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Evalution of Renal Involvement in Patients with Behçet Disease: Need to be Aware About Potential Hypertension in Long Term Follow Up?

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Backround: The aim of this study was to evaluate frequency and severity of kidney involvement with some clinical, ultrasonography and color Doppler measurements in patients with Behçet disease.

Material/Methods: This study was including 32 patients with Behçet disease and 32 healthy sex and age-matched control subjects. Patients were divided into two groups as period of disease 0-6 years and 7 years and above to evaluate effect of duration of disease. We evaluated some biochemical tests in both blood and urine related to renal functions, blood pressure values. Gray scale and color Doppler findings were noted.

Results: Renal artery volume flow in patients with a duration of 7 years or above was significantly decreased compared to control group ($p<0.05$). However, gray scale ultrasound and color Doppler measurements reveal there was not statistically significant change compared to control group. There was no biochemical abnormalities in any patient. Four patients had elevated blood pressure but mean blood pressure values were not statistically different compared to volunteers.

Conclusions: Renal involvement ratios varies in different studies but not common. End stage renal failure can be seen very rare. Furthermore, vasculitic changes can lead renal artery narrowness and can result to decrease in renal blood flow. It has a potential to activate renin angiotensin aldosterone cascade to elevate blood pressure. We must be aware about blood pressure of patients with Behçet disease, especially with long term follow up.

MeSH Keywords: Behçet Syndrome • Renal Artery • Ultrasonography, Doppler

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Background

Behçet disease (BD) is a systemic process of unknown etiology and protean clinical manifestations, including involvement of the mucocutaneous, ocular, articular, neurological, cardiovascular, gastrointestinal, and respiratory systems [1–5]. The disease is most often diagnosed in young adults between the ages of 20 and 40 years, generally in Mediterranean countries, the Middle East, and Japan, but it has been described worldwide. Mostly involved organs and systems are as follows: oral aphthosis (98%), genital aphthosis (73%), skin (74%), eyes (51%), joints (39%), neurological system (7.3%). Other systems are involved less frequently [6].

Vascular manifestations of BD, which consists of thrombosis, superficial phlebitis, and arterial involvements (aneurysm, stenosis, occlusion, etc.) have been added to update International Criteria of the Behçet disease (ICBD) since they are one of the major characteristics of BD. Trombosis is the most frequent vascular manifestation in BD and important factor of adverse prognosis [7]. Most vascular deaths are related to rupture of aneurysms [8]. Arterial complications are less common than venous ones in BD,

occurring in 1–7% of patients. The concept of ''vasculo-Behçet disease'' has been adopted for cases in which vascular complications are present and often dominate the clinical features. Patients with vasculo-Behçet disease are at a risk of multiple vessel-related complications [9–11].

Reports of Gharibdoost with 2068 patients, Shahram's survey of 3153 cases and a study of 4212 patients by Altiparmak et al. from Turkey revealed: frequency of urinary abnormalities in 6%, 11%, and 10.8%, respectively. The later study showed that renal biopsy confirmed GN in seven patients (0.16%) and end-stage renal failure developed in only one patient, concluding that urinary abnormalities are more frequent in BD. However, serious renal lesions develop in very few of them [12–14].

The aim of this study was to evaluate frequency and severity of kidney involvement with some clinical, ultrasonographic and color Doppler measurements in patients with Behçet disease.

Material and Methods

A total of 32 patients with BD referred from Eye Diseases and Dermatology Clinics, who were followed up with a control group consisting of 32 volunteers of similar age and gender for the purpose of comparison, were included in the study in Inonu University Turgut Ozal Medical Center between June 2001 and May 2002. Both groups included 18 males and 14 females. The process was explained to all patients in the study and informed consents were obtained.

Albumin, BUN, creatinine in blood and protein levels in urine were noted as biochemical parameters of renal involvement. Protein values above 30 mg/dL in spot urine were considered as proteinurea.

Sonographic examination was performed after 3 hours of fasting, by the same radiologist with four years of experience, and the patient in a prone position and holding a deep breath. Ultrasonography device was ATL HDI 5000 (Bothell WA, USA) and 3.5 Mhz sector probe.

Long and short axis in the sagittal plane of both kidneys were measured with the gray scale ultrasonography. Parenchymal echogenicity and structure, and the average thickness of the parenchyma were noted. Diameter of both renal arteries were measured.

Color Doppler examination of the proximal part of both renal arteries (after the aorta exit the first 2 cm) was performed. Attention was paid to cover the whole vessel while sampling window for measuring color Doppler parameters. Doppler angle of 30–60° was selected. Peak systolic velocity (PSV), end diastolic velocity (EDV), time average mean velocity (TAMV), systolic velocity/diastolic velocity (S/D), resistive index (RI), pulsatility index (PI), acceleration time (AT) and reno-aortic index (RAI) were noted as Doppler parameters.

Patients were divided into two groups, according to disease duration, i.e.: 0–6 years and 7 years and above to evaluate the effect of disease duration.

SPSS v10 (Chicago, IL, USA) software package was used for statistical analysis. Kolmogorov-Smirnov test was used to evaluate whether the group showed normal distribution or not. Variance analysis was used to compare the parameters of the group. A value of $p<0.05$ was considered as statistically significant.

Results

Mean age of BD patients was 34.88 years, range 17–54 years, whereas in the control group the mean age was 34.69 years and range 15–53 years. Those groups were identical by age. Both groups had a total of 32 individuals including 18 males and 14 females. Patients were divided into two groups according to the duration of the disease and each group had 16 patients.

All BUN and creatinine values in the BD group were within normal ranges. We did not find hematuria or proteinuria in any patient. Blood albumin values were normal. Systolic and diastolic blood pressure was elevated in 4 patients. There was no statistically significant difference in comparison of groups according to the systolic and diastolic blood pressure.

There was no statistically significant difference between patients with Behçet disease and control group as concerns kidney dimensions, parenchymal thickness, and renal artery diameter and reno-aortic index.

There was no statistically significant difference between patients with Behçet disease and control group concerning renal artery Doppler parameters (Table 1).

There was no statistically significant difference between Behçet group with disease duration of 1-6 years and control group when we compared gray scale ultrasounds of kidneys and renal artery Doppler parameters (Table 2).

Renal artery blood flow in patients with disease duration of 7 years or above was significantly decreased compared to control group ($p<0.05$). However, gray scale ultrasound and color Doppler measurements revealed there was not statistically significant change compared to control group (Table 3).

Discussion

BD, can be defined as multisystem vasculitis of young adults, which is endemic,showing the geographical distribution of countries, known as the Silk Road. Just as indicated by the geographical distribution, it has preferred organs to the body. The most common involvement sites are mouth, genitalia, skin and eye.

The major finding of this study is a significant decrease in renal artery volume flow in patients with disease duration of 7 years or more. This may be due to either development of subclinical renal artery involvement secondary to inflammatory vasculitis or impaired coagulation system. According to the recent studies, both overproduction of proinflammatory cytokines including interferon-gamma (IFNγ), tumor necrosis factor (TNF)α, interleukin (IL)1, IL6,

Table 1. Summary of data of Behçet and control groups.

Parameter	Behçet group (n: 32)	Control group (n: 32)	p
PSV mean (cm/s)	92.1	99.7	0.15
EDV mean (cm/s)	28.9	31.5	0.19
TAMV mean (cm/s)	36.9	38	0.26
S/D mean	2.54	2.60	0.39
RI mean	0.59	0.58	0.45
PI mean	1.08	1.05	0.37
AT mean	73.3	74.0	0.45
Renal artery flow mean (mL/min)	325.7	355.1	0.08

n – number.

Table 2. Summary of data of Behçet group with disease duration of 1–6 years.

Parameter	Behçet for 1–6 years (n: 16)	Control (n: 16)	p
Kidney long axis (mm)	102.2	104	0.32
Kidney short axis (mm)	40.1	39.1	0.22
Mean parenchymal thickness (mm)	12.55	12.82	0.27
Renal artery diameter (mm)	4.7	4.8	0.40
RAI	1.01	1.03	0.13
PSV mean (cm/s)	94.1	99.8	0.1
EDV mean (cm/s)	29.2	31.4	0.21
TAMV mean (cm/s)	37.3	38.1	0.16
S/D mean	2.52	2.6	0.17
RI mean	0.60	0.58	0.11
PI mean	1.02	1.04	0.30
AT mean	73.7	74	0.35
Renal artery flow mean (mL/min)	332.2	358.5	0.11

n – number.

IL8, IL12, and generalized derangement of CD4+ lymphocytes, monocytes and neutrophils have been observed in patients with Behçet disease [15,16]. These immunological and inflammatory factors may result in endothelial cell dysfunction and amplify the proinflammatory environment, promoting a prothrombotic state [15]. Because of systemic inflammatory vasculitis or impaired coagulation system, the same low volume flow is expected in different arterial systems. Indeed, Tasolar et al. reported that total vertebral artery volume flow was significantly lower in patients with Behçet disease [17].

Renal involvement shows a wide variation with a rate of 1–29% in various studies. Akpolat et al. reported edema – nephrotic syndrome in 12 patients, macroscopic hematuria in 1 patient, elevated serum creatinine and BUN in 20 patients and renal failure in 23 patients in their study of 33 BD patients with renal involvement [18]. In our study, no patient had renal failure.

Ardalan et al. reported that six patients had pathological biochemical values and 4 of them had positive hematuria and proteinuria in their study including 100 Behçet patients. This rate corresponds to 4% [19]. In our study, we did not observe any patients with hematuria or proteinuria. There was no patient with increased values of BUN and creatinine.

We observed an increase in systolic and diastolic blood pressure in 4 patients but did not find a statistically significant difference between BD and control group. Blood albumin levels were within normal limits in all patients.

Table 3. Summary of data of Behçet group with disease duration of 7 years and above.

Parameter	Behçet for 7 + years (n: 16)	Control (n: 16)	p
Kidney long axis (mm)	99.7	104	0.21
Kidneys short axis (mm)	39.5	39.3	0.39
Mean parenchymal thickness (mm)	12.4	12.76	0.13
Renal artery thickness (mm)	4.5	4.8	0.25
RAI	1	1.04	0.08
PSV mean (cm/s)	90.1	99	0.06
EDV mean (cm/s)	29.5	31.3	0.12
TAMV mean (cm/s)	35.6	38.7	0.23
S/D mean	2.49	2.6	0.11
RI mean	0.6	0.58	0.11
PI mean	1.01	1.03	0.29
AT mean	73.4	73.9	0.18
Renal artery flow mean (mL/min)	315.9	355.4	0.048

n – number.

As is well known, renal function should be substantially lost to patient's elevated values of BUN and creatinine. Glomerular filtration rate (GFR) is 120 mL/min while renal function is totally normal in healthy individuals with a body surface area of 1.73 m^2. Under these conditions, serum creatinine level is around 0.6 mg/dL. If GFR is about 40 mL/min to 90 mL/min, it indicates renal failure. Simultaneously, serum creatinine levels fall between 0.8 and 2 mg/dL. BUN and creatinine levels may remain within their normal values until the number of functioning nephrons falls to 10% of normal [20].

Mean serum creatinine levels of BD patients was 0.8 mg/dL, and 0.75 mg/dL in the control group. Generally, an increase in the level of serum creatinine of 0.05 mg/dL was seen, but the difference was not statistically significant.

Color Doppler ultrasound examination technique is an important modality for the evaluation of vascular pathology to provide flow information in addition to vascular morphology. The search for early warning signs is often made in vasculitic disease. Most important advantages are: it is technically easly applicable, cheap and non-invasive. However, Doppler examination is operator-dependent and there are also potential limitations of the abdominal examination, such as presence of bowel gas, obesity, and lack of co-operation [21]. Previous studies have reported that Doppler USG can provide us with earliest signs of vasculitis [21–24].

Renovascular Behçet disease, can be divided into two groups according to the type of vessel involvement: macroscopic (medium-sized arteries and veins] and microscopic (small arteries, arterioles, capillaries and venules). Akpolat et al. [25] observed 35 patients with renovascular involvement in their study with 132 patients. All 12 patients with renal artery aneurysms were male. In those patients, renal artery aneurysm were seen in the 2–10th year (average 5) of the disease. Renal artery stenosis was observed in 12, renal vein thrombosis in 7, and microscopic vascular invasion in 4 patients.

Our study showed a decrease in renal artery diameter in the BD group but the difference was not statistically significant. Stenosis is indicated as one of the types of arterial involvement in the literature. However, the flow rate of blood in a vessel is proportional to the square of the diameter of the vessel. The difference between the flow rate in our study may therefore have been statistically significant. There are not many studies showing the change of renal artery Doppler parameters in the literature.

Renal involvement in BD has a rate of 1–4% in different studies but a very small number of BD patients have severe renal insufficiency. Change in gray scale ultrasonography findings (kidney size and parenchymal average thickness) is generally observed in advanced stages of the disease [12–14]. In our study, there was no statistically significant difference between the BD and the control group, similarly to the literature.

Side effects due to treatment of renal involvement should be considered in the differential diagnosis of Behçet disease. Hemolytic uremic syndrome and thrombotic-thrombocytopenic purpura due to cyclosporine toxicity, have been reported in the literature [26]. Cyclophosphamide-induced bladder cancer [27], neurogenic bladder [28] was also defined. Patients who participated in our study were receiving treatment of corticosteroids and/or colchicine and there were no complaints mentioned. However, non-steroidal anti-inflammatory drugs and interferons are being

used in the treatment of BD and renal problems can be seen related to these drugs [29].

The most important limitation of our study was its small sample size. Another limitation was that our results were not supported by histopathological findings to show renal artery involvement. Recent studies with more patients may contribute to the subject.

Renal involvement ratios vary in different studies, but it is not common. End-stage renal failure is very rare. The only change in renal Doppler parameters we found was the reduction of renal blood with time. Long-term subclinical vasculitic changes can lead to renal artery narrowness and result in a decrease in renal blood flow. It has a potential to activate renin-angiotensin-aldosterone cascade to elevate blood pressure [30].

Conclusions

Since BD is a chronic vasculitis and patients with BD are followed up for a long period of time, we must monitor their blood pressure because all of them are potential candidates to hypertensive patients.

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