Original Article

The Role of Vestibular Evoked Myogenic Potential and the Video Head Impulse Test in Patients with Multiple Sclerosis without Radiologic Findings

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Abstract

Objective: The aim is to evaluate the vestibular system using the video head impulse test (vHIT) and vestibular evoked myogenic potentials (VEMP) in patients with multiple sclerosis (MS) without central vestibular involvement in magnetic resonance imaging (MRI), and to determine whether there was subclinical vestibular system impairment. **Materials and Methods:** The study comprised 27 patients with MS and 26 healthy participants. The participants had no lesions in the central vestibular system in an MRI taken in the past 3 months. Detailed neuro-otologic and neuro-ophthalmologic examinations were performed on all participants. Then, the Dizziness Handicap Inventory (DHI) was completed for subjective vestibular system evaluation. In addition, vHIT and cervical VEMP (cVEMP) were performed for objective vestibular system evaluation. The results were analyzed statistically. **Results:** The mean age of the patients in the MS group was 39.3 ± 11.4 years and 42.7 ± 9.7 years in the control group. The median DHI score was 4 (range, 0–8) in the MS group and 2 (range, 0–6) in the control group. There were no statistically significant differences between the DHI score averages of the groups. The mean vestibulo ocular reflex (VOR) gain in vHIT was 0.76 ± 0.21 in the MS group and 0.99 ± 0.13 in the control group. VOR gain was statistically significantly lower in patients with MS. The VOR gain cut-off level was considered as 0.8. Gain level was below the cut-off level in 53.7% of patients with MS. There was no cVEMP response in 31.5% of patients with MS. In addition, patients with MS had prolonged P1 and N1 latencies and decreased P1-N1 peak-to-peak amplitudes. **Conclusion:** We found subclinical involvement in electrophysiologic tests (vHIT and cVEMP) in patients with MS without MRI lesions and without subjective vestibular system symptoms. We believe that vHIT and cVEMP can be used for subclinical evaluation in patients with MS without central vestibular system involvement in MRI.

Keywords: *Cervical evoked myogenic potential, dizziness handicap inventory, multiple sclerosis, vestibular system, video head impulse test*

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). It is thought to be autoimmune and is characterized by local inflammation, demyelination, axonal loss, and gliosis in the brain and spinal cord, and by the formation of multiple plaques in the CNS. Today, there is no single clinical feature or diagnostic test that is sufficient for the diagnosis of MS. The diagnosis is mainly based on clinical findings.[1] Due to emerging technologies, the

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International Advisory Committee on Clinical Trials in MS updated the McDonald's 2010 criteria and published the 2017 revision.[2]

MS is the most common chronic CNS disease in young adulthood, and most patients experience their first symptoms by the age of 20–40 years. Intermittent or sustained disease activity leads to a gradual or slow increase in disability over time.[3] MS can lead to a wide variety of clinical presentations. Many signs and symptoms are characteristic, and few are pathognomonic for the disease. By contrast, some symptoms are atypical, and others are rare enough to lead to a different diagnosis.[4]

Dizziness is found at a rate of 49%–59% in patients with MS. Vertigo is seen in only 5% of patients. Vertigo severely affects the quality of life in these patients.[5] This symptom occurs due to impairment of peripheral or central vestibular pathways or combined impairment of both pathways.[6-8]

Today, 1.5 Tesla magnetic resonance imaging (MRI) is used as the gold standard for detecting MS lesions, but this technique fails in detecting small lesions that functionally affect patients.[9] However, electrophysiologic tests can be used to detect early demyelination.[10] In recent years, test batteries such as vestibular evoked myogenic potential (VEMP), which assesses the vestibulocollic reflex (VCR), and the video head impulse test (v-HIT), which assesses the vestibulo ocular reflex (VOR), have been used successfully in the evaluation of vestibular functions. Studies show that VEMP can be used to evaluate the central and peripheral vestibular system in patients with MS.[11,12]

vHIT is an objective test method that allows the evaluation of VOR arising from semicircular channels. It is generally affected by peripheral vestibular diseases, but it has also been shown to be affected in some central diseases.[13] It is the reflex arch that extends from the peripheral vestibular system to the brainstem, and thence to the extraocular muscles. It is the reflex mechanism that allows the image to reach the fovea in a constant manner. In the direction of the axis of the semicircular canal, that is being examined, a head movement with high acceleration and low amplitude is applied. Depending on the VOR induced by this movement, eye responses appear in the opposite direction of the head movement. It reflects the level of pathology in vestibular system diseases due to its relationship with the brain stem and central connections.

VEMP is the measurement of electromyogenic muscle activities arising from vestibular otolith organs following stimulation of the vestibular system. Cervical VEMP (cVEMP) is a reflex arch that begins from the saccular macula, is transmitted to the brainstem via the inferior vestibular nerve, and extends to the sternocleidomastoid (SCM) muscle via the accessory (XI) nerve in the brainstem. Basically, the VCR is evaluated. It is mostly used in peripheral diseases such as acoustic neuroma, Meniere's disease, but also provides information about the brainstem.

The aim of this study was to evaluate the vestibular system using vHIT and VEMP in patients with MS without brain stem involvement in MRI imaging and to determine whether there was subclinical vestibular system impairment.

Materials and Methods

This prospective and case–control study was conducted at the Neurology and Otorhinolaryngology Clinics of the University of Health Sciences, Umraniye Training and Research Hospital, between January 2018 and March 2020. This study was approved by the Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital (Date: 20.02.20220, number: B. 10.1.TKH.4.34.GP. 0.01/32). All participants gave written informed consent.

Study population

Twenty-seven patients with MS without any involvement in the brainstem, optic nerve, and central and peripheral vestibular systems, and 26 healthy volunteers who were admitted to the outpatient clinic due to tension headache and had no pathology in cranial MRI were included in the study. All patients met the McDonald MS Criteria, which were revised in 2017.[2] Patients with MS had no attacks for the past 30 days, did not use steroids, and had no central vestibular involvement in cranial MRI in the past 3 months.

A detailed clinical anamnesis was taken from all participants. Neurologic, neuro-otologic, and ophthalmologic evaluations were then performed. After the evaluations, all participants completed the Dizziness Handicap Inventory (DHI) for the subjective vestibular system evaluation. In addition, vHIT and cVEMP were performed for the objective vestibular system evaluation.

Patients who were aged under 18 years and over 60 years, who had previous or current middle ear disease, previous ear surgery or ablative therapy (steroids or gentamicin), additional vestibular and/or neurologic diseases, vision loss, musculoskeletal system diseases, diabetes mellitus, hypo or hyperthyroidism, attacks due to vertebrobasilar artery insufficiency, an MS attack in the past 30 days, and those on steroid treatment were excluded from the study. In addition, patients using vestibular suppressant medication were excluded.

Patients without demyelinating MS plaques in the brain stem, optic nerve, occipital lobe, cerebellum, and peripheral vestibular system, with a DHI score <16 and with normal pathology detected in neuro-otologic and neuroophthalmologic examinations were included in the study.

Magnetic resonance imaging

All MRIs were performed on a 1.5T MRI scanner (Siemens Healthcare, Erlangen, Germany). In cranial MRI, 2D/3D sagittal and axial fluid-attenuated inversion recovery; 2D/3D sagittal, coronal, and axial T2; axial diffusion-weighted imaging; and sagittal and axial T1 (noncontrast and postcontrast) sequences were performed. Axial and sagittal T1 and T2, postcontrast T1, phase-sensitive inversion-recovery (first cervical, then thoracic if necessary) sequences were evaluated in spinal MRI. Gadolinium chelate was used as a contrast agent. Within 30 s, 0.1 mmol/kg gadolinium was given, and a postcontrast examination was performed after waiting for at least 5–10 min.

Dizziness handicap inventory

All participants underwent evaluation with the DHI, which has been validated in Turkish.[14] The DHI is a personal disability questionnaire consisting of 25 questions used in the assessment of dizziness and vertigo. Each question is scored between 0 and 4 points, and the total score is in the range of 0–100 points. Both groups completed DHI questionnaires, and the total scores were evaluated. In the assessment, 0–14 points were accepted as normal, 16–34 points were accepted as mild dizziness, 36–52 points as moderate dizziness, and >54 points as severe dizziness.

Video head impulse test

The EyeSeeCam system (Interacoustics a/s, Middelfart, Denmark) was used for vHIT recordings. For the recording of the vHIT, light and tightly fitting glasses were used, on which a small video camera and a half-silver mirror reflecting the eye image (left side) were mounted. Patients were asked to focus on the target dot, which was placed on the wall at a distance of 1.2 m. Calibration was performed prior to each recording. For the test, a head impulse at a velocity of 1500–2000/s was applied to 15°–20° lateral side of the midline along both lateral semicircular canal axles in a random manner. Fifteen records were held separately on each side. VOR gains at 40–60 and 80 ms were recorded. Mean VOR gain at 60 ms was taken for evaluation. Normal values for VOR gain were considered 0.8–1.2.[15]

Cervical vestibular evoked myogenic potentials

cVEMP recordings were performed using an evoked potentials device (Eclipse EP-25/VEMP; Interacoustics, Denmark). The inverting (reference) electrode was placed at the upper two-third of the SCM muscle, noninverting (active) on the sterno-clavicular junction and ground electrode on the forehead.[16] The test was performed once in a silent environment and with the patient awake in the sitting position. The patients were instructed to turn their heads to the opposite side of the sound stimulus to contract the contralateral SCM muscle [Figure 1]. A note/alert sound was sent to the right and left ear, and ipsilateral records were obtained. Electrode impedance was <5 kΩ. The acoustic stimuli were 100 dB for 0.1 ms and delivered to each ear separately at 5 Hz. The electromyography signal was filtered in the range of 10–1000 Hz and averaged over a 100 ms interval. The average was calculated from 200 results. P13 and N23 positive/negative polarity were measured as peak waves. P13 and N23 peak latencies and P13-N23 inter-peak amplitudes were calculated.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 20 for Windows statistical software (SPSS Inc., Chicago, IL, USA). Descriptive statistical data were calculated. The relevance of the variables to normal distribution was analyzed through analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). The Mann–Whitney U test was used to compare the continuous variables between the two groups. The Type-1 error level was identified as 5% for statistical significance.

Results

Participants

The study began with a total of 30 participants in both groups. However, three patients in the MS group and four participants from the control group left the study. The

Figure 1: Cervical vestibular evoked myogenic potentials test was performed in the sitting position

study was completed with 27 patients in the MS group and 26 participants in the control group. The mean age of the patients in the MS group was 39.3 ± 11.4 years and 42.7 ± 9.7 years in the control group. In patients who had MS, the mean disease duration was 35.8 ± 19.5 (range, 12–84) months [Table 1]. The treatments that patients received for MS are shown in Table 2.

Dizziness handicap inventory

The median DHI score was found as 4 (range, 0–8) in the MS group and 2 (range, 0–6) in the control group. The scores in both groups were under <16 and within normal limits. There were no statistically significant differences between the DHI score averages of the groups [Figure 2].

Video head impulse test

Out of a total of 53 participants, 106 vHIT records were taken. The mean gain level was 0.76 ± 0.21 in the MS group and 0.99 ± 0.13 in the control group. VOR gain was statistically significantly lower in patients with MS [Table 3]. The VOR gain cut-off level was considered as 0.8. The gain level was below the cut-off level in 53.7% of patients with MS. This level was found to be statistically significantly higher compared with the control group [Table 4].

Cervical-vestibular evoked myogenic potentials

A total of 106 c-VEMP records were evaluated from both ears. P1 wave latencies in MS and control groups were measured as 17.08 ± 1.93 ms and 15.01 ± 0.63 ms, respectively. N1 wave latencies in the MS and control groups were measured as 26.48 ± 3.04 ms and 24.03 ± 0.94 ms, respectively. In patients with MS, P1 and N1 wave latencies were statistically significantly longer than in the control group. In addition, a statistically significant decrease in c-VEMP (P1-N1 peak to peak) amplitudes was present in patients with MS compared with the control group. P1-N1 amplitude averages in the MS and control groups were measured as 59.99 ± 61.62 μV and 129.38 ± 39.67 μV, respectively [Table 5]. When c-VEMP responses from both ears were evaluated, no response could be recorded in 31.5% of the total 54 cVEMP entries in patients with MS and 3.8% of the total 52 c-VEMP entries in healthy participants. No cVEMP response could

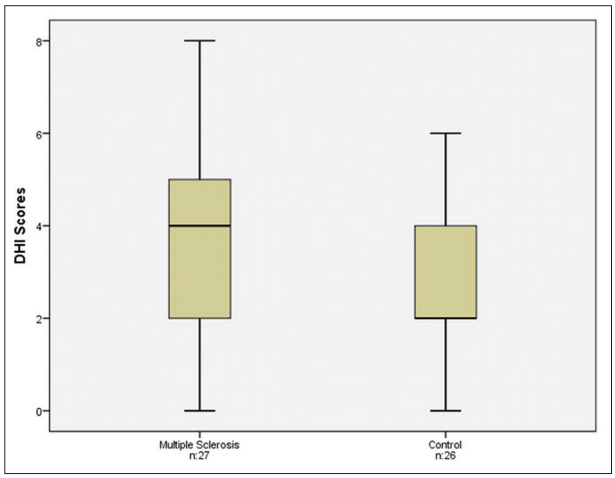

Figure 2: Dizziness handicap inventory scores. The mean values of both groups were in the normal range and there was no difference between groups (P = 0.086)

Table 1: Patient characteristics

Number of subjects	Multiple sclerosis (n=27)	Control (n=26)	P
Sex (male/female); n	6/21	7/19	0.47[a]
Age (year)			
Mean±SD	39.33±11.41	42.70±9.75	0.13[b]
Median (range)	39 (19-60)	44 (19-57)	
Time to disease (months)			
Mean±SD	35.78±19.58		
Median (range)	24 (12-84)		

[a]Fisher's exact test, [b]Mann-Whitney U-test, P<0.05. SD: Standard deviation

Table 2: Treatment of patients with multiple sclerosis (n=27)

Treatments	Patients (n=27)
Glatiramer acetate	6
Fingolimod	5
Interferon beta 1a	7
Interferon beta 1b	1
Ocrelizumab	4
Natalizumab	2
Dimethyl fumarate	2

Table 3: Horizontal-video head impulse test results of both groups

Number of subjects	Multiple sclerosis (n=27)	Control (n=26)	P
h-vHIT gain			
Mean±SD	0.76±0.21	0.99±0.13	<0.001*
Median (range)	0.76 (0.23-1.19)	0.97 (0.78-1.20)	

Mann-Whitney U-test. *P<0.05. There was no difference between the groups in terms of h-vHIT results (P<0.05). SD: Standard deviation, VHIT: Video head impulse test, h-VHIT: Horizontal-VHIT

Table 4: Abnormal value ratios measured in participants in both groups when the h-video head impulse test cut-off value was taken as 0.8

VHIT gain	Groups		P
	Multiple sclerosis	Control	
0-0.79, n (%)	29 (53.7)	2 (3.8)	<0.001*
0.8-1.2, n (%)	25 (46.3)	50 (96.2)	

Fisher's exact test. *P<0.05. h-VHIT abnormalities were present in about half of patients with multiple sclerosis. VHIT: Video head impulse test, h-VHIT: Horizontal-VHIT

Table 5: Cervical vestibular evoked myogenic potential results of both groups

Number of subjects	Multiple sclerosis (*n*=27)	Control (*n*=26)	*P*
P-Latency (onset) (s)			
Mean±SD	9.95±2.02	9.47±0.87	0.12
Median (range)	10.0 (4.67-14.67)	9.33 (8.0-11.0)	
P1 Latency (s)			
Mean±SD	17.08±1.93	15.01±0.63	<0.001*
Median (range)	16.67 (14.0-23.0)	15.0 (14.0-17.0)	
N1Latency (s)			
Mean±SD	26.48±3.04	24.03±0.94	<0.001*
Median (range)	26.33 (21.33-35.0)	24.0 (22.0-26.0)	
P1-N1 amplitude (μV)			
Mean±SD	59.99±61.62	129.38±39.67	<0.001*
Median (range)	45.75 (0.0-208.9)	141.00 (0.0-172.6)	

Mann-Whitney U-test. *P<0.05. SD: Standard deviation

be obtained on one side in five patients with MS and on two sides in six patients.

Discussion

The incidence of dizziness in MS varies between 49% and 59%. Dizziness and/or vertigo occur due to the involvement of central, peripheral or both pathways of the vestibular system. Although MRI is the most important diagnostic tool for diagnostic examination, it is insufficient for the detection of small lesions.[9] Wang *et al*. found that lesions were smaller than 3.5 mm in 20% and smaller than 8 mm in 80% of patients with MS.[17] Evoked potentials have been shown to reliably predict pathologies in patients with MS.[11] In our study, we found subclinical abnormal results in vestibular evoked responses in patients with MS, in whom no pathologic plaques were detected in central vestibular pathways such as brainstem, optic nerve, cerebellum, thalamus, and hypothalamus.

Studies showed abnormal vHIT results in many central vestibular pathologies except vestibular migraine.[18-22] There are a limited number of studies evaluating vHIT results in patients with MS. Pavlović *et al*. detected abnormal responses in 38% of patients with MS.[23] In our study, one-sided or two-sided abnormal responses were present in 53.7% of patients with MS in horizontal channel vHIT records. Unlike the study by Pavlović *et al*., the patients included in our study had no central vestibular lesion involvement in their MRI.

In our study, we found longer P1 and N1 wave latencies in cVEMP responses and decreased P1-N1 peak-to-peak amplitudes. We could not obtain a response in approximately one-third of cVEMP recordings. Di Stadio *et al*.[24] included 819 patients with MS in their systematic review, finding that vertigo was present in 37% of patients and abnormalities were present in 71% of cVEMP records. A notable finding was that MRI was normal in 35.4% of patients with cVEMP abnormalities. They concluded that this was due to peripheral vestibular system impairment, in which the diagnostic power of MRI was low. Our findings were similar to the findings of Di Stadio *et al*.[24]. In another study, Kavasoğlu *et al*. found that cVEMP was delayed in 38% of patients with MS with brainstem lesions.[25] They also concluded that cVEMP was not a sensitive test in brainstem involvement. Harirchian *et al*. found abnormalities in 70% of patients with MS, showing that these were associated with the duration of the disease.[26] Eleftheriadou *et al*. found that the abnormality rate was 50%, and when they added the P34-N44 waves, the abnormality rate increased up to 71%.[27] Skorić *et al*.[11] found brainstem findings in 25% of patients with MS during clinical examinations. However, they showed that, in MRI examinations, pathologic brainstem involvement was present in 40% of patients, and that electrophysiologic examinations with VEMP showed abnormal results in 63% of patients. This result shows that electrophysiologic examinations can be used to show subclinical involvement in the brainstem. In addition, Güven *et al*. reported that a cVEMP response was absent in 25% of the patients.[28]

Study limitation

The most important limitation of the study was the small number of patients without central vestibular system involvement in MRI.

Conclusion

We found subclinical involvement in electrophysiologic tests (vHIT and cVEMP) in patients with MS without MRI lesions and without subjective vestibular system symptoms. We believe that vHIT and cVEMP can be used for subclinical evaluation in patients with MS without central vestibular system involvement in MRI.

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Conflicts of interest

There are no conflicts of interest.

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