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Evaluation of myocardial perfusion in patients with Behçet's disease

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Aim: To estimate the prevalence of silent myocardial ischemia (SMI) in patients with Behçet's disease (BD) and to identify a subgroup of patients at higher risk for the presence of SMI. ***Materials and Methods:*** We evaluated 41 patients (mean age 42.8 ± 12.3 years) with BD and 35 healthy control subjects. Treadmill exercise test and thallium-201 myocardial perfusion single photon emission computed tomography (SPECT) were performed in all subjects. Coronary angiography was performed in all patients with a diagnosis of SMI in Behçet's group. ***Results:*** All subjects had normal resting electrocardiograms. Eight patients with BD (19.5%) had evidence of ischemia on exercise testing and myocardial perfusion SPECT. Only one SMI positivity (2.9%) was recorded in the control group. Significant coronary stenosis was not found with coronary angiography in the patients with a diagnosis of SMI in Behçet's group. SMI positivity was recorded in 2 of 18 female patients (11%) and in 6 of 23 male patients (26.1%) with BD ($p = 0.429$). The mean duration of BD was 13.8 ± 2.6 years in patients with SMI and 7 ± 4.1 in patients without it ($p < 0.001$). Seven of the 8 patients (87.5%) with SMI had a duration of BD of greater than 10 years. ***Conclusions:*** The results of this study show that the prevalence of SMI is high in patients with BD. Based on our findings, screening with myocardial perfusion scintigraphy may be recommended for patients with duration of BD greater than 10 years.

Key words: Behçet's disease, myocardial perfusion, scintigraphy, silent myocardial ischemia

INTRODUCTION

BEHÇET'S DISEASE (BD) is a generalized chronic inflammatory disease characterized by a triad of recurrent oral aphthous lesions, genital ulcers and uveitis.[1] However, involvement of many other systems is also observed.[2] Clinical reports have shown cardiac abnormalities in from 7 to 46 percent of cases.[3] Various cardiac abnormalities including pericarditis, myocarditis, endocarditis, aortic stenosis and insufficiency, aortic aneurysm, atrial fibrillation, thrombus, coronary arteritis, valvular dysfunction, acute myocardial infarction and cardiomyopathy have been described in patients with BD.[4–19] Silent myocardial ischemia (SMI) has also been reported in Behçet's patients.[20] But, there is little knowledge about SMI in BD. The aim of this study was to estimate the prevalence of SMI in patients with BD and to identify a subgroup of patients at higher risk for the presence of SMI.

MATERIALS AND METHODS

A total of 41 patients with BD (18 women and 23 men, mean age 42.8 ± 12.3 years; range, 20–69) were included in this study. BD was diagnosed according to the criteria reported by the International Study Group for Behçet's Disease.[2] All of the patients were in the inactive, remission phase of BD. From the start no patients had any clinical evidence of cardiac disease or abnormal electrocardiograms (ECG). Thirty-five sex and age matched healthy volunteers were selected as a control group. They were all free of cardiac and/or systemic disease. Their clinical and routine laboratory examinations and electrocardiograms were all considered normal. Subjects with hyperlipidemia, hypertension, diabetes mellitus, family

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history of coronary atherosclerosis, or history of smoking were not included in this study. Seven of 41 (17%) patients with BD had major vascular disease. All of the major vascular lesions were deep vein thrombosis.

Informed consent was obtained from all patients. Ethical committee approval was given and the study was conducted according to the ethical principles laid down in the latest version of the Declaration of Helsinki.

Treadmill exercise testing was carried out according to the Bruce protocol. Throughout the exercise testing the 12-lead ECG and blood pressure were monitored and recorded every minute. The response was considered to be positive when horizontal or downslopping ST-segment depression was ≥1 mm in magnitude from the baseline or upslopping depression was ≥1.5 mm at measurements obtained 0.08 seconds after J point. One hundred eleven MBq of thallium-201 was injected intravenously at near-maximal exercise. Imaging was initiated within 10 minutes after the injection of thallium. The redistribution image was obtained 4 hours later. We used a dual-headed rotating gamma camera (Optima, General Electric Medical Systems, Milwaukee, WI) equipped with a high resolution collimator to perform these studies. Thirty-two projections (40 seconds) were obtained over 180° arc from the 45° right anterior oblique to the left posterior oblique position in a 64 × 64 matrix with one zoom. Both stress and redistribution data were reconstructed after filtered back projection using a Hanning filter. One pixel thickness tomographic slices in short, vertical long, and horizontal long axis planes were obtained. We performed visual analysis of stress and redistribution images displayed on short-axis, horizontal-long axis and vertical-long axis views. The left ventricle was divided into seventeen segments using an apical, mid-, and basal short-axis slice as well as a mid-vertical long-axis view. Each segment was qualitatively scored using a 5-point scoring system (0: normal, 1: mild, 2: moderate, 3: severe reduction in photon activity, and 4: absence of photon activity). For each image, a summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores for all 17 segments. Images with an SSS greater than the respective SRS were classified as reversible. Myocardial perfusion scintigraphy was classified as normal (SSS < 4), mildly abnormal (SSS = 4–8), moderately abnormal (SSS = 9–13) or severely abnormal (SSS > 13). Results of myocardial perfusion scintigraphy were independently interpreted by two experienced observers who were unaware of the clinical presentation of the patients. Any disagreements were resolved by consensus.

Coronary angiography was performed within one month when any noninvasive test was positive. Fifty percent or more arterial narrowing was considered pathological.

Statistical analysis: Results are shown as mean ± SD values. A p value of <0.05 was considered significant. The comparison of sex between the patient and control groups was performed with Pearson chi-square test. The Mann-Whitney U test was used to compare differences between the groups for age and duration of disease. Comparison between the groups according to SMI posi-

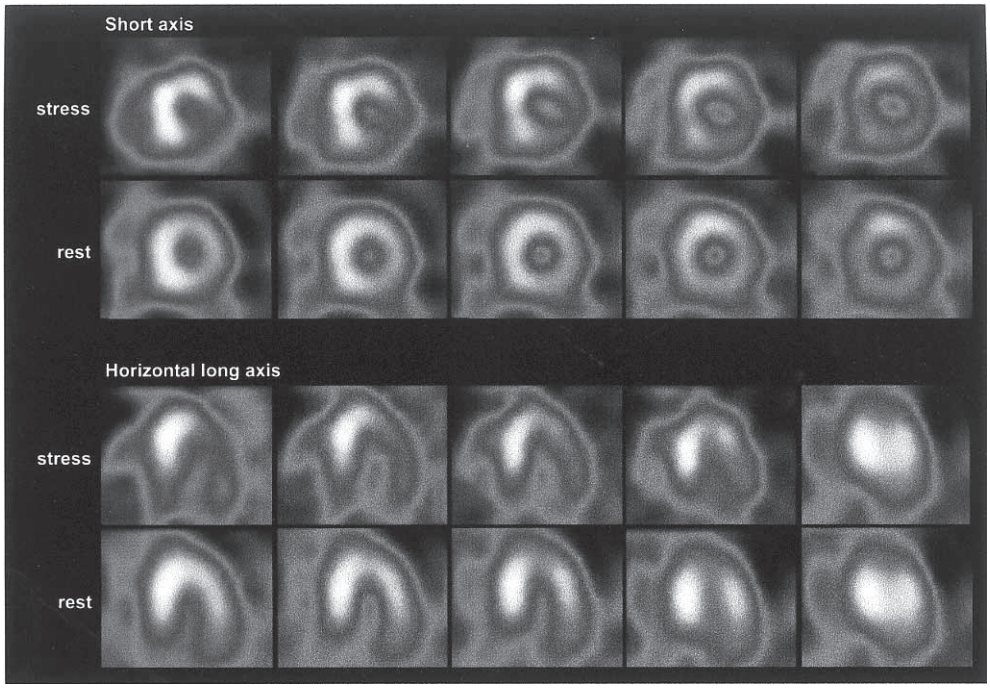

Fig. 1 (a) Short axis views, (b) Vertical long axis views at stress and redistribution. There is reversible ischemia identified in the lateral and inferolateral walls.

Table 1 General characteristics of the patients and control subjects

General characteristics	Patients (n = 41)	Control subjects (n = 35)	p value
Female/male ratio	18/23	15/20	NS
Mean age ± SD (years)	42.8 ± 12.3	42.2 ± 11.8	NS
Distribution of symptoms			
Recurrent oral ulcers	100%	–	
Eye lesions	61%	–	
Genital ulcers	83%	–	
Skin lesions	78%	–	
Arthralgia	54%	–	
Gastrointestinal involvement	20%	–	
Deep vein thrombosis	17.1%	–	
Positive pathergy test	66%	–	
Neurologic findings	7%	–	

NS: non-significant

tivity was performed with Fisher's exact test.

RESULTS

The physical characteristics of patients and controls are summarized in Table 1.

In all patients the ECG stress test was maximal, with heart rate 85% or more of the predicted maximal heart rate (MPHR: 220-age) for age. No patient experienced chest pain during the test. Results of exercise ECG were positive in 8 of 41 Behçet's patients and in 1 of 35 control patients. SMI was found in those 8 (19.5%) patients with BD and 1 (2.9%) in control group with thallium-201 myocardial perfusion scintigraphy. The difference was statistically significant between Behçet's and control groups (p = 0.033) (Table 2). According to the results of segmental analysis, abnormal perfusion (perfusion defect) was found at stress studies in 8 Behçet's patients and in one in the control group. All of the stress perfusion defects were moderate (SSS: 9–13) and showed complete filling at redistribution studies. Fixed perfusion defect was not seen. Reversible defects were inferior in 4 cases, anterior in 3 cases, and lateral and inferolateral (Fig. 1) in one on thallium-201 myocardial perfusion scintigraphy in patients with BD. In the control group, there was one case with inferior reversible ischemia on thallium-201 myocardial perfusion scintigraphy.

In Behçet's group, SMI positivity was recorded in 2 of 18 female patients (11%) and in 6 of 23 male patients (26.1%), but the difference between two groups was not statistically significant (p = 0.429) (Table 3).

The time from onset of BD to the time of testing for SMI ranged from 9 months to 16.3 years (mean, 8.3 ± 4.7 years). The mean duration of Behçet disease was 13.8 ± 2.6 years in the patients with SMI and 7 ± 4.1 in those without it. The difference in the duration of BD between the SMI positive and negative groups was statistically significant (p < 0.001) (Table 3). Seven of the 8 patients (87.5%) with SMI had a duration of BD greater than 10 years.

Table 2 Comparison of SMI incidence in Behçet's and control groups

	Behçet's group	Control group	p value
SMI + (%)	19.5	2.9	0.033
SMI – (%)	80.5	97.1	

SMI: Silent myocardial ischemia

There was no significant difference in age between the BD patients with and without SMI (Table 3). Major vascular involvement was found in 7 patients with BD. Two of 8 patients (25%) with SMI had major vascular involvement compared to 5 of 33 patients (15.2%) without SMI (p = 0.606). The prevalence of other types of involvement was not significantly different between the two groups (Table 3).

Coronary angiography was performed in all subjects with SMI, and significant coronary stenosis was not found in Behçet's patients. In the control group, the single case with SMI refused to undergo angiography.

DISCUSSION

Behçet's disease was first described in 1937 as a triple syndrome of oral and genital ulcers, uveitis, and cutaneous findings. Many organ systems may be involved.[2] The underlying basis for the lesions is believed to be vasculitis, especially in the microvascular circulation.[21] Involvement of the arteries and arterioles due to vasculitis in BD, with narrowing of their lumen by focal fibrinoid deposition and fibroelastic proliferation in the wall of the small vessel, is well known.[4]

The prevalence of cardiac involvement in BD has not been clearly defined. Ozkan et al.[16] reported that cardiac involvement in BD was rare; however, Morelli et al.[22] suggested that there was a high prevalence of cardiac abnormalities in patients with BD. Cardiac manifestations include pericarditis, myocarditis, endocarditis, aortic stenosis and insufficiency, aortic aneurysm, atrial

Table 3 Comparison of clinical characteristics of the patients with and without silent myocardial ischemia in Behçet's group

	with SMI (n = 8)	without SMI (n = 33)	p value
Sex (F/M)	2/6	16/17	0.429
Age (years) mean ± SD	43.1 ± 9.2	42.8 ± 13.1	0.834
Duration of BD (years) mean ± SD	13.8 ± 2.6	7 ± 4.1	< 0.001
Major vascular involvement	2/8	5/33	0.606
Recurrent oral ulcers	8/8	33/33	–
Eye lesions	5/8	20/33	1.000
Genital ulcers	6/8	28/33	0.606
Skin lesions	5/8	27/33	0.137
Arthralgia	4/8	18/33	1.000
Gastrointestinal involvement	2/8	6/33	0.642
Positive pathergy test	5/8	22/33	1.000
Neurologic findings	1/8	2/33	0.488

SMI: Silent myocardial ischemia
BD: Behçet's disease

fibrillation, thrombus, coronary arteritis, valvular dysfunction, acute myocardial infarction and cardiomyopathy.[4–19]

In the literature, it has been implicated that cardiac involvement due to BD can be seen frequently without symptoms.[1,23,24] Silent myocardial ischemia that is defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents has also been reported in patients with BD.[20] The pathophysiology of silent ischemia is unclear. Autonomic nervous system dysfunction has been reported in patients with BD[25,26] and it might be the factor responsible for SMI. There are some studies showing that silent ischemia is more prevalent in patients with autonomic neuropathy than in those with normal autonomic function.[27,28] The investigators suggested that the neuropathic damage to the myocardial sensory afferent fibers in the autonomic nerve supply reduced the individual's sensitivity to regional ischemia by interrupting pain transmission.[29] Despite being asymptomatic, SMI may have a poor prognosis.[30] Various screening methods for SMI are available, including continuous 24- or 48-h heart monitoring with the holter technique, exercise ECG, and myocardial perfusion scintigraphy.

In the literature, we could find a single report of SMI in patients with BD, in which the SMI prevalence was 25% in patients with BD.[20] Our results here, which are similar to those of Gullu et al.,[20] suggest 19.5% frequency of SMI in asymptomatic Behçet's patients.

Visual interpretation of thallium SPECT may dismiss the diffusely impaired microcirculation because the uptake of thallium represents only a relative reduction of the perfusion in the diseased territory compared with other non-diseased parts of the myocardium. The visual interpretation should be combined with quantitative analysis for the final decision. In addition, thallium washout analysis values may be helpful to pick up patients with a diffusely impaired microcirculation.

In our study, coronary angiography was performed in patients with SMI positivity, but we did not find any significant coronary stenosis in patients with BD. Myocardial perfusion scintigraphy positivity might have been related to an alteration of coronary vasomotor activity secondary to changes in endothelial function and/or coronary reserve due to intramyocardial microangiopathy. As a result of disturbance of the coronary microcirculation, small areas of myocardial fibrosis may develop.[4,15,20] This small vessel disease is like syndrome X that may be due to a variable response to exercise stress by the coronary vessels creating an apparent defect.

Major vascular involvement is well known in patients with BD. It may be arterial or venous. Arterial lesions of BD are characterized by the formation of aneurysms and thromboembolic occlusion of the lumen. Venous involvement may be variceal, but is usually occlusive.[31] Gullu et al. found a statistically significant difference in the presence of vascular involvement between the SMI positive (77.7%) and negative groups (14.8%). In their study, major vascular diseases in patients with SMI, were superior or inferior vena cava thrombosis, aneurysm and thrombosis in the pulmonary artery and its branches, and deep vein thrombosis.[20] In our study, the prevalence of major vascular lesions was higher in patients with SMI than those without it (25% vs. 15.2%, respectively). But, the difference between two groups with regard to major vascular involvement was not statistically significant. All of the major vascular lesions were deep vein thrombosis in our group.

Behçet's disease is a chronic disease. There may be a relation between cardiac involvement and its duration.[19,22,32,33] Komşuoğlu et al. and Gemici et al. found a good correlation between duration of disease and left ventricular diastolic dysfunction development.[19,32] Özdemir et al. suggested that there was a positive correla-

tion between the nocturnal decrease in systolic blood pressure, diastolic blood pressure, heart rate, heart rate variability parameters, diastolic dysfunction and duration of disease.[33] In our study, it was found that the prevalence of SMI was significantly higher in patients with long duration of disease. The duration of disease was greater than 10 years in 7/8 (87.5%) of the SMI positive patients.

The treatment of Behçet's disease is highly problematical, and one often has to resort to combinations of drugs in an attempt to control the various clinical manifestations. Treatment with corticosteroid and immunosuppressant drugs may cause microcirculation abnormality. It has been shown that long-term use of corticosteroids is associated with increased mortality from coronary heart disease.[34] Disease duration is a key for the development of silent myocardial ischemia in our study. This may be attributable to the medication exposure in this subset of patients. In our group, most of the patients received long-term medical treatment (colchicines, glucocorticoids, antiagregan, or non-steroid anti-inflammatory drugs) according to their clinical features and the content of medical treatment of the patients with and without silent ischemia was not significantly different.

In conclusion, the results of this study show that the prevalence of SMI is high in patients with BD. Based on our findings, screening with myocardial perfusion scintigraphy may be recommended for patients with a duration of Behçet's disease of greater than 10 years.

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