Original Article

Evaluation of vestibular system using c-VEMP and o-VEMP in patients with relapsing-remitting multiple sclerosis

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ABSTRACT

Objectives: This study aims to evaluate the role of vestibular evoked myogenic potentials (VEMPS; the cervical VEMP [cVEMP] and the ocular VEMP [oVEMP]) in the vestibular system in patients with relapsing-remitting multiple sclerosis (RRMS).

Patients and Methods: Between December 2016 and December 2017, a total of 42 ears of 21 RRMS patients (8 males, 13 females; mean age 41 years; range, 25 to 57 years) and 42 ears of 21 healthy controls (7 males, 14 females; mean age 44 years; range, 38 to 62 years) were included. All participants underwent neurological evaluation, brain magnetic resonance imaging (MRI), audiometry, tympanometry, and stapedial reflex testing. Their oVEMPs and cVEMPs were recorded.

Results: For cVEMP testing, the mean P1 and N1 latencies of the left ears of RRMS patients were significantly higher compared to the controls. There was no significant difference between patients and controls in terms of the P1-N1 interval or mean amplitude of the left ear ($p>0.05$). The P1 and N1 latencies and the mean P1-N1 interval of the right ears of RRMS patients were significantly higher than the controls ($p=0.019$, $p=0.001$, $p=0.004$; $p<0.05$, respectively). There was no significant difference in the amplitudes or amplitude asymmetry ratios (AARs) of either ear between patients and controls ($p>0.05$ for all). The P1 and N1 latencies were prolonged in 13 (42%) of 42 RRMS ears and 27 ears (64%), respectively. For oVEMP testing, eight patients (19%) had no response in the oVemp test of the right ear (n=4) and left ear (n=4) of RRMS patients. There was no significant difference in P1 or N1 latencies or the P1-N1 interval, amplitude or AAR of right ears between the patients and controls ($p>0.05$ for all). The P1 and N1 latencies were prolonged in 26 (62%) of RRMS ears and 27 ears (64%), respectively.

Conclusion: Based on our study results, VEMPs are useful for the evaluation of central vestibulopathies. The VEMP testing can diagnose brainstem lesions in RRMS patients quickly, easily, and safely without pain, although MRI shows no brainstem involvement. The VEMP testing is an electrophysiological test which can detect early stage pathologies of the vestibular system.

Keywords: Multiple sclerosis, vertigo, evoked potentials.

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS) which develops in young adults[1] and affects over one million patients worldwide.[2] It is more common in females than males (F:M ratio 1.4:3.1/1) and is most prevalent in those aged between 20 and 40 years.[3]

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Multiple sclerosis can involve various CNS sites including the brain, brainstem and optic nerve, and the its initial symptoms may reflect CNS demyelination. Patients may present to otolaryngologists with balance problems either before diagnosis or during the course of illness.[4] No single test or clinical finding can be used to diagnose MS. The Poser and McDonald diagnostic criteria are both commonly used and include magnetic resonance imaging (MRI) findings, cerebrospinal fluid and neurophysiological test results, and clinical course.[2,3] However, the correlation between clinical findings and MRI lesions has not been clearly understood, yet.[5]

The vestibular evoked myogenic potentials (VEMPs) are short-latency electromyographic responses to acoustic stimulation of the sternocleidomastoid muscle (SCM) and the extraocular muscles. They are a non-invasive and easy-to-perform electrophysiological test which is used to assess starting from the saccular and macula to the superior and inferior vestibular nerve, brainstem, and central connections. The VEMPs can be used to diagnose various otological and neurological diseases including Meniere's disease, superior semicircular canal dehiscence, vestibular migraine, brainstem involvement due to cerebrovascular disease.[6,7] A reflex response evident in the SCM is considered a cervical VEMP (cVEMP), while a response in the extraocular muscles is considered an ocular VEMP (oVEMP). The cVEMP is a marker for the integrity of the vestibulocollic reflex (VCR) pathway and the oVEMP denotes the integrity of the vestibuloocular reflex (VOR) pathway.[7-9] The VEMPs show a problem in the reflex pathway, even in the absence of a topographic analysis.

The brainstem is frequently involved in patients with MS being associated with symptoms of vestibular dysfunction. Functional tests such as evoked potentials (EPs) may facilitate MS diagnosis and treatment, as such tests can detect subclinical lesions and yield information on CNS function.[10] The EPs (the somatosensory EP, motor EP, visual EP and brainstem EP [BAEP]) can reveal functional deficits in MS patients.[11,12] However, no EP can confirm brainstem involvement. As the VCR and VOR arch pathways are located principally in the brainstem, the VEMP testing may yield information on brainstem lesions, although MRI shows no brainstem involvement.[6,13-16]

In the present study, we aimed to evaluate the role of cVEMP and oVEMP tests in the vestibular system in patients with relapsing-remitting MS (RRMS).

PATIENTS AND METHODS

Study design and sample

This study was carried out at Department of Otorhinolaryngology Head and Neck Surgery of Okmeydanı Training and Research Hospital between December 2016 and December 2017. A total of 42 ears of 21 RRMS patients (8 males, 13 females; mean age 41 years; range, 25 to 57 years) and 42 ears of 21 healthy controls (7 males, 14 females; mean age 44 years; range, 38 to 62 years) were included in the study. The VEMPs were measured during the remission period of patients. All participants were informed before testing. The MRI images of the brain and spinal cord of all patients were obtained. On MRI, patients had demyelinating plaques in the brain, but no involvement of the brainstem on MRI (Figures 1 and 2). All participants underwent otoscopic examinations, pure tone audiometry, tympanometry and stapedial reflex testing, and videonystagmography (VNG). Those having a

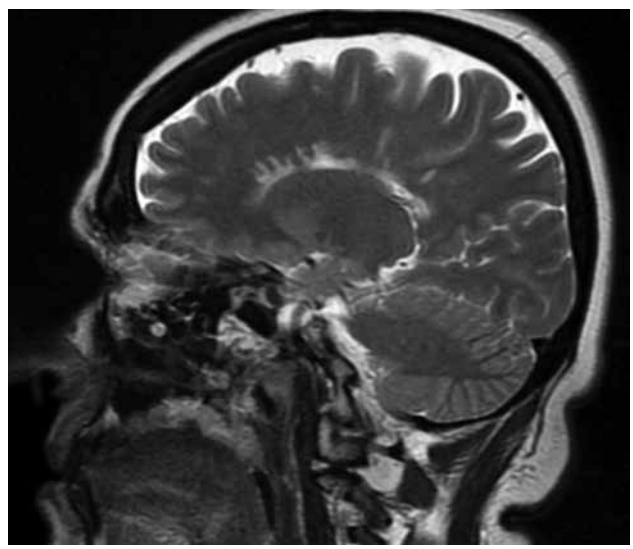

Figure 1. *A T_2-weighted magnetic resonance imaging of a patient showing a high-signal lesion in periventricular area.*

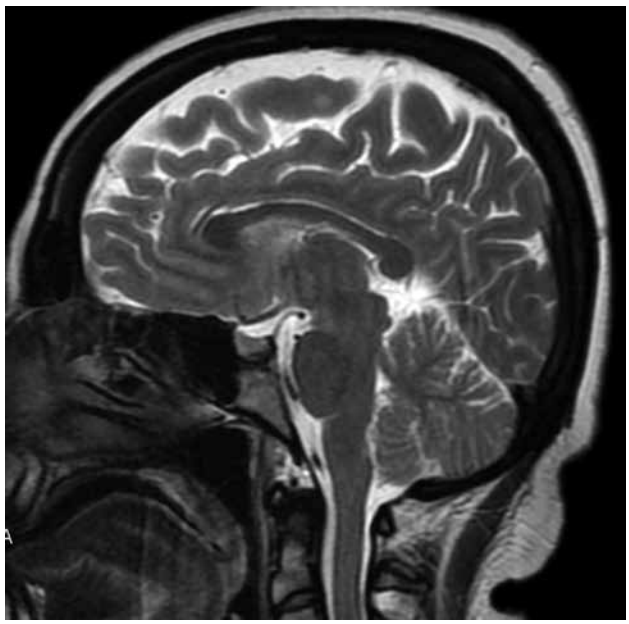

Figure 2. A T_2-weighted magnetic resonance imaging of a patient without no lesion in the brainstem.

SCM pathology or hearing loss or peripheral vestibular disorders were excluded. The VNG was performed in the remission period. Audiometric data were normal for all participants. No control subject had an otological or neurological disease.

Dizziness and vertigo were considered vestibular symptoms. The cVEMPs and oVEMPs were obtained to evaluate vestibular lesions. The VEMP recordings were made using a device (ICS-CHARTER EP 200 Evoked Potential System; GN Otometrics IL, USA). The RRMS group (42 ears) and the control group (42 ears) were compared in terms of the presence of VEMP waves; cVEMP (P1, N1) and oVEMP (N1, P1) latencies; P1-N1 and N1-P1 amplitudes; amplitude asymmetry ratios (AARs; AAR= 100 × (Ar-Al)/(Ar+Al) where Ar was the amplitude of the right ear and Al was that of the left ear). The patients having prolonged latencies and/or no response were considered abnormal. All patients were administered the Expanded Disability Status Scale (EDSS) for the evaluation of disability status.

A written informed consent was obtained from each participant. The study protocol was approved by the local Ethics Committee (19.12.2017: No: 48670771-514.10). The study was conducted in accordance with the principles of the Declaration of Helsinki.

cVEMP

A 500-Hz tone-burst stimulation with a rarefaction polarity loudness of 97 dB was used to stimulate airway conduction. The VEMP waves which occurred over a band transmittance range of 2 to 500 Hz with a repetition frequency of 5/s were recorded. Active electrodes were connected and placed just below the jugular notch of the sternum; the reference electrode was placed in the middle third of the SCM; and the ground electrode was placed on the nasion in the midline of the forehead near the scalp margin. An ICS Medical insert earphone (model ER 3A/5A; 300 Ohms) was used for stimulation. We ensured that the impedance difference between the electrodes was <3 kOhms. Each participant laying on his/her back was instructed to bring the head to 30° of flexion immediately on hearing a sound in the tested ear. In other words, the participant was asked to raise the head to look at his/her feet. If he/she became tired, we allowed rest. The line followed by the VEMP with sound stimulation consists of two biphasic wave complexes: the first biphasic potential has a positive peak (P1), followed by a negative peak (N1).

oVEMP

This test was performed in the sitting position. The participant was asked to keep the facial muscles relaxed and to look 30 to 40° upward. After stimulation, he/she was asked to look at a previously identified object 2-m distant and to hold the head stably in the neutral position. We, then, recorded the response of the contralateral eye. The active electrode was placed in the region of the infraorbital ridge, approximately 1-cm below the lower eyelid, and the reference electrode was placed approximately 2-cm below the active electrode. The ground electrode was placed on the forehead. The oVEMP scans consist of a series of negative and positive peaks. The initial negative-positive biphasic waveform is composed of peaks N1 and P1. The wave polarity reflects muscle activation, as does cVEMP. Surface positivity indicates inhibition of tone-active extraocular muscles, while surface negativity denotes muscle excitation.

Table 1. Baseline demographic characteristics of study population

	Study group			Control group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			41.6±8.7			44.9±9.4	0.240*
Gender							1.000**
Male	8	38.1		7	33.3		
Female	13	61.9		14	66.7		

SD: Standard deviation; * Student t test; ** Continuity (Yates) correction.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. The normality of the data distribution was assessed using the Shapiro-Wilks test. The Student's t-test was used for between-group comparisons of normally distributed parameters and the Mann-Whitney U test was applied to compare parameters that were not normally distributed. The paired-samples t-test was used to compare parameters that were normally distributed in both affected and non-affected ears. The Fisher's exact test, Yates' continuity correction, and McNemar's test were used to compare qualitative data. A *p* value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic characteristics of the patients and healthy controls are shown in Table 1. The EDSS scores were <5.5 in all RRMS patients.

Results of cVEMP testing

Five RRMS patients (2.1%) had no response in the cVEMP test of the right ear (Table 2). The mean P1 and N1 latencies of the left ears of RRMS patients were significantly higher than controls (p=0.009 and p=0.002, respectively). However, we found no significant difference between the patients and controls in terms of the P1-N1 interval or mean amplitude of the left ear (p>0.05). On the other hand, the P1 and N1 latencies, and mean P1-N1 interval of the right ears of patients were significantly higher than controls (p=0.019, p=0.001, p=0.004, p<0.05, respectively). However, we found no significant difference in the amplitudes or AARs of either ear between the patients and controls (p>0.05 for all). The P1 and N1 latencies were prolonged in 13 (42%) of 42 RRMS ears and 27 ears (64%), respectively (Table 3).

Results of oVEMP testing

Eight RRMS patients (19%) had no response in the oVEMP test of the right ear (n=4) and left ear (n=4) (Table 2). The P1 and N1 latencies and the P1-N1 interval of left MS ears were significantly

Table 2. Response rate in cVEMP and oVEMP tests of right and left ear of RRMS patients

		Right ear		Left ear		Total	
	Answer	n	%	n	%	n	%
cVEMP	+	16	76.2	21	100	37	88.09
	-	5	23.8	0	0	5	2.1
oVEMP	+	17	81.0	17	81.0	34	81.0
	-	4	19.0	4	19.0	8	19.0

cVEMP: Cervical vestibular evoked myogenic potential; oVEMP: Ocular vestibular evoked myogenic potential; RRMS: Relapsing-remitting multiple sclerosis.

Table 3. Results of cVEMP and oVEMP between affected ear and control groups

		Multiple sclerosis		Control		
	Parameters	Mean±SD	Median	Mean±SD	Median	*p*
cVEMP	Left					
	P1 latency	18.3±3.8		15.8±1.1		0.009*†
	N1 latency	28.5±4.0		25.3±2.0		0.002*†
	P1-N1 interval	10.3±2.2		9.5±1.64		0.196†
	Amplitude	209.1±154.3		200.1±150.4		0.849†
	Right					
	P1 latency	17.8±2.4		16.3±1.3		0.019*†
	N1 latency	29.3±3.5		25.8±2.5		0.001*†
	P1-N1 interval	11.5±2.3		9.5±1.7		0.004*†
	Amplitude	134±68.6		124.0±89.9		0.713†
	Amplitude asymmetry ratios	42.5±38.4	31.9	28.1±2.0	20.6	0.489‡
oVEMP	Left					
	P1 latency	16.6±0.9		15.1±1.0		0.000*†
	N1 latency	11.1±0.8		10.2±0.6		0.001*†
	P1-N1 interval	5.5±0.6		4.94±1.0		0.030*†
	Amplitude	5.5±2.5		8.7±7		0.065†
	Right					
	P1 latency	16.4±1.2		15.6±1.3		0.065†
	N1 latency	11.2±1.6		10.6±1.3		0.191†
	P1-N1 interval	5.1±0.8		5.1±0.9		0.990†
	Amplitude	8.4±6.3		7.7±4.3		0.681†
	Amplitude asymmetry ratios	45.7±38.5	28.9	26.3±18.2	19.3	0.203†

SD: Standard deviation; cVEMP: Cervical vestibular evoked myogenic potential; oVEMP: Ocular vestibular evoked myogenic potential; † Student t Test; ‡ Mann Whitney U test; * $p<0.05$.

higher than controls (p=0.000, p=0.001, p=0.030, respectively). However, we found no significant difference in the left ear amplitude between the patients and controls (p>0.05). In addition, we found no significant difference in the P1 or N1 latencies or the P1-N1 interval, amplitude or AAR of the right ears between the patients and controls (p>0.05 for all). The P1 and N1 latencies were prolonged in 26 (62%) of RRMS ears and 27 ears (64%), respectively (Table 3).

DISCUSSION

Multiple sclerosis is a chronic neurological disease affecting the brain, brainstem, and vestibulospinal tract. The majority of MS patients complain of dizziness and imbalance caused by vestibular dysfunction. Even when brainstem or cerebellar lesions are not evident on MRI, dizziness and imbalance are often caused by structural or functional damage to the vestibular system. Various degrees of functional impairment may occur involving the VOR and VCR pathways. Thus, cervical and ocular VEMP tests are useful to assess the VOR and VCR pathways in MS patients.[16] In the cVEMP test, the same-side (non-crossed) medial vestibulospinal tract (extending to the spinal accessory core and vestibular nuclei) is evaluated. The oVEMP test explores the functions of the vestibular nuclei and VOR pathways via the contralateral

oculomotor nucleus (the contralateral, medial, and longitudinal fascicular pathway).[17]

Several studies have described cVEMP testing of MS patients, although the oVEMP data are limited. Some reports described abnormal VEMP responses in MS patients, including latency extensions and even non-responses.[3-8,11,12,18] However, latency extension in the VEMP test and unresponsiveness also occur in those with acoustic neurinomas and Meniere's disease; such abnormalities are not specific to MS. Thus, the proportion of MS patients exhibiting abnormal VEMP responses widely varies (i.e., from 18 to 100%).[6,12-15]

In 2009, Eleftheriadou et al.[13] used MRI to divide 48 MS patients into those with and without brainstem lesions. Seven patients without brainstem involvement on MRI and 16 patients with such involvement yielded pathological findings on cVEMP testing.[13] Similarly, Bandini et al.[14] explored whether cVEMP was useful in detecting silent demyelinating lesions of the brainstem in patients with MS and P1 latencies were prolonged in patients with and without brainstem pathology.

In the present study, we found that 13 (30%) and 27 (64%) of 42 RRMS ears, respectively exhibited prolonged cVEMP P1 and N1 latencies; the respective figures on oVEMP testing were 27 (64%) and 26 (62%). Similarly, Gazioglu and Boz[6] used both cVEMP and oVEMP tests to evaluate 62 MS patients and 11 (18%) and 28 (45%) of them exhibited pathological cVEMP and oVEMP findings, respectively. In addition, the abnormal oVEMP rate was higher than the abnormal cVEMP rate, consistent with our study. However, Gabelić et al.[11] evaluated MS patients with or without clinical findings. The cVEMP score was higher than the oVEMP score in patients with clinical findings. Furthermore, the abnormal VEMP test rate was higher in MS patients with clinical findings. Both cVEMP and oVEMP testing yielded pathological results in 80% of the patients. Similarly, we recorded pathological VEMP test results in 90% of our patients. Crnošija et al.[17] subjected 121 MS patients to the brainstem functional system score, EDSS, MRI , and cVEMP and oVEMP testing and the cVEMP and oVEMP data did not significantly differ. The VEMP test was shown to be able to uniquely assess brainstem involvement in MS patients.[18]

In another study, Patko et al.[19] also found that 79% of the patients with unilateral acoustic neuromas exhibited pathological findings on VEMP testing. In addition, Murofushi et al.[20] reported similar results where 51% of the patients with Meniere's disease exhibited pathological findings. Also, Alpini et al.[21] evaluated 40 MS patients and reported abnormal cVEMP results in 28 patients (prolonged latency in 24 and no response in four). The cVEMP test was also found to be useful to diagnose MS in patients having a clinically silent disease, but having CNS lesions.[22] In our study, RRMS patients without brainstem involvement on MRI had higher rates of prolonged P1 and N1 latencies on cVEMP and oVEMP testing.

On the other hand, relatively small sample size who were in remission is the main limitation of the present study. Therefore, further studies with larger number of patients in remission and progression period would be helpful the definite role of VEMPs in the diagnosis of MS.

In conclusion, the use of combined cVEMP and oVEMP tests for the evaluation of MS patients allows assessment of both the ascending and descending vestibular pathways of the brainstem. The VEMPs is useful to diagnose brainstem lesions in MS patients quickly, easily, and safely without pain, although MRI shows no brainstem involvement.

Declaration of conflicting interests

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