Autonomic function assessment in Egyptian patients with Behçet's disease: a case–control study

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Background
Behçet's disease (BD) is considered a chronic multisystem disorder, where neurological manifestations are common. There is scarcity of investigations that have assessed the autonomic nervous system dysfunction in BD, with conflicting results.
Objectives
The current study aimed to identify presence of autonomic nervous system dysfunction using neurophysiological assessment in BD and to investigate the relationship between the indicators of autonomic function and the disease activity parameters.
Patients and methods
The study involved 30 patients with BD in accordance with the Universal Criteria for Behçet's Diseases and 25 controls, who were subjected to clinical evaluation and Palmar sympathetic skin response (SSR).
Results
Patients with BD had a significant difference in SSR ($P<0.001$) compared with controls. Moreover, a significant positive association was found among neuropathic pain and disease activity parameters.
Conclusion
The study confirms the presence of sympathetic autonomic dysfunction in BD, which related to disease activity using a simple noninvasive test such as SSR.

Keywords:
autonomic, Behçet's, electrophysiology

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Introduction

Behçet's disease (BD) is a chronic multisystem disease, mostly defined by mucous cutaneous lesion like oral and genital ulcers, erythema nodosum-alike and papulopustular lesions, and uveitis [1]. The prevalence of BD is estimated to be 5.2 per 100 000 populace (95% confidence interval 0.64–9.84), and although several studies were found in the literature concluding a high incidence of BD between females, this result is not approved in some other investigations [2].

BD was the commonest vasculitis in Egypt [3]. Moreover, higher frequency of BD was in Turkey, followed by Iran, Saudi Arabia, Iraq, and Japan [1].

It more frequently affects young males, throughout the third decade of lifetime [4,5]. It is clinically diagnosed depending on the International Study Group, and serological markers may be absent in many patients [6]. Furthermore, a number of additional manifestations may occur such as neurologic, gastrointestinal, pulmonary, vascular, articular, urogenital, and cardiac contribution [7].

The neurological manifestations of BD are a wide range of conditions and may be considered a major life problem [8]. NBD was reported in 5% of patients with BD [9,10] and represents a poor prognostic factor [11].

Dysfunction of autonomic nervous system (ANS) has been as well recorded in BD cases [12]. In spite of several studies that analyzed the ANS disfunction by means of several approaches, they showed disagreeing outcomes, with dissimilar degrees of involvements [13,14].

The sympathetic skin response (SSR) is a widely used method to evaluate ANS, as it includes exterior preganglionic and postganglionic sympathetically sudomotor fibers in addition to essential structures like the posterior hypothalamus, higher brain-stem reticulate making, and spinal cord [15]. It is considered as an easy and noninvasive testing founded

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on the modifications of the skin, possible elicited more commonly by electric stimulations of peripheral nerves. SSR voltage has a wave-form that is adjusted with closely repeating stimulations [16].

To our knowledge, there are scant previous studies about assessment of autonomic dysfunction in BD cases.

The current work aimed to employ an electrophysiological testing to study ANS functions in BD cases and to estimate any relations among the disease activities and the signs of autonomic affections.

Patients and methods

This was an observational case–control study, which included 30 cases that passed the adapted International Criteria for BD [17]. Moreover, 25 apparently healthy persons matching in sex and ages were recruited and considered as controls. The Ethical Committee of the Assiut University accepted this work, and each participant gave informed consent.

We excepted cases using interfering medications with autonomic function, for instance, beta-blockers and tricyclic antidepressant like amitriptyline, in addition to cases with severed skin lesion interfering with the technical operation of the current work.

Methods

All patients in this study had been subjected to the following:

(1) Clinical and neurological examination: it was done for justifying criteria of inclusion and exclusion and detecting the prevalence of the disease clinical manifestations.
(2) Visual analog scaling (VAS): it was employed to measure the joints and numbness pains in both upper and lower limbs with scores ranging between 0 and 10.
(3) Behçet's disease current activity form (BDCAF) [18,19]: it is an assessment tool that evaluates BD for activity during the last 4 weeks, by evaluating disease symptoms such as oral or genital ulcers, joint affection, fatigue, skin manifestations, vasculitis, gastrointestinal, and central nervous system (CNS) manifestations on scale from 0 to 12. Each score above four was considered to be active disease.
(4) Neurophysiological study:
    (a) Electrophysiological investigations of higher and lower limbs were implemented at the normal temperature, via Nihon Kohden Neuropack M1 QP-954 BK (Tokyo, Japan) electromyography machine, using surface electrodes for stimulation and recording. Assessment of sensory nerve conduction depended on the antidromic method. Digit2-wrist and Digit5-wrist segments were used for median and ulnar nerves conduction studies, respectively. During assessment of sural nerve conduction, the recording probe was positioned posterior to the lateral malleolus, whereas the reference probe was placed ~3 cm distally.

Regarding motor conduction study, the recording electrodes were positioned above the abductor pollicis brevis and the adductor digiti-minimi muscles for the assessment of middle and ulnar nerve, respectively. Moreover, assessing the peroneal nerves, these electrodes were placed over the extensor digitorum brevis muscle, whereas they were positioned over the abductor hallucis brevis muscle to assess the tibial nerves. The active recording probe was located on the belly of the muscles, whereas the reference probe was positioned at the inserting of the muscle tendon.

(1) Procedure of SSR:

Each participant relaxed in a relaxing wingchair but stayed awake. The room temperature was kept at 24±0.5°C as the heat is identified to influence conduction velocities of unmyelinated sympathetic fiber [20].

The techniques and recording depended on the operational steps stated by Shahani *et al.* [21]. The SSR was recorded from the palmar surfaces of both left and right hands for cases and controls (overall 110 hands). This was done using superficial probes (Ag-Ag Cl) and Nihon Khoden device (Neuropack X1, MEB 2300, 6 and 12-channels EMG/EP Measurement System, simple data base managing with Neuro-Work-bench program), with the position of the used probe being on the palmar aspect of hand, up of the third meta-carpal bones (at 3 cm of distal ending), the reference probe on the equivalent area of the dorsal aspect of the studied hands, and the ground probe at the distal skins crease at the wrist zone. We stimulated the median nerves at the wrist ipsilateral to the probe of record. Every stimulation was in the form of only one electric pulse (of length 0.5 ms). The stimulus intensity was fixed at 1.5 folds of the motor thresholds of the stimulated nerves, and it was brought to the wrist at an unregular period (30–35 s). The recording of traces was done from 0.5 s previously to 8 s afterward the triggers stimulation. We set the velocity of sweep at 1000 ms/D and the sensitivity of amplifier at 100 μV/div. The amplifier filters were used at 0.5 Hz and 2 kHz for

the lower-frequency and higher-frequency filters, respectively. We recorded five examinations from the palm with the highest amplitudes, and shortest latency was selected. We estimated peak-to-peak length and latency at the starting points of initial negative or positive of the baseline. To lessen the distortions of impulsive potentials, the baseline was observed on an oscilloscope before giving the electric pulse. To record extended latency response (with lower-frequencies component), there essential to be a very slow sweepy (0.5–1 s/division), a higher gaining (100 μv/division), and an extensive band passing (0.16–3 kHz).

The Euro Standard Telematic tool to Evaluating Electro-diagnostic Method was employed as a guideline [22] for assessment of individual neurophysiological nerve tests and polyneuropathy classification.

Statistical analysis

Data analysis was performed via the windows-based IBM SPSS-20.0. Mean and SD were employed for expressing quantitative data, whereas qualitative data were introduced in the form of frequency and percent. The mean values of SSR (latencies and amplitudes) were compared among cases and controls via Mann–Whitney *U* testing. The Spearman association coefficient was used to assess the association among SRR, peripheral neuropathy (duration, pain VAS, numbness VAS), and disease activity parameters [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)]. The statistically significant was determined at *P* value less than 0.05.

Results

A total of 30 patients with BD [23 (76.7%) men and seven (23.3%) women, with mean age of 34.63±7.96 years] were diagnosed as having neurological involvement (Table 1). The neurological manifestations were distributed as follows: six (20%) patients had hemiparesis or monoparesis, eight (26.7%) had bilateral pyramidal sign, four (13.3%) patients had seizures, 14 (46.7%) patients had peripheral neuropathy, 18 (60%) patients had headache, seven (23.3%) patients had cognitive affection, and three (10%) patients had psychosis and depression. Nonneurological involvements included oral ulcers (n=23), genital ulcer (n=14), arthritis and arthralgia (n=17), skin involvement (n=23), deep venous thrombosis (n=15), vascular and arterial ischemia (n=12), anterior and postuveitis (n=17), and panuveitis with retinal vasculitis and optic neuritis (n=11) (Table 2).

Mann–Whitney *U* testing revealed that there is a significant change among average latency and amplitude of SSR between Behçet's and control groups ($P \leq 0.001$), which indicates that there is significant autonomic dysfunction in BD (Table 3).

There is a significant positive moderate correlation between neuropathic pain and numbness on VAS and disease activity parameter (CRP, r=0.43, P=0.01 and r=0.40, P=0.02, respectively, and BDCAF, r=0.43, P=0.02, and r=-0.36, P=0.04, respectively), with no significant correlation with ESR. Moreover, there is a nonsignificant association between SSR (either latency or amplitude) and disease activity parameters (r=–0.26, P=0.15) (Table 4).

Discussion

It was known that, as early as we described, there is CNS involvement in BD, zones of focal

Table 1 Sociodemographic data of patient with Behçet's disease and control

Variables	Behçet's disease (N=30)	Control (N=25)	P value
Age			
Mean±SD	34.63±7.96	36.50±5.91	0.291
Sex			
Male	23 (76.7)	19 (76.0)	0.30
Female	7 (23.3)	6 (24.0)	0.21
Marital status			
Married	19 (63.3)	17 (68.0)	0.38
Single	11 (36.7)	8 (32.0)	0.24
Smoking			
Smoker	7 (23.3)	5 (25.0)	0.42
Nonsmoker	23 (76.7)	15 (75.0)	0.60
Smoking duration (years)	2.23±3.88	2.10±5.13	0.85
Disease-onset (years)	4.10±1.80		

Data are introduced as mean±SD, SE or median (interquartile ranges). *P* value less than 0.05 have a statistical significance (unpaired *t* testing, and Mann–Whitney testing).

Table 2 Clinical and laboratory data of patient with Behçet's disease

Variables	Frequency (*N*=30)	%
Neurological manifestations		
Hemiparesis or monoparesis	6	20
Bilateral pyramidal	8	26.7
Seizures	4	13.3
Headache	18	60
Peripheral neuropathy	14	46.7
Cognitive affection	7	23.3
Psychosis and or depression	3	10.0
Nonneurological manifestations		
Vascular arterial ischemia	12	40.0
Venous DVT	15	50.0
Erythema nodosum	22	73.4
Oral ulcer	23	76.7
Genital ulcer	14	46.7
Arthralgia and arthralgia	17	56.7
Anterior and postuveitis	21	70
Panuveitis with retinal vasculitis and optic neuritis/atrophy	11	36.7
BDCAF	5.14±1.59	
Peripheral neuropathy		
Duration in months	25.83±14.97	
Neuropathy pain VAS	6.33±1.71	
Numbness VAS	6.67±1.76	
ESR	26.13±13.24	
CRP	13.43±8.18	

BDCAF, Behçet's disease current activity form; CRP, C-reactive proteins; DVT, deep venous thrombosis; ESR, erythrocyte sedimentation rating; VAS, visual analog scaling.

Table 3 Values of sympathetic skin response in Behçet's disease group and controls

Variables	Behcet disease (*N*=30) (mean±SD)	Control (*N*=25) (mean±SD)	*P* value*
Average latency of SSR (ms)	1.73±0.07	1.47±0.07	<0.001
Average amplitude of SSR (mv)	1.43±0.22	2.77±0.56	<0.001

[a]Mann–Whitney *U* test. *Significant change among the studied groups, *P* value less than 0.05 is considered statistically significant. SSR, sympathetic skin response. Comparing sympathetic skin response test in Behçet's disease and controls groups.

Table 4 Correlation between disease activity parameters and peripheral neuropathy, sympathetic skin response in patients with Behçet's disease

	ESR		CRP		BDCAF	
Variable	*r*	*P* value*	*r*	*P* value*	*r*	*P* value*
Peripheral neuropathy						
Neuropathy duration (months)	0.19	0.30	–0.19	0.31	–0.19	0.31
Neuropathy pain VAS	–0.009	0.96	0.43	0.01	–0.36,	0.04
Numbness VAS	–0.01	0.91	0.40	0.02	0.43	0.02
Sympathetic skin response						
SSR latency	–0.06	0.73	–0.26	0.15	–0.15	0.29
SSR amplitude	–0.12	0.50	0.23	0.20	0.42	0.20

BDCAF, Behçet's disease current activity form; CRP, C-reactive proteins; ESR, erythrocyte sedimentations rating; SSR, sympathetic skin response; VAS, visually analog scale. *Spearman correlation shows there is a significant positive moderate correlation between neuropathic pain and numbness on VAS and disease activity parameter (CRP and BDCAF) (*r*=0.43, *P*=0.01; *r*=0.40, *P*=0.02; *r*=0.43, *P*=0.02; *r*=–0.36, *P*=0.04, respectively). Nonsignificant association with ESR, also there is no significant correlation between sympathetic skin response (either latency or amplitude) and disease activity parameters (*r*=–0.26, *P*=0.15).

inflammations could happen at various levels of the CNS. The brain stem, cerebral hemisphere, cerebellum, spinal cord, and meninges are the common locations of CNS involvements [23,24]. In circumstance of nervous system involvements, motor and sensory disorders have further consideration, as they are the more obvious complaints of the cases. There are few studies in the literature that target BD patient group for ANS evaluation [25–27].

So, the authors kept in mind the importance of ANS assessment, and many studies have assessed the ANS functions in patients with BD. ANS dysfunction in BD was difficult to be analyzed owing to using different methods of assessment such as (a) sympathetic skin potentials against consecutive nerve stimulation [27], (b) impaired time-domain heart rate variability parameters [26], (c) low sympathetic activity assessed by the electrodermal activities [28], and (d) using power spectral analysis of heart rate variability [29].

Various laboratory methods could be used to assess ANS functions, but most of these examinations are complicated, are not frequently appropriate for every-day evaluations, and frequently need specific equipment and qualified users, so physician might select not to execute them and might underestimate the autonomic involvements.

Thus, we built our hypothesis to investigate ANS function by using electrophysiological tests and validate the use of SSR as initial screening test for autonomic affection in patients with BD and to estimate the association among the disease's activity parameters and the signs of autonomic affections.

In the present study, a total 30 patients who fulfilled the inclusion criteria were recruited, with males (n=23, 76.3%) being more affected than females (n=7, 23.7%), and this is in agreement with other studies [30,31]. Moreover, we found that headache, peripheral neuropathy, pyramidally indicators, and cognitive affection were the most frequent neurological results in BD, and this was stated by previous studies [32].

Emam *et al*. [31] studied BD, and his study revealed that nearly 20% of patients with BD experienced clinical manifestations of peripheral neuropathy, and ~50% had peripheral neuropathy coupled with demyelinating changes, which were established electrophysiologically. This is concised with our findings, as we found that ~14 patients presented with symptomatic peripheral neuropathy, whereas neurophysiologically, ~21 patients presented with sensory manifestaions.

Birol *et al*. [33] studied 26 Behçet's patients and found that electrophysiologically determined peripherally neuropathy was concluded in more than 50% of the cases. The nerves disfunctions was of axonal types of distal polyneuropathy mainly comprising lesser limits.

In the present study, we found a statistically significant difference among average latency and amplitude of SSR between Behçet's and control groups, which indicates that there is significant autonomic dysfunction in patients with BD.

This finding supports those reported by other studies as Borman *et al*. [34], and Emam *et al*. [31]. So, the reduced sympathetic activity in our patients detected by SSR may represent a possible abnormality of the ANS.

Moreover, Karataş *et al*. [25] found that SSR latencies were delayed in their patients presented by both orthostatic hypotension and sweating abnormalities, and they suggested the coexistence of clinically and electrophysiologically indications of autonomic disfunction, supporting the involvements of the ANS in these cases.

The SSR is a temporary alteration in the electric voltage-induced reflexivity in the palms of the hands by electrical stimulation [35]. The summation of somatosensory medullated afferents, central coupling procedure, and various pathways represents the SSR latency [36]. The central pathway of the reflex was unknown precisely, but it perhaps includes the brain stem, thalamus, and hypothalamus [37]. The efferent phases of the reflexing latency principally consist of conducting in the postganglionic, unmyelinated sympathetically fibers of the sudomotor pathway [35]. Pathological situations influencing the somatosensory pathways in exterior neuropathy and/or central coupling might occur in SSR abnormalities [38].

ESR, CRP, and BDCAF are still consistent activity signs for BD. Clinically, disease activities were revealed to be accompanying with growths in laboratory markers such as ESR and CRP values, and these markers correlate well with disease activity in BD [39].

We determined a significant relation between laboratory parameters (ESR, CRP) and clinical neuropathic manifestations and a negative nonsignificant correlation with latency and amplitude of SSR of patients with BD, which might indicate dysfunction in sympathetic pathways in BD cases with active disease. Our finding is the same as that reported by Borman *et al*. [34].

The strength of our study includes assessment of sympathetic function in BD using simple noninvasive technique (SSR); however, the study had its limitations, including small sample size, and there was no assessment of the parasympathetic part of ANS.

In this study, we assessed the sympathetic function using SSR but we recommend the assessment of

the parasympathetic part of ANS and to assess which part of ANS is more affected in BD. The early detection of ANS dysfunction might be very significant to avoid excessive morbidities, and the use of simple, noninvasive electrophysiologically approaches is recommended to detect NBD cases at risks for symptomatically dysautonomia.

Conclusion

Our study confirms the presence of a sympathetic autonomically disfunction in BD cases, which might be correlated with disease activities. The ANS disfunction might be missed in BD cases owing to vague symptoms and difficult evaluation and quantification of ANS. Using simple noninvasive test as SSR could decrease this obstacle and help in the recognition of ANS dysfunction and hence early neurological involvement in BD.

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Conflicts of interest

There are no conflicts of interest.

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