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Frequency of Urinary Tract Infection and its Relationship with Disease Severity in Patients with Behçet's Disease

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Abstract: Although the importance of infections in the etiopathogenesis of Behçet's Disease (BD) has previously been reported, there are no studies in the literature concerning the frequency of urinary tract infections (UTIs) in the disease. The aim of this study was to investigate the frequency of UTIs and their association with disease severity in patients with BD. One hundred thirteen patients with BD were included in this retrospective cross-sectional study. Their files were reviewed and their symptoms on the date of admission and total urine analysis and urine culture results on that date were recorded. The frequency of UTIs and their relationship with disease severity were examined. One hundred thirteen patients with a median age of 38 (IQR: 29-47), 74.3% (n=84) of whom were women, were evaluated in the study. UTI was detected in 8.8% (n=10) of the patients. *Escherichia coli* (E. coli) was identified as the causative microorganism in 90% (n=9) and *Klebsiella spp.* in 10% (n=1) of the patients with UTIs. BD patients with UTIs were older, and UTIs were more common in those with longer disease durations (p=0.001 and p=0.005, respectively). No statistically significant relationship was detected between the severity of BD and the presence of UTIs (p>0.05). Dysuria and pyuria were detected more often in BD patients with positive pathergy test results and no UTIs (p=0.007 and p=0.038, respectively). Leukocyte esterase positivity was detected more frequently in BD patients with no urinary infections but with genital ulcers (p=0.039). Urinary system infection was detected in 8.8% (n=10) of the BD patients. Although no relationship was found between the severity of the disease and urinary system infection in the present study, we think that patients' complaints and culture results should be considered before administering treatment. ©2023 NTMS.

Keywords: Etiopathogenesis; Behçet's Disease; Urinary Tract Infection; Disease Severity; Microorganism.

1. Introduction

Behçet's disease (BD) is a chronic multisystemic vasculitis involving periods of exacerbation. It can affect the vascular, ocular, mucocutaneous, articular, gastrointestinal, and neurological systems [1]. Although BD is most commonly seen along the region of the Silk Road, extending from the Mediterranean region and the Middle East to Central and Eastern Asia, it can also be seen worldwide due to migration [2]. The etiopathogenesis involves inflammation triggered by environmental or infectious causes among genetically

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predisposed individuals. Inflammation occurs in the vascular endothelium.[3] The triggering effects of microorganisms in the development of BD have long been the subject of discussion. The first researcher to suggest that the condition might be associated with an infectious etiology was Professor Hulusi Behçet [4]. Some viral agents are known to be capable of causing UTIs However, no conclusive evidence has been found of a relationship with *Herpes simplex virus (HSV-1)*, *Cytomegalovirus*, *Epstein-Barr virus*, or *Hepatitis viruses*. Rather than active infection by the virus, inflammation has been implicated because of the altered immune response to the virus in BD. Researchers have also claimed that the cross-reaction between the heat shock proteins of some streptococcal species and human heat shock proteins may trigger an immune response in genetically predisposed patients. Toll-like receptor (TLR) can be stimulated after this cross-reaction, and T-cell expression increases [5]. Both adaptive and innate immune responses may play a role in the pathogenesis of BD. Microorganism lipopolysaccharides cause an increase in proinflammatory cytokines by stimulating the autoinflammatory response and thus interleukin-1β (IL-1β) synthesis through inflammasomes and TLR [6]. Previous studies have reported increased expression of pro–inflammatory cytokines, such as IL-1α, IL-1β, IL-6, IL-8, and tumor necrotic factor (TNF), in BD. However, low levels of IL-10, an anti–inflammatory cytokine, have been observed [7, 8]. While IL-23 increases the release of IL-17 from T-cells, IL-12 and interferon-γ (IFN-γ) cause a T-cell response in the Th1 direction. The release of IL-17 causes neutrophil accumulation in the affected organs in BD [9]. Research recently revealed that immunity against neurofilament-medium (NF-M) develops in patients with BD and that this and bacterial heat shock protein-65 (HSP) contain common epitopes [10]. Although numerous studies have investigated the pathogenesis of BD while focusing on the roles of microorganisms, none have addressed the frequency of urinary tract infections (UTIs) in BD and their effect on disease severity. The purpose of the current study was therefore to investigate the frequency of urinary infections in BD patients and their relationship with BD severity.

2. Material and Methods

2.1. Study Design

This research was designed as a retrospective, single-center, cross-sectional study.

2.2. Ethical Approval

The study was carried out in line with the principles of the Declaration of Helsinki after receipt of approval from the local ethics committee (No 5, Dated 29.12.2022).

2.3. Setting

The study was conducted between February 2020 and December 2022 among patients diagnosed with BD presenting to the dermatology clinic of our tertiary university hospital, which serves approximately 4.5 million people in Eastern Türkiye.

2.4. Participants and Study Protocol

One hundred thirteen active and inactive BD patients aged 18-70 who presented to the BD clinic between February 2020 and December 2022, were included in the study. Patients previously diagnosed with BD but with no complaints during routine control visits were considered inactive. Diagnosis of BD was based on international BD diagnostic criteria. The patients' demographic characteristics of the patients were recorded from patient registration forms. The patients' files were reviewed retrospectively, and their symptoms on the date of admission and total urinalysis and urine culture results were recorded. Our hospital's laboratory values were used as reference values for the urine laboratory tests. Analyses were carried out on automatic modular urine analyzers (model numbers H-800 and FUS-200, Dirui Industry, Changchun, China). Urinary system infection was diagnosed based on lower urinary system symptoms such as burning while urinating, increased frequency of urination, and feeling an urgency to urinate (dysuria, urgency, and frequency) as well as a leukocyte value of >10 cells/ml in urine culture and a causative microorganism value $>10^5$ colony-forming units/milliliter (cfu/ml). Patients with no growth in urine despite complaints of urinary system infection were not regarded as having UTI. Disease severity of BD was determined using Krause's BD clinical severity scoring system. Accordingly, one point was given for each mild symptom (oral or genital aphthous ulcer, arthralgia, erythema nodosum, papulopustular lesion, or folliculitis), two for each moderate symptom (arthritis, anterior uveitis, deep vein thrombosis in the legs, or gastrointestinal involvement), and three for each severe symptom (arterial thrombosis, retinal vasculitis, posterior uveitis/panuveitis, neuro-Behçet's, and bowel perforation). Once the total scores had been calculated, the patients were divided into three groups - mild (scores <4), moderate (4-6), and severe (≥7) based on the determined disease severity. Patients under 18 or who provided histories of another infection on the patient registration form, and pregnant and breastfeeding women were excluded from the study.

2.5. Statistical Analysis

All the study data were entered onto SPSS version 23 for Windows software (IBM, Chicago, IL, USA) for analysis. Categorical descriptive data were presented as frequency distribution and percentage, and continuous variables as median plus interquartile range. Chi–square and Fisher's Exact tests were used to compare categorical data between the groups, The non-parametric Mann–Whitney U and Kruskal-Wallis tests were used in the comparison of continuous data since the parametric hypothesis test conditions were not met. p values <0.05 were regarded as statistically significant.

3. Results

One hundred thirteen patients with BD, with a median age of 38 (IQR: 29-47), 74.3% (n=84) of whom women, were evaluated. UTI was detected in 8.8% (n=10) of the patients. *E. coli* was detected as the causative microorganism in 90% (n=9) of the patients and *Klebsiella spp.* in 10% (n=1). The distribution of the patient characteristics according to the development of urinary system infection is shown in Table 1.

Table 1: The distribution of patients' demographic and clinical characteristics of BD according to the presence of UTI.

Variables	No (n=13)	Yes (n=10)	P
Age, years, median (IQR)	36 (27-45)	49 (42-58)	0.001
Gender, female, n (%)	76 (73.8)	8 (80.0)	0.501
Presence of additional underlying disease, n (%)	18 (17.5)	4 (40.0)	0.102
Duration of complaints, months, median (IQR)	72 (36-144)	180 (84-315)	0.005
Age at disease onset, median (IQR)	28 (21-36)	34 (26-40)	0.125
BD organ involvement, n (%)			
Oral aphtha	73 (70.9)	6 (60.0)	0.349
Genital ulcer	22 (21.4)	1 (10.0)	0.354
Papulopustular lesion	54 (52.4)	7 (70.0)	0.234
Erythema nodosum	24 (23.3)	-	0.082
Vascular involvement	12 (11.7)	1 (10.0)	0.677
Superficial thrombophlebitis	5 (4.9)	-	
Deep vein thrombosis	4 (3.9)	-	
CNS vascular thrombosis	3 (2.9)	1 (10.0)	
Pathergy positivity	39 (37.9)	2 (20.0)	0.223
Joint signs	48 (46.6)	5 (50.0)	0.837
Arthralgia	39 (37.9)	5 (50.0)	
Arthritis	9 (8.7)	-	
Eye signs	29 (28.2)	4 (40.0)	0.325
Active	17 (16.5)	2 (20.0)	
Inactive	13 (12.6)	2 (20.0)	
CNS involvement	6 (5.8)	1 (10.0)	0.487
Disease activity, active	88 (85.4)	7 (70.0)	0.197
Disease severity index, median (IQR)			0.209
Inactive	14 (13.6)	3 (30.0)	
Mild	57 (55.3)	3 (30.0)	
Moderate	24 (23.3)	4 (40.0)	
Severe	8 (7.8)		
Number of skin and mucosal signs, median (IQR)	2 (1-3)	1,5 (0.75-2.25)	0.229
Treatment modality used, n (%)			
Drug use	97 (94.2)	9 (90.0)	0.487
Corticosteroid	2 (1.9)	-	0.830
Colchicine	95 (92.2)	9 (90.0)	0.580
Other immunosuppressive therapy	26 (25.2)	3 (30.0)	0.499
Biological agent	10 (9.7)	1 (10.0)	0.657

CNS: Central Nervous System, IQR: Interquartile range

Patients with UTIs were significantly older, and the duration of their BD complaints was significantly longer (p=0.001, and p=0.005, respectively). No significan relationship was observed between the presence of urinary system infection and the severity of BD (p>0.05). The symptom variations and laboratory findings according to the presence of UTI in patients with BD are shown in Table 2.

As anticipated, dysuria, frequency of urination, urinary leukocytes, leukocyte esterase, and nitrite positivity were significantly higher in patients with UTIs (Table 2). Leukocyte and erythrocyte counts in urine were also significantly higher in the presence of UTI (p<0.001). Relationships between the symptoms of BD in patients without diagnoses of UTI but with clinical findings of urinary system infection are shown in Table 3.

Table 2: The distribution of symptoms and laboratory findings according to the presence of UTI in BD patients.

Symptoms/n (%)	None (n=13)	Yes (n=10)	p
Dysuria	16 (15.5)	10 (100)	<0.001
Frequency	2 (1.9)	4 (40.0)	<0.001
Urgency	-	1 (10.0)	0.088
Laboratory parameters			
Median (IQR)			
Leukocyte count	7.12 (5.98-8.79)	7.21 (5.86-8.35)	0.976
Hemoglobin	14.0 (13.2-14.8)	13.0 (12.0-14.9)	0.195
Platelet count	281 (238-332)	273 (236-396)	0.746
Sedimentation	7 (5-15)	7.5 (6-25)	0.245
C-reactive protein	2.1 (1.1-5.4)	1.8 (1.0-5.1)	0.606
Creatine	0.63 (0.54-0.74)	0.6 (0.56-0.73)	0.980
Complete urinalysis			
Urine density, median (IQR)	1017 (1012-1023)	1017 (1012-1020)	0.812
Urine pH, median (IQR)	6.0 (5.5-6.0)	6.0 (5.5-6.0)	0.422
Leukocyte esterase positivity, n (%)	11 (10.7)	9 (90.0)	<0.001
Presence of protein, n (%)	3 (2.9)	1 (10.0)	0.131
Nitrite positivity, n (%)	-	2 (20.0)	0.007
Leukocyte positivity, n (%)	21 (20.4)	10 (100)	<0.001
Erythrocyte positivity, n (%)	33 (32.0)	5 (50.0)	0.210
Urine leukocyte count, median (IQR)	1 (1-2)	41 (14-123)	<0.001
Urine erythrocyte count, median (IQR)	2 (1-4)	24 (9-29)	<0.001

Table 3: The distribution of BD involvement according to clinical findings of urinary system infections in patients without such infections.

	Dysuria			**Frequency**		
BD organ involvement, n (%)	No (n=87)	Yes (n=16)	p	No (n=101)	Yes (n=2)	p
Oral aphtha	61 (70.1)	12 (75.0)	0.474	72 (71.3)	1 (50.0)	0.500
Genital ulcer	18 (20.7)	4 (25.0)	0.460	80 (79.2)	1 (50.0)	0.383
Papulopustular lesion	48 (55.2)	6 (37.5)	0.152	48 (475)	1 (50.0)	0.728
Erythema nodosum	20 (23.0)	4 (25.0)	0.542	78 (77.2)	1 (50.0)	0.413
Vascular involvement	10 (11.5)	2 (12.5)	0.591	89 (88.1)	2 (100)	0.780
Pathergy positivity	28 (32.2)	11 (68.8)	0.007	63 (62.4)	1 (50.0)	0.616
Joint signs	42 (48.3)	6 (37.5)	0.303	48 (47.5)	-	0.283
Eye signs	24 (27.6)	5 (31.3)	0.489	29 (28.7)	-	0.514
CNS involvement	4 (4.6)	2 (12.5)	0.233	6 (5.9)	-	0.886

Pathergy test positivity was significantly more frequent in patients with dysuria (p=0.007). Relationships between the symptoms of BD patients without diagnoses of urinary system infection and total urinalysis results are shown in Table 4. Urinary leukocyte esterase positivity and pathergy positivity were significantly in patients with BD with genital ulcers (p=0.039 and p=0.038, respectively).

Table 4: The distribution of BD involvement according to urinary system infection laboratory findings in patients without such infections.

	Leukocyte positivity in urine			Leukocyte esterase positivity in urine		
Behçet's disease organ involvement, n (%)	No (n=82)	Yes (n=21)	p	No (n=92)	Yes (n=11)	p
Oral aphtha	57 (69.5)	16 (76.2)	0.378	64 (69.6)	9 (81.8)	0.323
Genital ulcer	17 (20.7)	5 (23.8)	0.483	17 (18.5)	5 (45.5)	0.039
Papulopustular lesion	45 (54.9)	9 (42.9)	0.230	48 (52.2)	6 (54.5)	0.569
Erythema nodosum	20 (24.4)	4 (19.0)	0.422	20 (21.7)	4 (36.4)	0.232
Vascular involvement	10 (12.2)	2 (9.5)	0.540	10 (10.9)	2 (18.2)	0.376
Pathergy positivity	27 (32.9)	12 (57.1)	0.038	34 (37.0)	5 (45.5)	0.405
Joint signs	40 (48.8)	8 (38.1)	0.265	42 (45.7)	6 (54.5)	0.576
Eye signs	23 (28.0)	6 (28.6)	0.579	26 (28.3)	3 (27.3)	0.626

4. Discussion

Although many studies have investigated antigenic stimuli related to microorganisms in the etiopathogenesis of BD, none have specifically addressed the association between UTI frequency and the disease severity. In the light of the relationship with infectious etiology, this study was conducted to investigate the frequency of UTI and its effect on disease severity in these patients. Although no specific microorganism has been identified in the etiology of BD to date, studies have suggested that microorganisms may play an indirect triggering role in BD due to impaired immune system function. Microbiological studies have generally involved oral flora, ulcers, and skin lesions. *E. coli, Mycobacteria, Staphylococcus aureus, Borrelia burgdorferi, Streptococcal antigens, Helicobacter pylori, Mycoplasma fermentans,* and *Saccharomyces cerevisiae* have been described as potential triggering bacteria in the etiology of BD [11].

One of the studies of the possible association between BD and microorganisms involved pustular lesions. Although these have been were considered sterile in previous BD studies, subsequent research reported that *S. aereus* reproduced in 58% of these lesions [12]. A previous study reported that the occurrence of uveitis in patients after hypersensitivity testing with streptococcal antigens suggested that streptococci may be involved in the etiology.[13]Intradermal antigen tests applied with *E. coli, Pseudomonas aeruginosa,* and *Proteus vulgaris* revealed mild exacerbation in BD in another study [14]. BD has also been reported after *Streptococcus agalactiae* vaginitis [15]. Although antibiotics and antivirals are not routinely used in the treatment of BD, the improvement of symptoms observed with the use of these drugs supports the idea of an infectious etiology of BD. Another study showed that the combined use of benzathine penicillin and colchicine was more effective in ameliorating clinical symptoms compared to patients using colchicine alone [16].

In light of all these data supporting the idea of an infectious trigger in the etiopathogenesis of BD, 113 patients with BD were included in this study, with UTI being detected in 8.8% (n=10) of these. Urine culture results showed *E. coli* growth in 90% (n=9) of these patients and *Klebsiella spp.* in 10% (n=1).

UTIs can be seen in the form of simple cystitis or in complicated forms that can lead to septic shock and that have a very high incidence in the community. Involvement of the bladder and urethra is regarded as lower UTI, and that of the ureter, pelvis, and kidneys as upper UTI.[17]*E. coli* is the responsible microorganism in approximately 75-90% of cystitis or acute complicated UTIs.[18]Urine culture was performed on 29.2% (n=33) of the patients in this study, and growth was observed in only 10. *E. coli* growth wad determined in 90% (n=9) of those 10 patients, a figure compatible with the previous literature.

The diagnosis of UTI is accompanied by lower urinary systems symptoms such as a burning sensation during urination, increased frequency of urination, and a feeling of an urgent need to urinate (dysuria, urgency, and frequency), as well as >10 cells/ml leukocytes at urine testing, and $>10^5$ cfu/ml causative microorganisms in urine culture [19]. These criteria were considered when diagnosing UTI in our patients. The most common symptoms in the patients wıth UTIs were dysuria and frequency. Addıtıonally, as anticipated, leukocyte elevatıon, hematuria, leukocyte esterase, and nitrite positivity in the urine were the most common laboratory findings at total urinalysis.

Although BD causes epididymitis and sterile urethritis as well as genital ulcerations in the urogenital system, there is insufficient evidence to conclude that it exacerbates susceptibility to frequent UTIs [20]. In the present study, UTI developed more frequently in patients wıth prolonged durations of BD compared to other patients. This may be because BD can make the urogenital system more susceptible to infections in the long term or to receivıng immunosuppressive therapy for a longer period. Evaluation of the relationship between the severity of BD and the presence of UTI in this study revealed no statistical association between them. Among the BD patients with UTIs, 30% (n=3) were inactive, 30% (n=3) mild, and 40% (n=4) moderate. No statistically significant relationship was detected between BD patients with and without UTI in terms of the frequency of mucocutaneous symptoms (p=0.229). No significant relationship was also observed between the presence of UTI and the frequency of BD system involvement (p>0.05). Although 17.4% (n=18) of the patients had one or more UTI complaints, these were not considered to have UTI due to absence of growth in urine culture. Although no UTI was detected in our study, leukocyte esterase positivity was significantly higher, especially in patients with genital ulceration (p=0.039). This may be attributable to microorganisms secondarily infecting the ulcerated lesions in the genital area. A significant relationship was detected between the pathergy test positivity and the frequency of pyuria and dysuria in BD patients without UTI. Although this may be coincidental, we think that prospective studies with much greater participation should now be conducted to confirm such a relationship.

5. Conclusions

Although no statistically significant relationships were detected between the presence of UTI and the severity of the BD in the present study, microorganisms may be involved in the exacerbation of the disease. The frequency of UTI in BD patients was 8.8%. During the follow-up and treatment of BD cases, clinicians should therefore also investigate the presence of UTI complaints. We think that appropriate antibiotic therapy should be initiated depending on the urine culture results for patients with such complaints.

Limitations of the Study

The particular strength of this study is that it is the first to compare the frequency of UTI in BD, the severity of the disease, and the activity of symptoms. Another strength is that it was performed with a relatively large number of BD patients.

However, this study also has a number of limitations. The first involves the retrospective nature of the research. Second, despite the large participation in the study, the results cannot be generalized because of its single-center nature, and we think that further, multicenter prospective studies are now required.

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Conflict of Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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None.

Author Contributions

EP; The study concept and design, data collection, writing of the manuscript or critical review, and approval of the final version of the manuscript. ÖK; Statistical analysis, critical review of the literature, and approval of the final version of the manuscript.

Ethical Approval

The study was carried out in line with the Declaration of Helsinki Rules after receipt of approval from the local ethics committee (No. 5, Dated 29.12.2022).

The research was conducted in accordance with the principles of the Helsinki Declaration.

Data sharing statement

None.

Consent to participate and Informed Statement

Informed Statement was not obtained from the patients since the study was conducted retrospectively and was designed as an archive scan of all patient files.

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