Review

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Cardiac manifestations in Behcet's disease

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Summary **Behcet's disease (BD) is a chronic inflammatory disorder, with vasculitis underlying the pathophysiology of its multisystemic effects. Venous pathology and thrombotic complications are hallmarks of BD. However, it has been increasingly recognised that cardiac involvement and arterial complications are also important aspects of the course of the disease. Cardiac lesions include pericarditis, endocarditis, intracardiac thrombosis, myocardial infarction, endomyocardial fibrosis, and myocardial aneurysm. Treatment of cardiovascular involvement in BD is largely empirical, and is aimed towards suppressing the vasculitis. The most challenging aspect seems to be the treatment of arterial aneurysms and thromboses due to the associated risk of bleeding. When the prognosis of cardiac involvement in BD is not good, recovery can be achieved through oral anticoagulation, immunosuppressive therapy, and colchicine use. In this review, we summarise the cardiovascular involvement, different manifestations, and treatment of BD.**

Keywords: Behcet's disease, cardiac manifestations, treatment

1. Introduction

Behcet's Disease was named BD or Behcet's syndrome when it was first described by Turkish physician Hulusi Behcet in 1937 (*1*). BD involves widespread vasculitis with recurrent oral and genital ulcers and ocular symptoms as well as musculoskeletal, neurological, cardiac, pulmonary, and gastrointestinal system (GIS) involvement. The underlying pathology is an inflammatory response in the arteries and veins. The prognosis varies from patient to patient. Some patients manifest only skin and mucosal lesions, while others may manifest life-threatening central nervous system (CNS) and GIS involvement and pulmonary artery aneurysms (*2,3*). Cardiac involvement in BD is also referred to as cardiac BD. Cardiac involvement may occur in the form of intracardiac thrombus, endocarditis, myocarditis, pericarditis, endomyocardial fibrosis, coronary arteritis, myocardial infarction, and valvular disease (*4*). Recently, some studies have demonstrated that subclinical left ventricular dysfunction in BD progresses at an early stage (*5,6*). Based on this background, in this review, we summarise the cardiovascular involvement and its manifestations in BD.

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2. Epidemiology and pathogenesis

BD mostly affects ethnic groups of Mediterranean and East Asian origin that have historically settled along the historic Silk Road route regions. The prevalence of the disease is 80-370/100,000 in Turkey, whereas it is 13-20/100,000 in Japan, Korea, Iran, Iraq, and Saudi Arabia (*7*). In Europe, the estimated prevalence differs based on latitude, with higher prevalences in the south (*8*). Regional distribution not only affects prevalence, but also affects severity of the disease and organ involvement. For example, it has been reported that GIS involvement in Turkey is 5%, whereas it is 50% in Japan (*9*). The gene frequency of human leukocyte antigen (HLA)-B51, which is thought to play a key role in BD pathogenesis, is higher among those living along the Silk Road route than those living in other parts of the world (*8*). The disease is generally seen in the 3rd and 4th decades; it is rare for the disease to occur during adolescence or after the age of 40. BD is seen more commonly among

Table 1. International Study Group diagnostic criteria for the classification of Behcet's syndrome

- *Recurrent oral ulceration:* minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient recurring at least three times in a 12-month period
- *Plus two of the following:*
  Recurrent genital ulceration: aphthous ulceration or scarring observed by physician or patient
- *Eye lesions*: anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination, or retinal vasculitis observed by ophthalmologist.
- *Skin lesions:* erythema nodosum observed by physician or patient, pseudofolliculitis, papulopustular lesions, or acneiform nodules observed by physician in post-adolescent patients not on corticosteroid treatment.
- *Positive pathergy test:* read by physician at 24–48 h (findings applicable only in absence of other clinical explanations).

the family members of those who contract the disease in adolescence, yet the complications are fewer. The prevalence in males and females differs according to the region. In countries of the Middle East, the disease is seen more among males, whereas it is seen more among females in the countries of North Europe and the United States (*2,10*).

The aetiology of BD has yet to be determined. Viral, bacterial, genetic, environmental, toxic, and immune factors all have been proposed to play roles in its pathogenesis (*11*). The basic histopathological sign of BD is vasculitis in large, medium, and small veins. Lymphocytes, monocytes, and dense neutrophil infiltrations are evident in the lesions. It has been shown that antigenic peptides from strains of streptococcus and *Escherichia coli* can stimulate T cells from BD patients to produce higher quantities of interleukin (IL)-6 and interferon (IFN)-γ, respectively, compared to controls (*12*).

In recent years, there have been numerous findings about BD being an autoinflammatory disease rather than an autoimmune disease. Hypergammaglobulinemia and female dominance, seen in classic autoimmune diseases, are not observed in BD. BD typically has a more severe course in males. The serious complications of vascular disease, CNS disease, and pulmonary disease occur more often in males (*13*).

Today, the most accepted view about BD pathogenesis is an increased response of the innate and acquired immune systems against environmental antigens and autoantigens in addition to a genetic predisposition (*13*). The presence of anti-lymphocyte and anti-cardiolipin antibodies has been reported in BD (*14*), and they are used in the diagnosis of the disease. The fact that BD is seen more in some ethnic groups and has intrafamilial prevalence implicates the role of genetic mechanisms in its pathogenesis. The most discussed genetic indicator is HLA-B51, a subclass of HLA class I. HLA-B51 has been identified as the gene with the strongest association with BD (*7*). The proportion of people who suffer from cardiac involvement is not entirely clear; in previous studies, it was identified in 7-46% of patients (*15,16*).

3. Diagnostic Criteria

Due to the lack of specific clinical and laboratory diagnostic tests, several sets of diagnostic criteria have been proposed. Of these, the criteria of the BD Committee of Japan (1987, revised in 2003) (*17*) and the International Study Group for BD (1990) (*18*) (Table 1) are relatively well validated and used worldwide. Based on the International Study Group for BD criteria, diagnosis requires the presence of recurrent oral ulceration plus at least two other criteria (recurrent genital ulceration, ocular signs, skin lesions, positive pathergy test). The Japanese criteria include major (oral ulcers, skin lesions, including subcutaneous thrombophlebitis and cutaneous hypersensitivity, eye lesions, genital ulcers or scars) and minor criteria (arthritis, gastrointestinal lesions, epididymitis, vascular lesions, central nervous system complications). For a definite diagnosis, the presence of four major criteria is required.

Both sets of criteria lack an appreciation of the importance of various venous and arterial lesions, and thromboembolic complications, frequently reported as part of the initial, oligosymptomatic, or classical overt clinical presentation of BD. Diagnostic uncertainties also include the issue of cardiac involvement. Perhaps a diagnosis of cardio BD in young subjects originating from countries along the Silk Road route should be considered even in cases when the major (classical) criteria, such as oral ulcerations or a positive pathergy test, are absent. In these cases, a detailed analysis of the heart and large vessels structures and functions by echocardiography, magnetic resonance imaging (MRI), computed tomography (CT), and appropriate follow-up will be required.

4. Cardiac involvement in BD

The morphological basis of the systemic manifestations in BD, including cardiovascular involvement, is vasculitis (*19*). More specifically, some pathologists consider perivascular structures as the main target of T lymphocyte-mediated immune reactions, and perivasculitis as an essential part of the vasculopathy in BD (*20,21*). The venous and arterial wall lesions attract cytokinergic and neutrophilic reactions. Activated neutrophils cause destructive effects by excessive production of superoxide anion radicals and lysosomal enzymes. Neutrophilic infiltration and advanced vascular wall destruction with aneurysm formation cause local blood flow abnormalities. Endothelial

dysfunction, release of von Willebrand factor, platelet activation, enhanced thrombin and fibrin generation, antithrombin deficiency, and impaired fibrinolysis close the pathological chain of enhanced thrombocoagulation associated with vasculitis (perivasculitis) in BD (*22,23*).

Cardiovascular involvement in BD is estimated to range from 7% to 46%. In the disease, vasculitis lesions that may affect veins and arteries of all sizes are present. It has been reported that venous involvement is 29%, and arterial involvement varies from 8% to 18% (*24*). Endovascular and perivascular inflammation may result in stenosis, thrombus, and aneurysms. The typical form of arterial involvement manifests as a real or false aneurysm. The frequency of vascular involvement was reportedly 14.3% in 2,319 cases, and was significantly higher in males. The most commonly seen complication was superficial vein thrombosis, followed by deep vein thrombosis (*25*). Blockage of the superior and inferior vena cavae, Budd-Chiari syndrome (hepatic vein thrombosis), and dural sinus thrombosis are other vascular complications (*26*). In arterial involvement, which is less common than venous involvement, the carotid, pulmonary, aorta, iliac, femoral, and popliteal arteries are more commonly affected. Although less frequently, the renal arteries may also be involved. The prognosis of patients with arterial involvement is poor, with death rates of 13.5% in those with arterial lesions, especially when the pulmonary artery and thoracic aorta are involved (*27*).

Coronary aneurysms may be seen during angiography procedures in patients with BD. Some of these aneurysms are asymptomatic, whereas others manifest with acute coronary syndrome (*28,29*). These aneurysms are isolable, and most are evident together with coronary stenosis and are sometimes seen together with several arterial aneurysms (*30,31*). Sinus Valsalva aneurysms and aortitis are the most frequently reported cardiac complications, with BD particularly involving the root of the aorta (*31-33*). Sinus Valsalva aneurysms may be seen alone or with other sinus aneurysms, and may lead to acute or chronic aortic failure.

BD frequently leads to aneurysmal dilation of pulmonary arteries (*34,35*). Such pulmonary arterial involvement shows high mortality and morbidity. Aneurysms caused by the involvement of large proximal branches of pulmonary arteries often occur and are initially symptomatic with hemoptysis. Hemoptysis due to pulmonary arterial aneurysms (PAA) should be differentiated from pulmonary emboli. Anticoagulant and fibrinolytic treatments given, based on a presumption of pulmonary emboli, may result in the death of patients with aneurysms (*36*). The diagnosis is confirmed by pulmonary angiography and CT. In the study by Ma *et al.*(*26*), Bentall operations in BD (aortic valve replacement + ascending aorta replacement) were performed more frequently than in a normal population, and aortic valve separations were seen more frequently among these cases (*37-39*).

Heart involvement in BD may progress as endocarditis, myocarditis, pericarditis, intracardiac thrombosis, endomyocardial fibrosis, and valve diseases. Pericardial involvement has been reported as the most common manifestation of cardiac involvement in some series (*15,40*). The clinical presentation may be acute pericarditis, hemorrhagic pericardial tamponade, constrictive pericarditis, recurrent pericarditis, or even just a small, asymptomatic pericardial effusion (*41,42*). Endomyocardial involvement typically manifests as endomyocardial fibrosis on the right and/or left side of the heart (*15,43-45*).

Interatrial septum aneurysm, mitral valve prolapse, and mitral failure are rarely seen (*46*). Intracardiac thrombus is generally one of the serious cardiac complications, and may be one of the first findings of the disease with pulmonary emboli, or may cause cerebral emboli by passing through the patent foramen ovale. Often, the right ventricle is involved, but it has been demonstrated that the left ventricle can also be involved (*47-49*). In the study by Geri *et al*. (*46*), 807 BD cases aged 30 years on average were examined, and significantly more heart pathologies were found at a rate of 6% compared to the normal population. Of the heart conditions, 38% were pericarditis, 26% were endocarditis, 19% were intracardiac thrombus, 17% were myocardial infarcts, 7% were endomyocardial fibrosis, and 2% were myocardial aneurysm. Among the group with no heart involvement, which was a majority of the patients, BD was detected in the deep and superficial veins at a rate of 59%.

A component of BD is cardiomyopathy, which can be ischemic, non ischemic, or inflammatory in nature. Clinically, it can manifest as systolic or diastolic heart failure, or in a more subtle way, as asymptomatic systolic or diastolic dysfunction (*50,51*). In a study performed in our clinic, 30 BD patients were evaluated by conventional and tissue Doppler parameters. The parameters included peak early diastolic (E) velocity and deceleration time of early diastolic flow (DT), mitral annular early diastolic (Em), and late diastolic (Am) velocities, which were impaired in the early stages of the disease. The strain and strain rate values that showed left ventricular systolic and diastolic function were significantly decreased in the patient group compared to the healthy controls (*5*). In a similar study by Yağmur *et al*. (*6*), meaningful decreases were found in regional and mean longitudinal strain values in the early period in BD cases, but increases were seen in NT proBNP values.

5. Prognosis

BD is a chronic and inflammatory disease and shows relapses and remissions. Among young people and males, its progress may be more severe. As age advances, remissions lengthen and the severity of

relapses reduces. Among factors that affect BD morbidity, ethnicity, geographic, and genetic features have been most emphasised (*52*). The prognosis of mucocutaneous involvement in BD is generally good. Ocular involvement, which starts during the early years of the disease, is the most important cause of morbidity, whereas vascular involvement represents the most important cause of mortality. Neurological involvement is progressive among most patients, and is sometimes fatal. Annual mortality in BD varies between 2% and 4%. The most common causes of mortality are rupture of vascular aneurysms, intestinal ulcer perforations, and MSS involvement. PAAs and Budd-Chiari syndrome are associated with higher mortality rates. Overall survival in BD patients with cardiac involvement is poorer than in those without (*47*).

6. Treatment of BD with Cardiac Involvement

Because the aetiopathogenesis of BD is unknown, there is no specific treatment. Treatment of BD is still based on a low level of evidence (*i.e.*, expert opinions) (*53*). The aim of the treatment is to correct the symptoms, and to prevent the disease from causing permanent organ damage by repressing inflammation. Pharmacological agents used for the treatment of BS include corticosteroids, colchicine, azathioprine, and tumour necrosis factor-α inhibitors, among others. Pericarditis has always been treated with aspirin and immunosuppressive agents (*40*). In the setting of tamponade, emergency pericardiosynthesis may be necessary (*41*). Thrombus management is determined based on the mobility of the thrombus. If the thrombosis seems relatively immobile and is not susceptible to emboli, acetylsalicylic acid, warfarin, corticosteroids, and immunosuppressive agents may be used. However, more mobile thrombuses should be treated with thrombolytic agents (*48,54*). Acute myocardial infarction can be treated with percutaneous coronary intervention or surgical revascularisation (*46*). Myocardial involvement is almost always associated with endomyocarditis. Endomyocardial fibrosis in some cases has been cured with corticosteroids, colchicine, or immunosuppressive agents (*46,55*). High-dose prednisolone and azathioprine can be used, along with the routine treatment of cardiac failure, and in some patients, cardiac function has improved with these medications (*50*). The presence of PAA is associated with higher mortality rates (*56*). Prognosis in these patients becomes better with early diagnosis and intense immunosuppressive treatment (*56,57*). Transcatheter embolectomy has also proven beneficial (*34,35,58*). Oral anticoagulants and antiplatelets are often used to treat thromboembolic complications in BD. However, antithrombotic therapy should be administered cautiously, given the proneness of BD patients to bleedings, particularly from symptomatic or asymptomatic pulmonary aneurysms. Overall survival in BD patients with cardiac involvement is poorer than in those without. Complete remission of cardiac involvement has been associated with the use of immunosuppressants, colchicine, and anticoagulants.

7. Conclusions

BD is a disease with multi-organ involvement and thus shows signs and symptoms in many systems. The main cardiac features of BD include pericarditis, myocardial (diastolic and/or systolic) dysfunction, valvular, coronary (thrombosis, aneurysms, rupture), and intracardiac thrombus. Several cardiac manifestations may coincide in one patient. Cardiologists should always bear in mind the potential threats of symptomatic cardiovascular involvement in BD and consider diagnostic measures (echocardiography, CT, MRI) for its timely detection. The prognosis of cardiac lesions is poorer than that of lesions in others organs involved in BD, but anticoagulation, immunosuppressant agents, and colchicine seem to improve the prognosis of cardiac manifestations in BD.

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