Cardiac findings in patients with Behçet's disease: Facts and controversies

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Abstract

Behçet's disease (BD) is a systemic vasculitis of unknown etiology. It is characterized by recurrent oral and genital ulcers, uveitis, and a number of systemic manifestations. Although the disease is recognized worldwide, its prevalence is highly variable. A detailed review and analysis of the worldwide published reports on BD showed that not only the prevalence of the disease but also its cardiac complications differ according to the geographic distribution of the studied population. With the exception of France, Greece, Spain, and Italy, very few reports and studies regarding BD have been published from the western countries. Cardiovascular complications are an important cause of poor outcome in patients with BD. Over the past few years, many case reports and studies have been published, providing more facts about these complications. For example, peculiar echocardiographic findings in patients with aortic valve regurgitation and intracardiac thrombi secondary to BD were recently described. The role of these findings in the initial diagnosis of the disease, however, remains to be evaluated. On the other hand, some reports present contradictory results, especially concerning the left ventricular diastolic function, pathogenesis of coronary artery disease, and proper management of the cardiac complications in BD. Importantly, management of these complications is based mainly on the discretion of the treating physician due to the absence of large controlled studies and clear guidelines. This approach sometimes creates inconsistent data and allows controversies to persist. The review presented here will discuss some of the facts and controversies related to cardiac complications in BD. *(Anatol J Cardiol 2016; 16: 529-33)*

Keywords: Behçet's disease, aortic valve regurgitation, intracardiac thrombi, left ventricular function, coronary artery disease

Introduction

Behçet's disease (BD) is a systemic vasculitis of unknown cause that is recognized worldwide. Because of its peculiar geographic distribution, BD was known as the "silk route disease." The highest prevalence rates of the disease are seen in Turkey, Middle East, Japan, Korea, and China (1), and its occurrence seems to be related to both environmental and genetic factors (2).

Cardiac involvement has been previously documented in patients with BD (3, 4). Its exact incidence, nature, severity, and management, however, are not well established. There is a marked discrepancy between the types and response to treatment of such cardiac complications among the studied patients. While the most commonly published reports from Turkey, Middle East, and Mediterranean regions have described cases of BD with intracardiac thrombi (ICT), the aortic valve regurgitation and its surgical complications somehow remain restricted to the Asian countries, especially Japan, South Korea, and China. Published reports concerning cardiac complications among patients in the western countries, with few exceptions, are very sparse. Causes for such discrepancies might be partially related to the frequency of publication, geographic distribution, prevalence of the disease, genetic make up, or even, drugs used for the treatment of BD. Are we dealing with different forms of the same disease or two different diseases? The establishment of a regional or an international registry to thoroughly study these patients, recognize the variable cardiac findings among different countries, and accordingly improve the patients' outcome has been previously suggested and seems to be an appropriate tool for better understanding of the disease (5). In this review, the authors will discuss some interesting facts and controversies related to cardiac involvement in patients with BD.

Coronary artery disease

Coronary artery disease is extremely uncommon in BD, with a reported prevalence of 0.5% (6, 7). This complication poses several diagnostic and therapeutic challenges and occurs pre-

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dominantly in male patients (8, 9). Cases of coronary involvement in patients with BD were mainly published from Turkey, Mediterranean Basin, Middle East, and Asian countries (10–16). The age range at the time of presentation varied widely. A report from China described the occurrence of extensive anterior myocardial infarction in a young boy at the age of 12. This child additionally had an ascending aortic aneurysm (15). In another report from Italy, an acute coronary event was documented in an 80-year-old male patient with BD (12).

The majority of patients with coronary events were previously diagnosed with BD and were on regular treatment; less commonly, coronary complications may occur as the first manifestation of the disease. In a previous report, the diagnosis of BD was done several months following an index inferior myocardial infarction in a 40-year-old male patient who underwent percutaneous intervention of the right coronary artery and presented 4 months later with right femoral artery pseudoaneurysm necessitating surgical intervention. Despite the development of oral ulcers, the diagnosis was not made because of the lack of the other criteria for diagnosis. Only diagnosis was made histopathologically when 1 month later the patient developed left ventricular and right coronary artery pseudoaneurysms that required surgical repair (14).

The exact etiology causing acute coronary events is not well determined in patients with BD. Unlike patients with other autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis, increased atherosclerosis is not a prominent feature of BD, even among those with major organ involvement (7, 17). Angiographically, coronary aneurysms and stenotic lesions are the most frequently detected lesions. Local coronary vasculitis causing fibrous intimal thickening may result in coronary occlusion with subsequent development of symptoms of acute coronary syndrome, namely unstable angina and acute myocardial infarction (7). Occasionally, acute myocardial infarction might occur in patients with BD and angiographically normal coronary arteries. Impaired microvascular function is believed to be the cause of coronary events among these patients (18). A fresh floating thrombus in otherwise angiographically normal coronary arteries has also been documented, suggesting an underlying pro-thrombotic etiology (10). External compression of a coronary artery by an aneurysmal dilation of the left sinus of Valsalva has also been reported (19).

The proper management of coronary artery disease in patients with BD is controversial. One important reason for such controversy is the small number of patients and lack of large controlled studies to determine the best treatment strategy. Generally, in addition to the standard anti-ischemic medications, early initiation of immunosuppressive therapy is recommended. Corticosteroids, colchicine, azathioprine, and cyclophosphamide were the most commonly used agents in previous reports (16, 20, 21).

Management of these patients is not always uncomplicated. For example, the use of anticoagulants and thrombolytic agents may cause severe bleeding in patients with aneurysms (16). Additionally, the administration of corticosteroids following acute myocardial infarction is believed to interfere with the ventricular healing process and increases the risk of scar thinning and myocardial rupture (22).

Mechanical manipulation of the coronary vessels—whether percutaneously or surgically—during the active phase of vasculitis is risky and carries a higher possibility for development of complications (20). The long-term outcome and patency of percutaneously implanted coronary stents is not available (10).

In patients with BD who are scheduled for coronary artery bypass graft surgery, the following measures should be always taken to improve the outcome and reduce the incidence of complications. First, patients must receive adequate medical treatment prior to and after the surgery to reduce the inflammatory burden and allow better handling of the tissues. Second, all the vessels—whether arterial or venous—that could be implanted as grafts should be thoroughly, preoperatively screened to rule out associated vasculitis (23). Third, excessive aortic manipulation should be avoided (24).

There is a debate regarding the best implanted grafts in these patients. Some researchers recommend the use of in situ arterial grafts instead of free vein grafts to reduce the number of aortic puncture sites (24). Others, however, advice against the use of subclavian grafts because of the possible development of post-operative stenosis or occlusion secondary to vasculitis (23). Şişmanoğlu et al. (24) studied the 5-year patency of coronary grafts in three patients with BD. They found patent arterial grafts in two patients and an occluded venous graft in one (24). Large studies designed to assess the long-term outcome and patency of these grafts are required for clarification of facts in this regard.

Ventricular functions

While sporadic cases of myocarditis in BD have been reported, symptomatic systolic dysfunction does not appear to be a prominent finding. Several studies have recently proved subclinical left and right ventricular systolic affection using more recent imaging techniques (25, 26). On the other hand, there are several contradictory published data concerning the impairment of the left ventricular diastolic function in BD. In previous reports and compared with healthy controls, left ventricular diastolic function was unaffected in patients with BD regardless of the disease activity, co-morbidities, and used medical regimens (27, 28). Others documented impaired ventricular diastolic function among these patients (29, 30). The prevalence of left ventricular diastolic dysfunction, as documented by prolonged transmitral deceleration time, was documented more in patients with BD and history of vascular complications compared with those without. The authors explained this finding by the possible deleterious effect of proinflammatory cytokines on the left ventricular functions (30). One possible explanation for such discrepancy is the fact that the assessment of the left ventricular diastolic

function using various echocardiographic methods is generally not simple. Many factors, other than the ventricular diastolic dysfunction, may alter the variable velocities and indices widely used for the assessment of the diastolic function. Most important factors that are frequently encountered in patients with BD include tachycardia, anxiety, hypertension, drugs, and abnormal pre-load (31). Furthermore, the variable duration of the disease among the studied patients, presence of co-morbidity, disease activity, genetic makeup, and even, geographical distribution may affect the development of diastolic dysfunction and explain its presence/absence among some patients (32).

Aortic valve regurgitation

Aortic regurgitation secondary to BD occurs only rarely. It is widely accepted that annular dilation and sinus of Valsalva aneurysm secondary to aortitis, rather than abnormalities of the valve per se, are the main causes of aortic regurgitation in these patients. Disease-specific changes involving the aortic cusps in patients with BD such as cuspal aneurysmal changes, echocardiographic-free spaces, and mass-like lesions with or without annular dilation (both valvulitis and aortitis) have also been documented (33).

Severe aortic valve regurgitation can be the first clinical presentation of BD. It may occur even in the absence of other proposed criteria required for diagnosis of BD, resulting in a delayed diagnosis, inappropriate surgical procedures, and worse outcome. Jeong et al. (34) studied the mortality in 19 patients undergoing surgical intervention for management of severe aortic regurgitation secondary to BD. Mean follow-up duration from the index surgical procedure was 77.4±68.1 months (range, 9–271 months). Only seven patients were known to have BD preoperatively and were under medical treatment. They found that the overall mortality in these patients was high (47.3%), and it correlated with inflammatory markers, namely C-reactive protein and erythrocyte sedimentation rate. The concomitant administration of immunosuppressive therapy was associated with a significantly better 13-year event-free survival. Prosthetic valve endocarditis developed in four patients and was associated with poorer outcome. Histologic examinations showed evidence of both valvulitis secondary to involvement of the aortic valve and aortitis due to affection of the aortic root. Medial narrowing, thickened adventitia, and thrombotic occlusion of the vasa vasorum have also been documented. Interestingly, the examined specimens showed variable inflammatory reactions depending on the preoperative use of corticosteroids. All patients (n=12) who were not on corticosteroid therapy prior to the open heart surgery developed post-operative complications in the form of valvular detachment, endocarditis, interventricular dissection, paravalvular leakage, and progressive aortic regurgitation (34). These findings suggest the importance of preoperative diagnosis and medical control of the disease prior to any surgical intervention in order to avoid increased postoperative morbidity and mortality (35).

Surgical replacement of the aortic valve as well as the aortic root using a valved conduit is the standard surgical management of aortic regurgitation in BD, but results have not been satisfactory. Tissue fragility, paravalvular leakage, valve detachment, and pseudoaneurysm formation frequently occur after valve replacement. Many modified procedures such as the use of subannular ring reinforcement technique have been performed to reduce the incidence of post-operative complications (36–38).

Unfortunately and despite very poor surgical outcome compared with that in patients with rheumatic or other causes of aortic regurgitation, management of aortic regurgitation in patients with BD has not been addressed in the guidelines. What would be the best time to perform surgery, which drugs need to be given preoperatively to improve the outcome, how to preoperatively monitor the activity of the disease, and what are the predictors of early and late post-operative complications are important questions that need further research. Another issue that should be addressed is the possible consideration of the peculiar echocardiographic findings as criteria that can improve the early detection of BD in patients not previously diagnosed as having BD.

Intracardiac thrombi

While most of the cases of aortic regurgitation have been published from Asian countries, most of the cases with BD and ICT have been reported from Turkey, Mediterranean Basin, and the Middle East. The majority of reported cases show the evidence of right cardiac thrombi, with the right ventricle being more affected than the atrium. ICT were more commonly seen among young male patients (5, 39–45).

The presenting symptoms are usually the same among all patients, namely shortness of breath, fever, hemoptysis, and palpitation. Facial swelling, as a first presenting symptom, was also reported (46). ICT occurred more commonly in patients not previously diagnosed with BD, still others developed in patients on regular medical treatment. Some of the previously undiagnosed patients were diagnosed only following surgical removal of the thrombi. ICT may recur, especially following surgical removal (5).

Anemia, elevated erythrocyte sedimentation rate, and elevated C-reactive protein levels are frequent laboratory findings. The thrombi are variable in size and occasionally mobile. Recurrent deep and superficial thrombophlebitis affecting the veins of the lower limbs are the most commonly reported vascular abnormalities in patients with ICT. Less frequently, thrombosis may be detected in the superior and inferior vena cava. Concomitant arterial lesions are far less common, with the pulmonary arterial aneurysms and thrombosis being the most commonly diagnosed arterial abnormalities (40, 47).

Data in the literature about the proper management of these lesions are inconsistent, and the treatment of ICT in patients with BD remains largely dependent on the discretion of the treating physician and the experience of the center, rather than being based on large studies, guidelines, or evidence based

medicine. A long list of various drugs such as corticosteroids, colchicine, cyclophosphamide, warfarin, low-molecular-weight heparin, and occasionally, thrombolytic therapy were frequently used (40–43). The majority of cases received anticoagulants for the treatment of ICT, with satisfactory results; still, in a minority of patients, complete resolution of ICT was achieved using immunosuppressive agents without concomitant use of anticoagulants. Fear of development of hemoptysis secondary to the rupture of associated pulmonary arterial aneurysms was the most important reason why the treating physicians avoided the use of anticoagulation in these patients (39, 40). Anticoagulants alone—even after surgical removal of ICT—without concomitant administration of immunosuppressive agents failed to cause regression or disappearance of ICT (48).

The majority of researchers have warned against the surgical resection of these lesions because of the high risk of recurrence and worse post-operative outcome.

Conclusion

Cardiac complications in BD are rare and associated with a worse outcome. Due to the rarity of these complications, large controlled studies and clear guidelines concerning their proper management are lacking. Aortic valve regurgitation and cardiac thrombi necessitating surgical intervention may precede the other manifestations of BD. Since inflammation is the major underlying mechanism for development of these lesions, surgical procedures without preoperative diagnosis of BD and the concomitant use of immunosuppressive therapy are frequently complicated. These are important facts concerning cardiac complications in BD. On the other hand, questions regarding adequate immunosuppressive dosing, especially in patients with post-operative infective endocarditis; duration of therapy; use of combination therapy; and the most appropriate surgical procedure(s) in these patients require clear answers and recommendations. Furthermore, the use of anticoagulants in patients with cardiac thrombi associated with pulmonary arterial lesions is still under debate. Despite the available published studies and advances in cardiac imaging, controversies surrounding the impairment of the left ventricular diastolic function in BD remain. Moreover, there is insufficient data regarding the long-term patency of coronary stents and surgical grafts in BD. Recommendations based on large studies as well as national and regional database are required for prompt diagnosis and proper management of these patients.

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