European Archives of Oto-Rhino-Laryngology (2019) 276:1625–1632
https://doi.org/10.1007/s00405-019-05403-x

OTOLOGY

Audiological and vestibular measurements in Behçet's disease

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Received: 23 January 2019 / Accepted: 20 March 2019 / Published online: 30 March 2019

Abstract

Introduction Behçet's disease (BD) is a vasculitis that involves all small vessels and influences the multiple systems of the human body. This study aimed to evaluate the audio-vestibular system involvement of patients with BD and healthy individuals.

Materials and methods This study was designed as a prospective case–control blinded study. Thirty-one patients with BD and 31 healthy individuals were included. All the subjects were evaluated via pure tone audiometry (PTA), video head impulse test (vHIT), post head shake nystagmus test (PHSNT) and dizziness handicap inventory (DHI) to check for audio-vestibular system involvement.

Results Patients with BD showed higher PTA scores in both speech and high frequencies. The vHIT revealed pathological saccades, particularly in horizontal canals (right ear: $p=0.002$, left ear: $p=0.039$). The gain values of the patients were slightly lower than those of the control group; however, gain and gain asymmetry differed significantly in a few canals. In the spontaneous nystagmus test and PHSNT, pathological nystagmus was detected to be significantly higher in the patient group than control group ($p=0.001$); but the saccade presence in vHIT and nystagmus in PHNT did not differ among the patients ($p=0.106$). In addition, the DHI scores of the patients group were higher than those of the control group ($p<0.001$). No correlation was found between disease duration and saccade presence.

Conclusion The vHIT was used preliminary for evaluating the vestibular system in BD. This study showed the influence of BD on the audio-vestibular system, in particular isolated horizontal canal involvement was discovered in patients with BD.

Level of evidence Level III b.

Keywords Behçet's disease · Semicircular canals · Vestibulo-ocular reflex · Video head impulse test · Nystagmus · Dizziness handicap inventory

Introduction

Behçet's disease (BD), first described by Hulusi Behçet in 1937, is a systemic disorder that presents itself as recurrent aphthous ulcers (oral and genital) and eye and skin lesions [1, 2]. The prevalence of the disease varies in different geographical regions. BD is mostly seen along the ancient Silk Road route, which is between the Far East and the Mediterranean basin [2, 3].

Behçet's disease influences venous vessels rather than arteries [3]. The main etiology and pathogenesis of BD remained unclear until recent studies illuminated the autoimmune basis of this disease [2]. The inflammation of the venous vessels causes inflammatory thrombi which were thought to lead to the lumen being occluded. With regards to the arterial vessels, focal aneurysmal dilatation was mostly suspected and perivascular lymphocytic infiltration with

This study was orally presented in 9th National Audiology and Speech Disorders Congress, 11th–13th October, Istanbul, Turkey.

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corruption of medial elastic fibers was thought to lead to this pathology [3].

In recent literature, very few studies aimed to evaluate the audio-vestibular involvement of BD and hearing loss and determined an involvement at high frequencies [4, 5]. In addition, the vestibular impairment in BD was also proposed in prior studies and BD was suspected in vestibular dysfunction [4, 6, 7].

In the recent years, Halmagyi et al. researched a new vestibular test technique called the head impulse test that was commonly used to evaluate vestibular functions [8]. This technique evolved into the video head impulse test (vHIT) with high-speed cameras and proper software [8]. vHIT enables the detection of all three semicircular canals to understand the underlying reasons of different vestibular pathologies. According to our knowledge, the clinical results of the vHIT of patients with BD were never previously presented.

In the present study, it was aimed to preliminary examine the patients with BD via vHIT and other well-known audio-vestibular tests. In accordance with this purpose, a pure tone audiometer was used to evaluate the auditory system. Post head shake nystagmus test (PHSNT), dizziness handicap inventory (DHI) and vHIT, which is first used for the evaluation of the patients with BD, were utilized to determine the vestibular system effects of patients with BD and the obtained results were discussed in the light of recent literature.

Materials and methods

This study was designed as a prospective case–control blinded study.

Patient selection

All the patients were selected from the Medeniyet University Goztepe Training and Research Hospital Department of Dermatology between March 2017 and September 2017. Thirty-one patients and 31 healthy individuals, who were determined as control group, were involved in this study. The control group was selected randomly from healthy individuals, who had no history of vertigo or ear diseases and were similar to the patient group in terms of age and gender. The selection criteria for the patients were as follows:

- Confirmed diagnosis of Behçet's disease, excluding neuro-Behçet's disease.
- No history of

–air conduction hearing loss

– metabolic disorders (hypothyroidism, hyperthyroidism, diabetes mellitus, hypertension, cardiac diseases, anemia, etc.)

–previous vestibular disorders (benign paroxysmal positional vertigo, vestibular neuritis, acute/chronic otitis media, otosclerosis, ototoxicity, Meniere's disease, labyrinthitis, etc.)

–head and neck trauma or motility loss

– neurological disorders (multiple sclerosis, Parkinson's disease, meningitis, cerebral emboli, etc.)

- Patients currently receiving medical treatment were excluded from this study; except for those receiving colchicine (we did not find any related effects on the audio-vestibular system in current English literature).

Methods

All the clinical test results were evaluated blindly by the senior author (the cases were anonymously analyzed).

Audiometry

All the participants were tested with a calibrated clinical audiometer device (AC 40 Interacoustics®, Assens, Denmark) in a silent cabin (Industrial Acoustic Company Inc., New York, USA) at the Medeniyet University Goztepe Training and Research Hospital Department of Audiology. The pure tone thresholds of air conduction (AC) were evaluated at 500–8000 Hz (500, 1000, 2000, 4000, 6000, 8000 Hz) frequencies and bone conduction (BC) thresholds were tested in 500–4000 Hz (500, 1000, 2000, 4000 Hz). The related frequencies were assessed and grouped as speech frequencies (500, 1000, 2000 Hz) and high frequencies (4000, 6000, 8000 Hz) [4].

Vestibular tests

All the participants were evaluated with both vHIT, post head shake nystagmus test at the Baskent University Hospital Istanbul Faculty of Medicine vestibular laboratory by the same clinical audiologist and the test results were evaluated blindly by Dr. Ozluoglu.

- Video head impulse test: This test was performed with a calibrated device (OTOsuite Vestibular Software, ICS Impulse, GN Otometrics®, Taastrup, Denmark). Participants were placed 1 m away from a specific target and personal adjustments were made after the test goggles were put on to the participant. To evaluate the horizontal canals, the participant's head was positioned at ~ 20° anteflexion and head movements were generated randomly both sides with ~ 100° to 250°/s. After

the horizontal canal tests, the vertical canals were tested by rotating the head ~ 35° to 45° (right rotation for the right anterior and left posterior canals; left rotation for the left anterior and right posterior canals). Head impulse was generated vertically with the ~ 50° to 250°/s. All the canals were tested with 20 optimized impulses. The normal rate of vestibulo-ocular reflex (VOR) gains were accepted to be ≥ 0.8 for the horizontal (lateral) semicircular canals and ≥ 0.7 for vertical canals (anterior and posterior) [9]. The VOR gain values and existence of pathological saccades which are covert (the catch-up saccades which occur during head impulses) or overt (the catch-up saccades that occur after head impulses) were investigated (Figs. 1, 2). The overshoots were excluded from the dataset. Korsager et al. revealed that the occurrence of the saccades were more reliable than the gain at first place in vHIT [10]. Therefore, in the present study, the saccade presence was considered to describe the pathology.

- Spontaneous nystagmus test: This test was applied to the patients after the vHIT in the same sitting position and recorded with video nystagmography (Spectrum Software, Visual Eyes Binocular goggles, Micromedical Technologies®, IL, USA). Participants were asked to fixate on a specific target for 30 s and fixation was removed for 30 s, as well.
- Post head shake nystagmus test: This test was conducted after the spontaneous nystagmus test using the

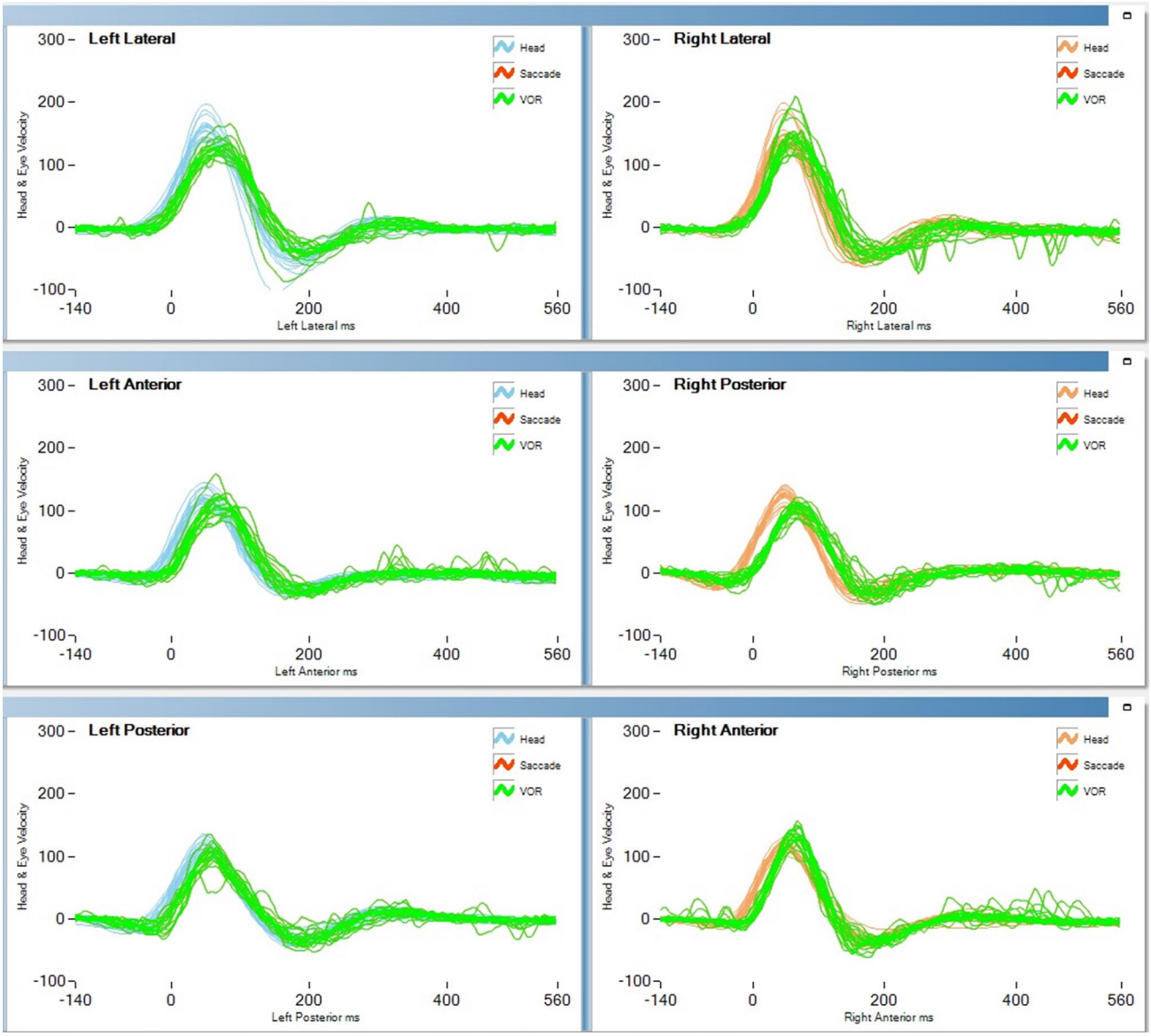

Fig. 1 Video head impulse test example of a normal case

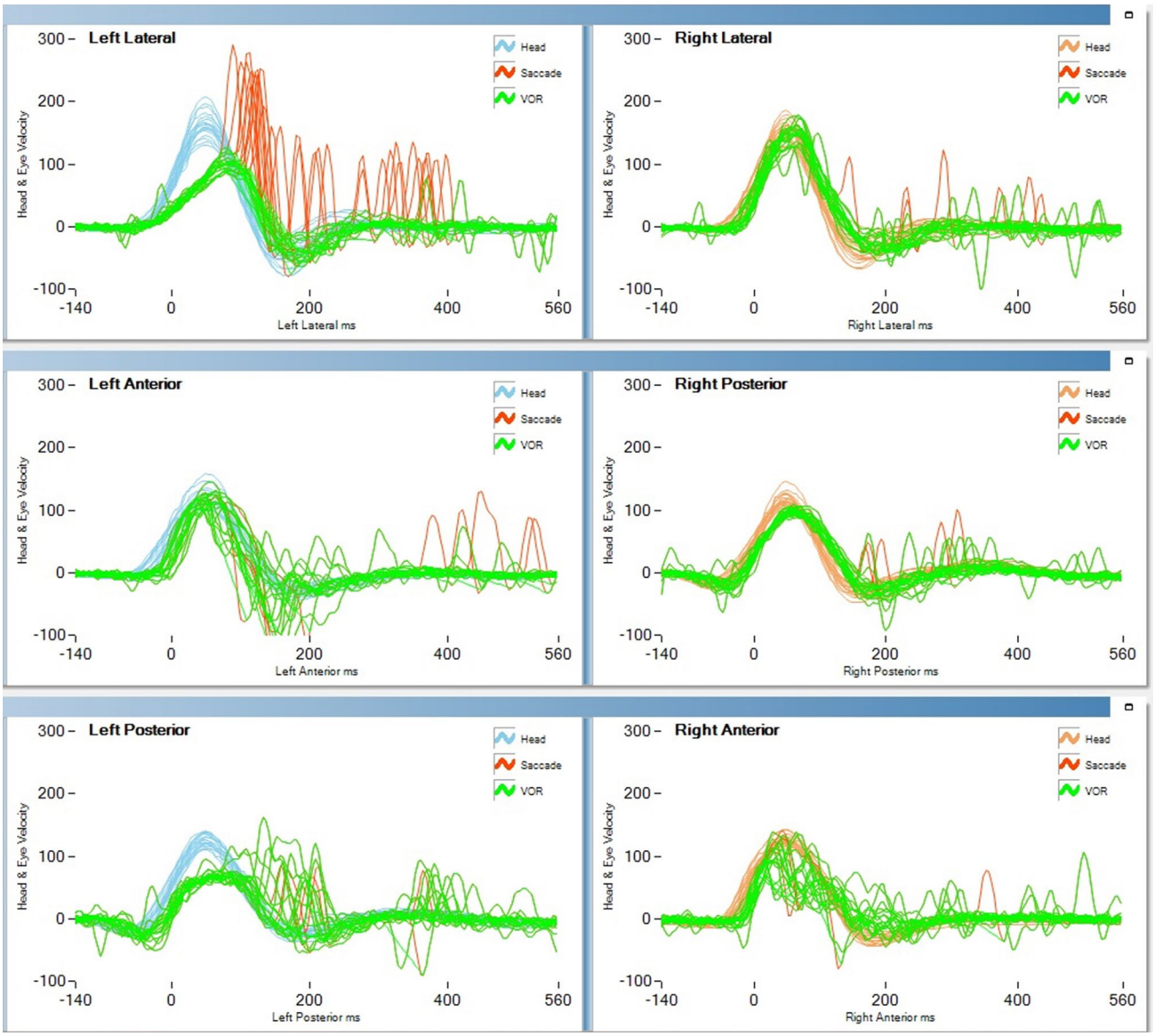

Fig. 2 Video head impulse test example of a patient (presence of overt, covert saccades and decreased gain levels)

same instruments. The examiner moved the participants' head 30° anteriorly and ± 45° horizontally oscillated 2 times/s (Hz) frequency for 20 cycles. Recorded nystagmus, which was persisted more than 5 s, was considered pathological.

Dizziness handicap inventory

The vestibular conditions of the participants were surveyed with the validated Turkish version of the Dizziness handicap inventory (DHI-TR) [11]. The survey was administrated to all the participants in a face-to-face format by a clinical audiologist. The scores obtained were used to determine the self-perceived handicap from the current status.

Statistical analysis

All the acquired data were assessed via SPSS v20 (IBM®, Chicago, IL, USA). The descriptive data were demonstrated with mean, standard deviation (SD), minimum and maximum values. The data distribution was checked for normality with the Kolmogorov–Smirnov test. The groups with normal distributed variables were compared by the independent samples *T* test. The non-normal data were assessed with the Mann–Whitney *U* test and Chi square test. Comparison of the categorical continuous variables

was performed with point-biserial correlation analysis. The p value of < 0.05 was considered to be statistically significant.

Ethical statement

This study was conducted after obtaining the approval of Baskent University Faculty of Medicine Ethics Committee for Clinical Investigations (Project number: KA17/136). Informed consent was obtained from all the participants involved in the study.

Results

The present study comprised of 31 patients with BD (*N*: 13 males 41.9%, 18 females 58.1%) and 31 healthy individuals (*N*: 9 males 29%, 22 females 71%). Age distribution ranged between 31 and 60 years for the patients (mean 45.16, SD 7.75) and 22 and 64 years for the control group (mean 42.81, SD 10.5). There was no significant difference between the groups regarding age ($p = 0.244$) gender ($p = 0.374$).

Table 1 The comparison of the audiometer results of patients with Behçet's disease and normal individuals

		Behçet's disease ($N = 31$)	Normal ($N = 31$)	p
Speech frequencies	R (dB)			
	Mean	17.61	10.16	0.004
	SD	14.04	3.71	
	L (dB)			
	Mean	17.23	10.06	0.001
	SD	11.58	3.01	
High frequencies	R (dB)			
	Mean	27.32	13.45	0.001
	SD	18.47	4.48	
	L (dB)			
	Mean	27.45	13.03	0.001
	SD	13.03	3.84	

Speech frequencies involved 500, 1000, and 2000 Hz; high frequencies involved 4000, 6000, and 8000 Hz

R right ear, *L* left ear, *SD* standard deviation, *N* number (Mann–Whitney *U* test; $p < 0.05$)

The pure tone audiometer results of the patients and control group were evaluated. The speech frequency and high-frequency pure tone averages of the patients were compared with those of the healthy group and significantly higher thresholds were detected (Table 1).

The vHIT results were evaluated for the presence of saccades, gain values and gain asymmetry levels for each semicircular canal. The presence of lateral saccades in horizontal canals were evaluated and patients with BD showed a significant number of pathologic saccades (overt, covert saccades), in fact none of the normal participants exposed pathological saccades (Chi square test; right ear: $p = 0.002$, left ear: $p = 0.039$) (Table 2). Conversely, saccades were detected in the vertical canals in very few patients. The left anterior semicircular canal of one patient and the left posterior semicircular canal on two different patients presented pathological saccades; however, the limited number of the patients prevented a statistical analysis. Other important factors were the gain and gain asymmetry of the three semicircular canals. The gain values of the patients were slightly lower than those of the control group but in the results lateral canal gain asymmetry values and gain values of the right anterior-left posterior canals showed statistical significance (Table 3).

All the participants were evaluated for the existence of nystagmus but neither the patients nor the healthy individuals showed spontaneous nystagmus. The presence of nystagmus in the patients with BD was sustained from the PHSNT. In contrast to the results of the patients, none of the healthy individuals showed nystagmus in the PHSNT. The difference between the patients and control group was found to be statistically significant (Chi square test; $p = 0.001$) (Table 4). In addition, saccade presence in vHIT and nystagmus in PHSNT did not differ significantly among the patients (Chi square test; $p = 0.106$).

The dizziness handicap inventory scores were 22.9 ± 13.35 and 0.16 ± 0.09 points for the patient and control groups, respectively. The results of the patient

Table 2 Lateral saccade statistics of both patients and normal participants (Chi square test; $p < 0.05$)

	Right lateral saccade				Total *N*	X^2; p	Left lateral saccade				Total *N*	X^2; p
	Saccade (−)		Saccade (+)				Saccade (−)		Saccade (+)			
	N	%	*N*	%			*N*	%	*N*	%		
Behçet's disease	23	74.19	8	25.81	31	9.185; 0.002	27	87.1	4	12.9	31	4.276; 0.039
Normal	31	100	0	0.00	31		31	100	0	0	31	
Total *N*	54	87.1	8	12.9	62		58	93.55	4	6.45	62	

N number

Table 3 This table shows the descriptive statistics and analysis of the vHIT results

	Behçet's disease ($N=31$)				Normal ($N=31$)				p*,**
	Mean	SD	Median	[a]	Mean	SD	Median	[b]	
Right lateral gain	0.96	0.08	0.94	1 3.2%	0.93	0.03	0.94	0	0.678*
Left lateral gain	0.84	0.66	0.84	5 16.1%	0.88	0.04	0.88	0	0.148**
Lateral gain asymmetry	− 6.4	3.67	− 5	–	− 2.72	2.41	− 3	–	< 0.001*
Left anterior gain	0.91	0.08	0.93	1 3.2%	0.92	0.06	0.91	0	0.807*
Right posterior gain	0.85	0.08	0.87	2 6.4%	0.91	0.08	0.90	0	0.16*
LARP gain asymmetry	3.37	5.05	4	–	0.89	4.14	1	–	0.326**
Right anterior gain	0.78	0.14	0.79	7 22.5%	0.88	0.06	0.89	0	0.001**
Left posterior gain	0.75	0.17	0.78	6 19.3%	0.87	0.06	0.88	0	0.001*
RALP gain asymmetry	− 2.86	15.72	− 1	–	− 0.31	3.2	0	–	0.682*

LARP left anterior right posterior semicircular canal, *RALP* right anterior left posterior semicircular canal, *SD* standard deviation

*p: Mann–Whitney U test, <0.05

**p: independent samples T test, <0.05

[a]Number of patients which has the lower gain value than the suggested cutoff value in the literature (horizontal canal 0.8, vertical canals 0.7)

[b]Number of normal individuals which show the lower gain value than the related literature values [9]

Table 4 The results of the nystagmus presence in post head shake nystagmus test (Chi square test; $p<0.05$)

	Post head shake test				Total N	X^2; p
	Nystagmus (−)		Nystagmus (+)			
	N	%	N	%		
Patient group						
Behçet's disease	20	64.52	11	35.48	31	13.373; 0.001
Normal	31	100.00	0	0.00	31	
Total N	51	82.26	11	17.74	62	

group were significantly higher than those of the control group (Mann–Whitney U test; $p<0.001$). Moreover, patients with saccades obtained higher scores (mean 29.45 ± 12.99, median 30) than patients without saccades (mean 19.30 ± 12.40, median 16) in vHIT (Mann–Whitney U test; $p=0.032$).

The comparison of saccade presence according to the disease duration was revealed to have no statistical difference ($p=0.468$) (Table 5).

Table 5 The correlation analysis between the disease duration and saccade presence in vHIT

	Duration of the disease (year)				
	Mean	Standard deviation	Minimum	Maximum	p
Saccade (+) $N=11$	13.63	8.60	3	35	0.141* 0.448**
Saccade (−) $N=20$	14.05	6.72	3	26	

N number (point-biserial correlation, $p < 0.05$)

*Point-biserial correlation score

**Significant p value

Discussion

Behçet's disease is a multi-systemic disorder that mostly involves the mucocutaneous areas, eyes, gastrointestinal tract, joints, lungs, central nervous system, and vascular structures. The audio-vestibular system involvement in BD attracts less attention due to the extensity of the effected systems and morbidity; so, very few studies have evaluated the possible effects of BD on the audio-vestibular system.

First, the auditory system involvement was reviewed, and hearing loss is a manifestation that demonstrates influence on this particular system. Choung et al. revealed hearing loss in a small group [7] and Erbek et al. mentioned hearing loss mostly in higher frequencies [4]. Sensorineural hearing loss was associated with the influence on the inner ear; however, the location of the pathology could not be defined. Sonbay et al. focused on hearing complexes and revealed the disruption on the cochlea in patients with BD [5]. In the present study correlated with previous studies with regard to the fact that higher pure tone, average results were found for both speech and high frequencies in the patients.

Second, the vestibular system involvement was evaluated. In their study, Choung et al. revealed abnormal results in vestibular tests (caloric tests, rotation tests) [7]. Kulahli et al. mentioned hypometric or hypermetric saccades in video nystagmography test related to vestibular dysfunction with central nervous system involvement [12]. Very few authors used the vestibular evoked myogenic potentials (VEMP) to shed light on the vestibular dysfunction in patients with BD, and they related the chronic inflammation on the sacculocollic pathways with central nervous system involvement [4, 13].

vHIT was a newly described test that enabled the identification of the overt and covert saccades and the gain of VOR of each semicircular canal to be studied. The originality of the present study lies in the fact that vHIT was preliminary used to assess this dilemma in patients with BD. According to the preliminary results of this study, the presence of pathological overt and covert saccades were elicited mostly in the horizontal canals, conversely the number of the saccades was relatively low on the vertical canals. Moreover, none of the normal individuals showed pathological saccades. The gain levels of the patients were also lower in most cases but made no statistical difference.

PHSNT is a well-known part of the video nystagmography test battery and useful to determine unilateral vestibular hypofunction. In the present study, it was found that the number of nystagmus detected in patients was statistically beyond the control group. In addition, the vHIT and PHSNT results were correlated with the patient group and a modest difference remained. This result also supports the hypothesis for vestibular hypofunction in patients with BD.

DHI is a useful survey, which numerically presents the self-reported inconvenience of balance disorders. In the present study, DHI was used to determine the patients' discomfort and according to our knowledge, it was the first time DHI was used for this purpose. According to the results, the scores of the patient group were higher than those of the control group and patients mentioned related inconvenience from the balance problems. The consultation of the patients suffering from balance problems may contribute to increase the patients' life quality in the long term.

The findings of studies regarding the correlation between disease duration and vestibular dysfunction are unclear [7, 13]. In the present study, this was analyzed, however, no correlation was detected between the two. The lack of this correlation can be interpreted as the irrelevance of the severity of vestibular dysfunction with disease duration.

Due to the anatomical nature of humans, cochlea and vestibular structures have a very limited blood supply. The common cochlear artery and the anterior vestibular artery are the main branches of the labyrinthine artery. BD is a vasculitis that can affect all kinds of vessels. The objective findings of the involvement of the cochlea and horizontal semicircular canals in the current study lead to the following hypothesis: BD might affect the labyrinthine artery or other end vessels such as the common cochlear artery or the anterior vestibular artery. Besides Choung et al. related the audiological impairments with the cochlear artery and vestibular dysfunction with the anterior vestibular artery involvements [7]. Another hypothesis due to the audio-vestibular effect on BD was central dysfunction. Erbek et al. presented prolonged cVEMP responses and related with a central disorder on the sacculocollic reflex [4]. Bayram et al. also studied to demonstrate a correlation with VEMP results and radiological findings (MRI) in patients; but found no correlation with central lesions [13].

In this study, we faced a limitation. We were unable to find any patients that had not received medical treatment. Some of drugs used in treatment of the BD such as cyclophosphamide and azathioprine were not certainly demonstrated for safety on the audio-vestibular system [14, 15]. As a nuance, colchicine remained as a drug which is not a reputation for the hearing loss in the literature. For this reason, patients taking medicine could not be included, excluding those taking colchicine.

Conclusion

The audio-vestibular involvement in BD has been a topic of debate for years and many studies have been carried out in this area. In the present study, the involvement of the all hearing frequencies in patients was discovered. Moreover, vHIT was first utilized as an instrument to describe the vestibular dysfunction and horizontal canal involvement came to the fore. Patients with BD also experienced dizziness; however, this symptom was perhaps ignored considering the other problems. The complete examination of the audio-vestibular system could be researched more thoroughly for the management of BD. Larger homogeneous patient groups are needed to clarify the exact effects of BD on the audio-vestibular system.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Financial disclosure No financial support was received for this study.

Ethical statement This study was carried out in accordance with the Helsinki Declaration and informed consent was obtained from all the participants involved in the study.

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