The pattern of cardiovascular manifestations in Egyptian Behçet’s patients and its relation to disease activity

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Abstract

Background: Behçet’s disease (BD) is also referred to as vascular BD when it frequently involves the heart and vessels. This study aimed to describe the cardiovascular manifestations in patients with BD and its correlation to disease activity. We conducted a cross-sectional study on 40 patients diagnosed with BD according to the International Criteria for Behçet’s Disease 2014. All the patients were subjected to detailed history taking, full clinical examination, lab investigations, resting electrocardiogram, trans-thoracic echocardiography, and carotid artery duplex for measuring intimal thickness, peripheral arterial and venous duplex, computed tomography pulmonary angiography, and full ophthalmological examination. Regarding the activity of the disease, it was assessed according to the score of Behçet’s Disease Current Activity Form (BDCAF).

Results: The most common cardiac manifestation was valvular lesion (67.5%) where the most frequently affected valve was the tricuspid valve (27.5%). Although 25% of patients had left ventricular diastolic dysfunction, only 5% had intracardiac masses. Approximately 52.5% of patients had vascular lesion (deep venous thrombosis 45%, arterial involvement 7.5% [as pulmonary artery thrombosis 5% and aneurysm 2.5%]). Increase in intima media thickness (IMT) was observed in 7.5% of patients, while 60% had abnormal lipid profiles. Hypercholesterolemia was the most common lipid abnormality (50%). BDCAF score range was 4–12, which was significantly correlated to multiple cardiovascular parameters as a mitral, tricuspid valve, and vascular venous involvement ($p < 0.05$), while not significantly correlated to lipid profile ($p > 0.05$).

Conclusion: Cardiovascular complications are frequent among patients with BD, even those who are asymptomatic; therefore, these complications must be screened for early detection and proper management.

Keywords: Behçet’s disease, Cardiovascular manifestations, Lipid profile, Disease activity score
Background

Behçet’s disease (BD) is a systemic vasculitis of uncertain etiology characteristically affecting blood vessels. It is diagnosed clinically by recurrent oral and/or genital aphthosis, mucocutaneous lesions, central nervous system manifestation, and ocular, vascular, articular, gastrointestinal, inflammatory eye lesions and tendency for thrombosis in young adults; however, diagnosis may be challenging. Treatment is difficult and should be individualized [1].

Cardiac involvement in BD is variable and is thought to occur in the range of 7–46% [2]. Moreover, it was observed that both cardiac and arterial complications are also important aspects of the course of the disease. Cardiac lesions that have been reported in the literature include pericarditis, endocarditis, intracardiac thrombosis, myocardial infarction, endo-mycocardial fibrosis, and myocardial aneurysm [3–5]. Treatment of cardiovascular involvement in BD is towards suppressing vasculitis [6].

Different types of vessels, predominantly veins, can be affected in BD. The frequency of vascular lesions in BD, such as superficial and deep venous thromboses, arterial aneurysms, and occlusions, ranges between 7–29% [7]. Different factors of thrombogenesis in BD are presented and discussed from positions of Virchow’s triad of venous thrombosis, particularly, pro- and antithrombotic endothelial and non-endothelial factors, factors of coagulation, and platelet activation [8].

BD has increased mortality specially among young males, while being not as severe as seen in females and old patients. Usually, the disease severity decreases with time. However, large- vessel vascular disease is considered as the most important cause of mortality in BD, particularly hemorrhage owing to pulmonary artery aneurysms [9].

Different Egyptian studies describe cardiovascular manifestations in BD [10–12]; however, the current study focused on both cardiac and vascular spectrum in BD patients in an Egyptian cohort and correlated them to disease activity.

The present study aimed to describe cardiovascular manifestations in patients with BD and its correlation to disease activity.

Methods

Patients

We conducted a cross-sectional study with 40 patients who were diagnosed with BD according to the International Criteria for Behçet’s Disease (ICBD) [13] aged 18–60 years, recruited from the Ain Shams University Hospital. We excluded patients with other associated autoimmune diseases, smokers, obese individuals (body mass index ≥ 30), and hypertensives or diabetics. We recruited patients from April 2019 to March 2020.

Ethical considerations

This study was conducted according to the criteria mentioned in the World Medical Association’s Declaration of Helsinki in October 2013. We obtained informed consent from each patient after demonstrating study’s aim and procedures. The local ethical committee of Ain Shams University approved our study protocol.

Clinical evaluation

Detailed history was obtained from all the participants including their age, sex, disease duration, and full clinical examination with special emphasis on signs and symptoms of BD.

Laboratory investigations

Laboratory investigations were done for all the patients including complete blood count (CBC), erythrocyte sedimentation rate (ESR), kidney function tests (serum creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP) with titer, liver enzyme alanine aminotransferase (ALT), aspartate aminotransferase (AST), lipid profile including low-density lipoprotein (LDL)-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol (a total cholesterol of > 240 mg/dl has been classified as elevated; triglyceride levels > 200 mg/dL have been classified as elevated; low HDL-C has been classified as < 40 mg/dL in men, and < 50 mg/dL in women; an LDL-C value > 160 mg/dL has been classified as high) [14].

Disease activity assessment

Disease activity was determined according to the score of Behçet’s Disease Current Activity Form (BDCAF) [15]. To calculate the BDCAF score, the presence of each general item accounts for one mark. The presence of any eye, neurological, or major vessel affection takes one mark as a whole even if all signs are present; therefore, the score is out of 12.

Imaging investigations

Echocardiography

All patients were examined with Philips iE33 echocardiographic machine (Philips Medical Systems, Andover, MA, USA). A broadband 2.5–3.5 MHz phased array transducer equipped with tissue Doppler imaging (TDI) mode was used. Two-dimensional imaging (2D) was performed, followed by Doppler. A single investigator had performed transthoracic echocardiography (ECHO) for > 5 years and had achieved level 3 training in echocardiography from cardiology department at Ain Shams University who was blinded to patient data.
Echocardiographic analysis
Two-dimensionally guided M-mode tracings were obtained from the parasternal short-axis view to measure the left ventricular (LV) dimensions and wall thickness. The LV ejection fraction (EF) was measured using the disk summation method. According to the guidelines from the American Society of Echocardiography (ASE), an EF ≤ 55% was considered abnormal [16].

To assess the LV diastolic function, the following Doppler parameters were measured: peak E velocity, peak A wave velocity, E/A ratio, and deceleration time of E velocity. Using the tissue Doppler imaging (TDI), the lateral mitral annular E’-wave velocity was obtained, and the E/E’ ratio was then calculated [17].

For assessment of the right ventricular (RV) systolic functions, the fractional area change (FAC), the tricuspid annular plane systolic excursion (TAPSE), and S wave velocity of the lateral tricuspid annulus were measured and analyzed according to the guidelines published by the ASE in 2010 [18].

The cardiac valves were assessed by 2D, color, and Doppler imaging. The severity of the aortic regurgitation was assessed by measurement of the vena contracta width as well as the proximal jet width obtained from the parasternal long-axis view and its ratio to the LV outflow tract diameter (LVOT). A ratio of proximal jet width to the LVOT diameter > 65% with a VC > 0.6 cm defined severe aortic regurgitation.

Detected pericardial effusion (PE) was described according to its amount, site, associated fibrinous shreds, and evidence of increased intrapericardial pressure. Severe PE was defined as an echo-free space of ≥ 1 cm seen surrounding the heart. Detected intracardiac masses were fully analyzed regarding their location, number, size, texture, and mobility. Other measurements were assessed as left ventricular end-systolic diameter, left ventricular end-diastolic diameter, interventricular septum diameter, left atrial diameter, pulmonary artery pressure, and right ventricular systolic diameters.

Carotid artery duplex
All patients underwent two-dimensional echo-color Doppler of the carotid arteries, adopting a high definition vascular echographic apparatus Philips Sonos 5500 Bothell (Washington, USA) and a 10–3 MHz linear electronic probe. During the procedure, patients were placed in a supine position, with the neck extended and turned, contralaterally by about 45 with a probe placed over the common carotid artery on both sides before carotid bifurcation with 1–2 cm for measuring IMT.

The intimal medial thickness was defined as the distance between the lumen-intima and media adventitia borders of the vessel, which was sonographically identified by a double hypoechoic line not projecting into the vessel lumen used for evaluation of the extent of carotid atherosclerotic vascular disease (cutoff value equal or greater than 1.1 mm) [19]. A value of 0.74 ± 0.14 mm was considered normal [20].

Peripheral arterial and venous duplex
Peripheral vascular arterial and venous duplexes were conducted where Doppler ultrasonography was performed in B-mode and color-mode spectral examinations using 13.5- and 9.4-MHz linear probes. The arterial and venous systems for both the upper and lower extremities were examined for venous insufficiency, thrombosis, arterial stenosis, and aneurysm. The venous insufficiency was determined by the presence of valvular incompetence that results in retrograde flow of blood (reflux) [21].

Computed tomography pulmonary angiography for assessment of pulmonary thrombosis and the pulmonary vascular aneurysm was performed. All were performed by trained staff members of the Radiology Department at Ain Shams University who were blinded to diagnosis.

A resting electrocardiogram (ECG) was also recorded for all patients.

Ophthalmological assessment
Complete ophthalmological examination were done for all the participants at the ophthalmology outpatient clinic of Ain Shams University, including assessment of their visual acuity, slit-lamp examination (for assessing the anterior chamber), and fundus examination (for assessing retina, choroid, and optic disk).

Statistical analysis
Data were handled using SPSS software version 20. We presented the qualitative data as frequencies and percentages and quantitative data as mean, standard deviation, range, and median. In order to compare two groups of quantitative data, we used unpaired Student’s t test while to examine the relationship between two qualitative variable, we used the chi-square test. For assessing the strength of association between two quantitative variables, correlation analysis was done using Pearson’s method and its symbol is “r” which defines both the strength and direction of linear relationship between the two variables.

We used the following criteria to determine the p value significance level:

- p value ≤ 0.05: significant.
- p value ≤ 0.001: highly significant.
- p value > 0.05: insignificant.

Results
Patients’ demographic and clinical characteristics
Considering demographic data, the age of the studied patients ranged between 19 and 47 years with a mean of
34.175 ± 6.891 years. There were 31 (77.5%) male and nine (22.5%) female patients with a ratio of 3.4:1 and disease duration ranged between 4 and 60 months with a mean of 21.65 ± 15.55 months. The distribution of cumulative clinical data among the studied patients with BD according to ICBD is presented in Table 1. BDCAF score was statistically significant with respect to mitral valve, tricuspid valve, and vascular venous lesions (p = 0.004, 0.034, 0.002, respectively), but not statistically significant with respect to lipid profile, ECG changes, carotid duplex changes, aortic, pulmonary valves involvement, diastolic dysfunction, intracardiac masses, and vascular arterial lesion (p > 0.05) (Table 3). The negative correlation between BDCAF score and left ventricular end-systolic diameter (p = 0.004) was significant (Fig. 2).

For comparing clinical data with lipid profile and cardiovascular manifestations, we found that a significant relation between anterior uveitis, vascular arterial, and venous involvement (p = 0.046, 0.002), respectively; meanwhile, lipid profile was significantly related to vascular arterial affection (p = 0.027).

### Table 1 Cumulative clinical data among the included Behçet’s patients and disease activity score (N = 40)

| Clinical data                        | N  | %   |
|--------------------------------------|----|-----|
| Oral ulcers                          | 40 | 100.00 |
| Genital ulcers                       | 32 | 80.00 |
| Ocular manifestations                | 31 | 77.50 |
| a) Anterior segment involvement      | 22 | 55.00 |
| b) Posterior segment involvement     | 9  | 22.5% |
| Vascular venous involvement (DVT)    | 18 | 45.00 |
| Pathergy test (positive)             | 11 | 27.50 |
| Neurological manifestations          | 10 | 25.00 |
| a) Transient ischemic attacks        | 7  | 17.50 |
| b) Hemiplegia (UMNL)                 | 3  | 7.50  |
| Skin lesions                         | 4  | 10.00 |
| a) Pseudofolliculitis                | 3  | 7.50  |
| b) Erythema nodosum                 | 1  | 2.50  |
| Vascular arterial involvement (pulmonary) | 3  | 7.50  |
| A) Pulmonary thrombosis              | 2  | 5     |
| B) Pulmonary aneurysma               | 1  | 2.5   |
| BDCAF score                          | Range | Mean ± SD |
|                                       | 4-12 | 7.7 ± 2.6 |

DVT deep vein thrombosis, UMNL upper motor neuron lesion

### Discussion

Behçet’s disease is a multi-systemic inflammatory disorder. Autoimmune factors are involved in its etiology. Immune fluorescence studies revealed IgM, IgG, and β1 globulin on the vascular endothelial walls and the serum contained increased amounts of IgD, IgG, IgM, C1, C2, C3, C4, and immune complexes. The increased prevalence of the HLA-B5 tissue gene group suggests a genetic role as etiological factor [22].

Behçet’s disease is a non-specific vasculitis involving both veins and arteries. Infiltration of lymphocytes, mononuclear cells, and mast cells can be observed around the blood vessels, causing endothelial swelling and fibrinoid degeneration. Cardiac involvement can be seen as pericarditis, acute myocardial infarction, valve lesion, and cardiomyopathy [23].

This cross-sectional study aimed to describe the cardiovascular manifestations for patients with BD and its correlation with disease activity.

Variable cardiac manifestations are presented in our study; cardiac valvular lesion was the most common cardiac features (67.5%). The commonest valvular lesion in this cohort was tricuspid regurgitation which was found in 27.5% of the participants, which was similar as reported by Lihong et al. where valvular affection was observed in 74.6% of patients [24]. However, aortic regurgitation was the most common valvular lesion reported by Abidov et al. in 64.9% of patients [25].

Up to date, there is no sufficient data regarding exact pathophysiology of the involvement of the heart valves that cause insufficiency among BD patients. It may be due to the inflammation that cause damage to the valve tissue which causes dilatation of both the ascending aorta and sinus valsalva aneurysm [26].

Moreover, patients with BD may also develop dilated cardiomyopathy; however, in this study, none of our
patients showed increased left ventricular diameter, which is disimilar to the Ulusan et al. study which found two (5.2%) patients with increased left ventricular diameter [23].

In our study, pulmonary artery hypertension (PAH) was present in 7.5% of patients, in contrast to Seyahi et al. where PAH was in 17% of patients [27]. These differences may be related to different numbers of patients included in the study.

Left ventricular diastolic dysfunction (LVDD) was detected in 25% of the participants, which may be considered as the most significant pathology in order to detect heart involvement in BD. This was in agreement with the studies by Bozkurt et al. and Gemici et al. and in contrast to the study by Farouk et al. who showed that LVDD is similar in Egyptian patients with BD and healthy controls and also the study done by Tunc et al. who reported no difference between diseased patients and healthy control regarding LVDD which may be explained by different demographic data of studied patients as regards age and disease duration [28–31].

Two of our Behçet’s patients (5%) had intracardiac masses. This was similar to the study done by Lihong et al. and Demirelli et al. [24, 32].

In our study, ECG abnormalities in the patients were as follows: left ventricular hypertrophy in (30%), left axis deviation (27.5%), left bundle branch block (12.5%), and right bundle branch block (2.5%). A lower percentage was observed in the study done by Bozkurt et al. who found that 11.1% of patients had left ventricular hypertrophy and only 1.8% had left-axis deviation; however, it is in concordance with Heper et al.’s study [28, 33].

In our study, abnormal lipid profile was found in 60% of patients, with high total cholesterol in 50%, high LDL-C level in 70%, abnormal lower HDL-C levels in 32.5%, and high level of triglycerides in 17.5% of patients. This was in concordance with the studies by Messedi et al. and Hammami et al., however, it is in contrast with Kayatas et al. who concluded that patients with BD in the active period may be less susceptible to atherogenic events than the controls [34–36].

We observed abnormal carotid duplex as increased IMT in 7.5% of patients. Many researches as those by Keser et al. and Hong et al. reported similar findings; however, a Korean study conducted by Rhee et al. reported no change in IMT of carotid artery in the studied patients with BD compared to controls [37–39] which may be explained by the difference between the pattern of clinical features in the Korean BD population from those in Middle East and Mediterranean regions.

In our study, vascular involvement in patients with BD was either arterial or venous (52.5%). The ratio was within proximity to many studies, as by El Mallahr et al. (39%) and El-Garfa et al. (58.9%); however, it is higher than that by Skef et al. (7–29%) [40–42].

Vascular lesions mainly consist in venous and arterial thrombosis and various types of arterial aneurysms. Venous lesions were more common in our cohort and reported in 45%, which is in agreement with Düzgün et al. findings which demonstrated that venous lesions are reported in 37.7%; however, Ulusan et al. reported only three cases (7.8%) with lower limb DVT [23, 43].

Arterial involvement was less common and found in only three (7.5%) patients in this cohort (two had pulmonary aneurysm [5%] and only one had pulmonary thrombosis [2.5%]). These findings were in agreement with the results obtained by Düzgün et al. who found them as 1.6%; however, El Mallahr et al. found that arterial affection was 17% [40, 43].

In our study, the BDCAF score was compared to multiple cardiovascular parameters where we found that it was significantly related to the mitral valve, tricuspid valve, and vascular venous affection (p = 0.004, 0.034, and 0.002), respectively. This was in concordance with
Table 2 Findings of ECG, carotid Doppler, and echocardiography among included Behçet’s patients (N = 40)

| ECG findings                  | N  | %   |
|-------------------------------|----|-----|
| Axis deviation                |    |     |
| Left                          | 11 | 27.50 |
| Right                         | 0  | 0    |
| Ventricular hypertrophy       |    |     |
| Left                          | 12 | 30.00 |
| Right                         | 0  | 0    |
| Bundle Branch block           |    |     |
| Right                         | 1  | 2.50  |
| Left                          | 5  | 12.50 |

| Carotid artery parameters    | N  | %   |
|-------------------------------|----|-----|
| Carotid duplex                |    |     |
| Abnormal (increased IMT)      | 3  | 7.50 |
| Normal                        | 37 | 92.50 |
| Carotid IMT (mm)              |    |     |
| Range                         | 0.5–1.2 |
| Mean ± SD                     | 0.785 ± 0.159 |

| Echocardiography parameters  |     |     |
| Ejection fraction            | Range | 56–78 |
| Mean ± SD                    | 65.575 ± 5.198 |
| RVSP (mmHg)                  | Range | 20–35 |
| Mean ± SD                    | 25.075 ± 2.664 |
| Left ventricular end systolic diameter (mm) | Range | 24–35 |
| Mean ± SD                    | 30.600 ± 2.468 |
| Left ventricular end diastolic diameter (mm) | Range | 39–55 |
| Mean ± SD                    | 47.975 ± 3.846 |
| Interventricular septum diameter (mm) | Range | 7–10 |
| Mean ± SD                    | 8.500 ± 0.934 |
| Left atrial diameter (mm)    | Range | 28–41 |
| Mean ± SD                    | 33.800 ± 3.674 |
| Pulmonary artery pressure (mmHg) | Range | 12–32 |
| Mean ± SD                    | 17.600 ± 4.471 |

| Valves, aortic root, and right ventricular systolic diameters | N  | %   |
|--------------------------------------------------------------|----|-----|
| Aortic valve                                                 | 4  | 10.00 |
| Mitral valve                                                 | 7  | 17.50 |
| Tricuspid valve                                              | 11 | 27.50 |
| Pulmonary valve                                              | 5  | 12.50 |
| Tricuspid and pulmonary valve                                | 3  | 7.5%  |
| Mitral and tricuspid valve                                   | 4  | 10%   |
| Mitral, tricuspid, and pulmonary valve                       | 2  | 5%    |
| Aortic root diameter                                         | 40 | 100.00|
| Right ventricular systolic diameter                          | 40 | 100.00|

| Other abnormalities                                          | N  | %   |
|--------------------------------------------------------------|----|-----|
| Diastolic dysfunction                                        | 10 | 25.00 |
| Pulmonary artery pressure                                    | 3  | 7.5%  |
| Pericardium                                                  | 40 | 100%  |
| Intracardiac masses                                          | 2  | 5.00% |

ECG electrocardiogram, RVSP right ventricular systolic pressure, AR aortic regurgitation, TR tricuspid regurgitation, MR mitral regurgitation, PR pulmonary regurgitation, SD standard deviation
Eldin and Ibrahim’s study [44]. These results reflected the importance of cardiovascular features as predictor parameters of disease activity score. We found a significant negative correlation between BDCAF score and left ventricular end-systolic diameter (LVDD) \((p = 0.004)\). Similar results were found in an Egyptian study conducted by Hassan and Ebaid who demonstrated a significant correlation between BDCAF and different echocardiographic parameters as LVDD and systolic and diastolic dysfunction [12]. Also, Ikonomidis et al. found BD with vascular complication to have more myocardial and aortic wall dysfunction and attributed this to a common pathophysiologic pathway that may elevate inflammatory cytokines as interleukin-2 (IL-2) and IL-6 [45].

These findings revealed that systolic function impaired even before the development of overt cardiac failure may be due to early affection of subendocardial longitudinal fibers with no distortion in circumferential function in BD due to the deterioration in coronary microvascular function, which is attributed to small vessel vasculitis [46].

Our study demonstrated a significant relationship between lipid profile and vascular arterial involvement \((p = 0.027)\) in this cohort and which was similar to the results of the studies by Ricart et al. and Musabak et al. who related increase of lipoprotein to the athero-thrombotic event in BD patients [47, 48].

We found a significant relationship between anterior uveitis and vascular involvement (either arterial or venous) \((p = 0.046, 0.002)\) respectively, which was similar to results reported by Yu et al. who concluded that the presence of vascular thrombosis is one of the bad prognostic factors of uveitis in BD patients; however, this was not also significant in our study for vascular venous affection \((p = 0.002)\).
Houman et al. reported the less frequent occurrence of DVT as well as a genital ulcer in patients with ocular involvement [49, 50].

Conclusion
Cardiovascular complications are significantly frequent among patients with BD, although asymptomatic; therefore, these complications must be screened for early detection and proper management to improve prognosis, quality of life and decrease the morbidity and mortality of the disease.

Abbreviations
BD: Behçet's disease; BDCAF: Behçet's Disease Current Activity Form; ICBD: International Criteria for Behçet's Disease; IMT: Intimal medial thickness; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ECG: Electrocardiogram; ECHO: Echocardiography; PAH: Pulmonary artery hypertension; LV: Left ventricular; LVDD: Left ventricular diastolic dysfunction; TDI: Tissue Doppler imaging; EF: Ejection fraction; ASE: American Society of Echocardiography; RV: Right ventricular; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; LVOT: Left ventricular outflow tract diameter; PE: Pericardial effusion; DVT: Deep venous thrombosis; CBC: Complete blood count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

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Authors’ contributions
NM conceived the idea and planned the research work. DF contributed to the design, supervised the finding, verified the analytic methods, and reviewed the manuscript. FB participated in writing the research, performed part of investigations, and supervised the work. MT carried out the data collection, statistical analysis, and writing and contributed to the work planning, data analysis, and manuscript writing. All authors discussed the result and contributed to the final manuscript. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study was approved by the local research ethical committee of the Faculty of Medicine at Ain Shams University in Egypt, reference number: FWU00007585 (No: FMSU 124/2019). All patients included in this study gave written informed consent to participate in this research.

Consent for publication
Consent for publication was taken from all participants.

Competing interests
The author(s) declare no potential conflicts of interest concerning the research, authorship, and/or publication of this manuscript.

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