Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behçet's disease

G. Keser, K. Aksu, S. Tamsel[1], M. Ozmen, G. Kitapcioglu[2], C. Kabaroglu[3], R. Killi[1], O. Bayindir[3], E. Doganavsargil

Departments of Rheumatology, Radiology[1], Public Health[2] and Clinical Biochemistry[3], Ege University School of Medicine, Izmir, Turkey.

Gokhan Keser, MD, Associate Professor; Kenan Aksu, MD, Associate Professor; Sadik Tamsel, MD, Specialist; Mustafa Ozmen, MD, Specialist; Gul Kitapcioglu, MD, Specialist; Ceyda Kabaroglu, MD, Specialist; Refik Killi, MD, Professor; Oya Bayindir, MD, Professor; Eker Doganavsargil, MD, Professor.

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Please address correspondence to:
Dr. Gokhan Keser, Mithatpasa cad.
No: 772/18, Nallıoglu apt,
35280, Izmir, Turkey.
E-mail: agkkeser@hotmail.com

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ABSTRACT

Objective. *Behçet's disease (BD), is a unique systemic vasculitis, which affects almost all types and sizes of blood vessels. Carotid intima-media thickness (IMT) is an endothelial cell dysfunction (ECD) parameter which may also be associated with atherosclerosis. We aimed to search carotid IMT and plaque formation in BD, using high-resolution B-mode Doppler ultrasonography (USG).*

Methods. *We studied 114 BD patients (M/F: 68/46; mean age 38.15± 9.44 years; disease duration 121 ± 79 months), being followed up by Ege University Rheumatology Department. Age and sex-matched, 77 healthy controls, and as the disease control group 46 non-matched SLE patients were also included. Exclusion criteria for all the study participants were hypertension, hyperlipidemia, diabetes mellitus, obesity and history of cardiovascular or cerebrovascular disease. Comparison of the three groups were made by ANOVA and for post-hoc confirmation, Bonferoni test was used.*

Results. *The carotid IMT in BD (mean ± SD, 0.55 ± 0.14 mm) was significantly higher than in healthy controls (0.48 ± 0.09 mm) (p = 0.004), but significantly lower than in SLE (0.66 ± 0.24 mm) (p = 0.001). Likewise, plaque frequency in BD (5/114) was significantly higher than in healthy controls (0/77), but significantly lower than in SLE (8/46) (p < 0.001).*

Conclusion. *Despite significantly higher carotid IMT and plaque frequency in BD compared with healthy controls, these parameters in BD were not as marked as in SLE. Less severe carotid artery abnormalities in BD, may partially explain why cardiovascular morbidity and mortality do not seem to be increased in BD, unlike in SLE.*

Introduction

Chronic inflammation is a non-traditional risk factor in the pathogenesis of atherosclerosis (1,2), and accelerated atherogenesis has previously been shown in inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (3-5). Vasculitis also plays an important role in atherogenesis (6), as has been shown in Takayasu arteritis (7, 8).

BD, which was first described as the triple symptom complex of recurrent oral and genital ulcers and iritis, is a unique systemic vasculitis, which affects almost all types and sizes of blood vessels (9). The disease severity and the resultant morbidity and standardized mortality ratios (SMR) are highest among the young males; however, the SMR tends to decrease significantly with the passage of time and in many patients, BD burns out as the years pass (10). Frequency of coronary atherosclerosis was found to be relatively low even in young male BD patients with major vessel disease (11).

On the other hand, endothelial cell dysfunction (ECD), defined as reduced arterial blood flow in response to a physiological stimulus (3), is widely regarded as the initial lesion in atherogenesis. ECD has been shown not only in antineutrophilic cytoplasmic antibody (ANCA) associated systemic vasculitis and in polyarteritis nodosa (12, 13), but also in Behçet's disease (BD) (14-16), as well. Recent studies showed that increased carotid intima-media thickness (IMT) was significantly correlated with ECD (17, 18). Besides, carotid IMT measurement was reported to be reliable and sensitive in assessing early atherosclerosis (19, 20). In BD, the presence of ECD together with inflammation and other vasculitis-related mechanisms, obviously have the poten-

tial to cause vascular changes, as in the case of silent myocardial ischemia (21). Therefore in this study we searched for carotid IMT and plaque formation in BD using high-resolution B-mode Doppler ultrasonography (USG). For comparison, we included age and sex-matched healthy controls, and non-matched SLE patients as the disease-control group. We also tried to evaluate the factors associated with carotid IMT and plaque formation in patients with BD.

Patients and methods

Patients and controls

In this cross-sectional study, 114 patients with BD (M/F:68/46; mean age 38.15±9.44 years; disease duration 121 ± 79 months), fulfilling the International Study Group criteria (22) were enrolled. As the healthy control group, 77 age and sex-matched healthy controls (M/F: 46/31; mean age 37.20 ± 7.87 years were included. As disease control group, 46 non-matched SLE patients (F/M: 40/6; mean age 40.7 ± 9.57 years), fulfilling the ACR 1982 criteria (23) were also included. All the patients were selected from consecutive patients, being followed up by the Outpatient Clinic of Rheumatology at Ege University Hospital. Written informed consent was obtained from all study participants. The Institutional Review Boards of Ege University Medical Center approved the study.

To avoid confounding by other known risk factors for atherosclerosis, we used the following exclusion criteria for all the study participants: hypertension (HT), as defined by blood pressure > 140/90 mmHg or use of antihypertensive medication; hyperlipidemia, as defined by levels of total cholesterol > 250 mg/dl, low-density lipoprotein (LDL) cholesterol >160 mg/dl, or triglycerides >200 mg/dl, or the use of lipid-lowering medication; diabetes mellitus (DM), as diagnosed according to the World Health Organization criteria (24) or use of anti-diabetic medication, body mass index (BMI) > 27 and history of ischemic heart disease or cerebrovascular events.

All of the BD patients were receiving multiple medications; colchicine 1.5 mg/day in 85 (75%), low dose aspirin in 68 (60%), azathioprine 2-3 mg/kg/day in 39 (34%), warfarin in 12 (10.5%) and cyclosporine A 3 mg/kg/day in 2 (1.7%) patients. Thirty-eight patients (33%) were on low to medium dose methylprednisolone at the time of study entry. Mean daily dose was 5.7 ± 3.5 mg/day; mean duration of steroid treatment was 16.5 ± 11.6 months, and the mean cumulative dose was 2.14 ± 1.23 gr.

Clinical assessments

Physical examination was performed in all study participants. Data were obtained on traditional cardiovascular risk factors, such as age, HT, DM, hypercholesterolemia, smoking, and history of cardiovascular or cerebrovascular disease. Height, body weight and body-mass index were noted. Smoking history was evaluated in pack years (1 pack year = 20 cigarettes/day for one year). On the day of ultrasound examinations, blood was drawn after an overnight fast and the sera were removed and stored at -70° until analyzed. Similarly, plasma samples were stored for homocysteine measurement. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and platelet cell count were measured by routine methods. Serum levels of total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were determined using an auto-analyzer (Technicon Dax-48; Bayer Diagnostics, Toshiba Japan). Serum vitamin B12 and folic acid were measured by chemiluminescence immunoassay (Access; Sanofi Diagnostics Pasteur, Marnes La Coquette, France). Homocysteine was measured in plasma samples by high-performance liquide chromatography (LC10A; Shimadzu, Kyoto, Japan) and the measurement was based on fluorometric detection, as previously described (25).

Carotid artery evaluation by B-mode ultrasound

The patient was placed in the supine position for ultrasonographic examination of the common carotid arteries. Carotid IMT and plaques were measured on both sides using high-resolution B-mode ultrasound (model ATL 5000, Buthal, USA) with an electric linear transducer (mid-frequency 10 MHz). To avoid inter-observer variability, all measurements were performed by the same examiner, who was unaware of the clinical characteristics of the subjects. The IMT was measured in the far wall of the arteries at sites of greatest arterial thickness on diffuse and continuous projection; the greatest distance between the *lumen–intima* interface and the *media–adventitia* interface in areas without atherosclerotic plaques was determined. Plaque was defined either as a distinct protrusion of > 1.5 mm into the vessel lumen or as definite echogenicity with a posterior echogenic shadow. All images were recorded digitally and reviewed later. All measurements were made manually from digitalized still images taken during scanning by high-resolution ultrasonography. Measurements were made three times and then averaged to produce a mean IMTfor each side. To find out intra-observer reliability, IMTmeasurements were repeated in 20 BD patients within 2 weeks of the first examination. The difference of mean IMT between the two measurements was 0.02 mm. Wilcoxon signed ranks test was made and correlation coefficient was found to be significant, ($r = 0.816$; $p = 0.0001$).

Statistics

Values were expressed as the mean ± SD unless indicated otherwise. Statistical package program was used to analyze the data. The comparison of the multiple parametric variables of the 3 groups was made by ANOVA, and Bonferoni test was used for *post-hoc* confirmation. The comparison of multiple nonparametric variables was made by Kruskal Wallis analysis.

Chi cquare analysis and Student's t test were used for the comparison of two parametric variables, while the Mann Whitney U test was used in the presence of nonparametric data. In Behçet's group, correlation between IMT values and various continuous variables were searched by Pearson correlation analyses. P values < 0.05 were accepted as significant.

Results

Clinical and laboratory characteristics of the three groups

The clinical and laboratory characteristics of each group were shown in Table I, and the clinical manifestations of BD group were given in Table II. Since HT, hyperlipidemia and BMI > 27 were among the exclusion criteria, there were no significant differences between the groups with respect to systolic and diastolic blood pressure, serum lipid levels and BMI. Plasma homocysteine levels in SLE group (40.58 ± 96.74 µmol/L) were significantly higher than both the BD group (11.57 ± 7.28 µmol/L) (p = 0.015) and the healthy controls (7.70 ± 1.70 µmol/L), (p< 0.001). Plasma homocysteine levels in BD group was also significantly higher than in healthy controls (p = 0.006). Serum folic acid levels in SLE group (8.37 ± 3.18 ng/ ml) were significantly lower than in BD group (10.7 ± 4.73 ng/ml) (p= 0.004) and in healthy controls (11.91 ± 3.98 ng/ml) (p < 0.004); however there was no significant difference between the BD group and healthy controls. With respect to other parameters, including serum CRP levels, serum B12 levels, platelet count and white blood cell count there were not significant differences between the groups.

Percentage of smokers in BD (40.4%) and in healthy controls (41.6%) was not significantly different from each other. The mean pack year of the 46 smoker Behçet's patients (10.86± 9.31) was also similar to the mean pack year of 32 smoker healthy controls (10.38 ± 4.63), (p >0.05). The percentage of smokers in SLE group (33%) was the lowest, among the three groups.

IMTs of the right and left common carotid arteries

Mean IMT values of the common carotid arteries both in BD (0.55 ± 0.14 mm) and in SLE (0.66± 0.24 mm) were significantly higher than in healthy controls (0.48 ± 0.09 mm), p values being 0.004 and 0.0001, respectively. The carotid IMT in BD (0.55 ± 0.14 mm) was significantly lower than in SLE (0.66 ± 0.24 mm) (p = 0.001) (Table I). Carotid plaque formation was detected in 5 (4.2%) among 114 Behçet's patients, in 8 (17.4%) of 46 SLE patients and in none of the healthy controls (Table III). Carotid plaque frequency in SLE was significantly higher than in BD (p=0.01). While comparing the BD and SLE groups, we made further analysis according to gender. Carotid IMT in 40 female SLE patients (0.66 ± 0.25 mm), was significantly higher than the 46 female BD patients (0.5 ± 0.15 mm) (p = 0.016). However, plaque frequency in female SLE patients (17.5%) was not significantly higher, compared with female BD patients (4.3%), (p= 0.075), (Table III). Likewise, neither carotid IMT nor plaque frequency was significantly different between male patients.

Correlation analysis of the factors associated with common carotid artery IMTin BD patients

Pearson correlation analyses were performed in the BD group to find out the parameters associated with carotid IMT. The mean carotid IMTvalues were positively correlated only with patient age (r = 0.477; p = 0.0001), disease duration time (r =0.408; p= 0.0001) and age at disease onset (r = 0.276; p = 0.003). We further investigated whether the positive association with disease duration still stands after correction for age. Linear regression analysis model showed a linear association between

Table I. Characteristics of Behçet's and SLE patients and healthy controls*.

	Behçet's patients (n = 114)	SLE patients (n = 46)	Healthy controls (n = 77)
Age (years)	38.15 ± 9.44 (23-57)	40.7 ± 9.57 (25-63)	37.20± 7,87 (27-54)
Sex (M/F)	68/46	6/40	46/31
Disease duration (months)	121 ± 79	128 ± 362.4	——-
Systolic BP(mmHg)	119.4 ± 8.3	126 ± 20.1	115.8± 18.9
Diastolic BP(mmHg)	75.3 ± 10.5	78.8 ± 10.1	74.1± 11.2
Carotid IMT(mm)	0.55 ± 0.14	0.66 ± 0.24	0.48± 0.09
Total cholesterol (mg/dL)	163.33 ± 28.56	156.13 ± 29.97	176.11± 27.73
HDLcholesterol (mg/dL)	46.41 ± 11.63	55.64 ± 23.81	52.66± 11.56
LDLcholesterol (mg/dL)	97.55 ± 25.26	89.5 ± 20.73	104.80± 29.52
Triglyceride (mg/dl)	95.55 ± 32.03	106.27 ± 35.91	90.64± 20.30
Homocysteine (µmol/L)	11.57 ± 7.28	40.58 ± 96.74	7.70± 1.70
B12 vitamine (pg/ml)	387.53 ± 231.58	530.91 ± 190.34	319.00± 90.12
Folic acid (ng/ml)	10.75 ± 4.73	8.37 ± 3.18	11.91± 3.98
CRP(mg/dL)	1.16 ± 2.01	0.84 ± 1.27	0.36± 0.13
Platelets (/mm^3)	247.864 ± 57.197	252.930 ± 65.558	259.600± 140.469
Number of smokers	46/114 (40.4%)	15/46 (33%)	32/77 (41.6%)

* Values were expressed as the mean ± SD.
BP: blood pressure; IMT: intima-media thickness; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table II. Clinical manifestations in 114 Behçet's patients.

	No. of pts. (%)
Oral ulcer	114 (100)
Genital ulcer	96 (84.2)
Skin lesions	73 (64.0)
Eye involvement	43 (37.7)
Arthritis	38 (33.3)
Large vessel involvement	38 (33.3)
CNS involvement	10 (8.8)
Pathergy positivity	43 (37.7)

carotid IMT and age. The formula of regression line was: mean IMT = 0.279 + (0.07 x age), (R = 0.477; R^2=0.228). This showed that 22.8% of the positive correlation between carotid IMT and disease duration could be explained by the patient age. On the other hand, since the data of homocysteine, CRP, platelets, leucocytes and vitamin B_{12} were not normally distributed, we used nonparametric Kruskal Wallis test in statistical analysis, and found no significant correlation between carotid IMT and these parameters.

Comparison of the carotid IMT and plaque frequency between different subgroups of BD

We compared 38 Behçet's patients receiving prednisolone with the rest of the group receiving no steroids, with respect to carotid IMT levels and plaque frequency. A similar comparison was also made between smoking and non-smoking Behçet's patients, but we could not find a significant difference between these subgroups (data not given). We also investigated whether carotid IMT or plaque frequency in BD was significantly higher in any clinical subgroup of BD, however, there was no significant difference between BD clinical subgroups.

Discussion

In the present study, we demonstrated that carotid IMT and the number of plaques were significantly higher in BD patients than in healthy controls. However, both of these parameters in BD group were significantly lower than in the SLE group. In other words, carotid abnormalities were present in BD, but these were less severe than in SLE. Recently, Alan S. *et al*. (26) also reported increased carotid IMT in 40 Behçet's patients, compared with healthy controls. However our study differs from this study, with regard to the much higher number of BD patients included and the exclusion criteria applied. We studied a larger group of BD patients without traditional atherosclerotic risk factors such as HT, hyperlipidemia, DM and obesity. The rationale for applying exclusion criteria was to find out whether the vasculitis itself in Behçet's disease might have caused atherogenic effects, independent from the contribution of traditional risk factors. However, we do accept that exclusion of patients with known cardiovascular risk factors from the study will have created a serious ascertainment bias, since traditional risk factors may synergize with the atherogenic effects of vasculitis. Unfortunately, smoking was not exclusion criteria, but both the percent of the smokers and the mean pack years were comparable between BD patients and healthy controls.

In the present study, we also found that in BD group, patient age, disease duration time and age at disease onset were positively correlated with increased carotid IMT. We wondered whether the positive association with disease duration still stands after correction for age. Linear regression analysis model showed that 22.8% of the positive correlation between carotid IMT and disease duration could be explained by the patient age.

Since the carotid arteries are easily accessible to ultrasound techniques, and carotid artery IMT measurement was shown to be reliable and sensitive in assessing early atherosclerosis (19, 20), we used B Mode Doppler USG in the present study. This technique was previously used in assessing subclinical atherosclerosis in autoimmune rheumatic diseases such as SLE (5) and RA (27-29) as well. Accelerated atherosclerosis in Wegener granulomatosus was also shown in a sonographic study, based on IMTmeasurement (30). However, we do accept that increased IMT can not be relied on solely as a marker of early atherosclerosis. In a recent study (31), it has been shown that intermittent exposure to markedly elevated systemic arterial pressure and increased tensile stress during exercise, may also cause increased carotid IMT in the athletes.

Knowing that atherosclerosis is a well-known feature of SLE (3, 5), we included SLE patients as the disease control group. Because of the gender differences between the SLE and BD groups, possibly we might have chosen another atherosclerotic disease, as the disease control group. In order to solve this problem, we made further analysis according to gender, and found that female SLE patients had significantly higher carotid IMT than the female Behçet's patients.

While interpreting the moderately increased carotid IMT and plaque frequency in BD compared with healthy controls, we should exclude the effects of major atherosclerotic risk factors. Because of the age and sex-compatibility, our findings can not be explained by age and sex differences. Likewise, because of the exclusion criteria, blood pressure and serum lipid levels were also comparable between the Behçet's patients and healthy controls. The smoking data was also similar between the groups. Whether treatment for BD affects the arterial system and causes atherosclerosis is also an important issue. Keeping in mind that 33% of BD patients were on low to medium dose me-

Table III. Plaque frequency in the SLE and BD groups.

	SLE (n = 46)	Behçet (n = 114)	Controls (n = 77)
Plaque frequency in the whole group	8/46 (17.4%)	5/114(4.2%)	0
Plaque frequency in females only	7/40 (17.5%)	2/46 (4.3%)	0
Plaque frequency in males only	1/6 (16.7%)	3/68 (4.4%)	0

thylprednisolone (mean daily dose 5.7 ± 3.5 mg/day; mean duration 16.5 ± 11.6 months), steroid treatment might have possibly contributed to the increased IMT in BD. On the other hand, plasma homocysteine levels in BD were significantly higher than in healthy controls, in line with a previous study by our group (25). But, in BD group, there was no positive correlation between carotid IMT and homocysteine. Anyway, high plasma homocysteine might have possibly contributed to increased carotid IMT, as also suggested in previous studies (32, 33).

After discussing the potential contribution of steroid treatment and homocysteine levels, we should consider the ECD, to explain the increased carotid IMT and plaque frequency in BD. ECD basically reflects depressed release or increased breakdown of nitric oxide, with consequent loss or diminution of the ability to produce vasodilatation in response to stimuli such as flow. In other words, the decrease in flow-mediated vasodilatation (FMD) reflects the presence of ECD (3, 34). The presence of ECD has been shown in various systemic vasculitis (12, 13), including BD (14-16). ECD and increased carotid IMT are two indicators of early cardiovascular disease (17,18). ECD is the earliest detectable physiological abnormality in atherosclerosis (12), and the cellular changes that result in increased IMT may be consequent to ECD. The relationship between ECD and carotid IMT was recently investigated in a large, community-based cohort study of 2109 healthy adults, aged 24 to 39 years (17). In this study, a multivariate model adjusted for age, sex and brachial vessel size, showed that ECD (reduced FMD) was significantly associated with increased carotid IMT ($P < 0.001$). Similar results were also reported in other studies, both in adults (18, 35,36) and in children (37,38). However, since all these studies were cross-sectional studies, none of them can prove a causal relation between these two variables.

The possible vasculitis-related mechanisms that may be involved in ECD include proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), sphingolipids and CRP (3). Although we could not measure serum TNF-α levels in this study, it has been well known that serum TNF-α levels are increased in BD (39). TNF—mediated sphingolipid release also appears to be a key event in diffuse ECD (3, 40). CRP, the most frequently measured acute phase protein, not only predicts future coronary events, but it has also been shown to correlate with ECD (3, 41). Since elevated CRP is a very close marker of ECD (3, 41), CRP should also be discussed while interpreting our results. In the present study, the CRP levels in BD was higher than in healthy controls, but this did not reach statistical significance ($p = 0.07$). We also could not find a positive correlation between carotid IMT and CRPin BD group. The absence of a significant association between carotid IMT and CRPmight be explained by our use of a conventional CRP assay, rather than a high-sensitivity CRP assay. Maybe, if we had used a high-sensitivity CRP assay, we might have found a positive correlation. Another possibility is that CRP may not be a reliable marker of disease activity in BD. The third possibility is that, serum CRP level as determined by conventional assay fluctuates in BD and median of serial measurements may be more reliable than a single measurement. On the other hand, in previous studies, positive correlation was shown between carotid IMT and cumulative CRP levels in RA (27). Likewise, in RA, serum CRP levels positively correlated with the annual increase in carotid IMT (29).

In conclusion, despite significantly higher carotid IMTand plaque frequency in BD compared with healthy controls, these parameters in BD were not as marked as in SLE. Although increased carotid IMT does not invariably mean atherosclerosis, together with the plaque frequency of 4.4% in BD, we believe that atherosclerosis, albeit mild to moderate, and obviously not as much as in SLE, may develop during the course of BD. On the other hand, whatever the etiology is, less severe carotid artery abnormalities in BD, may partially explain why cardiovascular morbidity and mortality is not high in BD, unlike in SLE. Likewise, these findings seem to be compatible with the previous reports of decreasing standard mortality ratio in BD with the passage of time (10).

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