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Gender-Specific Differences in Egyptian Behcet's Disease Patients

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Abstract

Background: Behcet's disease (BD) is a systemic inflammatory disease in which gender seems to have an influence on certain clinical findings, disease severity and outcome.

Aim of Study: To evaluate the impact of gender difference on disease presentation and outcome on a cohort of Egyptian patients with BD.

Patients and Methods: In this multi-center comparative study, 170 patients diagnosed according to the BD diagnostic criteria of the International Study Group in 1990 and following up in the Rheumatology Department, Faculty of Medicine of the Cairo University Hospital (116 patients), Fayoum University Hospital (44 patients), and Beni Suef University Hospital (10 patients) were enrolled and grouped according to gender.

Results: The patients' mean age was 35.8±8.5 years and the male to female ratio was 4.4:1. Vascular manifestations (p=0.014), especially arterial/venous thrombosis (p=0.004) and aneurysm formation (p=0.026) were detected to be statistically significantly higher in male compared to female BD patients. Female BD patients were found to have higher erythrocyte sedimentation rate (ESR) (p=0.006), lower hemoglobin and WBC count (p=0.001 and p=0.002 respectively). Cyclophosphamide and anticoagulation were significantly more frequently used by male BD patients (p=0.031 and p=0.045 respectively). No gender difference was observed regarding disease activity using BDCAF (p=0.158), whereas damage using vasculitis damage index (VDI) was significantly higher in male BD patients (p=0.038).

Conclusion: Vascular manifestations, the use of cyclophosphamide and anticoagulation as well as vasculitis damage index were significantly more frequent in male BD patients which may implicate poor outcome.

Key Words: *BD – Gender difference – BDCAF – Vascular involvement.*

Introduction

BEHÇET'S disease (BD) is a systemic vasculitis with relapses and remissions that can affect a variety of organs and systems, including the skin, joints, lungs, and blood vessels, as well as the central nervous system and gastrointestinal system [1].

The epidemiology of this illness shows dramatic differences in disease occurrence, with substantially higher prevalence in Turkey, Asia, and the Middle East as compared to European populations, which show a south-to-north diminishing gradient [2].

People who have HLA-B51 are more likely to develop BD, the risk of HLA-B51/B5 carriers developing BD is increased by a factor of 5.78 [3] and the condition is frequently more severe in HLA-B51 positive patients. Children are uncommonly affected. Because the HLA-B5 allele is more strongly linked to BD in men than in women, males, as well as patients with a younger age of onset and HLA-B51 positivity, had a more severe outcome with BD [4]. Male individuals are more likely to have ocular symptoms, vascular involvement, and neurologic manifestations [5]. Female patients are more likely to have oral and genital ulcers, skin rashes, and arthritis [6].

Vascular involvement is a major finding in BD, and it's related to higher rates of morbidity and mortality. It affects up to 40% of BD patients, primarily in the form of deep venous thrombosis (DVT) and superficial thrombophlebitis [7]. Although arterial vascular involvement is less common in BD than venous involvement, the prognosis is much worse [8].

Patients and Methods

In this multi-center comparative study, 170 patients diagnosed according to the BD diagnostic criteria of the International Study Group in 1990

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[9] who were following-up in the Rheumatology Department, Faculty of Medicine of the Cairo University Hospital (116 patients during the period from 2016 to 2018), Fayoum University Hospital (44 patients between 2019 and 2020), and Beni Suef University Hospital (10 patients between September 2021 and March 2022) were enrolled. Their medical record files were reviewed retrospectively.

Data about the demographic features of the patients, disease duration, manifestations of BD, laboratory findings, as well as the treatment received were collected. Disease activity according to the Behçet's Disease Current Activity Form (BDCAF) score was documented (as it could be collected from the file data) [10]. Vasculitis Damage Index score was also calculated [11].

The studied patients were divided into 2 groups according to gender: Group 1 (male BD patients) and group 2 (female BD patients).

The study was approved by the ethics committee of Fayoum University Hospital.

Statistical analysis:

Data management and analysis was performed using Statistical Package for Social Sciences (SPSS) vs. 25. Categorical data were described as numbers and percentages. Numerical data were checked for normality and were statistically described in terms of mean and standard deviation or median and range as appropriate. When comparing categorical data per gender, Chi square test or Fisher's exact test were used appropriately. For numeric data, independent Student's *t*-test was performed for normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables. All tests were 2 tailed, *p*-values <0.05 were considered statistically significant and 95% confidence level was used.

Results

This study enrolled 170 BD patients, 138 (81.8%) males and 31(18.2%) females with a male to female ratio of 4.4:1. Their mean age was 35.8±8.5 years. Their disease duration ranged from 1 to 38 years with a median of 7 years.

A comparison between both groups: Male and female BD was done regarding the demographic features and co-morbidities (Tables 1,2, respectively) and all parameters were similar.

Table (1): Demographic characteristics among Behcet patients per gender (n=170).

Characteristics	Males (n=139)	Females (n=31)	*p*-value
	Mean (SD)	Mean (SD)	
Age (years)	35.8 (8.3)	35.9 (9.6)	0.934 **a**
Disease duration (years), median (range)	8.0 (1.0-38.0)	6.0 (1.0-18.0)	0.514 **b**

a Student's *t*-test test. **b** Mann-Whitney U test.

Table (2): Comorbidities among Behcet patients per gender (n=170).

Comorbidity	Males (n=139)		Females (n=31)		*p*-value
	n	(%)	n	(%)	
Diabetes	9	(8.1)	2	(13.3)	0.501 **a**
Dyslipidemia	54	(48.6)	9	60.0)	0.409 **a**
Avascular necrosis	4	(2.9)	0	(0.0)	1.000 **b**
Osteoporosis	8	(5.8)	2	(6.5)	1.000 **b**
Cataract	46	(33.1)	14	(45.2)	0.204 **a**

a Chi-square test. **b** Fisher's Exact test.

Clinical characteristics and medications received are presented in Tables (2,5), respectively. Vascular manifestations (p=0.014), especially arterial/venous thrombosis (p=0.004) and aneurysm formation (p=0.026) were significantly higher in male BD patients (Table 3).

Table (3): Clinical characteristics among Behcet patients per gender (n=170).

Characteristics	Males (n=139)		Females (n=31)		*p*-value
	n	(%)	n	(%)	
Skin manifestations:					
Oral ulcers	132	(95.0)	29	(93.5)	0.750 **a**
Genital ulcers	110	(79.1)	22	(71.0)	0.324 **a**
Other skin manifestations	54	(38.8)	14	(45.2)	0.517 **a**
Vascular manifestations:	65	(46.8)	7	(22.6)	0.014 **a***
DVT	35	(25.2)	4	(12.9)	0.142 **a**
Venous insufficiency	13	(9.4)	0	(0.0)	0.076 **a**
Venous ulcers	4	(2.9)	0	(0.0)	1.000 **b**
Arterial/venous thrombosis	61	(43.9)	5	(16.1)	0.004 **a***
Aneurysm	19	(13.7)	0	(0.0)	0.026 **b***
Rupture aneurysm	0	(0.0)	0	(0.0)	
Neurologic manifestations:	23	(16.5)	6	(19.4)	0.707 **a**
Headache	14	(10.1)	8	(25.8)	0.018 **a***
Sensory affection	5	(3.6)	2	(6.5)	0.613 **b**
Cranial nerve affection	11	(7.9)	1	(3.2)	0.697 **b**
Ataxia	3	(2.2)	0	(0.0)	1.000 **b**
Sphincter affection	5	(3.6)	1	(3.2)	1.000 **b**
Confusion	0	(0.0)	0	(0.0)	
Coma	1	(0.7)	0	(0.0)	–
Seizures	1	(0.7)	0	(0.0)	
Stroke	13	(9.4)	3	(9.7)	1.000 **b**

Table (3): Count.

Characteristics	Males (n=139)		Females (n=31)		*p*-value
	n	(%)	n	(%)	
Ocular manifestations:	89	(64.0)	22	(71.0)	0.463 **a**
Single/paired involvement:					0.990 **a**
No involvement	50	(36.0)	11	(35.5)	
Single eye involvement	19	(13.7)	4	(12.9)	
Both eyes involvement	70	(50.4)	16	(51.6)	
Vision:					0.961 a
Normal	58	(41.7)	14	(45.2)	
Impaired vision	66	(47.5)	14	(45.2)	
Single eye blindness	8	(5.8)	2	(6.5)	
Both eyes blindness	7	(5.0)	1	(3.2)	
Uveitis	89	(64.0)	22	(71.0)	0.463 a
GIT manifestations	4	(2.9)	2	(6.5)	0.301 b
Chest manifestations	6	(4.3)	1	(3.2)	1.000 b
Arthritis	14	(10.1)	6	(19.4)	0.147 a

DVT: Deep venous thrombosis.
GIT: Gastrointestinal tract.
aChi-square test.
bFisher's Exact test.
* Statistically significant at *p*-value <0.05 level.

Cyclophosphamide and anticoagulation were more frequently used by male BD patients (p=0.031 and p=0.045, respectively) (Table 4).

Table (4): Treatment received by Behcet patients per gender (n=170).

Treatment	Males (n=139)		Females (n=31)		*p*-value **a**
	n	(%)	n	(%)	
Cyclophosphamide	70	(50.4)	9	(29.0)	0.031 *
Azathioprine	81	(58.3)	21	(67.7)	0.331
Cyclosporine	35	(25.2)	7	(22.6)	0.762
Biological treatment	22	(15.8)	4	(12.9)	0.683
Anticoagulation	48	(34.5)	5	(16.1)	0.045*

aChi-square test
*Statistically significant at *p*-value <0.05 level.

Erythrocyte sedimentation rate (ESR) (p=0.006) tended to be higher in female BD, while hemoglobin and WBC count were lower (p=0.001 and p=0.002, respectively) (Table 5).

Table (5): Laboratory data among Behcet patients per gender (n=170).

Laboratory data	Males (n=139)		Females (n=31)		*p*-value **a**
	Median	(Range)	Median	(Range)	
ESR (mm/h)	18.0	(2.0-70.0)	25.0	(5.0-85.0)	0.006*
Hb (g/dL)	13.2	(7.7-144.0)	12.0	(9.8-15.6)	0.001 *
WBC's ($x10^3/mm^3$)	8.7	(4.0-17.2)	6.0	(3.9-15.6)	0.002*
PLT ($x10^3/mm^3$)	248.0	(35.0-529.0)	230.0	(174.0-453.0)	0.721
AST (U/L)	23.0	(6.0-136.0)	24.0	(13.0-79.0)	0.408
ALT (U/L)	26.0	(6.0-189.0)	24.0	(11.0-208.0)	0.857
Creatinine (mg/dL)	0.8	(0.4-1.6)	0.9	(0.6-1.2)	0.193
Cholesterol	192.0	(106.0-277.0)	213.0	(157.0-260.0)	0.032*
Triglycerides	110.0	(38.0-313.0)	96.0	(55.0-321.0)	0.360

ESR : Erythrocyte sedimentation rate.
Hb : Hemoglobin.
WBC : White blood cell.
PLT : Platelet.
AST : Aspartate transaminase.
ALT : Alanine transaminase.
a Mann-Whitney U test.
* Statistically significant at *p*-value <0.05 level.

Discussion

BD is a systemic inflammatory disease characterized by recurrent oral ulcers, genital ulcers, cutaneous inflammation, uveitis, in addition to other potentially life-threatening lesions especially in the intestinal tract, blood vessels, and central nervous system **[12]**, in which gender seems to have an influence on certain clinical findings, disease severity and outcome and has been a topic of debate.

While most of the autoimmune diseases are common in females, the majority of the studies have shown either an equal gender distribution or a male predominance in BD. Until present time, the exact reason for the gender difference has not been determined. Gender is known to have an impact on its clinical findings and prognosis and may vary across ethnic backgrounds **[13]**. Male gender has been linked to more severe disease and higher mortality in BD **[14]**.

One theory was based on environmental risk factors such as smoking which was found to be prevailing among male patients with BD and has been implicated in the severity of clinical manifestations of BD including vasculitis and mucocutaneous lesions **[15-17]**.

A meta-analysis study by Maldini et al., indicated that human leukocytic antigen (HLA)-B51 was more common among male BD patients and was linked to disease severity suggesting a genetic basis for poor prognosis among men with BD [18]. Additionally, HLA-B5 was more frequently detected in male BD patients [5].

Aim of the work:

The aim of this study was to evaluate the impact of gender difference on Egyptian Behcet's disease patients, especially regarding clinical characteristics, laboratory findings, treatment, co-morbidities, and outcome.

The gender disparity regarding vascular manifestations especially thrombosis might imply a different pathophysiological mechanism of thrombosis in BD compared to common thromboembolic disease which in contrast to BD equally affects males and females [19]. However, this study did not differentiate between arterial and venous thrombosis.

Other explanations pointed to hormonal influences such as testosterone-induced neutrophil hyperactivity, especially regarding the prevalence of folliculitis and pathergy test positivity in male patients [20].

In accordance with several previous studies, our cohort confirmed the known male predominance in Egypt [21,22,23]. Male predominance was not only reported in parts of the old Silk Road such as Iran and Turkey, but also in other regions of the world such as Germany and Italy [24], possibly because of immigration. The opposite has been shown in Korea, Brazil, France, the United Kingdom (UK) and the United States of America (USA) [25,26], where females predominate. The gender difference showed a variable impact on the variant clinical manifestations.

In this study, cutaneous lesions including oral and genital ulcers, were similar in male and female BD patients, which is in agreement with the Turkish study by Yazici et al. [27], but in discordance with most of the performed studies, in which oral ulcers were found to be more frequent among females, especially in Korea and Turkey [28,29].

Also, a higher prevalence of genital ulcers in female patients with BD was shown in Turkey, Germany, Iran, Korea and Greece [6,24,29-33]. Possible explanations pointed to the aforementioned hormonal influences and the larger surface area of the genital tract mucosa in females [24].

Vascular manifestations were significantly more frequent in male patients in this study. Especially arterial/venous thrombosis as well as aneurysms significantly predominated in male BD patients. This is in conformity with the study by Cansu et al., who also described an overall higher vascular involvement in males including DVT and pulmonary/femoral aneurysms [1]. Furthermore, the study by Gheita et al., reported significantly higher occurrence of DVT in males [22].

Multiple other studies detected a higher prevalence of arterial involvement as well as peripheral and central venous disease in male patients with BD [24,27-31,34,35]. Vascular affection showed not only a widespread involvement in males but has been found to be a determinative of a worse disease prognosis [35,36] and is considered to be a major risk factor of death in BD [37,38].

The overall neurological involvement was more common among female BD patients in this study, however the difference was not significant. This is in discordance with Ucar-Comlekoglu et al., who reported neurological manifestations to be more prevalent in males [29], similar to other studies from Iraq, Tunesia, and Italy [31-34]. Among the neurological manifestations, we found headache to be significantly higher in female BD patients, which is in congruence with Cansu et al. [1]. Nevertheless, it is difficult to speculate whether or not headache has a direct association with BD as it has not been classified.

The comparable ocular involvement in males and females in the current study is in congruity with the Egyptian study by Gheita et al. [22], who also revealed no gender disparities regarding ocular manifestations. However, this result is in dissonance with studies from Korea, Turkey, Iran and Italy, where ocular disease was more commonly reported in men [1,27-31].

Also, a nearly equivalent frequency of pulmonary involvement in male and female patients was observed, similar to the study by Attia and Abdel Noor [23]. In contrast, other studies reported a higher frequency of pulmonary affection in men [30,39].

Regarding articular involvement, in accordance with another Egyptian study [23] no statistically significant difference was seen between male and female BD patients, while most previous reports revealed a female predominance [1,24,26,30,33].

In the current study, gastrointestinal involvement showed no gender difference, similar to three previous studies **[23,29,34]** unlike the multicenter study by Gheita et al., that showed a higher GIT affection in male BD patients **[22]**.

The BDCAF was comparable in males and females in accordance with the Egyptian study by Attia and Abdel Noor **[23]**. Nevertheless, the Vasculitis damage index was significantly higher in male BD patients, which goes in line with the overall more severe disease course and higher mortality among male patients previously described by Kural-Seyahi et al. **[37]**. VDI is correlated with most aggressive disease manifestations of BD **[40]**.

Regarding the co-morbidities, no statistically significant gender differences were documented in this study.

Concerning the laboratory data, several statistically significant differences were found: A higher ESR, higher cholesterol and lower hemoglobin level were detected in females. These results do not necessarily correlate with BD. The higher ESR and lower hemoglobin may be related to physiological changes such as menstruation, whereas the elevated cholesterol levels may be attributed to female obesity. According to the study by Aboulghate et al., obesity was more prevalent in adult females than adult males (49.5% of Egyptian adult females suffered obesity compared to 29.5% for males) **[41]**.

A significant male predominance was observed concerning the use of cyclophosphamide and anticoagulation, reflecting disease activity, and going in line with the higher prevalence of vascular involvement including thrombosis in male BD patients, and hence could be considered an indirect indicator of disease severity. The use of immunosuppressive drugs in general was significantly associated with VDI, especially cyclophosphamide, in addition to anticoagulant **[40]**.

The importance of this study is its confirmation of gender-associated clinical variation in BD, especially the association of male gender with vascular involvement as well as disease severity presented by the Vasculitis damage index, emphasizing the necessity of close monitoring and more frequent observation of male BD patients as well as the importance of developing more targeting and individualized therapeutic options.

Conflict of interest:

We have no conflict of interest to declare.

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الاختلافات المبنية على نوع جنس المريض فى متلازمة بهجت فى مجموعة من المرضى المصريين

متلازمة بهجت مرض مناعى مزمن حيث يلعب فيه جنس المريض دوراً فى النتائج الطبية وفى حدة المرض كما أيضاً فى الحصيلة المرضية. الهدف من هذا البحث هو تقييم اختلاف جنس المريض وأثره على الصورة المرضية والنتائج أو الحصيلة فى متلازمة بهجت فى مجموعة من المرضى المصريين عددها ١٧٠ مريض تم تجميعهم من ثلاث مستشفيات (جامعية) قصر العينى ـ الفيوم ـ بنى سويف. متوسط عمر المرضى ٨.٥±٣٥.٨ سنة ونسبة المرضى الذكور بالنسبة للاناث ١:٤.٤.

لقد أثبت البحث أن أمراض الأوعية الدموية خاصة الجلطات الوريدية والشريانية أكثر شيوعاً فى المرضى الذكور وكذلك تمددات الأوعية الد موية. أظهرت النتائج أن المرضى الاناث لديهم ارتفاعاً فى سرعة الترسيب وانخفاضاً فى نسبة الهيموجلوبين فى الدم مقارنة بالمرضى الذكور. لم يتم تسجيل اختلاف فى النشاط المرضى بين المجموعتين، أما بالنسبة لمقياس الضرر الناتج عن متلازمة بهجت على الأعضاء المختلفة فقد كان أعلى فى المرضى الذكور. كذلك أظهرت الدراسة أن استخدام السيكلوفوسفاميد ومضادات التجلط أكثر شيوعاً فى المرضى الذكور أيضاً مما يؤكد أن متلازمة بهجت أكثر شدة وخطورة فى المرضى الذكور.