The Characteristics of a Northern Israeli Cohort of Patients with Behçet's Syndrome

Fadi Hassan MD[1,4]*, Firas Sabbah MD[2,4]*, Rula Daood MD[1,4], Helana Jeries MD[1,4], Tamar Hareuveni MD[3,4], and Mohammad E. Naffaa MD[1,4]

[1]Rheumatology Unit, Galilee Medical Center, Nahariya, Israel
[2]Department of Rheumatology, Tzafon Medical Center, Lower Galilee, Israel
[3]Department of Ophthalmology, Galilee Medical Center, Nahariya, Israel
[4]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

ABSTRACT **Background:** Behcet's syndrome (BS) is a multisystem syndrome that typically manifests as recurrent oral and genital ulcers, as well as other systemic manifestations. Few studies describing the characteristics of BS among Israeli patients have been published.

Objectives: To describe the characteristics of BS patients and to compare Jewish and Arab subpopulations.

Methods: We retrospectively reviewed electronic medical records and extracted demographic, clinical, laboratory, and medication data for each patient. We compared the Jewish and Arab BS patients.

Results: The cohort included 98 patients. Males constituted 49 (50%); mean age at the time of diagnosis was 29.9 years; 71 (72.4%) were Arab and 27 (27.6%) were Jewish. Oral ulcers were evident in 93 patients (94.9%) and genital ulcers in 54 (55.1%). Involvement of the skin, joints, eyes, gastrointestinal tract, and neurologic and vascular systems were demonstrated among 42 (42.9%), 57 (58.2%), 47 (48.0%), 8 (8.2%), 10 (10.2%), and 15 (15.3%), respectively. HLA B51 was positive in 24 of 37 (64.9%). Pathergy was positive in 8 of 12 (66.7%). Colchicine was used in 82 (83.7%), azathioprine 47 (48%), methotrexate 16 (16.3%), apremilast 10 (10.2%), cyclosporine-A 8 (8.2%), adalimumab 26 (26.5%), infliximab 12 (12.2%), cyclophosphamide 1 (1.0%), tocilizumab 2 (2.0%), and anti-coagulation 6 (6.1%). The Arab and Jewish subpopulations were significantly different regarding male proportion, 40 (56.3%) vs. 9 (33.3%), $P = 0.042$.

Conclusions: BS is more common among Arabs in northern Israel, but no significant clinical or demographic differences were found except for a higher proportion of male patients among Arabs.

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*These authors contributed equally to this study

Behçet's syndrome (BS) is a multi-systemic syndrome that typically manifests as recurrent oral and genital ulcers with varying degrees of multi-systemic manifestations including skin as well as ophthalmic, gastrointestinal, musculoskeletal, and neurologic and vascular involvement [1]. Although BS has been reported all over the world, it has a unique geographic distribution with higher prevalence along the ancient Silk Road extending from Japan to the Mediterranean area [2-4]. The highest prevalence is reported to be in Turkey with estimation of up to 420 cases to 100,000.

Previous studies demonstrated that some of the disease manifestations are more prominent in specific geographic areas [5]. For example, gastrointestinal involvement is encountered more commonly in the Far East (especially in Japan) compared to the Mediterranean area, while seizures are less commonly encountered in Turkish patients [5,6]. Moreover, disease manifestations may also have sex predilection as vascular, ocular, and neurologic manifestations are more commonly reported among male patients than females while mucocutaneous involvement is more common in females. [7,8].

Israel is located along the ancient Silk Road. Krause and colleagues [9] evaluated the prevalence and clinical characteristics of BS patients in Israel more than 15 years ago and found an overall prevalence of 15 cases per 100,000 with increased prevalence among Arabs (26 cases per 100,000) compared to Jewish patients (8 cases per 100,000). Strikingly, the prevalence among the Druze subpopulation reached 146 per 100,000, which is the second highest reported prevalence worldwide [9]. Since the Krause study, few studies describing the characteristics of BS among Israeli patients have been published. Thus, we describe the characteristics of our patients with BS and compare demographic and clinical features between Jewish and Arab subpopulations.

PATIENTS AND METHODS

We retrospectively reviewed the electronic medical records of our BS cohort at two northern Israeli medical centers: the Galilee Medical Center and Tzafon Medical Center. Patients with BS were referred to our Behcet's clinic by family physicians until the end of 2022 and thereafter by family physicians and rheumatologists as well.

A large part of the Muslim subpopulation, and the majority of the Druze subpopulation, reside mainly in northern Israel. Most of the subpopulations are in geographical proximity to our medical centers. Electronic medical records were reviewed, and demographic (sex, ethnic background, age at diagnosis and smoking habits), clinical (oral and genital ulcers, ophthalmic, skin, gastrointestinal, neurologic, vascular, pulmonary manifestations and pathergy reaction), laboratory (HLA-B51), and medication prescription data were extracted for each patient. Baseline characteristics of the patients were evaluated using descriptive statistics. Furthermore, we compared the Jewish and Arab subpopulations (Muslim, Druze, and Christians) with regard to demographic and clinical features of BS.

STATISTICAL ANALYSIS

The categorical variables were analyzed using chi-square test or Fisher's exact test, as appropriate. The continuous variables were analyzed using Student's *t*-test or the Mann–Whitney test, depending on the specific variable distribution. A P-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 27 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Our cohort included 98 patients. Males constituted 49 (50%) of the cohort and the mean age at the time of diagnosis was 29.9 years (range 6–64) [Table 1]. Seventy-one (72.4%) patients were Arab (45 [45.9%] Muslims, 21 [27.6%] Druze, and 5 [5.1%] Christians). Jews constitut-

Table 1. Demographic and clinical characteristics of the cohort

Demographic variables	n (%)
Males	49 (50%)
Mean age at diagnosis (min-max)	29.9 (6–64)
Jewish	27 (27.6%)
Muslim	45 (45.9%)
Druze	21 (27.6%)
Christian	5 (5.1%)
Current smokers	23 (23.5%)
Mucocutaneous	
Oral ulcers	93 (94.9%)
Genital ulcers	54 (55.1%)
Skin	**42 (42.9%)**
Acne	7 (16.7%)
Erythema Nodosum	7 (16.7%)
Folliculitis	26 (61.9%)
Erysipelas like erythema	2 (4.3%)
Ophthalmic	**47 (48.0%)#**
Anterior uveitis	5 (10.6%)
Intermediate uveitis	3 (6.4%)
Posterior uveitis	1 (2.1%)
Panuveitis	15 (31.9%)
Uveitis not specified	17 (36.2%)
Neuroretinitis	4 (8.5%)
Blindness	3 (6.4%)
Musculoskeletal	**57 (58.2%)***
Arthralgia	39 (68.4%)
Arthritis	11 (19.3%)
Sacroiliitis	4 (7.0%)
Vascular	**14 (14.3%)**
Deep venous thrombosis	8 (57.1%)
Pulmonary art. thrombosis	4 (28.6%)
Cerebral vein thrombosis	3 (21.4%)
Budd Chiari	1 (7.1%)
Portal vein thrombosis	1 (7.1%)
Pulmonary art. aneurysm	1 (7.1%)
Superficial vein thrombosis	3 (21.4%)
Veno-occlusive (liver)	1 (7.1%)
Cardiac	**5 (5.1%)**
Intracardiac thrombus	2 (40%)
Pericarditis	1 (20%)
Dilated cardiomyopathy	1 (20%)
Myocardial infarction	1 (20%)
Congestive heart failure	1 (20%)
Neurologic	**9 (9.2%)**
Pseudotumor cerebri	2 (22.2%)
Stroke	5 (55.6%)
Encephalitis	1 (11.1%)
Sensory neural hearing loss	1 (11.1%)
Gastrointestinal	**8 (8.2%)**
Crohn disease	3 (37.5%)
Ulcerative colitis	3 (37.5%)
Terminal ileum aphthosis	3 (37.5%)
Pathergy test	**12 (12.2%)**
Positive	8 (66.6%)
HLA-B51	**37 (37.8%)**
Positive	24 (64.9%)

#macular edema (1), papillary edema (1), central retinal artery occlusion (2), central retinal venous occlusion (2)
*avascular necrosis of hip (1), back pain (2)

ed 27 (27.6%) [Table 1]. Oral ulcers were evident in 93 patients (94.9%) and genital ulcers in 54 (55.1%). [Table 1]. Involvement of the skin, joints, eyes, gastrointestinal tract, and neurologic and vascular systems were demonstrated among 42 (42.9%), 57 (58.2%), 47 (48.0%), 8 (8.2%), 9 (9.2%), and 14 (14.3%), respectively [Table 1]. Five (5.1%) patients had cardiac involvement, one patient (1.0%) had pulmonary hemorrhage, and two patients (2.04%) had orchiepididymitis. HLA B51 was performed in 37 (37.8%) patients and was positive in 24 (64.9%). Pathergy test was performed in 12 (12.2%) patients and was positive in 8 (66.7%). Psoriasis and FMF were evident in one patient each.

The Arab and Jewish subpopulations were significantly different with regard to males vs. females, 40 (56.3%) vs. 9 (33.3%), respectively, $P = 0.042$. No significant differences were observed regarding oral and genital ulcers, skin, ophthalmic, musculoskeletal, vascular, neurologic, gastrointestinal involvement or HLA-B51 positivity.

Colchicine was used in 82 (83.7%) cases, azathioprine in 47 (48%), methotrexate in 16 (16.3%), apremilast in 10 (10.2%), cyclosporine-A in 8 (8.2%), adalimumab in 26 (26.5%), infliximab in 12 (12.2%), cyclophosphamide in 1 (1.0%), tocilizumab 2 (2.0%), and anticoagulation in 6 (6.1%) [Table 2].

Table 2. Indications and drugs used to treat Behcet's syndrome

Drug	Indications	n (%)
Colchicine	Mucocutaneous, dermatologic, articular	82 (83.7%)
Azathioprine	Vascular, articular, ocular, dermatologic, neurologic, urologic	47 (48%)
Methotrexate	Articular, dermatologic, ocular	16 (16.3%)
Apremilast	mucocutaneous	10 (10.2%)
Cyclosporine-A	Ocular, vascular, mucocutaneous	8 (8.2%)
Adalimumab	Vascular, neurologic, gastrointestinal, articular	26 (26.5%)
Infliximab	Gastrointestinal, vascular, neurologic	12 (12.2%)
Cyclophosphamide	Cardiac	1 (1.0%)
Tocilizumab	Ocular	2 (2.0%)
Anticoagulation	Vascular	6 (6.1%)
Warfarin		3 (3.1%)
Enoxaparin		2 (2.0%)
Apixaban		1 (1.0%)

DISCUSSION

Our study showed that BS seems to be more prevalent among the Arab population compared to the Jewish population in northern Israel. No significant difference was observed regarding disease manifestations, except for higher proportion of males among Arabs.

Recurrent oral ulcers were evident in 95% of the cohort, emphasizing the higher sensitivity of this clinical manifestation among our patients. This prevalence signifies a small, but very challenging, group of patients without oral ulcers. A few case reports have been published describing BS patients presenting with vascular involvement without the pictorial recurrent oral ulcers making the diagnosis of BS very challenging [10]. Moreover, our cohort already included several patients presenting with major organ involvement (vascular, such as portal vein thrombosis, or neurologic) without recurrent oral ulcers. Thus, our results support the possibility of atypical presentations of BS such as sensorineural hearing loss, portal vein thrombosis, and Budd Chiari syndrome, necessitating vigilant clinical awareness even in the absence of the characteristic recurrent oral ulcers among patients with relevant ethnic backgrounds.

The association of pathergy reaction and HLA-B51 positivity with BS is well-documented, but their use in routine clinical practice remains very limited [11,12]. This finding is reflected in our cohort, where only 12% and 37% of patients underwent pathergy and HLA-B51 testing, respectively. While no significant difference in test positivity was observed between Arab and Jewish patients, this outcome may be attributed to the low number of patients being tested. Pathergy and HLA-B51 testing may be valuable tools, particularly in areas where BS is prevalent and when the presentation is atypical (such as vascular or neurologic involvement) [13,14]. In such cases, positivity to either test, or both, can significantly contribute to narrowing the diagnostic dilemma and facilitate earlier diagnosis and initiation of appropriate treatment. Thus, wider implementation of these tests could offer valuable diagnostic support and potentially allow earlier diagnosis of BS, at least, in certain situations.

Primarily residing in Syria, Lebanon, Israel, and Jordan, the Druze population exhibits a high degree of genetic isolation due to their historical marriage within the same community and closed religious system, which is strictly closed to new adherents [15-17]. Studies by Krause et al. [9] have reported a significantly elevated prevalence of BS among Druze individuals, estimated at 146 per 100,000. However, this prevalence is likely underestimated as their

study methodology captured patients followed at three specific hospitals divided by the size of the adult population served by the three medical centers. Thus, patients being treated outside the three medical centers were not captured and not counted in the estimation of prevalence. The substantial prevalence of BS within the genetically isolated Druze population underscores the potential role of genetic factors and possibly environmental influences in disease pathogenesis. The HLA-B51 positivity among Druze was estimated to be 100% according to the Krause study [9], highlighting the genetic factor.

One significant limitation of our study is the inability to directly compare the Druze subpopulation with Jewish and Muslim populations regarding demographic and clinical characteristics due to small sample size. Our analysis compared Arabs as a group and included Druze, Muslims, and Christians. As our cohort continuously grows, we may be able to compare the Druze subpopulation with Muslims and Jews.

Controversy still exists whether BS disease manifestations vary in different parts of the world and among different ethnic groups [5]. Although our study also demonstrated that BS seems to be more prevalent among Arab populations compared to Jewish populations, no significant differences were observed regarding disease manifestations except for ophthalmic complications, which trended toward being more prevalent among Arab patients even though statistical significance was not achieved. This finding was probably due to the relatively small sample size.

Several cohorts have shown that Japanese patients tend to have higher prevalence of gastrointestinal involvement (approximately 20%) compared to patients from other countries [5]. For example, among Turkish patients, the prevalence of gastrointestinal involvement is estimated to be between 0–5%, while in our cohort 8% had gastrointestinal involvement. Seizures attributed to BS have been reported to occur sevenfold higher in Caucasians and Middle Eastern patients compared to Turkish patients [9]. The pathergy reaction occurs more frequently in patients living along the Silk Road but is often negative in patients from Western countries. The frequency of HLA-B51 also varies considerably in different regions. Greek patients have a significantly higher prevalence of HLA-B51 compared to a lower prevalence in the United Kingdom [18]. However, Lewis and co-authors [19] found no differences in systemic manifestations comparing patients of different ethnic origins and concluded against different expressions of BS among different ethnic groups.

Our study demonstrated that the majority of the patients were treated with colchicine (approximately 83%), which is effective in the management of BS-associated mucocutaneous manifestations. Despite a relatively high prevalence of vascular involvement (14%) in our cohort, the use of anti-coagulation therapy was relatively low (approximately 6%). This apparent discrepancy can be explained by the underlying pathophysiology of vascular complications in BS. Unlike traditional thrombotic states arising from a hypercoagulable state, vascular thrombotic involvement in BS is primarily driven by inflammation that promotes thrombus formation tightly adherent to the vessel wall with very low risk of thromboembolism [20]. Consequently, the mainstay of treatment for vascular BS involves immunosuppressant medications instead of anticoagulation. In addition, the substantial proportion of patients receiving anti-TNF therapy (approximately 38%) underscores the presence of severe and potentially life- or organ-threatening BS manifestations within our cohort, as anti-TNF agents are typically reserved for more aggressive disease presentations.

Our study has several strengths. First, our cohort included full data about the patients with active frequent follow-up visits. Second, the frequency and prevalence of the demographic and clinical characteristics in our cohort are in accordance with the reported data regarding BS in different studies, adding to the validity and reliability of the cohort.

An important limitation of our study is that we could not calculate the prevalence of BS in the whole Israeli population because our cohort only represents northern Israel. Studying the prevalence and the incidence of BS among the whole Israeli population mandates the use of large population-based database that represents the wider Israeli population.

CONCLUSIONS

BS seems to be more common among Arabs compared to Jews in northern Israel, especially among Druze and Muslims, but no significant clinical or demographic differences were found except for higher proportion of male patients among Arabs. Further studies using large population-based databases to study the actual prevalence and incidence of BS among the whole Israeli population are warranted.

Correspondence

Dr. M.E. Naffaa
Rheumatology Unit, Galilee Medical Center, Nahariya 2210001, Israel
Phone: (972-4) 910-7038
Fax: (972-4) 910-7464
Email: mohammadn@gmc.gov.il

References

1. Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: disease manifestations, management, and advances in treatment. *Nat Clin Pract Rheumatol* 2007; 3 (3): 148-55.
2. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med* 1999; 341 (17): 1284-91.
3. Skef W, Hamilton MJ, Arayssi T. Gastrointestinal Behçet's disease: a review. *World J Gastroenterol* 2015; 21 (13): 3801-12.
4. Davatchi F, Chams-Davatchi C, Shams H, et al. Behcet's disease: epidemiology, clinical manifestations, and diagnosis. *Expert Rev Clin Immunol* 2017; 13 (1): 57-65.
5. Leonardo NM, McNeil J. Behcet's disease: is there geographical variation? a review far from the Silk Road. *Int J Rheumatol* 2015; 2015: 945262.
6. Joseph FG, Scolding NJ. Neuro-Behçet's disease in Caucasians: a study of 22 patients. *Eur J Neurol* 2007; 14 (2): 174-80.
7. Ucar-Comlekoglu D, Fox A, Sen HN. Gender differences in Behçet's disease associated uveitis. *J Ophthalmol* 2014; 2014: 820710.
8. Zouboulis CHC, Djawari D, Kirch W. Adamantiades-Behçet's disease in Germany. In: Godeau P, Wechsler B, eds. Behçet's Disease. 1st edn. Amsterdam: Elsevier Science; 1993: 193-6.
9. Krause I, Yankevich A, Fraser A, et al. Prevalence and clinical aspects of Behcet's disease in the north of Israel. *Clin Rheumatol* 2007; 26 (4): 555-60.
10. Omara A, Alkhuboli M, Nauman J, Al Nokhatha S, Almarshoodi M. Case report: deep vein thrombosis as the sole clinical feature of Behcet's syndrome. *Front Med (Lausanne)* 2023; 10: 1276867.
11. Yazici H, Yurdakul S, Hamuryudan V. Behçet's syndrome. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, eds. Oxford Textbook of Rheumatology. Oxford: Oxford University Press; 1998: 1394-402.
12. Dilşen N, Koniçe M, Aral O. Important implications of skin pathergy test in Behçet's disease. In: Wechsler B, Godeau P, eds. Behçet's Disease. International Congress Series 1037. Amsterdam, London, New York, NY, Tokyo: Excerpta Medica; 1993: 229-33.
13. Takeno M. The association of Behçet's syndrome with HLA-B51 as understood in 2021. *Curr Opin Rheumatol* 2022; 34 (1): 4-9.
14. Alibaz-Oner F, Direskeneli H. Update on the diagnosis of Behçet's disease. *Diagnostics (Basel)* 2022; 13 (1): 41.
15. Aharon-Peretz J, Badarny S, Ibrahim R, Gershoni-Baruch R, Hassoun G. Essential tremor prevalence is low in the Druze population in Northern Israel. *Tremor Other Hyperkinet Mov (N Y)* 2012; 2: tre-02-81-390-1.
16. Amer-Alshiek J, Alshiek T, Amir Levy Y, Azem F, Amit A, Amir H. Israeli Druze women's sex preferences when choosing obstetricians and gynecologists. *Isr J Health Policy Res* 2015; 4: 13.
17. Faraj Falah J. The development of the status of Druze women in the 21st century. *Front Sociol* 2023; 8: 1206494.
18. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of Behçet's disease: an international collaborative study. *British Journal of Ophthalmology* 2007; 91 (12): 1579-82.
19. Lewis K. A., Graham E. M., Stanford M. R. Systematic review of ethnic variation in the phenotype of Behcet's disease. *Scand J Rheumatol* 2007; 36 (1): 1-6.
20. Seyahi E, Yurdakul S. Behçet's syndrome and thrombosis. *Mediterr J Hematol Infect Dis* 2011; 3 (1): e2011026.

Capsule

Lymph nodes get a remodel

Fibroblastic reticular cells are stromal cells that coordinate structural remodeling and immune responses within lymph nodes and other secondary lymphoid organs. Using single-cell transcriptomics and high-resolution microscopy, **Lütge** and colleagues comprehensively characterized the stromal cell landscapes in human lymph nodes during quiescence and inflammation. Inflammation drove lymph node remodeling, which included macrophage-guided the expansion of perivascular peptidase inhibitor 16 (PI16)+ fibroblastic reticular cells and enabled the enlargement of immune cell niches. These findings provide insight into how inflammation affects the stromal cell architecture of human lymph nodes to support immune responses.

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Eitan Israeli

Capsule

Detangling ancestry effects on disease

Recent progress in human genomics has resulted in vast databases of genetic and clinical data that are then used to inform the diagnosis and treatment of medical conditions. Unfortunately, most of the individuals included in these databases are of European descent, making it more difficult to apply precision medicine for individuals of other ancestries. To overcome this challenge, **Smith** and colleagues developed a machine learning method called PhyloFrame, which can distinguish ancestry-specific and disease-specific genetic signatures and help identify ancestry-specific genetic variants that affect disease risk. This approach avoids reliance on self-identification and the assumption that individuals come from uniform ancestral backgrounds, which is particularly important in a world of increasingly admixed populations.

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