oVEMPs was performed separately (monaurally) in the right and left ears. The test was recorded as the subject contracted the inferior oblique muscle by elevating the eye 30º (for optimal muscle tension) to maintain gaze fixation on the target that was premeasured for angle of the eye gaze. The waveform n1 and p1 peak to peak amplitude in μV and latencies in ms were measured for all participants.

Statistical Analysis

The VEMPs results of pseudotumor cerebri patients and normal subjects were submitted to statistical analysis using a Statistical Package for the Social Sciences (SPSS) file version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics include the mean; standard deviation and independent t test which were used to compare the results. The criterion for statistical significance was set at $p<0.05$. The analysis was carried out in relation to the latencies of cervical (p13 and n23) and ocular (n1 and p1) VEMPs as well for the amplitude values of p13-n23 and n1-p1 of the cervical and ocular VEMPs waveforms respectively. Correlation and linear regressions of the cVEMPs and oVEMPs as a function of age were also assessed on the above mentioned parameters in both groups.

RESULTS

In this study, the mean age for the control group was 35.4±10.4 years while it was 35.6±9.5 years for the study group. There was no statistically significant difference between pseudotumor cerebri and normal subjects age (t test value = 0.93, $p>0.05$). The mean pure-tone audiogram for pseudotumor cerebri and normal subjects at frequencies 0.25, 0.5, 1, 2, 4, and 8 kHz as a function of hearing threshold level in dBHL for study and control group is displayed in Figure **1**.

Figure **2** shows the prevalence of pseudotumor cerebri symptoms: headache, transient visual obscuration, tinnitus, diplopia, photopsia, retrobulbar pain and visual loss among the patients. The most common symptom was headache while the least was visual loss.

Table **1** shows the mean latencies (n1 and p1; p13 and n23) and amplitudes of n1-p1 and p13-n23 responses of oVEMPs and cVEMPs respectively in the study and control group. While, Table **2** reveals the mean of the right and left recorded sides for latenices and amplitude of oVEMPs and cVEMPs in both groups.

Table **3** shows t-test of the right versus left sides and control versus study groups as a function of oVEMPs and cVEMPs. It was noticed in this study that

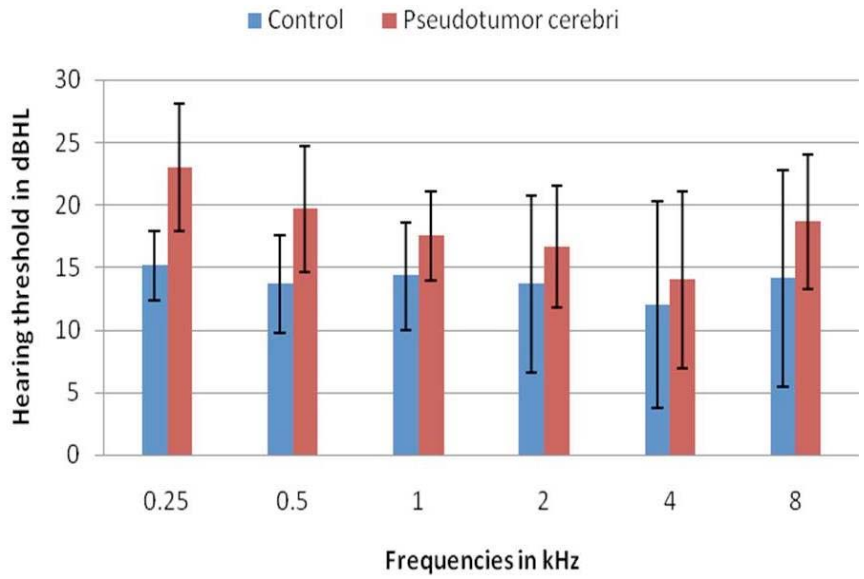

Figure 1: The mean pure tone audiogram in dBHL of the control group and pseudotumorcerebri patients. Error bars represent 1 SD above and below the mean.

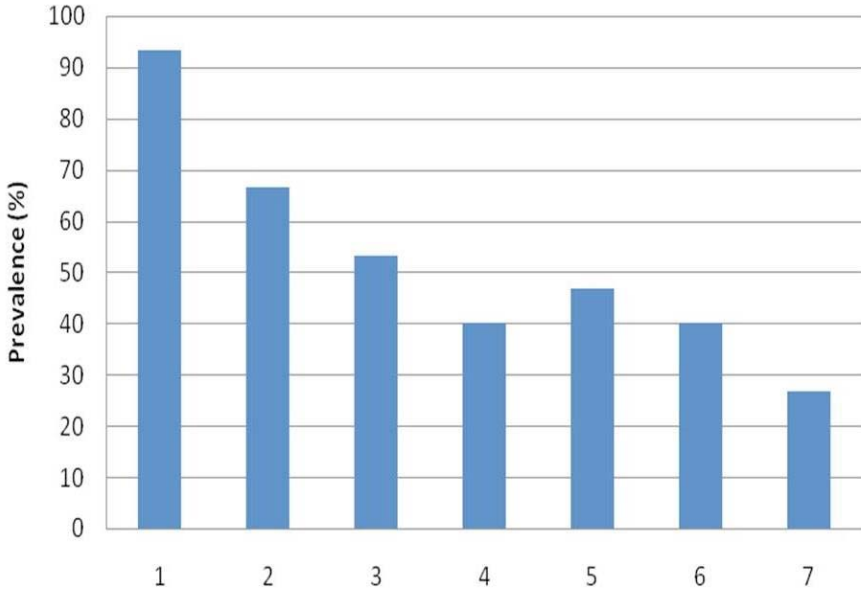

Figure 2: Prevalence of pseudotumor cerebri symptoms. Bars represent the percentage of patients who reported each symptom. Symptoms key (1) headache, (2) transient visual obscuration, (3) tinnitus, (4) diplopia, (5) photopsia, (6) retrobulbar pain and (7) visual loss.

Table 1: The Mean (SD) of cVEMPs and oVEMPs in the Study and Control Group

	cVEMPs			oVEMPs		
	p13 (ms)	**n23 (ms)**	**p13-n23 (μV)**	**n1 (ms)**	**p1 (ms)**	**n1-p1 (μV)**
Control group	13.6 (1.48)	24.19 (3.16)	176.73 (43.45)	10.85 (1.2)	16.51 (1.42)	6.64 (1.49)
Study group	14.14 (1.17)	25.1 (2.22)	156.56 (34.59)	11.45 (1.28)	16(1.58)	5.84 (1.38)

ms = milliseconds; μV = microvolt; SD = standard deviation.

Table 2: The Mean (SD) of Right and Left Recorded Sides for p13, n23, n1 and p1 Latencies and the Amplitudes of p13-n23 and n1-p1 Responses of cVEMPs and oVEMPs in the Study and Control Group

	cVEMPs						oVEMPs					
	p13 (ms)		n23 (ms)		p13-n23 (μV)		n1 (ms)		p1 (ms)		n1-p1 (μV)	
	R	L	R	L	R	L	R	L	R	L	R	L
Study group	14.17 (1.16	14.11 (1.19)	25.1 (2.09)	25.1 (2.36)	157.2 (35.26)	155.93 (33.92)	11.39 (1.27)	11.52 (1.3)	16.92 (1.59)	16.94 (1.58)	5.84 (1.48)	5.83 (1.51)
Control group	13.58 (1.48)	13.63 (1.49)	24.01 (3.06)	24.38 (3.26)	176 (45.04)	177.46 (41.87)	10.83 (1.25)	10.88 (1.16)	16.47 (1.47)	16.56 (1.37)	6.52 (1.38)	6.77 (1.38)

R = right; L = left; ms = milliseconds; μV = microvolt; SD = standard deviation.

Table 3: t-Test of the Right Versus Left Sides and Control Versus Study Groups as a Function of cVEMPs and oVEMPs

	cVEMPs			oVEMPs		
	p13	n23	p13-n23	n1	p1	n1-p1
Right versus left sides						
Control	0.932	0.753	0.927	0.905	0.868	0.62
Study	0.89	0.948	0.92	0.789	0.963	0.962
Control versus study group	0.123	0.076	0.047	0.06	0.281	0.369

there were no significant statistical differences between sides (right and left) and control versus study groups as a function of the latencies and amplitudes for the ocular and cervical VEMPs.

Figure **3** shows the scatter plot of the latencies of oVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age. Whereas, Figure **4** reveals correlations of the amplitudes of oVEMPs evoked by 500 Hz tone burst in the control and study groups as a function of age. It was noticed that the amplitude of oVEMPs decrease as the age increase.

Figure **5** shows the scatter plot of the latencies of cVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age. While, Figure **6** reveal correlation of the amplitudes of cVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age. It was noticed that the amplitude decrease as the age increase.

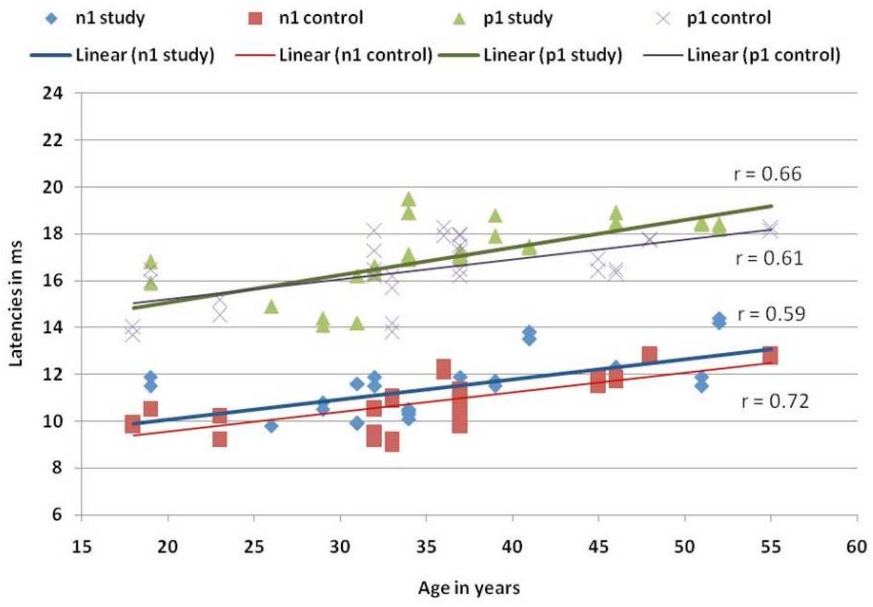

Figure 3: The latencies of oVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age.

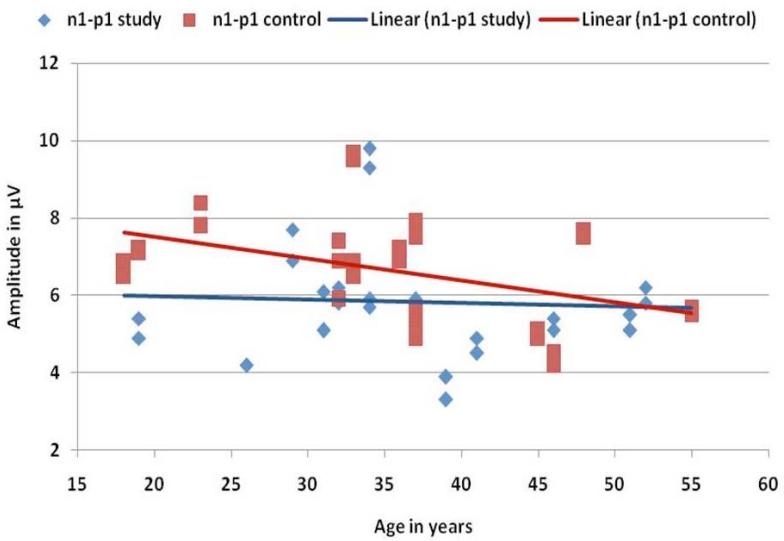

Figure 4: The amplitudes of oVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age.

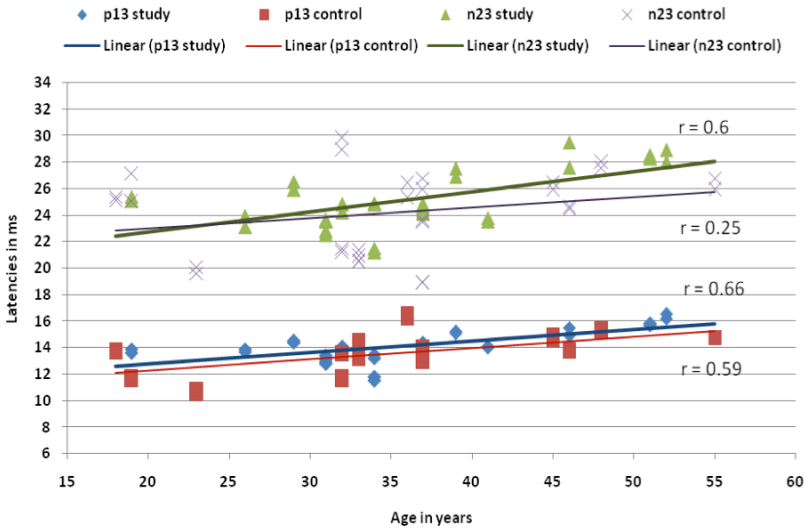

Figure 5: The latencies of cVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age.

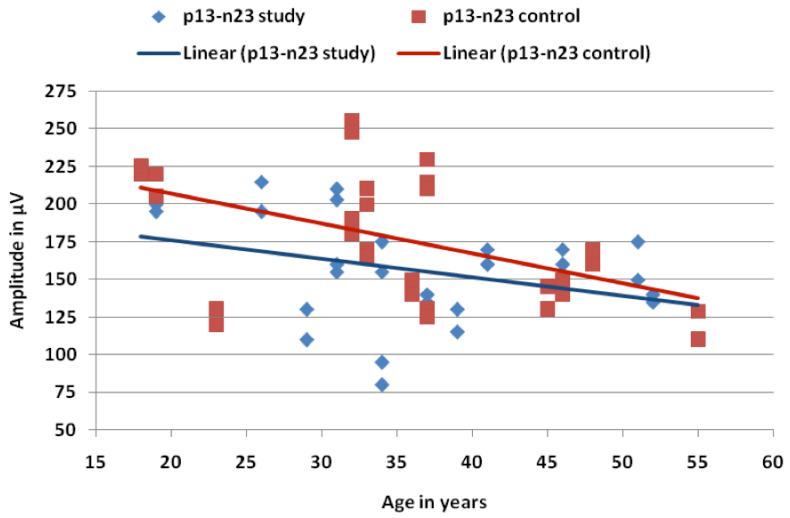

Figure 6: The amplitudes of cVEMP evoked by a 500 Hz tone burst in the control and study group as a function of age.

DISCUSSION

The cVEMPs can be elicited with loud sounds by stimulating the ear. The response to the stimulus could be recorded from the sternocleidomastoid muscles which can be elicited from both sides and it indicates the integrity of vestibule-colic reflex arc. Whereas, the oVEMPs originates from the otolithic organs *via* superior vestibular nerve to vestibular nuclei, and then crosses to the opposite extra-ocular muscles, especially inferior oblique and inferior rectus muscles [21]. Murofushi *et al*., 2010 suggested that oVEMPs in response to air-conducted sound reflect functions of a population of the peripheral vestibular system different from those reflected by cVEMPs, perhaps predominantly utricular in origin [22]. The procedure evaluates the ascending vestibular pathway as crossed VOR [23].

The effectiveness of air conducted tone bursts can be attributed to vestibular activation in normal adults which is highly reproducible between experiments and more symmetrical than activation by head taps or bone conducted vibration [24]. Furthermore, conventional instrument for evoked potentials is generally equipped with a maximum level of 70 dBnHL for bone-conducted sound, which is lower than the normal threshold for eliciting VEMPs [13]. In this study, a comparison between the results of VEMPs (cervical and ocular) in pseudotumor cerebri patients and normal subjects were performed.

Air conducted tone bursts were used as a stimulus for eliciting the responses. VEMPs can be elicited optimally for tone burst frequencies from 250 Hz to 2 kHz, provided age-matched control data are available. In this study, air conducted 0.5 kHz tone bursts (1 ms rise/fall time and 2 ms plateau) were used to elicit the responses in both the ocular and cervical VEMPs. An increase in amplitude with increasing stimulus duration, using 500 Hz stimuli can be observed however, there is no definite benefit in using longer stimuli than 2 ms to elicit the responses. Shorter stimuli also minimize subject exposure to sound [25]

Wang *et al*., 2009 found that oVEMPs n1-p1 waveforms were recorded with maximal amplitudes from the electrodes located below the eyes contra-lateral to the side of acoustic stimulation while the subject was gazing upward [26]. Therefore, the active and reference electrodes in this study were placed below the eye contra-lateral to the side of acoustic stimulation. In this study, although the amplitude of VEMPs (ocular and cervical) varies among subjects, it was reproducible and stable intrasubjects. This finding was in agreement with that of Iwasaki *et al*., 2008 [21].

Although the mean latencies for pseudotumor cerebri were longer and the mean amplitudes were less than that of the normal control for ocular and cervical VEMPs, they were still statistically non-significant ($p > 0.05$). But, we cannot roll out vestibular affection on subclinical level in patients with pseudotumor cerebri due to increased intra cranial pressure. Furthermore, the results were compared between sides (right or left) and it was found that there were no statistical significant side differences in both ocular and cervical VEMPs. On the other hand, it was noticed that the amplitudes decreases and latencies prolonged for ocular and cervical VEMPs as a function of age.

For cVEMP and oVEMP, several studies have described decreased amplitudes and increased thresholds in older individuals [27-30]. Janky and Shephard, 2009 reported a stronger correlation between age and cVEMP amplitude or threshold when using 500-Hz tone bursts [28]. An age-related decline in neuronal populations [31], and hair cell populations [32, 33], as well as a reduction in the number and density of otoconia [34] has been postulated as the possible cause for VEMPs age related changes. This reduction as a function of age should be taken into account to avoid increased false-positive rates when interpreting tuning shifts in older patients.

The air conducted ocular and cervical VEMPs are reliable and repeatable procedure. It provides another diagnostic tool for assessing the integrity of VOR. Hence, it can be used as a test that may contribute as a part for the evaluation of the vestibular system in pseudotumor cerebri patients. However, further studies are needed to investigate and compare (ocular and cervical) VEMPs in pseudotumor cerebi and different vestibular lesions.

CONCLUSION

Although, the latencies were longer and there were a reduction in amplitude of pseudotumor cerebri in comparison with that of normal female subjects, it shows no statistical significant differences. But the encountered differences although statistically non-significant, asserting a query on affection of the vestibular system secondary to increased intra cranial pressure in those patients which require further studies.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to this article.

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