Renal Involvement in Behcet’s Disease

Mohammad Reza Ardalan1, Shahram Sadreddini2, Hamid Noshad1, Aliasghar Ebrahimi2, Mahsheed Molaeefard2, Mohammad Hossein Somi3, Mohammadali Mohajel Shoja4

Department of 1Nephrology, 2Rheumatology, 3Liver and Gastrointestinal Research Center and 4Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ABSTRACT. There are conflicting reports about the renal involvement in Behcet’s disease (BD). In this study we aimed to study the frequency and type of renal involvement in a group of patients with BD in Azerbaijan province that is one of the prevalent areas of BD in Iran. All cases of BD were prospectively followed between June 2004 and January 2007, and evaluated for renal dysfunction (serum creatinine > 1.7 mg/dL), glomerular hematuria and proteinuria. Those patients with proteinuria > 500 mg/day and serum creatinine level > 2 mg/dL, underwent renal biopsy. From a total number of 100 patients, six patients (6%) had obvious renal involvements. Four patients had glomerular hematuria and proteinuria. Renal biopsy in two of them revealed mesangial proliferative glomerulonephritis with IgA deposit in one of them and membranoproliferative glomerulonephritis in another one. Two remaining patients had serum creatinine > 2 mg/dL without any hematuria or proteinuria. Serologic study for viral agents and collagen vascular disease were negative in all patients with renal involvements. In conclusion, renal involvement in BD is not infrequent, although in most cases it is mild in nature and may be missed.

Keywords: Behcet’s Disease, Glomerulonephritis, Hematuria

Introduction

Behcet’s disease (BD) is a multi system disorder that affects younger population from Mediterranean, the Middle East and Far East region connected with ancient Silk Road. Its major manifestations are recurrent oral and genital ulcers and uveitis. Central nervous system disturbances, thrombophlebitis, large-vessel vasculitis and myocarditis could occur less frequently. There are conflicting reports about the renal involvement in BD. Four decades ago in 1963, Oshima et al first reported the occurrence of minor proteinuria and hematuria in 13 of 65 patients with BD.1 Twelve years later it was claimed that BD does not involve the kidney.2 But shortly thereafter Rosenthal et al showed that it is not rare, although in most instances it is mild in nature.3,4 In 1980 the diagnostic criteria of Zhang inclu-
Renal involvement in Behcet’s disease

Table 1 A and B. Clinical and laboratory characteristics of the patients with Bechet’s disease and renal involvements

<table>
<thead>
<tr>
<th>Patients</th>
<th>K. size</th>
<th>Scr</th>
<th>24h/P</th>
<th>GH</th>
<th>K biopsy</th>
<th>Type of BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 30y/M</td>
<td>R; 110/L; 112</td>
<td>1.7 mg/dL</td>
<td>700 mg</td>
<td>++</td>
<td>_</td>
<td>O/G</td>
</tr>
<tr>
<td>2. 40/M</td>
<td>R; 103/L; 110</td>
<td>1.1 mg/dL</td>
<td>200 mg</td>
<td>+</td>
<td>_</td>
<td>O/G</td>
</tr>
<tr>
<td>3. 25/F</td>
<td>R; 120/L; 115</td>
<td>1 mg/dL</td>
<td>900 mg</td>
<td>++</td>
<td>MSPGN</td>
<td>O/G/J</td>
</tr>
<tr>
<td>4. 42/M</td>
<td>R; 115/L; 118</td>
<td>1.4 mg/dL</td>
<td>1200 mg</td>
<td>++</td>
<td>MPGN</td>
<td>Neuro</td>
</tr>
<tr>
<td>5. 44/M</td>
<td>R; 105/L; 103</td>
<td>2.3 mg/dL</td>
<td>150 mg</td>
<td>_</td>
<td>_</td>
<td>Ocular</td>
</tr>
<tr>
<td>6. 28F</td>
<td>R; 121/L; 80</td>
<td>2.1 mg/dL</td>
<td>280 mg/dL</td>
<td>_</td>
<td>_</td>
<td>O/G/J</td>
</tr>
</tbody>
</table>

Table 1B

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>WBC (µL)</th>
<th>Hgb (g/dL)</th>
<th>HBSAg</th>
<th>HCVAb</th>
<th>HIVAb(ELISA)</th>
<th>C3 (90-180mg/dL)</th>
<th>C4 (10-40 mg/dL)</th>
<th>CH50 (70-150 unit)</th>
<th>ANA (&lt; 1 unit/L)</th>
<th>Anti-dsDNA (&lt; 45U/L)</th>
<th>P-ANCA (MPO) (&lt; 0.4 U/mL)</th>
<th>C-ANCA (PR3) (&lt; 3.1 U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30y/M</td>
<td>6400</td>
<td>13.5</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>110</td>
<td>14</td>
<td>90</td>
<td>0.7</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>40/M</td>
<td>8000</td>
<td>13.3</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>156</td>
<td>20</td>
<td>110</td>
<td>0.5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>25/F</td>
<td>9100</td>
<td>13.5</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>124</td>
<td>22</td>
<td>110</td>
<td>0.1</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>42/M</td>
<td>7000</td>
<td>12.5</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>51</td>
<td>18</td>
<td>140</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>44/M</td>
<td>7500</td>
<td>13</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>160</td>
<td>29</td>
<td>130</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>28/M</td>
<td>7700</td>
<td>11.8</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>140</td>
<td>&lt; 50</td>
<td>120</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


ded urinary problems including bladder ulceration, hematuria and epididymitis as minor criteria of BD.5 The finding of severe renal involvement in BD led to histological study of the kidney by Hermann et al in 1982.6

In most of the later reports, transient asymptomatic hematuria and proteinuria was the main presentation.7 Despite of the weak recognition several important renal problems have been associated with BD including; glomerular and vascular involvements and complications of drug therapy.3,8

Proliferative glomerulonephritis, IgA nephropathy, focal necrotizing glomerulonephritis and renal amyloidosis are the reported findings in BD.8 The aim of this study is to determine the frequency, clinical and pathologic features of renal involvements in a group of patients with BD from Azerbaijan province in North West of Iran where BD is most prevalent.9

Materials and Methods

In this prospective study during a period of three years (June 2004 and January 2007), all cases of BD who had the International criteria and were under the follow up in outpatients rheumatologic clinic of Tabriz University of medical science were included. Following information were recorded, including: gender, age, medications, history of renal problem and duration and type of BD. Urine analysis and serum creatinine levels were measured in each individual during their regular follow up. Patients with a serum creatinine level of greater than 1.7 mg/dL or those with dipstick proteinuria or he-
maturia underwent further evaluation including; urine examination for dysmorphic red blood cells, urine culture, twenty four hours urine collection for quantifying proteinuria, renal and bladder ultrasound for measuring the renal size and ruling out any renal or bladder stones. In those with glomerular hematuria and greater than 250 mg/24 hours proteinuria, serologic examination for hepatitis B virus (HBV), Hepatitis C virus (HCV) and HIV, Autoimmune workup including: ANA, dsDNA, complements, ANCA, antiphospholipid antibodies, cryoglobulins and anti-basement membrane antibody were performed. In those with accelerated and malignant hypertension, flank pain, worsening proteinuria, and renal size asymmetry; Doppler Ultrasound study for possible renal artery or renal vein thrombosis was performed. Echocardiography was also performed to rule out endocarditis as a possible cause of secondary glomerulonephritis. A complete history of medications was also obtained.

Renal biopsy was considered in those with active urine sediment including dysmorphic red blood, red blood cell casts, 24 hours protein excretion greater than 500 mg/day and serum creatinine levels greater than 2 mg/dL.

**Results**

A total of 103 Behcet patients were enrolled in this study. Two of them withdrew consent at the start and another during the study. In the remaining 100 patients (M/F 63/37 age: 18-48 years) in 68 patients (68%) had oral and genital aphthous lesion as the main presentation of BD, 27 (27 %) patients had ocular BD, and 5 patients (5%) had various degree of neurological involvements. Glomerular hematuria (figure 1), proteinuria or renal function impairment were detected in 6 (6%) patients (5M, 1F) only. (Table 1A). None of them had any history of macroscopic hematuria and the patients and their physicians were unaware about their kidney problems. Urine culture was negative in all these six patients and there was no evidence of renal or bladder stones on ultrasound examination.

Two patients had an elevated serum creatinine levels, without hematuria or proteinuria (table 1A: patient no. 5 and 6). One of them (patient 5) was receiving cyclosporine for treatment of ocular-BD (uveitis) for more than one year with a high cyclosporine blood level of 250 ng/mL. The second patient (table 1A, patient 6) had a history of oral and genital aphthous ulcer and right knee arthritis and was taking prednisolone and Azathioprine. Ultrasound in this patient revealed small left kidney and increased echogenicity of right kidney. Doppler ultrasound in this patient was negative for left renal artery stenosis.

Autoimmune workup was negative in all except patient no. 4, who had depressed C3 and CH50 levels (table 1B). No evidence was endocarditis was seen on echocardiographic study.

None of our patients had any history of peripheral arterial or vein thrombosis, or pulmonary embolism or any recent history of exacerbating or malignant hypertension.

Renal biopsy was performed in two patients (table 1, patient no. 3 and 4). Light microscopic and immunofluoresent studies of renal biopsy disclosed mesangial proliferative glomerulonephritis and a mild granular mesangial deposit of C3 (+1) and more prominent IgA (+3) deposit in in one patient (table 1A, patient 3 and figure 2).
Membranoproliferative glomerulonephritis with a granular mesangial deposit of C3 (+2) and IgM (+2) were found in the other patient (table 1A, patient 4 and figure 3). Based on the biopsy findings the first patient received angiotensin receptor blockers, angiotensin converting enzyme inhibitors and prednisolone and the other was prescribed intravenous cyclophosphamide pulse (500 mg monthly/for six months). None of these patients with renal involvement reached an end stage renal failure during the study period.

Discussion

We detected an obvious renal involvement in 6% of our patients with BD. Microscopic glomerular hematuria and mild proteinuria were the most frequent presentation in our patients. Membranoproliferative glomerulonephritis and mesangial proliferative glomerulonephritis with IgA deposits were the pathological findings that we found in two of our patients.

We did not perform renal biopsy in two patients with urinary findings suggestive of glomerulonephritis, the third patient was thought to have cyclosporine nephrotoxicity and the fourth was felt to have BD related chronic kidney disease.

Reports of Gharibdoost in 2068 patients and Shahram in a survey of 3153 cases of BD from Iran and a study 4212 patients with BD by Altiparmak et al from Turkey revealed urinary and renal abnormalities in 6%10, 11%11 and 10.8% respectively. The later study had 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 only very few of these patients.12

Similar to our study several case reports and case series report the occurrence of various types of Gn in BD.3,8,13-17

Glomerulonephritis with nephritic picture is common at early diagnosis of renal disease in BD whereas secondary amyloidosis is a late sequelae of chronic inflammation.8,18-20 In a report from Turkey the most common cause of renal failure in BD was amyloidosis.19 Shahram et al reported that amyloidosis among the Iranian patients with BD is extremely rare.9 None of our patients had a nephritic proteinuria or any other sign of systemic amyloidosis.

Although vascular involvement including veno-occlusive, arterial aneurysm and arterial occlusion are the leading cause of death in BD, renal
vascular disease is found in less than 1% of patients with vascular BD. Renal artery may be involved at any level throughout the renal artery resulting in main renal artery aneurysm or intra renal microaneurysm. Microscopic hematuria can result from renal micro-infarcts and proteinuria as a sign of renal vein thrombosis in these patients.

Renal replacement therapy in BD is also associated with a high risk of surgical vascular complication and failure of A-V fistula. Theoretically peritoneal dialysis could be a more preferred choice. None of our patients reached the end stage renal state.

In conclusion, the present study suggests that renal involvement in BD is not infrequent, although in most cases it is mild in nature. Dermatologists, rheumatologists and ophthalmologists taking care of most of these patients should be aware about this possibility of renal involvement and therefore periodic urine examination and serum creatinine level measurement should be part of the management protocol.

References