



## Doppler Microembolic Signals in Behcet's Disease with Nervous System Involvement

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### ABSTRACT

**Background:** Behçet's disease (BD) is a multisystemic inflammatory vasculitis of unknown etiology, and vasculitis being its major pathological feature. **Objectives:** We studied the prevalence of microembolic signals (MES) in patients with diagnosis Behçet's disease. We also tried to determine the frequency of MES in BD patients with or without neurological involvement.

**Materials and Methods:** This study enrolled 40 patients who fulfilled the diagnostic criteria of International Study Group for BD during 2012 to 2013. Bilateral transcranial Doppler ultrasound of the middle cerebral arteries was performed by multigate method. MES were identified based on the criteria of International Consensus group on Microembolus Detection.

**Results:** We found MES in none of our patients with BD. We measured intima-media thickness in all patients.

**Conclusion:** It seems that in our population core histopathologic phenomenon to be other than MES and vasculitic phenomenon may be implicated as a pathophysiologic factor for central nervous system involvement. The clarification of this subject needs further investigations on Iranian BD patients.

**Keywords:** Behçet's Disease; Transcranial Doppler; Microembolic Signals

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## Introduction

**B**ehçet's disease (BD) is a multisystemic inflammatory vasculitis of unknown etiology, and vasculitis being its major pathological feature (1,2). Neurological involvement is one of the most dangerous manifestations of BD (neuro-BD). This complication may occur by primary brain parenchymal lesions (neuro-BD) or be secondary to major vascular involvement (vascular BD) (3-6). In patients with neuro-BD, neurological focal deficits may be seen either acutely or by gradual onset, and they usually progress in a halting manner with periods of acceleration and incomplete remission and with neurological deficits such as transient ischemic attacks, stroke, bulbar, and pseudobulbar palsy, cerebral venous thrombosis, and pseudotumor cerebri (7-10). The pathophysiology of vascular BD is not clear, and knowledge is limited by data derived from pathological and angiographic studies (11-15). Transcranial Doppler (TCD) studies showing solid and gaseous microembolic materials may be an alternative method to search for the pathophysiology of BD (16-18). So we performed TCD in BD patients, to ascertain detection of microembolic materials in a case series of BD patients.

## Materials and Methods

This study is a case series on patients with BD. The study samples were enrolled consecutively from patients with BD who had been admitted to the Neurology or Rheumatology Department of Mashhad University of Medical Sciences in 2012 and 2013. The diagnosis of patients was assessed according to the criteria of the International Study Group for Behçet's Disease, requiring

the presence of oral ulceration plus any two of the following four criteria; genital ulceration, typical defined eye lesions, typical defined skin lesions, and a positive pathergy test. Patients were categorized into a classical BD group (classical BD) without neurological involvement and a neuro-BD group with neurological deficits such as hemispheric, brainstem signs or symptoms, pseudotumor cerebri, and cerebral venous thrombosis.

All patients underwent neurological and general physical examination; computed tomography and magnetic resonance imaging (two to three examinations in 3–7 days) were performed in patients with neurological deficits; noninvasive studies, including extracranial and transcranial Doppler sonography and well as duplex sonography were performed in all cases; and cardiac investigations consisting of clinical examination, 12-lead electrocardiography, and transthoracic echocardiography were performed in all cases.

### *Embolic signal monitoring*

MES were detected and measured according to the criteria of International Consensus Group on Microembolus Detection (11). Flow velocity monitoring was performed with the use of a multigate transcranial pulsed Doppler system (Multi-Dop X4, DWL, with multirange embolus detection software TCD-8 for MDX, version 8.00K) in patients and controls. Both MCAs were insonated simultaneously with a 2-MHz probe through the transtemporal window at an insonation depth of 50–60 mm. In multigate Doppler examinations, an integrate distance of 5 mm was used. Recordings were performed with the patient in a supine position with monitoring of blood

pressure and heart rate. All patients had a temporal window. Doppler signals were recorded for 30 min. Differentiation of embolic signals (MES) from artifacts was based on criteria of the recent consensus conference. All signals with atypical crisp sound and signal intensity greater than 9 dB spectral broadening intensity were evaluated. Artifacts were assumed if signals were recorded simultaneously on both sides or were bidirectional and only short signals showing integrate latencies were classified as ES. The examiner was blind to the status of all subjects. Two to three investigations were done to test the reproducibility of the method.

Atherosclerotic plaques were studied by ultrasound examination of both carotid arteries using a high-resolution ultrasound scanner (Medison, SA8000EX) equipped with a linear-array transducer. The maximum intima-media thickness in common and internal carotid arteries was measured on frozen B-mode images. Like our previous MES detection study (19). TCD evaluation was performed using an Atys TCD

ultrasonographic instrument (Atys Medical, St. Genislaval, France) equipped with a 2 MHz probe and Spencer head frame. Both MCAs were monitored for 30 min using the Bilateral Multigate mode. The results were reviewed off-line, and MES were defined as being random, unidirectional, high intensity, and short duration signals, with an associated characteristic chirping sound.

## Results

Among the patients with BD, no one had MES. We have shown radiologic characteristics of patients with neuro-BD and non neuro-BD (Table 1). There were two women in neuro-BD group and 16 women in non neuro-BD group ( $p=0.11$ ). The mean age in neuro-BD and non neuro-BD groups was 36 years and 31.87 years respectively ( $p<0.05$ ). Disease duration was  $8.33\pm 3.5$  years and  $7.33\pm 3.1$  years respectively ( $p>0.05$ ).

We also measured intima-media thickness that has been shown in previous mentioned table.

**Table 1.** Radiologic characteristics of patients with neuro-BD and non neuro-BD

	Neuro-BD group (N=5)	Non neuro-BD (N=35)	<i>p-value</i>
Plaque formation	0	1	
IMT* Right CCA (mm)	0.39±0.08	0.343±0.04	$p =0.12$
IMT Right ICA (mm)	0.32±0.05	0.377±0.76	$p =0.32$
IMT Left CCA (mm)	0.37±0.12	0.38±0.07	$p =0.18$
IMT Left ICA (mm)	0.39±0.11	0.36±0.07	$p =0.43$
MES**	0	0	
Deep venous thrombosis	0	0	
Pseudotumor cerebri	0	0	
Basal ganglia lesion	2	0	
Upper brainstem lesion	2	0	
Cerebellar lesion	0	0	
Cerebral venous thrombosis	1	0	

\*: Intima-media thickness; \*\*: Microembolic signals

## Discussion

Involvement of central nervous system is one of the most serious manifestations of BD, either by parenchymal or vascular involvement (16,17). In parenchymal involvement, the abnormal mechanism occurs primarily within the nervous parenchyma by a slight inflammation. In patients with vascular BD, the overt lesions and clinical features usually correspond well to main vascular territories. However, the pathological process in the vascular system of patients with BD is not clear. None of patients with BD had MES; there was not increased frequency of MES in patients with CNS involvement. The high prevalence of MES in patients with cerebral venous thrombosis may be explained by generalized activation of thrombotic system due to immunopathological process in the blood but this process was not found in our patients may be because of limited number of patients.

There are no data on the source of MES in patients with BD. In previous studies, pathological examination showed lymphocytic infiltration progressing from the adventitia toward the intima, possibly causes thrombus formation (18). It is probable that in some patients with BD immunological aetiology propagates the formation of microthrombus, and then leads to embolization of distal vascular system.

It should be stated that documented cerebral arteritis in BD is extremely rare and is even debatable as a mechanism for central nervous system involvement. However, some cases have been reported with typical appearance of arteritis – with multiple segments of stenosis, occlusion, and dilatations of internal and external carotid arteries (16). Postmortem study of patients

with vascular BD showed inflammation and destruction occurring in the media and adventitia (11). In our patients, MES were not seen in cases with lesions involving brain stem and basal ganglia. Previous studies have shown an activation of blood coagulation, such as shortening of prothrombin time, decreases in concentrations and activities of plasma antithrombin III, and elevated levels of plasma thrombin antithrombin-III complex. Moreover, increased plasma levels of protein C and total protein S levels, plasminogen activator activity, and decreased levels of a 2-plasmin inhibitor also indicate an activation of fibrinolysis in these patients (5, 6). We did not study coagulation and fibrinolytic activities, but, as showed by previous studies, thrombosis formation by activated platelets and endothelial injuries are the potential causes of MES in BD.

In our patients, MES are not seen and was not related to a previous clinical event or silent brain infarctions, in disagreement with other related studies who have reported MES to be correlated with a previous recent event (15). Our different findings might be due to the lower number of patients and genetic differences.

The detection of MES provides important pathophysiological information in a variety of disorders, but their clinical importance and possible therapeutic implications is still the subject of discussion. The origin of MES in BD is also a matter of debate. Vasculitis of the small vessels hypercoagulability and early atherosclerosis are some of the proposed mechanisms.

## Conclusion

In conclusion, we have shown by TCD that despite other studies, there is not MES in

patients with neurological deficits and those without CNS involvement. Further studies are required to highlight the core histopathologic phenomenon in CNS involvement of BD patients.

In the absence of MES, like our population in this study, a vascular-inflammatory central nervous system disease with focal or multifocal parenchymal involvement and small vessel vasculitis may be an important etiology.

### Conflict of Interest

The authors have no conflict of interest.

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