Caspian Journal of Neurological Sciences
http://cjns.gums.ac.ir

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

Mirfeizi Zahra (MD) [1] , *Ghabeli-Juibary Ali (MD)* [2] , *Moohebati Mohsen (MD)* [3] , *Azarpazhooh Mahmoudreza (MD)* [4] , *Sasannejad Payam (MD)* [5*]

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 1 October 2015
Accepted: 18 May 2016
Available online: 30 June 2016
CJNS 2016; 2 (5): 36-41

1. Assistant Professor of Rheumatology, Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
2. Resident of Neurology, Student Research Committee, Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Assistant Professor of Cardiology, Department of Cardiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
4. Associate Professor of Neurology, Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
5. Assistant Professor of Neurology, Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Corresponding author:
Assistant professor of Neurology Department of Neurology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Email: sasannejadp@mums.ac.ir

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 transcranialDoppler 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 andvasculiticphenomenonmay 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

➢ ***Please cite this paper as:***
Mirfeizi Z, Ghabeli-Juibary A, Moohebati M, Azarpazhooh M, Sasannejad P. Doppler Microembolic Signals in Behcet's Disease with Nervous System Involvement. Caspian J Neurol Sci 2016; 2(5): 36-41.

Introduction

Behçet's disease (BD) is a multisystemic inflammatoryvasculitis of unknown etiology, and vasculitis being its majorpathological feature (1,2). Neurological involvementis one of the most dangerous manifestations of BD (neuro-BD). This complication may occur by primarybrain parenchymal lesions (neuro-BD) or be secondaryto major vascular involvement (vascular BD) (3-6). In patients with neuro-BD, neurological focal deficits maybe seen either acutely or bygradual onset, and they usuallyprogress in a halting manner with periods of accelerationand incomplete remission and with neurological deficitssuch as transient ischemic attacks, stroke, bulbar,and pseudobulbar palsy, cerebral venous thrombosis,and pseudotumorcerebri (7-10). The pathophysiologyof vascular BD is not clear, and knowledge islimited by data derived from pathological and angiographicstudies (11-15). Transcranial Doppler (TCD) studies showing solid and gaseous microembolic materialsmay be an alternative method to search for the pathophysiologyof 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 enrolledconsecutively from patients with BD who hadbeen 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, pseudotumorcerebri, 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 patientswith neurological deficits; noninvasive studies, includingextracranial and transcranial Doppler sonography and well as duplexsonography were performed in all cases; and cardiac investigationsconsisting 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 multigatetranscranial pulsed Doppler system (Multi-Dop X4, DWL, with multirange embolus detection software TCD-8 for MDX, version8.00K) 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 ultrasoundexamination of both carotid arteries using a high-resolutionultrasound scanner (Medison, SA8000EX) equipped with alinear-array transducer. The maximum intima-media thicknessin common and internal carotid arteries was measured on frozenB-mode images. Like our previous MES detection study (19). TCDevaluation was performed using an Atys TCD ultrasonographicinstrument (Atys Medical, St. Genislaval, France) equipped witha 2 MHz probe and Spencer head frame. Both MCAs weremonitored for 30 min using the Bilateral Multigate mode. Theresults were reviewed off-line, and MES were defined as beingrandom, 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±3.5 years and 7.33±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)	*p-value*
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	
Pseudotumorcerebri	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 abnormalmechanism occurs primarily within the nervous parenchyma by a slightinflammation. 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 immunologicaletiology propagates the formation of microthrombus, and then leads to embolization of distalvascular system.

It should be stated that documented cerebral arteritisin BD is extremely rare and is even debatable as amechanism for central nervous system involvement. However, some cases have been reported with typical appearanceof 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 occurringin the media and adventitia (11). In our patients, MES were not seen in cases with lesions involving brain stemand basal ganglia. Previous studies have shown an activation of blood coagulation, such as shortening of prothrombintime, 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 fibrinolysisin these patients (5, 6). We did not study coagulationand fibrinolytic activities, but, as showed by previousstudies, 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.

References

1. Saip S, Akman-Demir G, Siva A. Neuro-Behçet Syndrome. Handb Clin Neurol 2014;121:1703-23.
2. Dutra LA, Gonçalves CR, Braga-Neto P, Pedroso JL, Gabbai AA, Barsottini OG, et al. Atypical Manifestations in Brazilian Patients with Neuro-Behçet's Disease. J Neurol 2012;259(6):1159-65.
3. Noel N, Bernard R, Wechsler B, Resche-Rigon M, Depaz R, Le ThiHuong, et al. Long-term Outcome of Neuro-Behçet's Disease. Arthritis Rheumatol 2014 May;66(5):1306-14.
4. Miller JJ, Venna N, Siva A. Neuro-Behçet Disease and Autoinflammatory Disorders. Semin Neurol 2014;34(4):437-43.
5. Sula B, Batmaz I, Ucmak D, Yolbas I, Akdeniz S. Demographical and Clinical Characteristics of Behcet's Disease in Southeastern Turkey. J Clin Med Res 2014;6(6):476-81.
6. International Study Group for Behçet'sdisease Criteria for Behçet's Disease. Lancet 1990;335:1078-80.
7. Noel N, Bernard R, Wechsler B, Resche-Rigon M, Depaz R, Le ThiHuong, et al. Long-term Outcome of Neuro-Behçet's Disease. Arthritis Rheumatol 2014 May;66(5):1306-14.
8. Miller JJ, Venna N, Siva A. Neuro-Behçet Disease and Autoinflammatory Disorders. Semin Neurol 2014;34(4):437-43.
9. Taşolar S, Doğan M, Taşolar H, Kahraman A, Kamışlı S, Doğan A, et al. Evaluation of Vertebral Artery Involvement by Doppler Sonography in Patients with Behçet Disease. J Ultrasound Med 2014;33(5):811-6.
10. Yoon DL, Kim YJ, Koo BS, Kim YG, Lee CK, Yoo B. Neuro-behçet's Disease in South Korea: Clinical Characteristics and Treatment Response. Int J Rheum Dis 2014 May;17(4):453-8.
11. Ringelstein EB, Droste DW, BabikianVL, Evans DH, Grosset DG, Kaps M, et al. Consensus on Microembolusdetection by TCD. International Consensus Group on Microembolus Detection. Stroke1998; 29:725-9.
12. Shakir RA, Sulaiman K, Kahn RA, Rudwan M. Neurological Presentationof Neuro-Behçet's Syndrome: Clinical Categories. Eur Neurol 1990;30:249-53.
13. Sibley C, Yazici Y, Tascilar K, Khan N, Bata Y, Yazici H, et al. Behçet Syndrome Manifestations and Activity in the United States Versus Turkey a Cross-sectional Cohort Comparison. J Rheumatol 2014;41(7):1379-84.
14. Wolf SM, Shotland DL, Phillips LL. Involvement of Nervous Systemin Behçet's Disease. Arch Neurol 1965;12:315-25.
15. Kumral E, Evyapan D, Oksel F, Keser G, Bereketoğlu MA, Balkir K. Transcranial Doppler Detection of Microembolic Signals in Patients with Behcet Disease. J Neurol 1999;246:592-6.
16. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical Carotid Atherosclerosis in Patients with Rheumatoid Arthritis. Ann Intern Med 2006;144(4):249-56.
17. Azarpazhooh MR, Velayati A, Chambers BR, Mashhadi-Nejad H, Sasan-Nejad P. Microembolic Signals in Subarachnoid Hemorrhage. J Clin Neurosci 2009;16(3):390-3.
18. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium. Basic Identification Criteria of

Doppler Microembolic Signals. Stroke 1995;26:1123.
19. Azarpazhooh MR, Mokhber N, Orouji E, Chambers BR, Hatef MR, Rezaieyazdi Z, et al. Microembolic Signals in Patients with Systemic Lupus Erythematosus. Can J Neurol Sci 2010;37(3):371-5.