Renal involvement in Behçet’s Disease

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Abstract

Renal involvement in Behçet’s Disease (BD) has a wide clinical spectrum. The most common causes of renal failure in BD are amyloidosis (AA-type), glomerulonephritis and macroscopic/microscopic vascular diseases. Renal involvement is mild and detected in routine urine analysis and serum creatinine measurements in the majority of the patients. However, a small number of patients may have renal failure and also end-stage renal failure requiring renal transplantation. We aim to make a brief overview of the renal problems seen in Behçet’s Disease.

Key words: Kidney, Behçet’s disease

Introduction

Behçet’s Disease (BD) is a multisystem disorder characterized by vasculitis. It was first described in 1937, as the triad of recurrent uveitis, recurrent oral and genital ulcers [1]. Behçet’s Disease characterized by mild proteinuria and hematuria was first reported by Oshima et al. in 1963 [2]. Later, two other chronic nephritis patients with similar renal findings have been reported [3]. Amyloidosis and glomerulonephritis (GN) were first described in 1958 and 1973, respectively [4,5]. In a prospective study by Rosenthal et al., mild proteinuria and hematuria were found at 16 of 51 (31%) patients with BD in 1978 [6]. Behçet’s Disease can make involvement in almost all tissues and organs. Although Chajek and Fainaru [7] made a conclusion as “BD does not effect the kidney” in their BD series including 683 patients, in 1975, and numerous reviews [8,9] did not mention about renal involvement in BD, renal involvement in BD firstly suggested in case reports [10-12] and then reported in some clinical studies conducted in a small number of patients (6-33 patients) [13-18]. The clinical spectrum of renal BD varies in a wide range from asymptomatic hematuria/proteinuria to end-stage renal failure. Asymptomatic hematuria and proteinuria are the most often clinical findings of renal BD, and also there may be other clinical forms of...
renal BD such as amyloidosis (AA-type), GN and vascular involvement [14]. The incidence of renal symptoms in BD varies between 1% and 29% [13]. The differences in the incidence values may be associated with the variety of parameters (hematuria, proteinuria, microalbuminuria, GN, amyloidosis, renal vasculitis) used by different researchers.

Male gender was suggested to be a risk factor for renal BD, but there are also some other studies that claim the opposite of it [14,19]. Only a few studies have control groups. Karci et al. compared BD patients (n=500) with control group (n=506), and did not find any significant difference in terms of chronic renal failure and glomerular disease [20]. Sahin et al. designed a study on 28 BD patients in comparison with a healthy control group (n=27), and they found that microalbuminuria and beta2-microglobulin excretion were higher in BD patients, as the markers of renal damage, but it was not statistically significant [21].

Which patients with BD have higher risk of renal involvement? Kavala et al. from Turkey reported that the incidence of microalbuminuria was higher in BD patients who had the BD for more than 10 years and with neurological involvement [18]. In another study by Choi et al. from Korea informed a higher incidence of hematuria in patients with high erythrocyte sedimentation rates and genital ulcers, and relatively elderly female patients. In the same study, authors also reported higher incidence of proteinuria in patients with higher erythrocyte sedimentation rates [19]. This difference from two studies may be due to geographical conditions. Indeed, amyloidosis is common in Familial Mediterranean Fever patients from Mediterranean Region and Middle East, but rare in patients from Japan.

**Amyloidosis**

Sherf et al. first described renal amyloidosis in BD in 1964 [5]. In the meta-analysis by Akpolat et al., renal amyloidosis were found in 42.7% of 253 renal BD patients, and reported as the first most common specific renal lesion in patients with renal BD [13]. Akpolat et al. also reported that amyloidosis (n=21) was the most common specific renal involvement in their own patient series (n=33) [13]. Amyloidosis is also the most common reason that causes renal failure in BD patients [13,22]. However, amyloidosis can be isolated or together with other renal problems (such as renal vein thrombosis) in these patients [13,14].

Male gender is dominant in patients with amyloidosis [14]. Mean period of developing amyloidosis has been reported as 9.6 years (1.3-27 years) in the literature and is also reported that amyloidosis occurs in a shorter period in men compared to women (9 years vs. 13 years, p<0.02) [14].

Amyloidosis is usually together with renal failure and 5-year survival of these patients is 46% [14]. These cases mostly have been reported from Middle East and Mediterranean countries [13]. And this data indicates the importance of genetic/environmental factors in the development of amyloidosis as previously known. The most frequent MEFV mutations are M694V, M684I, V726A, M680I and E148Q [13]. However, Kutlay et al. didn’t find any MEFV mutations in patients with BD and amyloidosis [23]. In another study conducted in 19 patients with amyloidosis related to BD, MEFV mutation frequency reported as 32%, were not statistically significant [24].

Serum amyloid A-1 (SAA) gene is associated with AA-type amyloidosis and Utku et al. showed that SAA-1 α/α genotype is a risk factor for the development of amyloidosis in BD [25]. In another study by Dilşen et al., amyloidosis frequency were found higher in patients with genital ulcers, ocular involvement, thrombophlebitis, peripheral arthritis, neuropsychiatric symptoms, and positive pathergy test [26].

Amyloidosis is one of the prognostic factors affecting the survival of patients with renal BD. Patients with vascular involvement are at high risk for the development of amyloidosis. Therefore it may be useful to start colchicine treatment in these patients with vascular involvement [14].

**Glomerulonephritis**

It is the second most common specific lesion in patients with renal BD. The average time of development of GN in BD patients was reported as 8 years (2 months-22 years), and this period has been found to be shorter in women than men (5.9 years vs. 8.8. years, p<0.05), in contrast to the complication of amyloidosis [14]. Renal findings of GN has a very wide range. Any kind of renal signs, from asymptomatic hematuria and/or proteinuria to rapidly progressive glomerulonephritis, may be
found in these patients [14,27]. A wide variety of types of GN can be seen in BD patients [13,28]. These are as follows:

- Diffuse proliferative GN,
- Focal and segmental glomerulosclerosis,
- Mesangial proliferative GN,
- IgA nephritis,
- Membranoproliferative GN,
- Crescentic GN,
- Minor glomerular lesion,
- Membranous GN,
- Proliferative GN,
- Fibrillary GN.

As can be seen, there isn’t any specific glomerular lesion in patients with BD. But, crescentic GN and IgA nephropathy are seem to be the most common ones [19,27,29]. In two large patient series of BD, GN frequency have been reported as <1% (7/4212 and 13/5059 patients) [15,30]. This rate is very low compared to the other vasculitis. In these two studies, hematuria/proteinuria frequency was found to be 10%, and this shows the prevalence of mild glomerular disease in BD.

In immunofluorescence microscopy, mainly IgA, IgM and C3 depositions were seen, but electron microscopy findings are nonspecific [15,31-36].

Immunocomplexes are thought to be triggering mechanism in the pathophysiology of glomerular lesions in BD [37]. Although the development of GN associated with circulating immunocomplexes have been reported [38-41], other opinions against this hypothesis are also available in the literature [42,43]. Although it has been reported that anti-neutrophil cytoplasmic antibodies may play a role in the pathogenesis of renal involvement observed in BD patients [44,45], but it could not be proven yet [46].

How should we treat GN in patients with BD? According to an opinion, renal biopsy should be performed in patients with protein excretion >1 g/day [47]. Immunosuppressive therapy consisting of steroids and/or cyclophosphamide should be considered if there is crescentic or focal sclerosing GN and especially the presence of abnormal renal function test results. Indeed, immunosuppressive therapy has been successfully used in these patients [39,41,43,48]. However, because of the possibility of spontaneous recovery even in severe GN [42,49,50] some of the authors are against any specific treatment for these patients [48,51].

As a result, BD patients who developed GN has good prognosis, and the disease progresses to end-stage renal disease in only very few patients [15,27,52]. Prognosis of GN with silent clinical presentation (isolated hematuria and/or proteinuria) is not exactly known, but it seems to be favorable, and the treatment of these patients is also unknown [14].

**Vascular Involvement**

Vascular involvement is a leading cause of death in BD patients. Prevalence of vascular involvement in BD varies between 2-37%, and it is more common in men [14,53]. Incidence of renal vascular involvement has been reported as less than 1% in BD patients [53]. It is specifically the third most common renal lesion in renal BD patients. Renal vascular involvement in BD patients can be in three types:

- Venous occlusion,
- Arterial aneurysms,
- Arterial occlusions.

The venous lesions are more common than arterial lesions and subcutaneous venous thrombophlebitis is the most common form of involvement [14].

Renal arter aneurysms is the most common one amongst the problems of the renal arter [54-64]. The main finding of renal arter aneurysms, stenosis and occlusion is hypertension. Renal arter aneurysms may occur anywhere along the renal arter from the beginning of the renal arter to intrarenal microaneurysms. Flank pain is the primary complaint in the presence of renal arter aneurysm. Magnetic resonance imaging and magnetic resonance angiography are safe, noninvasive and effective imaging methods in the study of arterial and venous lesions in BD patients. Selective transcatheter embolization in addition to immunosuppressive drugs is a promising treatment option for BD patients with aneurysms including renal arter aneurysms [65,66]. In addition to the immunosuppressive drugs, angioplasty and stent implantation can be performed in BD patients in the presence of renal arter stenosis [67].

Renal vein thrombosis has been reported in BD patients [68-71]. The most important characteristic of these patients with BD and renal vein thrombosis is that they usually have
accompanying another major vascular disorder [14]. There may be an underlying renal vein thrombosis in patients with nephrotic syndrome associated with BD [14].

**End Stage Renal Disease**

Amyloidosis and GN are the most important two causes of renal failure due to BD. Crescentic GN is a major cause of end-stage renal disease [27]. In patients who have end-stage renal disease has been observed that the BD activity decreased with the onset of hemodialysis [22.72]. This situation may be associated with immunosuppression due to uremia as also occurs in systemic lupus erythematosus [73]. However, in BD patients undergoing hemodialysis, problems such as thrombosis are common at venipuncture places [22]. Despite this, renal transplantation and hemodialysis are safe treatment options in end-stage renal disease associated with BD [22.52].

Cyclosporine used in the treatment of BD also keeps an important part in the etiology of renal failure in these BD patients [13,22]. For this reason, BD patients receiving cyclosporin should be closely followed in this regard.

**Bladder Involvement**

In BD patients, urological problems such as epididymitis and sterilit urethritis are rarely seen in contrast to genital ulcers which is one of the most important diagnostic parameters [74]. Bladder involvement may also exist in BD patients. Çetinel et al. reported the incidence of bladder involvement in BD as 0.07% [75]. Mostly storage symptoms [75-81], and sometimes urge incontinence were found in these patients [76,77,79,80,82]. However, symptoms associated with bladder emptying [4,8,9,11] and also urinary retention may also be experienced [78,81]. In BD patients with bladder involvement, frequency and urgency are more common, and this may be due to the involvement of pontine micturition center with vasculitic process [77].

Treatment of patients with bladder involvement is the same in patients with and without BD. So, clean intermittent catheterization is used to treat emptying failure and anticholinergic agents and sometimes augmentation cystoplasty are used to treat patients with storage problems [83].

**Other Renal Lesions in Behçet’s Disease**

Interstitial nephritis have been reported in BD patients [14,84]. Acute tubulointerstitial nephritis accompanied by acute renal failure and Fanconi Syndrome has been identified in a 46-year-old women with recurrent oral ulcers, uveitis and arthralgia [84]. However, many more patients must be able to mention about correlating of interstitial nephritis with BD [13,14].

Oğuz et al. reported a BD patient with renal cortical scarring demonstrated by computed tomography [85]. The reason for this radiological finding is thought to be renal microinfarction.

Although they are rarely reported, other renal problems in BD patients are cyclosporine nephrotoxicity [31], renal cancer [86], and thrombotic thrombocytopenic purpura [87].

**Conclusion**

Renal BD patients have some nonspecific but special clinical features. In BD patients, renal involvement is actually more common than expected, but most cases are mild manner. Routine urinalysis and serum creatinine measurement is required for early diagnosis of renal involvement in BD. Rectal biopsy should be performed prior to the renal biopsy, since the most common cause of nephrotic syndrome is amyloidosis. Just like in Familial Mediterranean Fever patients, colchicine should be started as early as possible and recommended to be used for a long time for both prevention and treatment of amyloidosis in BD patients [14,26]. If there are nephrotic syndrome, flank pain, or severe hypertension then it should be suspected of renal vein thrombosis and/or renal arter aneurysm. Multidetect computed tomography, arteriography, magnetic resonance imaging and magnetic resonance angiography are very good alternatives to evaluate renal vascular disease, but the selection of the method to use, depends on the state of the patient and experience of the medical center.

The therapy of renal involvement is the same in patients with and without BD. There is no data about the treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on the effect of urinary protein excretion in BD patients. Embolization and/or vascular interventions such as angioplasty may be used for the treatment of renal vascular involvement, but these methods should be performed together with immunosuppressive drugs. Despite some difficulties, hemodialysis and renal transplantation are safe treatment options for uremia associated with BD.
Increased awareness of renal problems by physicians dealing with BD, especially such as rheumatologists, dermatologists and ophthalmologists, will show us the prevalence and importance of renal involvement in BD more accurately.

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