Research Article

Assessment of Saccular and Semicircular Canal's Function in Behcet's Disease

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Highlights

- Peripheral and unilateral vestibular disorders are common in Behcet's disease
- The vestibular disorders in BD are due to the inflammatory process of the disease
- Colchicine may have an ototoxic effect and influence on cVEMP and vHIT test results

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ABSTRACT

Background and Aim: Behcet's disease (BD) is a multisystemic, chronic and progressive disorder with a relatively high prevalence in Iran. Therefore, this study aimed to compare the vestibular function between Iranian BD patients and normal subjects using cervical vestibular-evoked myogenic potentials (cVEMPs) and video head impulse test (vHIT).

Methods: In this cross-sectional study, 44 patients with definitive BD in the inactive stage of disease and 30 age and sex matched normal subjects were evaluated via cVEMP and vHIT tests and dizziness handicap inventory (DHI). Then the parameters of the tests were compared between the two groups by statistical methods. Moreover, the effects of DHI scores and other contextual variables on the test results were examined.

Results: In terms of the cVEMP test, the response rate and mean latency of p13 in the left ear were significantly lower, the amplitude of the cVEMP wave in the left ear and the amplitude asymmetry ratio were significantly higher in BD patients compared to normal subjects ($p<0.05$). Fifteen BD patients had abnormal amplitude and nine patients had abnormal latency of cVEMP responses. In terms of the vHIT test, the mean vestibule-ocular reflex gain of the left posterior semicircular canal and the mean gain asymmetry ratio of lateral canals were significantly higher in BD patients than in the controls ($p<0.05$).

Conclusion: the vestibular system of some patients with BD is disturbed and the results of this study indicate the presence of unilateral vestibular weakness in BD. So vestibular assessment can be helpful for these patients.

Keywords: Cervical vestibular evoked myogenic potentials; video head impulse test; saccule; semicircular canals; behcet's disease

Introduction

Behcet's disease is a rare, multisystemic, chronic and progressive disease of unknown etiology. It was first described by a Turkish dermatologist named Hulusi Behcet as a triad of recurrent oral and genital aphthous ulcers and uveitis in 1937 [1, 2]. In the course of this disease, with the cellular secretion of monocytes and lymphocytes around the blood vessels, with or without fibrin deposition in the vessels wall, inflammation of vessels and necrosis of the surrounding tissues occur. So Behcet's disease (BD) is known as a systemic leukocytoclastic vasculitis (Inflammation caused by the secretion of immune cells in the walls of the blood vessels) that can affect both arteries and veins of almost any organ, but usually affects small capillary [2-8]. The exact pathogenesis of BD is currently unclear, but it is usually known as an autoimmune disorder that may have a family or genetic predisposition [3, 5].

The highest prevalence of BD is in the Silk Road and its peripheral countries, including Japan, Korea, Iran, and Turkey [9]. This disease often occurs in the third and fourth decades of life and the overall prevalence of the disease is equal in men and women [1, 3]. However, in some studies, it has been reported that BD is more common in men than women [3, 4]. According to studies, Iran with an annual average of 280 new infections and an overall

prevalence of 68 per 100000, is in the second place after Turkey in terms of the prevalence of BD [9-11].

Treatment for BD often includes anti-inflammatory or immunosuppressive drugs such as Colchicine, Methotrexate, Cyclosporine, anti-tumor necrosis factor (TNF), etc. that prevent the symptoms and manifestations of the disease and its serious complications such as blindness [1, 3].

Although the manifestations of Behcet's disease are heterogeneous and can occur anywhere in the body, the involvements are more common in some organs and tissues such as mucous membranes, skin, eyes, joints and the central nervous system. [1, 3]. The disease can involve the audio-vestibular system and cause symptoms such as tinnitus, hearing loss and dizziness through central nervous system (CNS) involvement, dural sinus thrombosis, increasing intracranial and inner ear fluids pressure, damage to the endolymphatic sac which is the main processing center for inner ear antigens and thus reducing the immune response of the inner ear, or damage to the peripheral supplies of the inner ear (anterior vestibular artery and common cochlear artery) [2, 3, 12, 13]. In other words, inner ear involvement is not uncommon in autoimmune rheumatic disorders [9]. The prevalence of vestibular disorders in BD was reported to be between 20-40% [14].

The first cases of inner ear involvement in BD were reported in 1961 [1, 2]. Everekliogl et al. identified hearing loss as the seventh and dizziness and vertigo as the fifth most common complaint in patients with BD [15]. Vascular inflammation or neuropathy due to chronic inflammation are probable causes of vestibular disorders in BD [6]. So, if there are symptoms such as hearing loss, tinnitus or dizziness, hearing and balance assessments are necessary [1]. Despite the large number of audiological studies performed on patients with BD, so far vestibular disorders have been studied in very few articles [3].

Cervical vestibular-evoked myogenic potentials (cVEMPs) are inhibitory electromyographic potentials that are recorded from the sternocleidomastoid muscle (SCM) in response to sound, vibration, or electrical stimulation The neural pathway of this reflex that begins with stimulation of the saccular afferents and inferior vestibular nerve and terminates in the SCM muscle through the 11th cerebral nerve (subsidiary nerve), is called sacculocollic or vestibulo-collic reflex (VCR) [2, 6, 16]. Normal cVEMP responses that are recorded ipsilaterally from the stimulated ear, appear as biphasic waves (positive-negative), usually, their peaks are named with p13 and n23. These responses that specifically examine the saccule and lower vestibular nerve, are recorded only from the vestibular system and if this system is healthy, it can be recorded even in deaf people [2, 16, 17]. Injury or damage to any part of the neural pathways that trigger this potential, including multiple sclerosis (MS), vestibular neuritis, brainstem lesions in stroke and BD can cause abnormal cVEMP responses [2]. The advantages of this test are the need for short recording times, few negative side effects and not being affected by hearing impairment [2, 6]. However, so far there is limited information about the results of cVEMP evaluation in BD, which are contradictory. Erbek et al. and Abdel Baki et al. reported an increase in peak latency of p13 and n23 in patients with BD [6, 18]; while Bayir et al. reported a decrease in response rate and latency of n23 peak and Bayram et al. reported no difference in cVEMP responses between patients with BD and normal controls [2, 14].

The video head impulse test (vHIT) is also a useful clinical tool for assessing semicircular canals (SCCs) and ves-

tibulo-ocular reflex (VOR). In this test, eye movements in response to sudden, inactive, and unpredictable head rotations in the direction of the horizontal and vertical semicircular canals' planes are recorded [19]. This test can evaluate the performance of all three semicircular canals on both sides (six SCCs) and because of the use of physiological stimuli, it is superior to the caloric test [20]. In addition, one of the unique advantages of vHIT over the videonystagmography (VNG) and rotatory chair tests is that it can record very small backup saccades that are indicative of disorder in the central vestibular system and therefore can differentiate between peripheral and central lesions of the vestibular system. Many studies have confirmed the use of this test in the diagnosis of neurological disorders [21, 22]. The most valid method for evaluating the function of the anterior and posterior SCCs involves combining the vHIT and scleral coil technique [17]. However, only two studies have performed this test in patients with BD. Ertugrul et al. reported a reduction in VOR gain in the stimulation of right anterior-left posterior (RALP) SCCs and also a higher asymmetry ratio in the test of lateral canals in BD patients than the controls [22]; while Tutar et al. reported only a reduction of the VOR gain of left anterior, left posterior and right posterior SCCs, and found no difference in the asymmetry ratio of BD patients and normal controls [23].

As mentioned above, the prevalence of Behcet's disease in Iran is relatively high, but the incidence and characteristics of vestibular disorders in Iranian BD patients have not been studied so far. Therefore, this survey aimed to study the function of the peripheral and central vestibular system in Iranian BD patients using the results of cVEMP and vHIT tests. Some previous researchers have assessed the effect of factors such as age, duration of disease and complaints of dizziness on cVEMP and vHIT tests in BD. Due to the differences in the manifestations and symptoms of BD in different geographical areas, in addition to the aforementioned factors, we have assessed the influence of other factors such as gender, race, age of onset, subjective complaints of dizziness and other balance symptoms, medications at the time of evaluation, organs involved from the onset of disease to the time of evaluation, results of Pathergy, C-reactive protein (CRP) and erythrocyte sedimentation ratio (ESR) tests at the time of evaluation on the results of cVEMP and vHIT tests in Iranian BD patients.

Methods

In this cross-sectional (from February 2020 to March 2021), comparative and non-interventional study, 44 patients with BD (23 men and 21 women) with definite diagnosis by a rheumatologist using the International Criteria of Behcet's Disease (ICBD) who were all registered in Behcet's unit of Shariati Hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran, along with 30 age and sex matched normal subjects (15 men and 15 women) in the age range of 18 to 60 years were examined.

The subjects were selected by convenience sampling method. Prerequisites for inclusion were no cervical disorders such as osteoarthritis, no neck pain or limited mobility, absence of metabolic disorders, no autoimmune diseases unrelated to BD, no connective tissue disorders, no disease in outer and middle ears, no history of head trauma, absence of any otological and neurological disorders not related to BD (such as Meniere's disease) and no taking ototoxic drugs (in patients with BD, the use of BD treatment wasn't stopped) in both control and BD groups and no history of dizziness or any balance disorder or hearing loss in the control group. This information was obtained through history taking using a simple questionnaire. Also, by reviewing the medical records of BD patients, information such as race, age, age of onset and duration of disease, organs involved from the onset of disease to the time of the study, results of blood tests (ESR and CRP) and medications used in the time of the study were extracted. After obtaining written and informed consent from all subjects and completing the vestibular history form and dizziness handicap inventory (DHI) questionnaire by BD patients, basic audiological assessment including otoscopy (Riester, Germany), immittance audiometry (including tympanometry and acoustic reflex) using Zodiac901(Denmark) and pure-tone audiometry; air conduction (AC) and bone conduction (BC)) at the frequency range of 250-8000 Hz using two-channel audiometer (harp inventis, Italy) were performed for all participants to ensure the health of the outer and middle ear. Thresholds greater than 20 dB HL at two or more frequencies were considered sensorineural hearing loss [6]. Moreover, if the difference between AC and BC auditory thresholds were equal to or greater than 10 dB nHl (air-bone gap >10 dB nHL) it was considered a conductive hearing loss and the test results of patients with conductive hearing loss were excluded from the study. After ensuring the health of the outer and middle ear, vestibular tests including spontaneous nystagmus, cVEMP and vHIT tests were performed by an experienced audiologist for all participants in the study as follows:

Spontaneous nystagmus

Spontaneous nystagmus was assessed by Eye dynamics VNG device, Canada. For this purpose, the patient's eye movements were recorded for 30 seconds with visual fixation and 30 seconds without visual fixation. Less than 3° of spontaneous nystagmus can be considered within the normal range. All cases had no spontaneous nystagmus.

Cervical vestibular-evoked myogenic potentials test

This test was performed using the evoked potentials system (Biologic, USA.), in the supine position and with head elevation, using disposable plate electrodes. After cleaning the electrodes' placement site with a special cleaner, the positive (non-inverting) electrode was placed on the upper half of the SCM muscle symmetrically, the negative (inverting) electrode was placed on the center of the sternal manubrium and the ground electrode was placed on the forehead. It was then ensured that the impedance between the electrodes and skin was less than 5 kΩ and the difference in impedance of the electrodes with each other was less than 2 kΩ. The stimuli were delivered ipsilaterally using the insert earphone ER-3A. The stimulus was a 500 Hz tone burst with 2 ms rise-fall time and 0 ms plateau time with rarefaction polarity, 95 dB nHl intensity and a rate of 5 (5.1). Amplifier gain was ×5000, the band-pass filter was 10-1000 Hz, analyzing window was –20 to 100 ms and 150 sweeps were used. Directly monitored minimum tonic electromyographic levels for the SCM muscle activation were 50 μV. To ensure the reproducibility of the responses, the test was performed twice at each intensity level. The participants were also given a break after each stage of the test. To obtain the thresholds, the stimulus intensity level started from 95 dB nHL, then decreased in 10 dB steps and increased in 5 dB steps. Finally, we considered the lowest intensity at which the two repetitive responses were recorded as a threshold. When no reproducible p13-n23 was present in 2 runs (if amplitude was lower than 25 μV), we regarded it as an absent response. When a reproducible p13-n23 was present and the cVEMP asymmetry ratio (AR) (%) was greater than the normal upper limits (VEMP asymmetry ratio (VARs) >45%), we regarded it as a decreased response [16].

The p13 latency is defined as the positive polarity of the biphasic wave that appears at approximately 13 ms, and the n23 latency is defined as the negative polarity of the biphasic wave that appears at approximately 23 ms.

The amplitude is defined as the peak-to-peak p13-n23 maximum energy in μV. VAR is defined as the ratio of the inter-aural amplitude difference to the sum inter-aural amplitude. Previous studies have indicated that normal individuals have VARs<45% of the amplitudes of both ears [16].

Finally, the percentage of occurrence and threshold of cVEMP response, the latency of p13 and n23, p13-n23 interpeak latency, and amplitude of p13-n23 complex were measured in both groups and the asymmetry ratio of the amplitude in two ear's response waves was calculated and recorded.

Video head impulse test

Video HIT test was performed using the impulse device (ICS Otometrics, Denmark). The person sat on a special chair, goggles were placed over his/her eyes and instructed to look at the marked spot on the wall that 1 meter away from him/her and equal to the height of the eyes. Calibration was performed before each step of the test. To check the condition of horizontal and vertical semicircular canals, the examiner stood behind the patient and delivered at least 20 rapid impulses of 15-20 degrees in the direction of the SCCs and each impulse had a minimum velocity of 100 degrees per second (the head velocities ranged between 100 to 300 and on average higher than 150 degrees per second). After each impulse, the head remained in the final position and did not return to its original position to prevent the covert saccades from being covered. The timing and direction of head impulses varied to prevent the patient's prognosis [24]. Patients were also given rest between evaluating any semicircular canals. Finally, VOR gain was recorded for each SCCs and both the gain asymmetry ratio for each pair of SCCs as well as the occurrence of covert and overt corrective saccades were investigated. VHIT gain cut-offs of 0.7 and 0.8 and below have been used for diagnosing vestibular loss in the horizontal and vertical canals, respectively. only a series of saccades (not just one) after the 50-ms suppression point (50–450 ms from head-impulse onset) were included in this analysis since earlier saccades are probably due to the visual fixation task. Covert saccades are made earlier than head velocity returning to 0, usually during the high-velocity part of the head movement. As covert saccades are made before the head comes to rest there must be some predictive aspect to them. Overt saccades are mainly made after the head is fairly still and visual feedback is available.

Statistical analysis

In descriptive statistics, descriptive indicators were used to describe the data, which included the number and percentage for qualitative data and the mean, standard deviation and range of changes for quantitative data. In the analytical statistics, in order to investigate the effect of BD on cVEMP and vHIT response parameters, to compare the qualitative variables chi-square-Pearson test (for the occurrence of cVEMP response) and Fisher's exact test (for the occurrence of covert and overt corrective saccades in vHIT) were used. An independent group t-test was used to compare quantitative variables if the sample size was more than 30 people in both groups (Central limit theorem).

In addition to the main results in this study, the effect of clinical characteristics of patients with BD including gender, race, subjective complaints of dizziness, medications taken at the time of the study, results of ESR and CRP tests at the time of the study, organs involved since the onset of disease to the time of study on different parameters of cVEMP and vHIT tests were investigated. For this purpose, patients with BD were divided into four groups in terms of race: Persian, Turk, Lur and Kurd. Drugs used during the study the effect of which on the test results were examined, included Colchicine, Methotrexate, Prednisolone and anti-TNF drugs. Mann-Whitney and Kruskal Wallis tests were used for the statistical analysis of data. In addition, the correlation of quantitative variables of the cVEMP and vHIT tests with age, age of onset and duration of disease as well as functional, emotional, physical and total scores of the Persian version of the dizziness handicap inventory (DHI) [25] in patients with BD was examined by Spearman correlation coefficient test. Statistical analysis was performed using SPSS software version 26 and at the significance level of 0.05.

Results

In the present study, cVEMP response parameters including occurrence percentage (i.e. the incidence rate), threshold, absolute latency of p13 and n23, inter-peak latency of p13-n23, peak-to-peak amplitude and amplitude asymmetry ratio as well as vHIT response parameters including VOR gain of each semicircular canal, VOR gain asymmetry ratio of each pair of canals and incidence of covert and overt corrective saccades, were compared in Behcet patients and normal subjects. The mean age±SD was 41.367±9.611 in the control and 46.273±9.364 in the BD group. The age of disease onset varied between 7–46 years and its mean±SD was 25.205±8.685. The mean disease duration±SD was 21.136±12.273 (varied between 1–48 years). Behcet's disease was silent and under control in all patients. The clinical characteristics of patients with BD are summarized in Table 1.

Spontaneous nystagmus was not observed in any of the control and BD group subjects. The cVEMP response was recorded in both ears of all normal subjects, But 9 out of 44 BD patients (20.45%) didn't have a cVEMP response in one or both ears. In other words, the occurrence of cVEMP response in BD patients was significantly lower than in control ($p=0.006$). It should be noted that the difference was significant only in the left ear ($p=0.037$) and the right ear didn't show a significant difference. Table 2 shows the mean and standard deviation of the quantitative parameters of the cVEMP response, including threshold, absolute and inter-peak latencies, amplitude and amplitude asymmetry ratio for each ear of BD and control groups. As can be seen in Table 2, there was a statistically significant difference in the p13 latency in the left ear of the two groups ($p=0.047$). In fact, the mean p13 latency in the left ear of BD patients was lower than controls. In addition, the p13-n23 amplitude in the left ear ($p=0.031$) and the amplitude asymmetry ratio ($p<0.001$) were significantly higher in BD patients than in normal subjects.

In the vHIT test, only the VOR gain of the left posterior canal ($p=0.038$) and the gain asymmetry ratio of lateral canals ($p=0.041$) were significantly increased in patients with Behcet's disease. There was no significant difference in terms of the occurrence of covert and overt corrective saccades in the stimulation of any of the SCCs in patients and controls. The mean and standard deviation of quantitative parameters of the vHIT test including the VOR gain for each canal and also the gain asymmetry ratio for each pair of canals are shown in Table 3.

In the present study, the influence of various factors including gender, race, subjective complaints of dizziness or vertigo, medications used at the time of the study, results of the Pathergy test, CRP and ESR, involved organs from the onset of disease to the time of the study, functional, emotional, physical and total scores of dizziness handicap inventory on cVEMP and vHIT responses, as well as the correlation between age, age of disease onset and duration of disease on the test results were examined. Factors of disease onset age, race, pathergy and CRP tests had no significant effect on the test results. The impact of other factors is summarized in Tables 4, 5, 6 and 7.

Table 1. Clinical characteristics of patients with Behcet's disease (n=44)

		Patients	
		No	%
Gender	Male	23	52.27
	Female	21	47.73
Race	Turk	24	54.54
	Persian	12	27.27
	Lur	6	13.63
	Kurd	2	4.54
Disease manifestations	Oral AU	44	100
	Genital AU	33	75.00
	Eye	30	68.18
	Skin	28	63.63
	Joint	24	54.54
	Vertigo	21	47.7
	CNS	5	11.36
	Artery	3	6.81
Laboratory	CRP	7	15.90
	ESR	3	6.81
Medications	Prednisolone	29	65.90
	Colchicine	25	56.81
	Methotrexate	12	27.27
	Anti-TNF	3	6.81

AU; aphthous ulcers, CNS; central nervous system, CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, Anti-TNF; tumor necrosis factor inhibitors

Discussion

In the present study, the characteristics of cVEMP response including the incidence rate, threshold, absolute and interpeak latency, peak-to-peak amplitude and amplitude asymmetry ratio were measured and compared in Behcet patients and control groups. The results showed that the incidence rate of response, absolute latency of p13 and peak-to-peak amplitude of p13-n23 in the left ear of patients with BD and the control group were significantly different. Also, the amplitude asymmetry ratio of cVEMP waves in BD patients was significantly higher than in normal individuals. Threshold, absolute n23 latency and inter-peak latency of p13-n23 were not statistically significant in BD and normal groups.

As mentioned above, the rate of cVEMP response in Behcet patients was significantly lower than in the normal group. This finding is consistent with the study of Bayir et al., which reported a lower rate of cVEMP in BD patients than normal [2]. Other studies have not reported the effect of Behcet's disease on the rate of cVEMP response [6, 14, 18]. However, the occurrence of the p13-n23 complex is affected by the pattern and intensity of stimulus and test position and is reported to be between 70-100% in normal individuals [2]. In our study, the cVEMP response was recorded in 100% of

Table 2. Comparison of mean and standard deviation of cervical vestibular-evoked myogenic potential response parameters of right and left ears in Behcet and control groups

Parameter		Mean (SD)		p*	Confidence interval (95%)		Test's power	Effect size**
		Control (n=30)	Behcet (n=40)		Lower limit	Upper limit		
Threshold (dB nHL)	Right	83.00 (6.38)	82.12 (7.24)	0.601	–2.44	4.19	0.08	0.13
	Left	85.17 (5.33)	83.61 (6.61)	0.303	–1.44	4.55	0.18	0.26
Absolute latency (ms)	Right p13	16.09 (1.93)	17.03 (2.03)	0.056	–1.89	0.02	0.48	0.47
	Left p13	16.69 (1.89)	15.65 (2.22)	0.047	0.017	2.07	0.52	0.50
	Right n23	24.97 (2.26)	25.81 (2.61)	0.159	–2.04	0.34	0.33	0.35
	Left n23	25.34 (2.81)	24.49 (2.90)	0.235	–0.56	2.26	0.22	0.30
Inter-peak latency (ms)	Right p13-n23	8.87 (2.51)	8.79 (2.16)	0.880	–1.03	1.20	0.05	0.04
	Left p13-n23	8.64 (2.61)	8.84 (1.71)	0.726	–1.31	0.92	0.06	0.09
Peak-to-peak amplitude (μv)	Right p13-n23	309.27 (139.37)	364.07 (244.67)	0.241	–147.30	37.70	0.20	0.27
	Left p13-n23	289.47 (138.90)	407.98 (282.88)	0.031	–225.90	–11.13	0.56	0.53
Amplitude asymmetry ratio (%)		11.57 (11.62)	33.26 (34.74)	<0.001	–33.25	–10.13	0.93	0.84

* indipendent group t-test was used for comparisons, ** Cohen's D

normal subjects and 88.4% of BD patients and despite the rate of more than 70% in BD patients, the difference between the two groups was significant. Lack of cVEMP response may be due to pathology affecting the peripheral or central components of the vestibulocollic reflex pathway and can't be attributed to a lesion in a particular part of the vestibular system [16, 17].

The mean latency of p13 was shorter in BD patients compared to normal subjects. However, Erbek et al. and

Table 3. Comparison of mean and standard deviation of video head impulse test response parameters of right and left ears in Behcet's and control groups

Parameter		Mean (SD)		p*	Confidence interval (95%)		Test's power	Effect size**
		Control (n=30)	Behcet (n=42)		Lower limit	Upper limit		
VOR gain	RL SCC	0.94 (0.09)	0.99 (0.19)	0.131	–0.12	0.02	0.30	0.35
	LL SCC	0.96 (0.13)	1.02 (0.17)	0.099	–0.13	0.01	0.39	0.41
	RP SCC	0.88 (0.16)	0.88 (0.22)	0.909	–0.09	0.10	0.05	0.02
	LA SCC	0.71 (0.18)	0.69 (0.23)	0.639	–0.08	0.12	0.08	0.12
	RA SCC	0.85 (0.15)	0.85 (0.25)	0.911	–0.1	0.09	0.05	0.03
	LP SCC	0.97 (0.15)	1.07 (0.22)	0.038	–0.19	–0.01	0.57	0.52
Gain asymmetry ratio (%)	Lateral	6.08 (4.10)	9.26 (8.61)	0.041	–6.23	–0.13	0.49	0.47
	LARP	14.72 (11.02)	18.33 (19.48)	0.326	–10.89	3.67	0.15	0.23
	RALP	11.08 (9.24)	16.07 (16.29)	0.104	–11.04	1.05	0.34	0.38

VOR; vestibulo-ocular reflex, RL; right lateral, SCC; semicircular canal, LL; left lateral, RP; right posterior, LA; left anterior, RA; right anterior, LP; left posterior, LARP; left anterior-right posterior, RALP; right anterior-left posterior

* indipendent group t-test was used for comparisons, ** Cohen's D

Abdel Baki et al. reported a significant increase in p13 and n23 latency in BD patients [6, 18]. In addition, Bayir et al. reported a decrease in the n23 latency and Bayram et al. stated that none of the parameters of cVEMP response were significantly different in BD and control groups [2, 14]. Latency of cVEMP waves shows the transmission process of the CNS along the afferent and efferent pat hways of the sacculocollic reflex. In other words, the late cVEMP waves are indicative of retrolabyrinthin damage to the vestibulospinal tract, but now there is not enough justification for reduced latency of the cVEMP response.

In this study, the peak-to-peak amplitude in the left ear and the amplitude asymmetry ratio were significantly increased in BD patients. While none of the previous studies have reported significant differences in the amplitude and amplitude asymmetry ratio of cVEMP responses recorded in BD patients and controls. Larger p1 and n1 amplitude are often suggestive of third window pathologies (superior or lateral canal dehiscence and fistulas). However, the cVEMP amplitude is very variable and depending on the stimulus intensity and contraction of the sternocleidomastoid muscle can be 25 to more than 200 µv [16]. Due to this high variability, the absolute amplitude of cVEMP waves is not an important factor in differential diagnosis, but the cVEMP amplitude asymmetry ratio is a clinical feature of unilateral vestibular loss [17]. The mean amplitude asymmetry ratio is between 20-45% in normal individuals. Clinical studies in normal individuals less than 60 years of age, have reported amplitude asymmetry ratio up to 34%-35% and higher val-

Table 4. Evaluation the effect of different factors on cervical vestibular-evoked myopgenic potential test parameters (n=44)

Factor	Groups	n		Threshold (dB nHL)		Absolute latency (ms)				Inter-peak latency (ms)		Peak-to-peak amplitude (µv)		Amplitude asymmetry ratio (%)
				Right	Left	Right p13	Left p13	Right n23	Left n23	Right	Left	Right	Left	
Gender	Male	23	p*	0.421	0.791	0.020	0.743	0.099	0.171	0.768	0.029	0.708	0.628	0.185
	Female	21	Power	0.10	0.06		0.06	0.37	0.32	0.06		0.14	0.17	0.15
			ES			0.52					0.69			
				Absolute latency of right p13 and inter-peak latency of left p13-n23: male>female										
Race	Turk	24	p**	0.464	0.221	0.886	0.920	0.709	0.953	0.365	0.881	0.452	0.303	0.232
	Persian	12	Power	0.23	0.34	0.06	0.05	0.11	0.09	0.15	0.13	0.27	0.41	0.51
	Lur	6												
	Kurd	2												
				No effect										
Subjective complaint of vertigo	Yes	21	p*	0.390	0.498	0.611	0.987	0.039	0.937	0.520	0.863	0.421	1.000	0.075
	No	23	Power	0.14	0.11	0.20	0.07		0.11	0.11	0.09	0.11	0.06	0.30
			ES					0.46						
				Absolute latency of right n23: yes>no										
ESR	High	3	p*	0.401	0.625	0.175	0.705	1.000	0.872	0.273	0.512	0.557	1.000	0.577
	Low	41	Power	0.13	0.08	0.39	0.05	0.05	0.06	0.18	0.14	0.13	0.06	0.11
				No effect										
CRP	High	7	p*	0.754	0.605	0.702	0.852	0.835	0.918	0.651	0.885	0.442	0.442	0.426
	Low	37	Power	0.06	0.07	0.10	0.09	0.05	0.05	0.08	0.09	0.08	0.17	0.10
				No effect										

Factor	Groups		n		Threshold (dB nHL)		Absolute latency (ms)				Inter-peak latency (ms)		Peak-to-peak amplitude (μv)		Amplitude asymmetry ratio (%)
					Right	Left	Right p13	Left p13	Right n23	Left n23	Right	Left	Right	Left	
Medications	Prednisolone	Yes	29	p*	0.180	0.562	0.624	0.078	0.624	0.679	0.171	0.518	0.685	0.079	0.703
		No	15	Power	0.22	0.10	0.11	0.31	0.12	0.06	0.35	0.22	0.11	0.18	0.06
					No effect										
	Colchicine	Yes	25	p*	0.570	0.115	0.090	0.312	0.182	0.107	0.914	0.040	0.745	0.131	0.418
		No	19	Power	0.08	0.50	0.47	0.10	0.15	0.44	0.10		0.08	0.53	0.15
				ES								0.69			
					Inter-peak latency of left p13-n23: yes<no										
	Methotrexate	Yes	12	p*	0.939	0.886	0.058	0.168	0.158	0.693	0.569	0.428	0.818	0.472	0.423
		No	32	Power	0.05	0.05	0.51	0.45	0.22	0.09	0.08	0.27	0.06	0.15	0.17
					No effect										
	Anti-TNF	Yes	3	p*	0.741	0.495	0.926	0.114	0.697	0.917	0.877	0.317	0.282	0.317	0.929
		No	41	Power	0.08	0.15	0.05	0.15	0.05	0.05	0.05	0.16	0.30	0.88	0.16
					No effect										
Involved organs	Eye	Yes	30	p*	0.510	0.359	0.318	0.435	0.332	1.000	0.092	0.220	0.944	0.710	0.722
		No	14	Power	0.06	0.25	0.13	0.28	0.17	0.12	0.53	0.10	0.05	0.05	0.08
					No effect										
	Joint	Yes	24	p*	0.141	0.657	0.672	0.214	0.713	0.465	0.374	0.849	0.005	0.005	0.365
		No	20	Power	0.37	0.08	0.06	0.12	0.06	0.15	0.09	0.08			0.15
				ES									0.88	1.06	
					Peak-to-peak amplitude in both ears: yes<no										
	CNS	Yes	5	p*	0.937	0.610	0.337	0.543	0.071	0.021	0.244	0.073	0.524	0.366	0.970
		No	39	Power	0.05	0.14	0.12	0.10	0.26		0.16	0.54	0.20	0.32	0.05
				ES						1.11					
					Absolute latency of left n23: yes>no										
	Arterial involvement	Yes	3	p*	0.296	1.000	0.492	0.476	0.962	0.549	0.461	0.242	0.524	0.318	0.371
		No	41	Power	0.19	0.05	0.23	0.20	0.08	0.12	0.08	0.12	0.13	0.26	0.05
					No effect										

ES; effect size, ESR; erythrocyte sedimentation rate (high>30, low<30), CRP; C-reactive protein (high>6, low<6)

TNF; tumor necrosis factor, CNS; central nervous system

* Mann-Whitney U test was used, ** Kruskal-Wallis test was used

Table 5. Evaluation of the correlation between age, age of disease onset, disease duration and dizziness handicap inventory scores with cervical vestibular-evoked potential test parameters (n=44)

Factors	n		Threshold (dB nHL)		Absolute latency (ms)				Inter-peak latency (ms)		Peak-to-peak amplitude (µv)		Amplitude asymmetry ratio (%)
			Right	Left	Right p13	Left p13	Right n23	Left n23	Right	Left	Right	Left	
age	44	p*	0.193	0.053	0.811	0.920	0.272	0.841	0.440	0.903	0.002	0.000	0.423
		r	0.21	0.32	0.04	0.02	0.18	–0.03	0.13	0.02	–0.47	–0.59	0.13
			Peak-to-peak amplitude of both ears: increased age=decreased amoplitude (inverse correlation)										
Age of disease onset	44	p*	0.782	0.329	0.335	0.273	0.954	0.131	0.186	0.191	0.407	0.951	0.421
		r	–0.04	–0.17	0.16	0.19	0.01	0.26	–0.21	0.22	–0.13	0.01	0.13
			No effect										
Disease duration	44	p*	0.234	0.051	0.765	0.743	0.285	0.328	0.113	0.436	0.039	0.004	0.994
		r	0.19	0.33	–0.05	–0.06	0.17	–0.17	0.25	–0.13	–0.33	–0.47	0.00
			Peak-to-peak amplitude in both ears: increased duration=decreased amoplitude (inverse correlation)										

Table 6. Evaluation the effect of different factors on video head impulse test parameters (n=44)

Factors	Groups	n		VOR gain						VOR gani asymetry ratio (%)		
				RL	LL	RP	LA	RA	LP	Lateral	LARP	RALP
Gender	Male	23	p*	0.068	0.006	0.457	0.262	0.186	0.040	0.013	0.036	0.068
	Female	21	Power	0.29		0.06	0.26	0.36				0.55
			ES		0.91				0.73	0.88	0.74	
			VOR gain of LL and LP SCCs+gain asymmetry ratio of lateral and LARP SCCs: male<female									
Race	Turk	24	p**	0.727	0.919	0.818	0.937	0.235	0.714	0.881	0.383	0.559
	Persian	12	Power	0.13	0.09	0.12	0.09	0.27	0.18	0.07	0.25	0.15
	Lur	6										
	Kurd	2										
			No effect									
Subjective complaint of vertigo	Yes	21	p*	0.537	0.338	0.230	0.206	0.734	0.588	0.011	0.575	0.580
	No	23	Power	0.11	0.21	0.31	0.23	0.07	0.01		0.15	0.11
			ES							0.91		
			Gain asymmetry ratio of lateral SCCs: yes>no									
ESR	High	3	p*	0.009	0.124	0.652	0.372	0.397	0.111	0.026	0.723	0.166
	Low	41	Power		0.38	0.10	0.10	0.13	0.40		0.05	0.22
			ES	1.60						1.11		
			VOR gain of RL SCC: high<low/gain asymmetry ratio of lateral SCCs: high>low									

Factors	Groups		n		VOR gain						VOR gani asymetry ratio (%)		
					RL	LL	RP	LA	RA	LP	Lateral	LARP	RALP
CRP	High		7	p*	0.053	0.869	0.370	0.697	0.122	0.974	0.446	0.282	0.335
	Low		37	Power	0.34	0.05	0.12	0.10	0.32	0.05	0.05	0.39	0.19
					No effect								
Medications	Prednisolone	Yes	29	p*	0.762	0.589	0.730	0.533	0.571	0.096	0.802	0.121	0.947
		No	15	Power	0.05	0.06	0.06	0.11	0.10	0.40	0.25	0.43	0.12
					No effect								
	Colchicine	Yes	25	p*	0.303	0.021	0.068	0.361	0.770	0.611	0.387	0.832	0.509
		No	19	Power	0.08		0.55	0.06	0.07	0.08	0.22	0.07	0.09
				ES		0.80							
					VOR gain of LL SCC: yes>no								
	Methotrexate	Yes	12	p*	0.433	0.573	0.372	0.767	0.967	0.288	0.518	0.989	0.670
		No	32	Power	0.07	0.06	0.20	0.06	0.06	0.11	0.07	0.16	0.08
					No effect								
	Anti-TNF	Yes	3	p*	1.000	0.124	0.944	0.795	1.000	0.818	0.275	0.519	0.890
		No	41	Power	0.06	0.43	0.05	0.05	0.06	0.05	0.17	0.05	0.07
					No effect								
Involved organs	Eye	Yes	30	p*	0.947	0.163	0.596	0.454	0.553	0.782	0.535	0.167	0.405
		No	14	Power	0.07	0.48	0.11	0.09	0.06	0.05	0.26	0.11	0.09
					No effect								
	Joint	Yes	24	p*	0.440	0.111	0.365	0.379	0.063	0.613	0.230	0.358	0.047
		No	20	Power	0.05	0.28	0.23	0.23	0.39	0.09	0.38	0.27	
				ES									0.50
					Gain asymmetry ratio of RALP SCCs: yes>no								
	CNS	Yes	5	p*	0.043	0.371	0.382	0.783	0.215	0.394	0.443	0.048	0.157
		No	39	Power		0.20	0.15	0.09	0.24	0.18	0.06		0.54
				ES	0.84							1.07	
					VOR Gain of RL SCC: Yes>No/Gain asymmetry ratio of LARP SCCs: yes<no								
	Artery	Yes	3	p*	0.062	0.345	0.213	0.519	0.782	0.927	0.124	0.832	0.610
		No	41	Power	0.42	0.18	0.28	0.09	0.10	0.06	0.31	0.07	0.15
					No effect								

VOR; vestibulo-ocular reflex, RL; right lateral, LL; left lateral, RP; right posterior, LA; left anterior, RA; right anterior, LP; left posterior, LARP; left anterior- right posterior, RALP; right anterior- left posterior, ES; effect size, SCCs; semicircular canals, ESR; erythrocyte sedimentation rate (high>30 , low<30),CRP; c-reactive protein (high>6, low<6), TNF; tumor necrosis factor, CNS; central nervous system

* Mann-Whitney U test was used, ** Kruskal-Wallis test was used

Table 7. Evaluation of the correlation between age, age of disease onset, disease duration and dizziness handicap inventory scores with video head impulse test parameters (n=44)

Factors		n		VOR gain						VOR gani asymetry ratio (%)		
				RL	LL	RP	LA	RA	LP	Lateral	LARP	RALP
Age		44	p*	0.897	0.339	0.676	0.312	0.537	0.723	0.567	0.081	0.382
			r	–0.02	–0.15	0.07	–0.16	–0.10	–0.06	–0.09	0.28	0.14
No effect												
Age of disease onset		44	p*	0.641	0.417	0.296	0.707	0.593	0.809	0.113	0.820	0.635
			r	0.07	–0.13	0.17	–0.06	–0.08	0.04	–0.25	0.04	0.07
No effect												
Disease duration		44	p*	0.625	0.922	0.706	0.448	0.767	0.554	0.514	0.153	0.895
			r	–0.08	0.02	-0.06	-0.12	-0.05	-0.09	0.10	0.23	0.02
No effect												
DHI Scores	Functional	44	p*	0.820	0.028	0.908	0.776	0.751	0.091	0.067	0.874	0.151
			r	0.04	0.34	–0.02	–0.05	–0.05	0.26	0.28	-0.03	0.23
VOR gain of LL SCC: increased functional scores=increased gain (direct correlation)												
	Emotional	44	p*	0.688	0.006	0.966	0.976	0.778	0.199	0.076	0.933	0.301
			r	–0.06	0.42	0.01	–0.00	–0.04	0.20	0.28	–0.01	0.16
VOR gain of LL SCC: increased emotional scores=increased gain (direct correlation)												
	Physical	44	p*	0.534	0.254	0.194	0.639	0.935	0.325	0.079	0.559	0.983
			r	0.10	0.18	–0.21	–0.07	0.01	0.16	0.27	–0.09	0.00
No effect												
	Total	44	p*	0.656	0.072	0.448	0.637	0.841	0.207	0.039	0.484	0.459
			r	0.07	0.28	–0.12	–0.08	–0.03	0.20	0.32	–0.11	0.12
Gain asymmetry of lateral SCCs: increased total scores=increased gain asymmetry (direct correlation)												

VOR; vestibulo-ocular reflex, RL; right lateral, LL; left lateral, RP; right posterior, LA; left anterior, RA; right anterior, LP; left posterior, LARP; left anterior-right posterior, RALP; right anterior-left posterior, DHI; dizziness handicap inventory, SCCs; semicircular canals

* Spearman's correlation coefficient test was used

ues are considered unilateral saccular dysfunction [16]. In our study, the mean asymmetry ratio was 11.569 in the control group and 33.259 in the BD group, and there was a significant difference between the two groups. It is always recommended in clinical trials that each clinic has its norm values, so although the mean asymmetry ratio in BD patients was less than 45%, the significant difference between the BD and control groups is important and it can be said that unilateral vestibular loss is common in Behcet's disease. Pollak et al. also reported that vestibular loss in BD was mainly unilateral [3]. In addition, abnormal cVEMP amplitude was observed in 15 and abnormal latency was observed in 9 BD patients. Peripheral vestibular lesions such as Meniere's disease or vestibular neuritis often affect the amplitude of cVEMP responses and even may eliminate the response [6]. So,

we suggested that peripheral involvement of the vestibular system is more probable in our Behcet's patients group. Gemignani et al. also reported the same finding [26], but Belkahia et al. reported that central vestibular disorders are more common in BD. Of course, they examined 16 patients with neuro-Behcet's disease, which may be the cause of their findings [27].

Regarding the vHIT test, the findings of the present study showed that the mean VOR gain of the left posterior SCC and the gain asymmetry ratio (%) in the stimulation of lateral SCCs in BD patients (1.072 and 9.264 respectively for VOR gain and asymmetry ratio) were significantly higher than the control group (0.972 and 6.084 respectively for VOR gain and asymmetry ratio). So that the VOR gain for the left lateral SCC was higher than the right. The other variables of the vHIT test were not significantly different between the two groups. Only one previous study showed that VOR gain increases in BD patients [1], but in the study of Ertugrul et al. the RALP VOR gain was significantly lower and the gain asymmetry ratio of lateral SCCs was significantly higher in BD patients compared to the control. They also reported a significant occurrence of pathological covert and overt saccades in lateral SCCs stimulation in BD patients [22]. However, in our study, the percentage of covert and overt corrective saccades was higher in vertical canals than the horizontal canals, while there was no significant difference between the two study groups in terms of the occurrence of corrective saccades. In the study of Tutar et al. the VOR gain of left and right anterior and right posterior SCCs in BD patients were significantly lower than normal subjects [23]. The difference in affected SCCs in studies may be because vasculitis caused by BD affects different canals. There may be an association between increased gain in vHIT with decreased p13 latency and increased p13-n23 amplitude in cVEMP in patients with BD.

Based on our findings, with increasing age and duration of disease in BD patients, the amplitude of the cVEMP response decreases in both ears. Brama and Fainaru also stated that inner ear involvement is often seen in elderly BD patients with a longer duration of disease despite the health of the CNS [28]. Other researchers found no correlation between age and disease duration with audio-vestibular disorders [1, 3, 6, 14, 22].

Erythrocyte sedimentation rate (ESR) is the rate at which red blood cells settle in the laboratory and is used as a non-specific test to detect the presence of inflammation in the body. We observed that the VOR gain of the right lateral canal was lower and the gain asymmetry ratio of lateral canals was higher in the vHIT test of patients with high ESR. This finding could confirm that vestibular system disorders in Behcet's disease are caused by the inflammatory process of the disease.

Other studies found no correlation between vestibular disorders with hearing loss and other systemic manifestations in BD patients [2, 3, 6]. However, it was found in our study that in patients with articular involvement, the cVEMP amplitude was lower and the RALP gain asymmetry ratio was higher than in other patients and this may be related to a decrease in patient's ability to contract SCM muscle and smaller neck range of motion (despite no specific involvement of the cervical vertebrae). In addition, we found that CNS involvement affects the n23 latency and the VOR gain. Kulahi et al. showed by MRI that the vestibular disorders observed in Behcet's disease may be due to CNS involvement in the disease [29]. Bayram et al. also reported pathological findings of cranial MRI in 2 out of 10 patients with abnormal cVEMP and 1 in 7 patients with abnormal oVEMP, but they didn't find a significant correlation between MRI and VEMP results [14].

Finally, by examining the effect of 4 drug groups on the cVEMP and vHIT tests results, it was found that only Colchicine may have an ototoxic effect and affect these tests. Side effects of this drug include neuritis and CNS disorders. However, so far non of the studies have examined the effect of BD treatment on the results of vestibular tests and more studies should be done in this field.

It is noteworthy that this study had the largest sample size compared to previous studies, but we recommend more studies be done with larger sample sizes. In addition, radiological evaluations such as cranial MRI can also confirm the involvement of the CNS in BD.

Conclusion

According to the results, we concluded that peripheral and unilateral vestibular disorders are common in Behcet's disease (BD). Decreased vestibulo-ocular reflex gain of the right lateral canal and increased gain asymmetry ratio of lateral canals in patients with high erythrocyte sedimentation ratio, can indicate that vestibular disorders in BD are due to the inflammatory process of the disease. Due to the effect of Behcet's disease on the vestibular system as well as the effect of colchicine on central nervous system and the results of vestibular tests of our study, examination of the vestibular system of BD patients before and after drug administration is recommended.

Ethical Considerations

Compliance with ethical guidelines

It should be noted that the study was approved by the committee on ethics in medicine (IR.TUMS.FNM.REC.1399.047).

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Authors' contributions

ZHS: Study design, acquisition of data, interpretation of the results, statistical analysis, drafting the manuscript; FH: Study design, interpretation of the results, drafting the manuscript; RH: Study design, Interpretation of the results; STF: Diagnosis and identification of patients; SJ: Statistical analysis.

Conflict of interest

The authors declare that there is no conflict of interest to be reported.

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