

# Findings of Carotid Artery Color Doppler Ultrasonography in Patients With Behcet Disease

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Received: April 11, 2014; Revised: April 28, 2014; Accepted: May 4, 2014

**Background:** The Behcet disease is a multisystemic disease with involvement of vessels.

**Objectives:** Our aim is to evaluate the frequency of carotid artery disease in asymptomatic carotid artery involvement in patients with Behcet disease and compare the results with a control group.

**Patients and Methods:** Fifty patients with Behcet disease who were asymptomatic for any vascular involvement and 50 healthy volunteers participated in this study. We compared intima-media thickness (that is measured manually) and plaques in carotid arteries.

**Results:** Mean intima-media thickness in the patient group was  $0.562 \pm 0.133$  mm in the right and  $0.566 \pm 0.140$  in the left common carotid artery. In the control group, mean intima-media thickness was  $0.526 \pm 0.127$  in the right and  $0.500 \pm 0.105$  in the left common carotid artery. The only significant difference between groups was the larger intima-media thickness of the left common carotid artery in the patients ( $P = 0.009$ ). No plaque was seen in the carotid arteries of the control group.

**Conclusions:** Behcet disease may be associated with subtle increased intima-media thickness in the carotid artery, so it can be a predisposing factor for atherosclerotic arterial disease.

**Keywords:** Behcet Syndrome; Carotid Artery; Ultrasonography, Doppler, Color

## 1. Background

Behcet disease is a multisystemic disorder with a remitting and relapsing course. The disease involves vessels of different sizes in various organs. The disease is seen worldwide but is more common in the eastern Mediterranean and the eastern rim of Asia, with the highest rate in Turkey (80–370 per 100 000 person) (1, 2). The prevalence of behcet disease in Iran is rather high. Large vessel involvement is seen in 8.5% of the patients with Behcet disease (3, 4). Venous involvement including deep vein thrombosis and superficial thrombophlebitis is seen frequently (8.2%). Arterial involvement is rare (0.5%), and arterial aneurysm is more common than arterial thrombosis (3, 4).

The diagnosis is primarily based on the clinical criteria, as no specific diagnostic laboratory test is available and the findings of histopathology are nonspecific. According to the International Study Group for Behcet Disease (ISGBD), the diagnosis is based on the presence of recurrent oral ulcers plus at least two signs of the following features: recurrent genital ulcers, eye lesions, skin lesions,

or a positive pathergy test (5). One of the main complications of Behcet disease is vascular involvement, which affects both the arterial and venous systems (4). Depending on the ethnicity of the population, the prevalence of vascular involvement varies from 7.7% to 43% (6-10). Venous thrombosis, the most common manifestation, occurs in 6.2% to 33% of the patients with Behcet disease (11, 12). The main presentations of venous involvement are superficial thrombophlebitis, deep-vein thrombosis (more frequently in the lower extremities), superior vena cava syndrome, Budd-Chiari syndrome, and dural sinus thrombosis (13-15). Involvement of the arterial system is less common than venous involvement, and may present as true or false aneurysm, or, less frequently, as arterial thrombosis. The prevalence of arterial involvement reportedly ranges from 2.5% to 3% of patients with Behcet disease (16, 17). Arterial occlusion is a rare manifestation in Behcet's disease and accounts for only 1.5% of all forms of vascular involvement (17, 18).

Determining the extent of vascular involvement in Be-

### Implication for health policy/practice/research/medical education:

Behcet disease is not uncommon in our country. To our article it can increase chance of atherosclerosis in carotid arteries, so color Doppler ultrasonography can be a useful modality for assessing these patients.

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Behcet disease is important as it can affect the prognosis. Sudden death may occur in patients with Behcet disease with the rupture of an aortic aneurysm or large arterial aneurysm (16). Duplex and color Doppler ultrasonography are noninvasive methods that can be used to evaluate possible vascular involvement and its patterns in Behcet disease. Ocular vascular involvement in both symptomatic and asymptomatic patients has been studied previously (19). In addition, a few studies have evaluated the superior and inferior mesenteric and peripheral arteries in asymptomatic carotid artery involvement in patients with Behcet disease (3, 20). To our knowledge, only a few studies have evaluated carotid artery involvement in Behcet disease (7, 9, 21-24).

## 2. Objectives

Because vascular involvement is one of the leading causes of morbidity in this disease, we designed the present study to evaluate possible carotid artery and jugular vein involvement in asymptomatic carotid artery involvement in patients with Behcet disease by color Doppler ultrasonography.

## 3. Patients and Methods

This is a case control study. From those patients with Behcet disease who referred to our Behcet Disease Clinic during a five-month period from October 2008 to February 2009, after excluding the criteria that might affect the carotid arteries, 50 patients were enrolled in the study as the case group. Written informed consent was obtained from each patient. All patients fulfilled the criteria of the ISGBD. According to these criteria, the diagnosis is based on the presence of recurrent oral ulcers plus at least two of the following features: recurrent genital ulcers, eye lesions (anterior and posterior uveitis and retinal vasculitis), skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, and acneiform nodules), or a positive pathergy test (nodule or pustule formation 24-48 hours after skin prick) (5). A complete physical exam and paraclinical workup for each patient were used to rule out possible vascular-related causes other than Behcet or concomitant diseases. The exclusion criteria were disease duration less than one year, a history of ischemic heart disease or cerebrovascular accident, and atherosclerotic risk factors such as hypertension, diabetes mellitus and hyperlipidemia (LDL more than 130, Triglyceride more than 150). Patients who smoked up to two years before the study, and patients with liver disease (elevated liver transaminase more than normal levels and cirrhosis) or renal failure, were also excluded from this study. All available previous images obtained with computed tomographic angiography, magnetic resonance angiography and color Doppler ultrasonography were reviewed to exclude patients with previously diagnosed vascular involvement.

The patients were then examined to exclude symptomatic vascular involvement. All the patients were evaluated for positive clinical findings including local tenderness, swelling or bruit on vessels, weakness or absence of pulses, and any other changes in favor of ischemia in the upper and lower extremities, abdominal and neck vessels. Thus only patients with Behcet disease who were free from vascular symptoms were included as the case group. Control individuals were 50 persons who referred to radiologist by rheumatologist; among those who visited the rheumatologist for minor reasons other than Behcet disease and other vasculitis that might affect the IMT of carotid arteries. They participated voluntarily in our study after explaining the study to them and written informed consent were obtained from them and the same exclusion criteria were considered for them as the case group.

The patients were then referred to a radiologist who was blind about the disease for color Doppler examination of the carotid arteries and jugular veins. Color Doppler examination of both of the common carotid arteries (CCA), internal carotid arteries (ICA), external carotid arteries (ECA) was done with a GE Logique seven machine and linear probe (6-10 MHz frequency range). We measured intima-media thickness (IMT) approximately 2 cm proximal to the carotid bulb in the posterior wall of the CCA from the blood-intima interface to the media-adventitia interface manually (22-24). Any focal irregularity or increase in thickness was assessed. Any plaque was investigated for location, size, echogenicity (hyperechoic, intermediate echoic or hypoechoic) and homogeneity versus inhomogeneity. Particular attention was given to any abnormal narrowing, thrombosis, dilatation and aneurysm. Color flow mapping and spectral analysis of bilateral CCA, ICA and ECA were done and peak systolic velocity and end diastolic velocity of the arteries were recorded. Particular attention was given to any abnormal patterns of spectral analysis. The data were analyzed using the Statistical Package for Social Sciences software, version 11 (SPSS Inc. Chicago, IL, USA). Two independent samples t-tests, paired samples, t-tests and regression analysis were also used. A P value of < 0.05 was considered statistically significant.

## 4. Results

Of the 50 patients, 30 were women (60%) and 20 were men (40%). Mean age of the patients was  $37 \pm 8.3$  years, and range was 25 to 56 years. Mean duration of the disease was  $8.9 \pm 6.0$  years, and range was 1 to 30 years. Mean age in the control group was 35 years (no significant difference from the patient group,  $P = 0.17$ ). The control group consisted of 23 (46%) men and 27 (54%) women: sex ratio did not differ significantly with respect to the patient group ( $P = 0.5$ ). In the group of patients, mean IMT was 0.562 mm in the right and 0.566 mm in the left CCA, with a range of 0.3 to 1.0 mm considering both vessels. In

the control group, mean IMT was 0.526 mm in the right and 0.500 mm in the left CCA. There was no significant difference between the patients and the control group in IMT of the right CCA ( $P = 0.172$ ), but IMT of the left CCA in patients was larger than in the control group ( $P = 0.009$ ). The IMT of the right and left CCA in control groups did not differ significantly ( $P = 0.15$ ), nor did the IMT in the right and left CCA in the patients ( $P = 0.82$ ).

Regression analyses were conducted to provide contribution of age, disease and its duration to increase in IMT. The larger IMT of left CCA in patients was not associated with duration of the disease ( $r = 0.000$ ,  $P = 0.78$ ) or age ( $r = 0.001$ ,  $P = 0.07$ ). The larger IMT of the left CCA in patients was, however, associated with presence of the disease itself ( $r = 0.005$ ,  $P = 0.025$ ). Among the 50 patients, three (6%) showed carotid artery involvement consisting of an increase in IMT of more than 0.08 cm (4%) and the presence of plaque (4%). One of the patients showed both increased IMT and plaque (2%). Two of them were women (4%) and one (2%) was a man. One man (5% of the subgroup of men) had both increased IMT and plaque. One woman (3.3% of the subgroup of women) had plaque, and another woman (3.3%) had increased IMT. Bilateral CCA were evaluated in all the patients for IMT; we found no significant difference in mean IMT  $\pm$  SD between the right ( $0.562 \pm 0.139$  mm) and left CCA ( $0.566 \pm 0.141$  mm,  $P = 0.821$ ). There was no statistically significant difference between men and women with Behcet disease in the increase in IMT. ( $P = 0.932$ ). In the patient group, plaque was seen in the carotid artery in one out of 20 men (5%) and in one out of 30 women (3.3%). In the patient group, the frequency of plaque did not differ significantly between men and women ( $P = 0.645$ ). Overall, the frequency of plaque did not differ significantly between the patient group and the control group ( $P = 0.07$ ).

## 5. Discussion

We evaluated the frequency of asymptomatic carotid artery involvement in patients with Behcet disease, compared to a sample of healthy individuals. We examined carotid arteries by color Doppler imaging to determine the prevalence of carotid artery, such as increased IMT as well as the presence of plaque in the carotid arteries. The only statistically significant change we found was the increased IMT of the left CCA ( $P = 0.009$ ). Compared to the earlier studies, the mean IMT in our sample was within the range of values reported in earlier studies ( $0.51 \pm 0.09$  mm,  $0.86 \pm 0.18$  mm) (Table 1) (7, 9, 21-24). The highest IMT to date was reported by Ozturk et al. (23, 24) however, these authors did not use the same exclusion criteria as we did in the present study. For example, risk factors that we considered as exclusion criteria, such as smoking during the previous two years and hyperlipidemia, were not among their exclusion criteria. Moreover, we excluded patients with renal or liver dysfunction. The differences between studies of IMT may thus have been due to our use of more rigid exclusion criteria. Moreover, the research done in Turkey may have been influenced by local epidemiological factors. However, two other studies also done in Turkey reported a smaller mean IMT values ( $0.51 \pm 0.09$  mm,  $0.55 \pm 0.14$ ) (21, 22).

Mean duration of the disease was  $8.9 \pm 6$  years in the present study, and was  $7.3 \pm 5.3$  years and  $7.0 \pm 5.2$  years in two other studies. Among studies that reported higher mean IMT values, we found only one (22) which showed a relationship between vascular involvement in Behcet disease and disease duration, whereas two other studies (7, 23) failed to find this relationship. Mean duration of the disease in our patients who had plaque in the carotid artery or increased IMT were  $11.3 \pm 4.3$  years; however, we found no statistically significant difference

**Table 1.** A Comparison Between Studies Using Color Doppler Ultrasonography on Carotid Arteries <sup>a, b</sup>

Studies	Number of Asymptomatic Patients	Number of Patients With Vascular Involvement	Rolled Out Risk Factors	Mean IMT in CCA	Plaque Assay	Number of Patients With Plaque	Duration of Disease, mo/y
Hong et al. (7)	40	-	A, B, C, D, E, F, G	$0.71 \pm 0.22$	not done	-	$5.2 \pm 4.0$ , y
Rhee et al. (9)	41	-	A, C, D	$0.52 \pm 0.09$	not done	-	$78.1 \pm 57.4$ , mo
Keser et al. (22)	114	5	A, C, D, E, H	$0.55 \pm 0.14$	-	5/114	$121 \pm 79$ , mo
Ozturk et al. (24)	34	6	A, C, D, E, G, I	(R), $0.81 \pm 0.17$ (L), $0.82 \pm 0.16$	-	6/34	$7.0 \pm 5.2$ , mo
Ozturk et al. (23)	21	-	A, C, D, E, G, I	$0.86 \pm 0.18$	not done	-	$7.3 \pm 5.3$ , y
<b>Our study</b>	50	3	A, B, C, D, E, F, G, H, I, J, K	(R), $0.562 \pm 0.133$ (L), $0.566 \pm 0.140$	-	2/50	$8.9 \pm 6.0$ , y

<sup>a</sup> Abbreviations: CCA, common carotid artery; IMT, intima media thickening; L, left; R, right.

<sup>b</sup> A, History of ischemic heart disease; B, risk factors for coronary heart disease; C, hypertension; D, diabetes mellitus; E, history of cerebrovascular accident; F, smoking; G, anti hyperlipidemic therapy; H, obesity; I, taking steroids more than six month; J, renal disease; K, liver disease.

between groups in the association between duration of the disease and increased IMT.

We found only two reports that investigated arterial plaque in patients with Behcet disease. One study (22) reported the presence of plaque in five patients out of 114 (4.4%). Mean duration of the disease in this sample was  $121 \pm 79$  months, and mean age was  $38.1 \pm 9.4$  years. Another study (23) reported the presence of plaque in six of 34 patients (17.6%). Mean duration of the disease in that study was  $7.0 \pm 5.2$  months, and mean age was  $34.6 \pm 8.5$  years. In our sample, plaque was detected in 2 of 50 patients (4%), and in none of the participants in the control group; this difference was not significant ( $P = 0.07$ ). We found a marginal increase in the risk of atherogenesis (increased IMT in the left CCA) in patients with Behcet disease who were asymptomatic for any vascular involvement. It should be recalled that we used rigid exclusion criteria for participants with any risk factor of atherosclerosis or any disease which had association with atherosclerosis.

We did not assess the effect of disease activity and atherogenic drugs such as steroids in our sample; although, our primary hypothesis is that there may be a correlation between them and vascular involvement. Accordingly, we recommend further studies to investigate the usefulness of color Doppler ultrasonography of the cervical arteries in asymptomatic carotid artery involvement in patients with Behcet disease. Behcet disease may be associated with subtle increased intima-media thickness in the carotid artery, so it can be a predisposing factor for atherosclerotic arterial disease.

## Acknowledgements

We thank Dr. Zahra Shaian for the data analysis, K. Shashok (AuthorAID in the Eastern Mediterranean) for improving the use of English in the manuscript, and M. Gholami at the Center for Development of Clinical Research of Namazi Hospital for research assistance.

## Authors' Contribution

Sepideh Sefidbakht, Elham Aflaki, Zahra Habibagahi developed the original idea and the protocol and analyzed data. Mohsen Agah developed the protocol, abstracted analyzed data and wrote the manuscript. Amin Abolhasani Foroughi, Masoume Nazeri contributed to the development of abstracted data, analyzed data, and prepared the manuscript.

## Financial Disclosure

There is no financial interest.

## Funding/Support

This study was supported by Shiraz University of Medical Sciences as a residency thesis.

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