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ORIGINAL ARTICLE

The subclinic autonomic dysfunction in patients with Behçet disease: an electrophysiological study

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Abstract Studies that have evaluated autonomic nervous system (ANS) function in Behçet disease (BD) are rare and have indicated conflicting results with different degrees of involvement. The aim of this study was to investigate ANS function by using electrophysiological tests in patients with BD and to determine the relationship between the disease activity parameters and the indicators of autonomic activity. We included 70 BD patients and 50 healthy controls. Demographic characteristics including age, sex, and disease duration were recorded. A detailed neurological examination was performed, and clinical autonomic symptoms were recorded. The Behçet Disease Current Activity Form (BDCAF) was used to determine the disease activity. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were determined for laboratory activity. The electrophysiological assessments of ANS function were performed by sympathetic skin response (SSR) and R-R interval variation (RRIV) tests. The mean values of sympathetic (SSR latency and amplitude) and parasympathetic (RRIV at rest [R%] and deep breathing [D%], D% − R%, and D%/R%) parameters were compared, and any correlations between ANS parameters and clinical disease characteristics were determined. Seventy BD patients (23 males, 47 females) with a mean age of 41.2±10.01 years and 50 control subjects (18 males, 32 females) with a mean age of 39.5±8.94 years were included in the study. All the subjects were totally symptom free with respect to ANS involvement, and the subjects in both groups had normal neurological examination findings. The demographic characteristics were similar between the groups. The mean latency of SSR was increased (1.4±0.4 vs 0.7±0.8), and R% (0.3±0.3 vs 0.5±0.4) and D% (0.3±0.3 vs 0.6±0.5) values were decreased in BD patients compared to control subjects. No correlation was found between BDCAF scores and ANS variables. However, there was a significant correlation between SSR latency and ESR and CRP values ($p<0.01$, $r=-0.25$, $r=-0.31$, respectively) in the patient group, indicating a more sympathetic dysautonomia in patients with active laboratory parameters. In conclusion, our study indicates a subclinical sympathetic and parasympathetic autonomic dysfunction in patients with BD, which may be related with disease activity. As the early recognition of abnormalities in ANS may be very important in order to prevent excessive morbidity, simple electrophysiological methods are suggested to identify Behçet patients at high risk for symptomatic dysautonomia.

Keywords Autonomic nervous system · Behçet disease · Disease activity

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Introduction

Behçet disease (BD) is an inflammatory multisystemic disease of unknown etiology, characterized by aphthous stomatitis, genital ulcers, uveitis, and skin lesions [1]. It is well-known that many other systems might be involved in

the disease and that vasculitis is the main physiopathologic process responsible for the lesions. Arthritis, thrombosis, arterial aneurysms, gastrointestinal manifestations, and central nervous system involvement are less commonly found in this chronic condition [2, 3]. Neurological findings, both central and subclinical peripheral nerve involvement, may occur in up to 30% of the patients, and these findings usually manifest late in the disease course [3, 4]. In addition to some neurologic manifestations, autonomic nervous system (ANS) dysfunction has also been reported in patients with BD [5–12]. However, studies that have evaluated ANS function in BD are not common, and most of them analyzed ANS dysfunction using various methods and indicated conflicting results with different degrees of involvement [5–11, 13]. The aim of this study was to investigate ANS function using electrophysiological tests in patients with BD and to determine any relationships between the disease activity parameters and the indicators of autonomic activity.

Materials and methods

We included 70 of 85 eligible BD outpatients from the Rheumatology Unit of the Physical Medicine and Rehabilitation and Dermatology clinics, Ankara Training and Research Hospital, who were seen between January 2010 and December 2010. All patients fulfilled the International Study Group criteria for the diagnosis of BD [14]. The control subjects included 50 healthy subjects (18 males, 32 females) recruited from hospital staff and age-matched (within ±2 years). Exclusion criteria for patients and controls were systemic diseases that may affect the nervous system or cardiovascular function, such as diabetes mellitus, hypo-hyperthyroidism, uremia, cardiac failure, and cardiac arrhythmia, or the use of any medications that would influence the ANS (i.e., antidiabetic drugs, beta adrenergic blockers, channel blocker agents, peripheral and central antihypertensive drugs, diuretics, nitrofurantoin, and tricyclic antidepressants). A detailed neurological examination was performed, and clinical autonomic symptoms including feeling faint on orthostatic change of posture, distal vasomotor dysfunction, sweating abnormalities, and gastrointestinal, genital, or urinary disorders were recorded in all participants. Subjects with neurological findings and/or autonomic symptoms were not included in the study. The study was approved by the local ethical committee, and all the participants gave informed consent prior to testing.

Demographic characteristics including age, sex, education, body mass index, drug intake, disease duration, smoking habit, and exercise status were recorded. The blood samples of the BD patients were taken to determine erythrocyte sedimentation rate (ESR) using the Westergren method and C-reactive protein (CRP) by turbidimetric method. Visual analog scale was used to assess pain in the joints, with scores ranging between 0 and 10. We used the validated Turkish version of Behçet Disease Current Activity Form (BDCAF-2006) [15, 16] to determine the disease activity. This activity form scores (from 0 to 4) the duration of clinical features (headache, oral ulcers, genital ulcers, skin lesions, arthralgia, arthritis, skin lesions, gastrointestinal symptoms), which were present during the 4 weeks prior to the day of assessment. The eye activity was assessed for the presence or the absence of blurring of vision, pain, or redness in either eye over the last 4 weeks and scored if the symptoms were new. Nervous system and major vessel involvement was defined if the patients had related symptoms over the last 4 weeks and if there was any evidence of new active nervous system involvement and major vessel inflammation. The BDCAF score was calculated by adding the score of each index and ranged between 0 and 12. The patients and physicians also rated their assessments of the overall disease activity within the preceding 4 weeks by indicating it on a scale consisting of seven faces with different expressions on the BDCAF [16]. An informative handout advising subjects to stop caffeine and alcohol intake and to have a restful sleep 1 day before the electrophysiological study was given to all participants.

Electrophysiological assessments

The electrophysiological assessments of ANS function were performed by sympathetic skin response (SSR) and R-R interval variation (RRIV) at rest and during deep breathing, and recorded according to the methods described by Shahani et al. [17–19]. All subjects were studied in the supine position using Nihon Kohden Neuropack M1 QP-954 BK (Tokyo, Japan) by the same physician (FT) who was blinded to the subjects' identity and clinical data. All electrophysiological sessions were completed in the morning at least 2 h after a light breakfast in a quiet semi-darkened room with an ambient temperature between 23°C and 26°C and an extremity skin temperature over 31°C.

The levels of RRIV at rest and deep breathing were used for parasympathetic function assessment and were recorded using the disk electrodes placed on the chest wall across the cardiac position with a ground electrode on the right axial line at the lowest rib. The band pass was 20–1,000 Hz, sensitivity 0.5 MV, and sweep duration 0.2–1 s. Using the triggering mode and adjusting the sweep speed, two QRS complexes (mainly R waves) of electrocardiography were simultaneously displayed on the screen. Because the first displayed complex represented the triggering potential, the variation in the timing of the second complex represented the variation in the R-R interval. Twenty traces were

recorded and superimposed, and a printout was made for subsequent measurement. The range in the 20 pairs of R-R intervals is termed as "a" and the mean of the 20 pairs of R-R intervals is termed as "b." RRIV was expressed as the percentage of the average R-R interval using the formula $\mathrm{RRIV} = a/b \times 100$. Five groups of 20 sweeps were recorded at rest and two during forced deep breathing at six breaths per minute. The average of five recordings at rest was termed as R% and that of two recordings during deep breathing as D%. The difference between D% and R% (D% − R%) and the ratio of D% to R% (D%/R%) were also calculated. The recordings and calculations were performed using computer software [17, 19].

SSR was used to measure the sympathetic function. SSR recordings were performed using disk electrodes of the same device. The active electrode was attached to the palm and the reference electrode to the dorsum of the right hand. The electrical stimuli as single square wave pulses of 0.1 s duration and 10–20-mA intensity were applied to the dominant median nerve at the wrist portion. Latency and amplitude of the response were analyzed. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection of the signal baseline, and the amplitude was measured peak to peak. The normative values of SSR and RRIV were determined in the 50 healthy volunteers who constituted the control group [18, 19].

Statistical analysis

The demographic properties of patients and control subjects, as well as the characteristics of disease activity, were summarized by descriptive statistics. The results were expressed as mean±SD (range). The differences between the groups were assessed by Mann–Whitney *U* test. The mean values of sympathetic (SSR latency and amplitude) and parasympathetic (D%, R%, D% − R%, and D%/R%) parameters were compared using Mann–Whitney *U* test. The Spearman correlation matrix was used to evaluate the correlation between ANS parameters and clinical disease characteristics. The statistical significance was determined at $p \leq 0.05$. All statistical analysis was performed using SPSS version 11.0.

Results

Seventy BD patients (23 males, 47 females) with a mean age of 41.2±10.01 years and 50 control subjects (18 males, 32 females) with a mean age of 39.5±8.94 years were included in the study. All the subjects were totally symptom free with respect to ANS involvement, and the subjects in both groups had normal neurological examination findings. The demographic characteristics were similar between the groups. The demographic and clinical characteristics of the groups are summarized in Table 1. No patient had central nervous system involvement; 12 patients (17.1%) had vascular, two (2.9%) had gastrointestinal, and 39 (55.7%) had ocular involvement. Arthralgia and/or arthritis was present in 46 (65.7%) patients, and dermatological lesions were recorded in 51 (72.9%) patients. In the BD group, 68 patients (81.4%) were taking colchicum-dispert and/or nonsteroidal anti-inflammatory drugs. Ten patients (14.3%) were on azathioprine treatment, and two patients (2.9%) were receiving sulfasalazine.

The electrophysiological ANS test results including sympathetic and parasympathetic variables are shown in Table 2. The mean latency of SSR, RRIV during rest (R%) and deep breathing (D%), and D% − R% values were

Table 1 The demographic, clinical, laboratory, and disease activity characteristics of Behçet patients and demographic variables of control group (mean±SD)

	Behçet's disease $n=70$	Control $n=50$	p
Male/female (*n*)	23/47	18/32	0.412
Age (years, (mean±SD)	41.21±10.01	39.5±8.94	0.60
BMI (kg/m^2, mean±SD)	27.53±5.52	26.45±3.91	0.30
Duration of education (years, mean±SD)	4.2±3.6	4.6±3.7	0.382
Smoking (*n*, %)	23 (32.9)	20(40)	0.42
Regularly exercise (*n*, %)	15(21.4)	10 (20)	0.85
Disease duration (years, mean±SD)	8.37±6.60		
VAS (cm, mean±SD)	50.20±20.94		
ESR (mm/h, mean±SD)	16.20±14.74		
CRP (mg/dl, mean±SD)	0.68±0.61		
Patient's impression of disease activity (0–6)	2.92±1.65		
Doctor's impression of disease activity (0–6)	2.52±1.42		
BDCAF score	4.7±2.2		

BMI body mass index, *VAS* visual analog scale, *BDCAF* Behçet disease current activity form, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

Table 2 The electrophysiological ANS test results (SSR latency, amplitude, and mean values of RRIV) of the patients and control subjects

	Behçet's disease group $n=70$	Control group $n=50$	p
SSR latency (ms)	1.4±0.4	0.7±0.8	0.001
SSR amplitude (mV)	2.1±1.6	2.0±1.3	0.97
R%	0.3±0.3	0.5±0.4	0.05
D%	0.3±0.3	0.6±0.5	0.006
D% − R%	0.0±0.4	0.2±0.5	0.05
D%/R%	2.8±4.2	2.1±2.2	0.42

SSR sympathetic skin response, *RRIV* R-R interval variation, *D* RRIV at deep breathing, *R* RRIV at rest

significantly different between BD patients and control subjects. Although the mean D%/R% level was higher in BD patients, the difference was not statistically significant between the patient and the control groups. The mean latency of SSR was higher and the mean R-R values at rest and deep breathing were lower in BD patients than in control subjects, indicating both sympathetic and parasympathetic dysautonomia in BD patients. When we analyzed the results according to gender, we observed that D% and D%/R% values were significantly higher in female BD patients than in male patients, indicating a more prominent parasympathetic dysfunction in female patients with BD. No other ANS variable was found to be different between male and female patients (Table 3). In the control group, the mean level of SSR amplitude was found to be higher in female subjects (2.9± 1.3 mV vs 1.5±1.1 mV, $p<0.001$).

We could not find any correlation between BDCAF scores and electrophysiologically determined ANS variables. Demographic variables were not found to be correlated with BDCAF scores or ANS variables. However, there was a significant correlation between median SSR latency and ESR and CRP values in the BD group, indicating a sympathetic dysautonomia in patients with active laboratory parameters. Patient and physician assessments of disease were also not correlated with any of the measured ANS parameters (Table 4). The mean BDCAF score of the patients was correlated with the patient and physician assessment scores ($p<0.001$, $r=0.39$, $r=0.41$, respectively), while no correlation was observed between laboratory activity parameters (ESR and CRP) and BDCAF scores ($p>0.05$).

Discussion

Autonomic dysfunction has previously been reported in several rheumatologic conditions [19–22]. Unlike other types of vasculitis, neurologic involvement in BD is rare and can manifest as both central and peripheral nervous system involvement [2–4]. The most common neurological findings in neuro-Behçet are pyramidal signs and hemiparesis; however, peripheral and ANS involvement are also mentioned in the literature with different degrees of involvement [4–12]. Several studies in the literature have evaluated ANS functions in patients with BD and reported conflicting results [5–13]. Gulturk et al. [10] assessed ANS function by measurement of the sympathetic skin potentials against consecutive nerve stimulation and reported a delayed habituation in 12 patients with BD. Ozdemir et al. [9] reported impaired time-domain heart rate variability (HRV) parameters indicating ANS dysfunction in 45 patients with BD. Akyol et al. [8] assessed the electrodermal activities in 16 patients and indicated low sympathetic activity in BD that may reflect an ANS dysfunction. Aksoyek et al. [6] evaluated ANS function in BD using power spectral analysis of HRV and reported asymptomatic ANS dysfunction. However, Karataş et al. [7] and Kırımlı et al. [11] could not indicate a significant difference in ANS parameters between their Behçet patients and control subjects. Tellioğlu and Robertson [12] were also unable to demonstrate a clear autonomic abnormality in their Behçet patient. The literature review of previous studies evaluating ANS function in BD is shown in Table 5.

Table 3 The BDCAF scores and ANS variables of female and male Behçet patients

	Female Behçet patients $n=47$	Male Behçet patients $n=23$	p
BDCAF score	5.0±2.0	4.3±2.4	0.51
SSR latency (ms)	1.3±0.3	1.4±0.5	0.29
SSR amplitude (mV)	2.3±1.6	1.6±1.3	0.12
D%	0.2±0.2	0.4±0.4	0.08
R%	0.3±0.2	0.4±0.3	0.47
D% − R%	0.1±0.3	0.5±0.4	0.20
D%/R%	3.5±2.2	1.2±1.1	0.01

BDCAF Behçet disease current activity form, *SSR* Sympathetic skin response, *D* RRIV at deep breathing, *R* RRIV at rest

Table 4 The correlation coefficients between clinical and disease activity parameters and ANS variables in patients with Behçet disease

	SSR median latency		SSR median amplitude		R%		D%		D%/R%	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
BDCAF score	−0.07	0.51	0.11	0.36	0.20	0.09	0.08	0.50	−0.20	0.09
Patient's impression of disease	0.08	0.50	0.03	0.77	0.13	0.29	0.07	0.54	−0.09	0.43
Doctor's impression of disease	−0.01	0.89	0.004	0.93	0.15	0.20	0.08	0.49	−0.07	0.53
ESR	−0.25	0.033*	0.05	0.67	0.04	0.73	0.09	0.46	−0.05	0.66
CRP	−0.31	0.008*	−0.04	0.69	−0.15	0.21	−0.01	0.91	−0.11	0.37

BDCAF Behçet disease current activity form, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *SSR* Sympathetic skin response, *D* RRIV at deep breathing, *R* RRIV at rest, * $p<0.05$

To the best of our knowledge, our study is the first to assess ANS function electrophysiologically with a large number of BD patients and control subjects. Furthermore, our study is the first to assess the disease activity and report the relationship of clinical and laboratory activity parameters and ANS dysfunction in patients with BD. According to our data, we have determined a decreased sympathetic and parasympathetic dysfunction in Behçet patients compared to healthy controls. Though many new laboratory markers have been defined for BD, including interleukin-8, oxidation protein products or angiopoietin-1, ESR and CRP are still reliable activity markers for BD. Clinical disease activity was shown to be associated with increases in ESR and CRP values in several studies, and these markers correlate well with disease activity in BD [23, 24]. Although no relationship was observed between BDCAF levels and ANS parameters, we determined a significant relation between laboratory activity parameters and sympathetic functions, which may indicate a more prominent dysfunction in sympathetic pathways in BD patients with active disease. The reason for the absence of a relationship between BDCAF scores and ANS variables, as well as the discordance between laboratory activity parameters and BDCAF levels, may be explained by the BDCAF scoring system and the heterogeneous nature of organ involvement. BDCAF scores reflect primarily the new and current involvement of different organ systems in BD patients, and may not express a comprehensive measure of disease activity [15]. As none of our patients had clinical symptoms of autonomic disturbance, our results indicate a subclinical

Table 5 The literature review of ANS assessment studies in Behçet disease

Study	Patients (*n*)	Controls (*n*)	Method	Findings
Bayramlar et al. [5]	21	41	Pupillometric technique	Pupil cycle time, pilocarpine drop test, phenylephrine drop test results, and dark adaptated pupil size are different in BD patients
Aksoyek et al. [6]	71	26	Power spectral analysis of heart rate variability (HRV)	Increased subclinic sympathetic, decreased parasympathetic modulation in BD patients
Kırımlı et al. [11]	28	25	HRV, by Holter electrocardiography (ECG)	No difference in reliable HRV values between BD patients and control subjects
Karatas et al. [7]	25	25	Electrophysiologically determined SSR, R%, D%, D% − R%, and RRIV	No difference between SSR, R%, D%, D% − R%, and RRIV values of BD patients and control subjects
Akyol et al. [8]	16	16	Skin potential recordings (SPR)	Reduced skin potentials and skin potential responses in BD patients
Ozdemir et al. [9]	45	35	Ambulatory and rest blood pressure at day and night HRV by ECG	Absence of normal decrease in systolic diastolic BP and impaired HRV parameters in BD patients
Gulturk et al. [10]	12	12	Sympathetic skin potential records and habituation rate by electrodermal activity	Delayed habituation rate in BD patients
Kaya et al. [13]	30	50	Heart rate recovery index by ECG and stress test	Impaired heart rate recovery index and reduced parasympathetic activity in BD patients
Current study	70	50	Electrophysiologically determined SSR, D%, R%, D% − R%, and D%/R% values	Increased SSR latency and decreased D%, R%, and D% − R% levels in BD patients

ANS dysfunction that may be related with disease activity in patients with BD. The abnormality in autonomic cardiovascular reflexes may also be due to physical deconditioning [25], but our study group was all ambulant and the mean number of subjects performing regular exercise was similar between the BD and control groups.

ANS function can be detected by various clinical and electrophysiological methods, including visual evoked potential, motor evoked potential, brainstem auditory evoked potential, electrodermal activities, heart rate variability, or pupillometric studies [5–13]. However, most of these tests are complex, often require specialized equipment, and may not be suitable in routine practice. SSR and RRIV at rest and deep breathing are reliable and reproducible simple, inexpensive, and noninvasive electrophysiological tests that can be easily performed in the electromyography laboratory [7, 19].

The SSR is a polysynaptic reflex and reflects the integrity of the small unmyelinated autonomic fibers, as the function of these fibers cannot be tested by routine nerve conduction studies of motor and sensory nerves. SSR is a transient change in the electrical potentials evoked by reflex in the palm or sole by electrical stimuli. As the amplitudes of this response might be too variable even in the same patient, they were neglected, and latencies were considered to be more important in the interpretation of the results of the SSR test [26, 27]. SSR latency represents the integration of the somatosensory myelinated afferents, central coupling process, and efferent pathways [7, 28]. BD is a vasculitis, and areas of focal inflammation can occur at different levels of the central nervous system. Pathologic conditions affecting the somatosensory pathways in peripheral or central centers may result in the abnormalities of this response and can be present in cases with subclinical involvement without neurological signs or symptoms. R-R intervals and variation at rest and deep breathing indicate the function of the vagal autoimmune system. Normal individuals at rest show variation in heart rate induced by respiration, and the normal control of RRIV with respiration depends on an intact parasympathetic reflex arc that is integrated at the medullary level [7, 8, 29]. Expansion of the lungs during inspiration stimulates the pulmonary stretch receptors in the trachea and bronchioles, and the stimuli are transmitted to the related centers, which is followed by the decrease in efferent vagal tonus and an accelerated heart rate [7]. The prolonged latencies of SSR and decrease in R-R interval at rest and with deep respiration indicate the involvement of both sympathetic and parasympathetic pathways in our BD patients.

The ANS dysfunction in autoimmune inflammatory rheumatic conditions was mainly reported to be due to secondary complications of inflammation in nerves leading to suppressive nerve signaling, but in recent years other alternative mechanisms were also suggested. It was reported that the dysfunction in ANS pathways might be a primary proximal event that enables the overproduction of cytokines in response to an otherwise innocuous stimulus. Whether the inflammatory process in the affected vessels is a consequence of autonomic dysfunction requires further studies, which will provide additional insight into the pathogenesis of BD [8, 19, 30, 31].

There is debate as to whether or not gender differences occur in sympathetic and parasympathetic reflex responses; most reports suggest that males demonstrate greater cardiovascular responses to different stressors, while orthostatic intolerance was reported to be more common in females. Females were reported to have greater parasympathetic withdrawal during head-up tilt test [19, 32, 33]. There are no data in the literature about the expected difference between the results of ANS test in males and females with BD. In our study, we found significant gender differences with regard to parasympathetic ANS parameters in BD patients and a sympathetic variable in the control group. However, we cannot compare our results with the previous data, and our study subgroups are not large enough to draw definitive deductions regarding gender differences.

In conclusion, our study indicates a subclinical sympathetic and parasympathetic autonomic dysfunction in patients with BD, which may be related with disease activity. The ANS dysfunction may be underestimated in Behçet patients, as the evaluation and the quantification of ANS regulation represent a difficult area of clinical neurophysiology. However, the early recognition of abnormalities in ANS may be very important in order to prevent excessive morbidity, and it seems crucial to follow BD patients closely for ANS dysfunction. Therefore, simple noninvasive electrophysiological methods are suggested to identify Behçet patients at high risk for symptomatic dysautonomia.

Disclosures None

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