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ORIGINAL ARTICLE

Evaluation of Eustachian tube function in Behçet's disease: A case-control study

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ABSTRACT

Objectives: The purpose of this study was to evaluate Eustachian tube function in patients with Behçet's disease (BD).

Patients and methods: Forty-six patients (22 males, 24 females; mean age: 42.1±11.3 years; range, 19 to 64 years) with BD and 46 (21 males, 25 females; mean age: 38.5±14.8 years; range, 19 to 63 years) age- and sex-matched audiologically healthy individuals were enrolled in this cross-sectional, case-control study between June 2023 and August 2023. Demographic and clinical characteristics of participants were recorded from electronic health records. All participants completed the Eustachian tube function test and the Eustachian tube dysfunction questionnaire 7 (ETDQ-7). Binary logistic regression analysis was employed to identify the factors that predict Eustachian tube dysfunction in patients with BD. Additionally, the association between disease duration and ETDQ-7 scores was evaluated using Spearman's rank correlation.

Results: The median ETDQ-7 scores were significantly higher in patients with BD than in controls (10 (7-32) *vs.* 7 (7-9); p<0.001). The number of ears with Eustachian tube dysfunction was also significantly higher in the BD group than in the controls (n=22, 47.8% *vs.* n=7, 15.2%; p=0.007). Regression analysis did not reveal statistically significant factors that predicted Eustachian tube dysfunction. Moreover, no statistically significant correlation was observed between Eustachian tube dysfunction and disease duration (R=–0.067; p=0.525).

Conclusion: This study showed that Eustachian tube dysfunction is more prevalent in patients with BD than in the healthy controls. However, clinical and demographic variables were not found to be associated with Eustachian tube dysfunction.

Keywords: Behçet's disease, ETDQ-7 questionnaire, Eustachian tube function test, Eustachian tube.

Behçet's disease (BD) is a multisystemic vasculitis first described in 1937 by Dr. Hulusi Behçet and is characterized by recurrent oral and genital mucosal ulcers and uveitis.[1] The etiology is unknown, although it is a genetically based autoimmune inflammatory disease.[2] It affects both sexes equally.[2,3] Regarding the International Study Group (ISG) criteria, classification of BD relies on recurrent oral ulcers, together with at least two of pathergy test positivity, ocular lesions, genital ulcers, and cutaneous lesions.[4] BD also affects the pulmonary, gastrointestinal, central nervous, and cardiovascular systems.[1-3]

The Eustachian tube is an important pneumatic component of the head and neck region.[5] Its essential functions are the ventilation of the middle ear and the provision of pressure balance, protecting the middle ear from pathogens and sounds, and providing mucus clearance.[6] Eustachian tube dysfunction can be observed in 1% of adults and 40% of children.[7] Smoking and inflammatory states, such as chronic rhinosinusitis, allergic rhinitis, and laryngopharyngeal reflux are thought to contribute to the development of obstructive-type tube dysfunction.[8] Vasculitides are similarly known to be capable of causing inflammation in the Eustachian tube mucosa.[9] In BD, a panvasculitis, otorhinolaryngological manifestations include symptoms and signs in the mouth, nose, sinus, larynx, and ear.[10]

Therefore, it is recommended that the ear, nose, and throat be periodically examined in patients with BD.[11]

Behçet's disease has been reported to cause audiologic involvement, including sensorineural hearing loss and vestibular dysfunction,[12-14] as well as impaired sense of smell and recurrent rhinosinusitis due to nasal involvement.[15-18] These pathologies may also lead to a possible dysfunction of the Eustachian tube.

To the best of our knowledge, the effect of BD on Eustachian tube functions has not been studied in the literature. Based on a review of the literature, this study hypothesized that microvasculitic involvement of the Eustachian tube, a structure with mucosal tissue, may occur in BD. Therefore, the purpose of this study was to evaluate Eustachian tube function in adult patients diagnosed with BD using the Eustachian tube function test and Eustachian tube dysfunction questionnaire 7 (ETDQ-7).

PATIENTS AND METHODS

Forty-six patients with BD who were followed up in the rheumatology clinic of the Kastamonu Training and Research Hospital met the ISG criteria[4] and 46 age- and sex-matched audiologically healthy individuals (a total of 184 ears) were included in this cross-sectional, case-control study between June 2023 and August 2023. The ISG criteria for BD comprise five categories: oral aphthae, genital ulcers, ocular involvement, skin involvement, and a positive pathergy test.[4] BD is diagnosed when an individual presents with at least two of these clinical findings in addition to oral aphthae.[4] Participants were excluded from the study if they had outer or middle ear disease, a history of otologic surgery, were using ototoxic medications, or were younger than 18 or older than 65 years of age. Furthermore, participants with other pathology-causing Eustachian tube dysfunction (e.g., deviated septum, nasal polyps, sinusitis, and nasopharyngeal lesions) were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Kastamonu University Clinical Research Ethics Committee (date: 17.05.2023, no: 2023-KAEK-57). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The demographic and clinical characteristics of patients with BD were recorded from electronic health records. The demographic data of patients with BD include information on patient age, sex, disease duration, smoking, and comorbidities, such as diabetes mellitus. In addition, clinical manifestations of BD were recorded, including oral aphthae, genital ulcers, papulopustular lesions, erythema nodosum, pathergy test positivity, ocular involvement, musculoskeletal involvement, intestinal involvement, neurological involvement, and vascular involvement.

After the ear, nose, and throat examinations, Eustachian tube function tests and the ETDQ-7 were performed for the evaluation of Eustachian tube functions. The Eustachian tube function test involved taking a tympanogram graph at 0 daPa pressure (P1), followed by two more tympanogram graphs during the Valsalva maneuver (P2) and the Toynbee maneuver (P3). The test recorded the peak pressure of the three tympanograms, as well as the P1-P2 and P1-P3 pressure differences, and the maximum pressure change (Pmax). Eustachian tube dysfunction is defined as a P1-P2 pressure difference exceeding 10 daPa or a Pmax exceeding 15 daPa.[19] The measurements were conducted using a 226 Hz acoustic immittance meter (AT 235 H; Interacoustics, Middelfart, Denmark).

The ETDQ-7 is a 7-point Likert scale used to assess the presence and severity of Eustachian tube dysfunction in adults over 18 years of age. Patients were asked to report if they had experienced pressure, pain, a feeling of congestion in their ears, muffled hearing, sinusitis, increased ear symptoms during colds, or crackling and ringing in the ears in the previous month. A score of 1 indicated no problem, while a score of 7 indicated a severe problem. The possible scores ranged from 7 to 49, with higher scores indicating greater severity.[20]

Statistical analysis

The sample size of each group was calculated as 46 in line with the Cohen test (effect size=0.3)

by G*power version 3.1.9.4 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), with a power of 80% and a two-sided significance level of 0.05.[21]

Statistical analyses were performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) and RStudio version 2022.02.1+461 software. Descriptive statistics

Table 1. Demographic data, clinical characteristics, and ETDQ-7 scores in the BD and control groups

	Controls (n=46)					Behçet's disease (n=46)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			38.5±14.8					42.1±11.3			0.190a
Sex Male Female	 21 25	 45.7 54.3				 22 24	 47.8 52.2				1.000b
Disease duration (year)				-	-				9.5	1-43	-
ETDQ-7 score				7	7-9				10	7-32	<0.001c
Oral aphthous	-	-				46	100				-
Genital ulcer	-	-				37	80.4				-
Erythema nodosum	-	-				26	56.5				-
Uveitis	-	-				18	39.1				-
Pathergy positivity	-	-				31	67.4				-
Vascular involvement	-	-				7	15.2				-
Arthralgia/arthritis	-	-				34	73.9				-
Neuroparenchyma involvement	-	-				2	4.3				-

ETDQ-7: Eustachian tube dysfunction questionnaire 7; BD: Behçet's disease; SD: Standard deviation; a: Independent samples t-test; b: Pearson's chi-square test; c: Mann-Whitney U test.

Table 2. Results of the Eustachian tube function test in the BD and control groups

	Controls (n=46)				Behçet's disease (n=46)				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
P1									
Right			–23	–72-64			–10	–118-159	0.066
Left			–22	–97-43			–16	–130-196	0.203
P2									
Right			–22	–148-120			–5	–116-185	0.128
Left			–27	–240-155			–13.5	–211-218	0.480
P3									
Right			–42	–147-127			–13	–132-78	**0.031**
Left			–43	–301-64			–18	–192-169	**0.020**
Eustachian dysfunction									
Right	4	8.7			9	19.6			
Left	3	6.5			13	28.3			**0.007**
Total	7	15.2			22	47.8			

BD: Behçet's disease; Values in bold are significant at p<0.05.

for the numerical variables were presented as mean ± standard deviation (SD) for normally distributed variables and as median values (min–max). Categorical variables were presented as frequency (percentage) values. The normality assumption was assessed using the Kolmogorov-Smirnov test and graphical methods. Comparisons between the controls and patients with BD were performed using Pearson's chi-square test for categorical variables and the independent sample t-test or the Mann-Whitney U test for numerical variables. The correlation between disease duration and ETDQ-7 scores was evaluated using Spearman's rank correlation coefficient. To account for intrapatient dependency (each patient as a cluster and ear unit), Eustachian tube dysfunction was compared between the controls and patients with BD using the adjusted chi-square approach. The relationship between Eustachian tube dysfunction and different covariates in patients with BD was assessed using binary logistic regression analysis. The package's "aod" (function "donner") and "ggplot2" were used.[22]

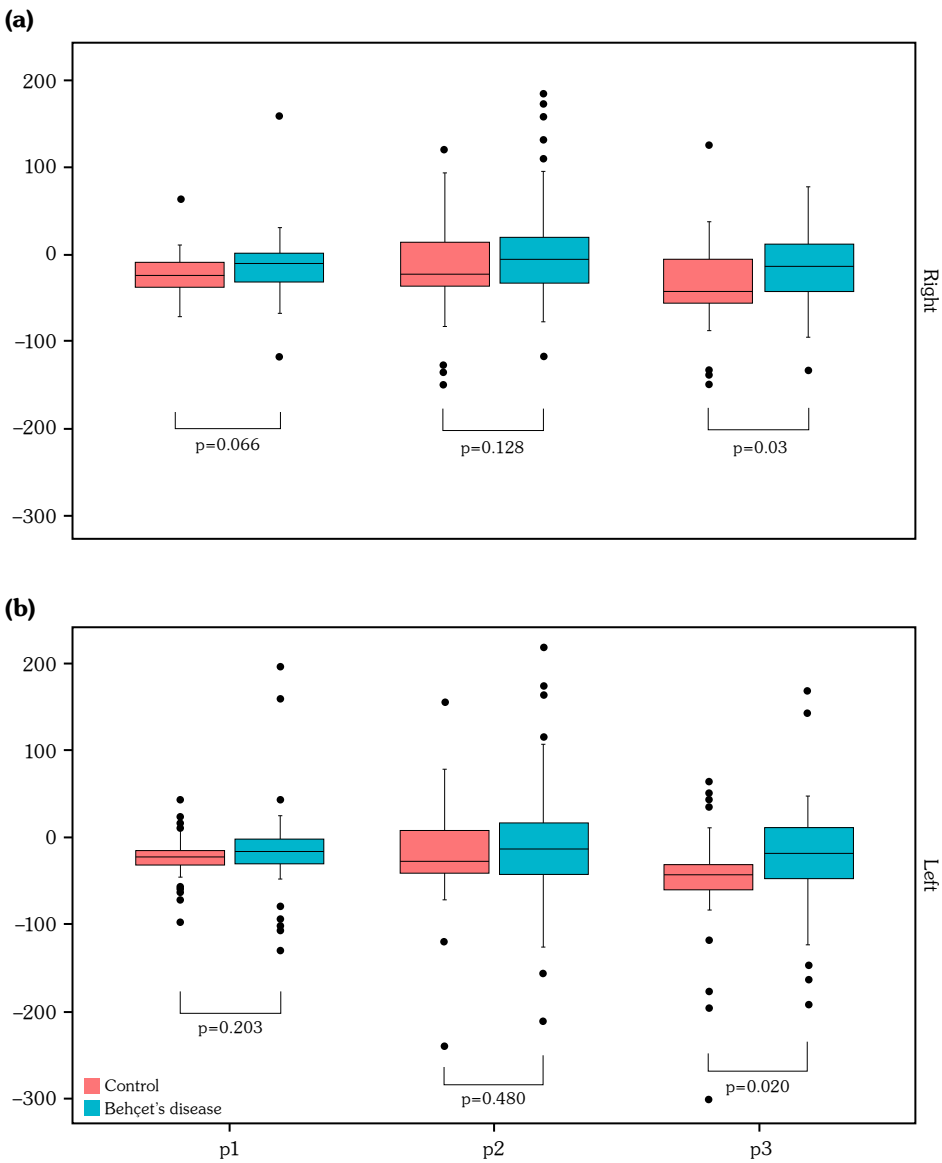

Figure 1. **(a)** Comparisons of P1, P2, and P3 values for the left and right ears between the controls and Behçet's disease patients. **(b)** The upper box reflects the comparison of the right ear result; the lower box demonstrates the left ear results.

Table 3. Results of binary logistic regression analysis between Eustachian tube dysfunction as the dependent variable and different covariates in BD patient

						95% CI for OR	
Variables	B	SE	Wald	*p*	OR	Lower	Upper
Age	–0.088	0.104	0.713	0.398	0.916	0.747	1.123
Sex Male	0.863	1.206	0.513	0.474	2.371	0.223	25.180
Disease duration	0.169	0.104	2.633	0.105	1.184	0.966	1.452
Smoking	1.225	1.595	0.590	0.442	3.405	0.149	77.592
Diabetes mellitus	–2.121	2.852	0.553	0.457	0.120	0.000	32.124
Colchicine dose	–0.426	0.531	0.643	0.423	0.653	0.230	1.850
Glucocorticoids dose	0.327	0.314	1.083	0.298	1.387	0.749	2.568
Azathioprine dose	–0.531	0.567	0.876	0.349	0.588	0.194	1.787
Genital ulcer	–0.265	1.605	0.027	0.869	0.767	0.033	17.825
Erythema nodosum	–0.165	1.379	0.014	0.905	0.848	0.057	12.657
Uveitis	0.251	1.655	0.023	0.879	1.286	0.050	32.941
Pathergy positivity	–0.875	1.345	0.423	0.516	0.417	0.030	5.821
Vascular involvement	–2.996	2.132	1.974	0.160	0.050	0.001	3.265
ETDQ-7 score	–0.102	0.108	0.884	0.347	0.903	0.730	1.117
Constant	2.136	4.289	0.248	0.618	8.469		

BD: Behçet's disease; CI: Confidence interval; OR: Odds ratio; SE: Standard error; ETDQ-7: Eustachian tube dysfunction questionnaire 7. Generalized estimating equation parameter estimates for the dependent variable: Eustachian tube dysfunction. Significant level at p<0.05. *Model summary:* –2loglikelihood= 29.788; model χ^2=15.69, p=0.333; Hosmer and Lemeshow test χ^2=24.39 (df=7, p=0.001).

A p-value <0.05 was considered statistically significant.

RESULTS

There 21 male and 25 female participants among controls, and there were 22 male and 24 female participants among patients with BD. The mean ages were 38.5±14.8 years (range, 19 to 63 years) for the controls and 42.1±11.3 years (range, 19 to 64 years) for the patients with BD. There was no statistically significant difference between the groups in terms of age and sex (p=0.190 and p=1.000, respectively; Table 1). The median ETDQ-7 score of patients with BD was significantly higher than that of controls (10 (7-32) *vs.* 7 (7-9), p<0.001). The other clinical characteristics of patients with BD are shown in Table 1.

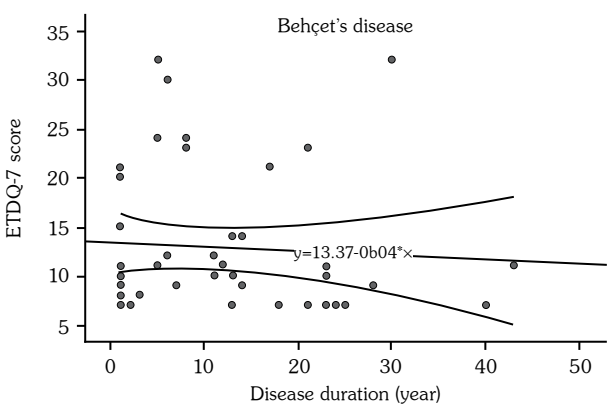

Figure 2. Correlation between disease duration and ETDQ-7 score in Behçet's disease patients.
ETDQ-7: Eustachian tube dysfunction questionnaire 7.

According to the results of the Eustachian tube function test, P3 values of patients with BD were statistically higher than controls on both sides (p=0.031 and p=0.020 for right and left sides, respectively). However, there was no statistically significant difference between P1 and P2 values between the groups (Table 2, Figure 1). In addition, we found that patients with BD (n=22, 47.8%) had a significantly higher number of ears with

Eustachian tube dysfunction compared to the control group (n=7, 15.2%; p=0.007).

Binary regression analysis was conducted to assess the factors influencing Eustachian tube dysfunction in the BD group. The analysis revealed no statistically significant relationships between Eustachian tube dysfunction and any of the covariates (Table 3). Furthermore, in the Spearman correlation analysis, we found no statistically significant correlation between disease duration in patients with BD and their ETDQ-7 scores (rho=−0.067, p=0.525; Figure 2).

DISCUSSION

The study demonstrated a higher prevalence of Eustachian tube dysfunction in patients with BD than in healthy controls. Furthermore, there was no association between Eustachian tube dysfunction and the clinical manifestations or demographic characteristics of the patients.

Behçet's disease is a multisystemic vasculitis that affects several different systems.[1] Oral and oropharyngeal ulcers were most frequently observed in a previous study investigating ear, nose, and throat symptoms in patients with BD, followed by audiovestibular symptoms, such as high-frequency sensorineural hearing loss, bilateral vestibular hypofunction, and vertigo.[12-14] BD also affects the nasal mucosa. A previous study investigating the effects of BD on smell function, nasal mucosa, and nasal symptoms reported an association between smell perception function disorder and BD.[18] In addition, worsening of smell perception function disorder and correlation between disease duration and dysfunction severity are known to occur in neuro-BD, particularly in the presence of parenchymal involvement.[15] A study investigating the frequency of chronic rhinosinusitis in patients with BD reported a greater frequency in such patients than in healthy controls.[17] The fact that inflammatory conditions, such as chronic rhinosinusitis, also contribute to the development of obstructive-type Eustachian disorder has led to the need to investigate Eustachian tube functions in patients with BD.[8] In our study, both Eustachian tube function test results and ETDQ-7 scores were significantly higher in patients with BD than in controls.

Another study of nasal involvement reported ulcers in the nasal mucosa, nasal obstruction, epistaxis, pain, a burning sensation, itching, and dysosmia in patients with BD, although the difference was not statistically significant.[16] Due to most BD clinical symptoms resolve spontaneously, the prevalence of nasal involvement was thought to be underestimated.[16] In another study, nasal mucociliary clearance times were longer in patients with BD than in control subjects and were positively correlated with the duration of the disease.[23] The authors also emphasized that these patients should be closely monitored for prolonged respiratory diseases and sinonasal and middle ear infections.[23] These data suggest the need for an examination of Eustachian tube functions in patients with BD. Within this context, the frequency of Eustachian tube dysfunction was higher in our patients with BD. None of the factors that could influence Eustachian tube function, including duration of disease, smoking, diabetes mellitus, medications, and BD's clinical features, were significant in the regression analysis. However, the presence of oral aphthae in all patients and neuroparenchyma involvement in only two patients prevented the evaluation of their effect on Eustachian tube dysfunction.

Behçet's disease is a genetically based autoimmune vasculitis.[1] Several systemic autoimmune diseases result in ear, nose, and throat symptoms that create diagnostic difficulties for clinicians and can be overlooked.[24] Otological symptoms are frequently observed in vasculitis and can even be the initial presentation symptom.[25] Recent studies have focused on hearing loss and vestibular symptoms in systemic vasculitides.[25] Hearing losses are generally sensorineural, although conductive and mixed-type losses can also be observed.[9] Autoimmune diseases are thought to cause conductive hearing loss due to effusion in the middle ear, inflammation in the Eustachian tube mucosa, and ossicular chain involvement.[9] Although several studies have investigated sinonasal and audiological involvement in BD,[9,24,25] its impact on the Eustachian tube and middle ear functions has not been previously established. To the best of our knowledge, this study is the first to

examine Eustachian tube functions in patients with BD.

This study has some limitations. The objective detection of clinical nasal involvement in BD was not possible, which prevented the evaluation of its effect on Eustachian tube function. Additionally, the small number of patients with neuroparenchyma involvement limited the ability to perform subgroup comparisons and variable analyses. However, this study is noteworthy for being the first to compare Eustachian tube dysfunction in patients with BD and for testing factors (clinical involvement, medications, and comorbidities) that may have an impact on Eustachian tube dysfunction.

In conclusion, this study indicates that Eustachian tube dysfunction is more prevalent in patients with BD than in healthy controls. However, no association was found between Eustachian tube dysfunction and clinical or demographic variables. More detailed studies are required to clarify the mechanism involved in Eustachian tube dysfunction in BD.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization, formal analysis, methodology, writing-review and editing: M.Y., F.A., A.K., Z.Y.; Investigation: M.Y., F.A., A.K.; Supervision: F.A., A.K., Z.Y.; Writing-original draft: M.Y., F.A.

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