



Assessment of Carotid-vertebral Artery and Renal Artery Doppler Ultrasound in the Behçet's Disease with Cutaneous Lesions

Kutanöz Lezyonları Bulunan Behçet Olgularında Karotis-vertebral Arter ve Renal Arter Doppler Ultrasonografi Bulgularının Değerlendirilmesi

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ABSTRACT

Objective: Behçet's disease (BD) is a chronic multisystem inflammatory disease of unknown etiology defined as recurrent aphthous oral and genital ulcers, skin lesions, and uveitis. BD is a type of systemic vasculitis that can affect arteries regardless of origin and size-the co-occurrence of chronic systemic vasculitis and acute systemic inflammation results in an endothelial abnormality of the vessels. The morphological thickness of the arterial wall is a crucial feature of atherosclerosis. Carotid intima-media thickness (IMT) is an endothelial cell dysfunction parameter associated with atherosclerosis. This study aimed to evaluate the hemodynamic properties of carotid-vertebral and renal arteries of BD with cutaneous lesions to prove the effects of subclinical morphology of atherosclerosis.

Methods: The study consisted of 23 BD patients with oral and genital aphthae or cutaneous lesions. Color Doppler and B-mode ultrasonography examinations of the carotid-vertebral and renal arteries were performed in all patients. The assessment of the vascular structures included IMT, plaque thickness, resistive index, pulsatility index, peak systolic velocity, end-diastolic velocity, and the volumes of both kidneys were measured in the study. In addition, the flow rates of both vertebral arteries were calculated.

Results: The most intriguing findings of our study were the detection of non-stenotic plaque in 3 patients, mild intimal thickening in most patients, and vertebra basilar insufficiency in 12 patients. In addition, hemodynamic alterations of the patient's carotid arteries were compatible with the reported findings in the literature. Age, gender, disease duration, ophthalmic and neurological involvement, and IMT correlation were evaluated with the chi-square test, and no statistically significant correlation was found in this study. However, in the Mann-Whitney U test, a significant positive correlation was detected between kidney volume and IMT ($p < 0.035$).

Conclusion: We found no significant differences in vascular changes secondary to early atherosclerosis compared with the average population and literature in Behçet patients with cutaneous lesions. The increase in kidney size may be one of the early signs of atherosclerosis in Behçet's cases.

Keywords: Behçet's disease, carotid-vertebral Doppler, intima-media thickness, renal artery Doppler

ÖZ

Amaç: Behçet hastalığı (BH), etiyolojisi bilinmeyen, esas olarak tekrarlayan aftöz oral ve genital ülserler, deri lezyonları ve üveit ile karakterize, kronik, tekrarlayan, multisistemik enflamatuvar bir hastalıktır. BH, insan vücudundaki orjini ve büyüklüğü ne olursa olsun her arteri etkileyebilen bir sistemik vaskülitir. Akut sistemik enflamasyon ve kronik sistemik vaskülitin birlikte ortaya çıkması damarın endotel disfonksiyonuna neden olabilir. Arteriyel duvarın morfolojik kalınlığı aterosklerozun önemli bir özelliğidir. Karotis intima-media kalınlığı (İMK), ateroskleroz ile ilişkili bir endotelial disfonksiyon parametresidir. Bu çalışmada, kutanöz lezyonları olan Behçet hastalarının karotis-vertebral ve renal arterlerinin hemodinamik özelliklerinin karşılaştırılarak aterosklerozun subklinik morfolojisinin etkilerinin kanıtlanması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya oral ve genital aft veya kutanöz lezyonları olan 23 Behçet hastası alındı. Hastalara karotis-vertebral ve renal arterlerin renkli Doppler ve B-mod ultrasonografi incelemeleri yapıldı. Vasküler yapıların incelenmesinde İMK, plak kalınlığı, pik sistolik hız, diyastol sonu hız, rezistif indeks, pulsatilite indeksi değerlendirilerek her iki böbreğin hacimleri ölçüldü. Ek olarak, her iki vertebral arterin akım hızları hesaplandı.

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Bulgular: Çalışmamızın en ilgi çekici bulguları 3 hastada stenotik olmayan plak, çoğu hastada hafif intimal kalınlaşma ve 12 hastada vertebrobaziler yetmezlik saptanmasıdır. Hastaların karotis arterlerindeki hemodinamik değişiklikler literatürde bildirilen bulgularla uyumluydu. Ki-kare testi ile yaş, cinsiyet, hastalık süresi, oftalmik ve nörolojik tutulum ve İMK korelasyonu değerlendirildi. Çalışmamızda istatistiksel olarak anlamlı korelasyon saptanmadı. Ancak Mann-Whitney U testinde böbrek hacmi ile İMK arasında anlamlı pozitif korelasyon saptandı ($p < 0,035$).

Sonuç: Behçet'in kutanöz lezyonlu hastalarında erken ateroskleroza sekonder vasküler değişikliklerde normal popülasyona ve literatüre göre anlamlı bir fark bulunamadı. Böbrek büyüklüğündeki artış, Behçet olgularında damar sertliğinin erken belirtilerinden biri olabilir.

Anahtar Kelimeler: Behçet hastalığı, karotid-vertebral arter Doppler, intima-media kalınlığı, renal arter Doppler

INTRODUCTION

Turkish dermatologist Hulusi Behçet (1889-1948), who identified and published a triad of symptoms in 1937, is credited with giving the disease its name, Behçet's disease (BD), a multisystem inflammatory condition with an unknown cause. BD is more common in populations carrying the *HLA-B5* gene (1). Aphthous mouth ulcers, genital ulcers, and skin lesions are the main symptoms of BD, a multisystemic inflammatory condition that is chronic, recurring, and has an unknown etiology (2). A wide range of systemic organ involvement occurs in BD, such as in the vascular, ophthalmic, central nervous system, musculoskeletal, and gastrointestinal systems. Obliterative vasculitis is the central lesion in BD, which may be brought on by aberrant immune complexes that circulate in the blood (2,3).

Deep vein thrombosis (DVT), myocardial infarction, arterial aneurysm, and formation of an arterial thrombus have all been documented in about 20-35% of instances in patients with BD, primarily in male individuals (2). These complications usually occur in male patients (2). A defining aspect of BD is histological evidence of vasculitis with endothelial cell activation or damage (4). Carotid intima-media thickness (IMT) is a parameter associated with atherosclerosis and endothelial vessel dysfunction (4).

This study assessed the vascular involvement of BD patients with cutaneous lesions. We assumed that BD patients might have a greater risk in the cardiovascular system; thus, the morphological evidence of subclinical atherosclerosis was investigated and evaluated with high-resolution B-mode ultrasonography (U/S) and Doppler U/S of the carotid, vertebral, and renal arteries.

METHODS

Study Design and Patients

Twenty-three cases with oral and genital aphthae or cutaneous lesions diagnosed with BD and followed up at the department of dermatology in a university hospital were included in this study. All of our cases were under treatment and had mild symptoms. Of the patients, 12 were women

and 11 were men, with a mean age of 39 years for women and 46 years for men. Exclusion criteria for all participants were defined as wholly healed cutaneous lesions and/or patients with BD with no clinical manifestation of cutaneous lesions.

Patient Evaluation

The same radiologist performed all Doppler U/S exams without knowing the clinical condition of the patients and used the same scanner: a Toshiba (Applio 500; Toshiba, Tokyo, Japan) equipped with a 14-mm-wide, 7.5-MHz linear array transducer. Duplex and color Doppler U/S was examined on the patients' and the control groups' carotid and renal arteries. Doppler U/S examinations of all patients were lying down in the supine position, and the carotid and renal arteries were evaluated; for the common carotid artery (CCA) and internal carotid artery (ICA), flow measurements were taken 2 cm proximal and 2 cm distal to the bulb, respectively, measuring the peak systolic (PSV), end-diastolic (EDV), and time-averaged edged mean (Vmean) velocity for each artery. The system computed the resistance (RI) and pulsatility index (PI) from these measurements. During the Doppler U/S evaluation, none of the patients took any medicine (including oral and topical anti-inflammatory drugs, etc.) that would have affected the findings. The Bezmialem Vakıf University Ethics Committee approved the study with reference number 2022/338 (date: 24.01.2023). Informed consent of all study participants was obtained before the U/S evaluation.

Carotid Artery Evaluation by B-mode Ultrasound Measurement Technique

The intima-media complex is represented by the leading margins of the lumen-intima and media-adventitia interfaces (the "double-line pattern") of the arterial wall in longitudinal pictures of the carotid arteries used for IMT measurements (5,6). Normal common carotid IMT was typically 0.4 to 0.5 mm at age 10, but by the fifth decade of life, it had increased to 0.7 to 0.8 mm or more (7). The plaque was characterized as either an apparent protrusion of more than 1.5 mm into the artery lumen or as clear echogenicity with a posterior echogenic shadow (4,8).

Statistical Analysis

Descriptive statistics include frequency, percentage, and median (minimum-maximum). Analyses were made with Fisher's exact chi-square test and Mann-Whitney U test in the SPSS 28 V program. The significance level was taken as $\alpha=0.05$.

RESULTS

The median age was 40.0 (25.0-66.0) years for 23 people with BD included in our study, and the median disease duration was 8.0 (2.0-23.0) years for these patients. The study control group had the exact number and similar proportion of healthy individuals. Previous clinical findings of BD are shown in Tables 1 and 2. The demographic and clinical characteristics of the participants are shown in Table 1. The clinical features of the patients were compared according to whether they showed any sign of neurological symptoms, and their findings are given in Table 2. No statistically significant difference was observed among neuro-Behçet's diseased patients who manifested neurological signs or not and Behçet's patients with increased intimal thickness and ophthalmic findings ($p>0.05$). However, kidney size was significantly increased in patients with an increased intimal thickness of the carotid arteries ($p=0.035$).

In our cases, three smooth-surfaced atherosclerotic soft plaques, which were hemodynamically insignificant, were observed in the CCA bulb. The largest of them was measured at 7.7x1.7 mm. None of the BD patients in this study had a hemodynamically significant atherosclerotic plaque. The IMT of the correct CCA was counted as 0.8 mm in 17 of our cases, 1.0 mm in 2 cases, 1.1 mm in 1 case, 1.2 mm in 2 points, and 1.3 mm in 1 patient. IMT was measured 0.8 mm in 19 of the left CCA, 0.9 mm in 1 case, 1.0 mm in 1 point, and 1.2 mm in 2 cases (Figure 1). There was no disease activity during and in the month before the study. In BD patients, Carotid IMT values were slightly higher than in the control group [0.80 (0.80-1.30) vs. 0.7±0.1 mm]. However, cardiac and significant vessel involvement were not detected. In 12 cases, the total vertebral artery flow rate was less than 200 mL/min, consistent with vertebrobasilar insufficiency. In our study, IMT values did not correlate with the duration of the disease, neuro-BD, or ophthalmic and vascular involvement. In the spectral examination of both kidneys of our BD patients, RI (RI 0.60±0.05) and PI (1.05±0.18) values were within normal limits.

DISCUSSION

In the literature, BD is accepted as an unclassified vasculitis affecting arteries and veins of all sizes (9). Clinical

manifestations of BD include mucocutaneous, ocular, articular, vascular, and neurological involvement, along with all other organ systems (10). Mucocutaneous involvements, which include oral ulcers, genital ulcers, and cutaneous lesions, are thought to be the "fingerprint" of the disease because they are the most common and frequently the first symptoms to manifest (10,11).

Table 1. Demographic and clinical informations of patients with Behçet's disease

| | Median (minimum-maximum) (n=23) n (%) |
|-------------------------------------|---------------------------------------|
| Age, years (mean) | 40.0 (25.0-66.0) |
| Disease duration (years) | 8.0 (2.0-23.0) |
| Gender | |
| Female | 12 (52.2) |
| Male | 11 (47.8) |
| Skin and mucosal involvement | |
| Aphthous oral and genital ulcers | 21 (91.3) |
| Presence of nodules | 2 (8.7) |
| Neuro-Behçet's | |
| Negative | 4 (17.4) |
| Neurologic symptoms | 19 (82.6) |
| Vascular involvement | |
| Negative | 16 (69.6) |
| Trombophlebitis | 5 (21.7) |
| Retinopathy | 2 (8.7) |
| Ophthalmic involvement | |
| Negative | 14 (60.9) |
| Positive | 9 (39.1) |
| Iridocyclitis | |
| Negative | 19 (82.6) |
| Positive | 4 (17.4) |
| Uveitis | |
| Negative | 17 (73.9) |
| Positive | 6 (26.1) |
| R_carotis intimal thickness | |
| Mild | 14 (60.9) |
| Increase | 9 (39.1) |
| L_carotis intimal thickness | |
| Mild | 18 (78.3) |
| Increase | 5 (21.7) |

Table 2. Clinical comparisons by neuro-Behçet's condition

| | Neuro-Behçet's | | p-value |
|------------------------------------|--|---|---------|
| | Negative (n=4) | Neurologic symptoms (n=19) | |
| Disease duration (years) | 9.0 (5.0-23.0) | 8.0 (2.0-19.0) | 0.745 |
| R_carotis intimal thickness | | | |
| Mild | 2 (50) | 12 (63.2) | 1.000 |
| Increase | 2 (50) | 7 (36.8) | |
| L_carotis intimal thickness | | | |
| Mild | 3 (75.0) | 15 (78.9) | 1.000 |
| Increase | 1 (25.0) | 4 (21.1) | |
| Ophtalmic involvement | | | |
| Negative | 2 (50) | 12 (63.2) | 1.000 |
| Positive | 2 (50) | 7 (36.8) | |
| Uveitis | | | |
| Negative | 4 (100.0) | 13 (68.4) | 0.539 |
| Positive | 0 (0.0) | 6 (31.6) | |
| Ophtalmic involvement | | | |
| Negative | 3 (75.0) | 16 (84.2) | 1.000 |
| Iridocyclitis | 1 (25.0) | 3 (15.8) | |
| Renal volume | Bilateral carotis intimal thickness increase (n=9) 287.0 (167.0-387.0) | Bilateral carotis intimal thickness normal (n=14) 243.5 (188.0-377.0) | 0.035 |

Data are shown as median (minimum-maximum) and frequency and percentage

BD eye involvement presents as non-granulomatous, bilateral, and recurrent inflammation of the anterior uvea. There are three primary forms of posterior segment changes: retinitis, widespread vascular leakage, and retinal vasculitis, predominantly affecting veins (2,3). In addition, bilateral eye involvement and recurrent episodes of uveitis may cause progressive vision loss (3,10). Neurosyndrome Behçet is the term used to describe the predominant neurological involvement in BD (neuro-Behçet's syndrome) (12).

Recurrent inflammation defines BD, which is an occlusive vasculitis (3,13). Venous involvement exceeds arterial participation by 75% to 25% (2-4). Therefore, the most frequent symptom is DVT in the lower extremity (4).

Chronic inflammation is an infrequent risk factor for the development of atherosclerosis (4,13). Nowadays, atherosclerosis is mainly perceived as a persistent, low-

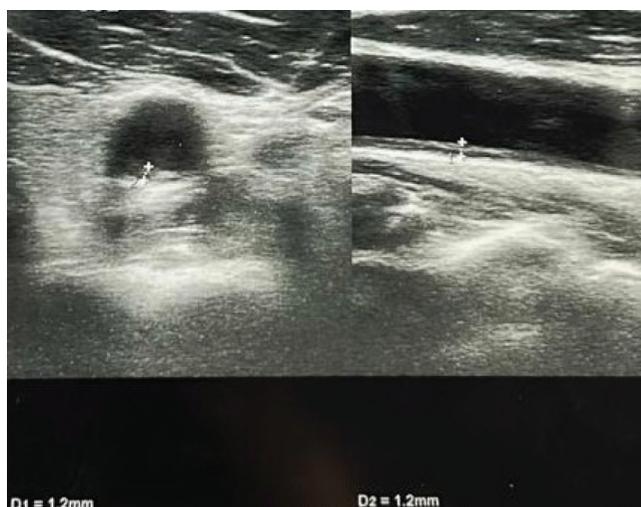


Figure 1. Intimal thickness measurement from the carotid artery

grade inflammatory condition. Endothelial damage is a crucial stage in atherogenesis and a defining trait of BD (4,6,14). Due to this fact, in this study, carotid arteries in BD patients were assessed. Blood vessels of all diameters are affected by BD, a systemic disease (14).

Doppler ultrasound has emerged as a popular, simple, manageable, affordable, quick, precise, and noninvasive tool for measuring vascular hemodynamics. We reasoned that since vascular illness affects all vessel diameters and is a prevalent clinical characteristic of BD, the carotid arteries may be affected (14).

Subclinical atherosclerosis can be detected by measuring carotid IMT using high-resolution B-mode U/S. Endothelial injury is a critical event in atherogenesis. A crucial characteristic of atherosclerosis is the morphological thickness of the arterial wall (15). Unfortunately, we could not show a relationship between carotid IMT and disease severity scores in patient groups. Similar to the current study, only 3% to 4% of the carotid arteries in Behçet patients had atherosclerotic plaques (14). Our study found a similar proportion of atherosclerotic plaques in CCA. Akçar et al. (14) reported no atherosclerotic plaques in the carotid arteries of 41 BD patients.

Various studies have reported significantly higher IMT in BD patients than in controls (4,8,15,16). However, in another study, the authors reported no difference in IMT measurements between her BD patients and controls (2). In our study, BD carotid artery IMT scores were slightly higher than those of healthy subjects, but not significantly. Similarly, Messedi et al. (2) we found no significant association between IMT and clinical and therapeutic disease features in our BD patients.

In addition, our study could not find a statistically significant relationship between IMT and clinical involvement areas.

Among the various parameters, only age was positively correlated with carotid IMT in both BD patients and controls (15). Similarly, we could not show a correlation between the clinical severity of the disease and carotid IMT in our patient group.

In BD patients, higher IMT was substantially linked with signs of endothelial dysfunction, according to a recent study (4). However, according to the research, there was disagreement on the connection between IMT measures in individuals with BD and cardiovascular risk factors (2).

Typical or nontraditional risk factors for cardiovascular disease do not predict increased IMT during this systemic vasculitis. Furthermore, the immunosuppressive medication, the length of the illness, or clinical signs were not linked to increased artery wall thickness. These findings imply that BD might result in elevated IMT (2).

Moreover, vascular involvement, posterior uveitis, or retinal vasculitis have all been linked to IMT by other authors (2). Although plaque incidence was often higher in BD than in healthy controls, this difference was not statistically significant. This divergence in IMT-related parameters in BD patients seen in the literature may be caused by variations in vascular risk factors among various ethnic groups (2). These vascular risk factor variations between ethnic groups are most likely hereditary. These findings suggest that atherogenesis may be influenced by prolonged systemic inflammation (2).

Renal involvement associated with BD varies significantly in different studies (17,18). Akpolat et al. (18) In their study of BD patients with renal involvement, the most prominent findings were edema-nephrotic syndrome, macroscopic hematuria, and proteinuria. More rarely, renal vasculitis, glomerulonephritis, amyloidosis, and chronic renal failure have been reported (18). Our study showed no statistically significant change in RI, PI, PSV, and EDV values on renal artery Doppler examination. Only B-mode U/S examination revealed a positive correlation between kidney volume and carotid IMT. We did not observe hematuria, proteinuria, or renal failure in the cases in our study. Not many studies in the literature show changes in renal artery Doppler parameters.

In this study, the carotid IMT of BD patients was the only positively correlated with age. However, there was no correlation between disease duration and neurological and vascular involvement. Also, in our study, it was very intriguing to find a positive correlation between carotid IMT and increase in kidney volume size in BD.

This study had some limitations. First of all, this study had a relatively small sample size. Second, it was impossible to avoid patient selection bias because all data were obtained from a single center. The exclusion of patients with further types of carotid and renal pathology, diabetes mellitus, systemic hypertension, or background with any systemic disease was another study constraint. Finally, whether illness severity raises the likelihood of subclinical atherosclerosis in BD patients cleared from further research on people with more severe diseases.

CONCLUSION

The carotid IMT was higher in the BD patients than in the healthy control group in those without substantial cardiovascular involvement. Our findings show the morphological evidence of subclinical atherosclerosis in BD. However, atherosclerosis started before clinical symptoms and may present for years. Hence, future clinical atherosclerosis events in BD may not always be predicted by increased carotid IMT and increased plaque prevalence in the carotid arteries.

ETHICS

Ethics Committee Approval: The Bezmialem Vakif University Ethics Committee approved the study with reference number 2022/338 (date: 24.01.2023).

Informed Consent: Informed consent of all study participants was obtained before the U/S evaluation.

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