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Immunological Evaluation of Children with Behçet's Disease

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Abstract

Objective: Behçet's disease (BD) is a rare, chronic, systemic inflammatory condition characterized by features of both autoinflammation and vasculitis. This study aimed to investigate the clinical manifestations, laboratory findings, and immunological features of children with BD, and to evaluate their treatment response.

Methods: A retrospective analysis was conducted of the medical records of 50 children with BD, aged 0–18 years, followed at a single pediatric rheumatology center between January 2011 and 2023. Demographic, clinical, laboratory, and immunological data were collected, including serum immunoglobulin levels (interpreted according to age-specific reference values), lymphocyte subsets, and treatment response.

Results: The cohort comprised 24 males (48%) and 26 females (52%). The mean age at diagnosis was 11.12±4.24 years, with an average diagnostic delay of 2.08 years. A family history of BD was present in 20 patients (40%). Oral aphthous ulcers were the most common manifestation (96%), followed by gastrointestinal involvement and genital ulcers (each 34%), musculoskeletal involvement (58%), uveitis (18%), neurological (18%), and vascular involvement (10%). HLA-B51 was positive in 39 patients (78%), and MEFV variants in 5 of 16 tested (31.2%). Before treatment, 13 of 34 patients (38.2%) showed a reduction in at least one serum immunoglobulin (IgG in 5, IgM in 6, and IgA in 2, all below −2 SD); one patient with low IgG developed multisystem inflammatory syndrome in children (MIS-C) after COVID-19 and received intravenous immunoglobulin for 6 months. Decreased T, B, and/or natural killer (NK) cells in the lymphocyte subset were detected in 15 out of 30 patients (50%). Although changes in lymphocyte subgroup counts and/or decreased immunoglobulin levels were detected in patients with oral aphthous ulcers and gastrointestinal involvement, immune tests were normal in most patients with neurological or vascular involvement. Colchicine was the most frequently prescribed medication (90%), followed by systemic corticosteroids (24%) and biological agents (18%); clinical improvement was observed in 32 patients (64%), and of the nine patients with uveitis, eight received treatment, of whom five achieved complete recovery.

Conclusion: In our study, we observed antibody deficiencies and alterations in lymphocyte subsets, particularly in patients with gastrointestinal mucosal involvement and oral and genital aphthous ulcers. These findings suggest that immunological assessment may contribute to the monitoring of children with BD; however, controlled studies are needed to determine whether it can inform treatment decisions.

Keywords: Behçet's disease, Children, Immunoglobulins, Lymphocytes

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Behçet Hastalığı olan Çocukların İmmünolojik Değerlendirilmesi

Öz

Amaç: Behçet hastalığı (BH), hem otoinflamasyon hem de vaskülit özellikleriyle karakterize, nadir, kronik, sistemik inflamatuar bir hastalıktır. Bu çalışma, Behçet hastalığı olan çocukların klinik bulgularını, laboratuvar bulgularını ve immünolojik özelliklerini araştırmayı ve tedavi yanıtlarını değerlendirmeyi amaçlamıştır.

Yöntemler: Ocak 2011 ile 2023 yılları arasında tek bir çocuk romatolojisi merkezinde takip edilen, 0–18 yaş aralığındaki BH tanılı 50 çocuğun tıbbi kayıtları retrospektif olarak analiz edildi. Demografik, klinik, laboratuvar ve immünolojik veriler toplandı; bunlara serum immünoglobulin düzeyleri (yaşa uygun referans değerlerine göre yorumlandı), lenfosit alt grupları ve tedavi yanıtı dâhildi.

Bulgular: Kohort 24 erkek (%48) ve 26 kız (%52) hastadan oluşuyordu. Tanı anındaki ortalama yaş 11,12±4,24 yıl olup, ortalama tanı gecikmesi 2,08 yıldı. Yirmi hastada (%40) ailede Behçet hastalığı öyküsü mevcuttu. Oral aftöz ülserler en sık görülen bulguydu (%96); bunu gastrointestinal tutulum ve genital ülserler (her biri %34), kas-iskelet sistemi tutulumu (%58), üveit (%18), nörolojik (%18) ve vasküler tutulum (%10) izledi. HLA-B51, 39 hastada (%78) pozitifti ve MEFV varyantları test edilen 16 hastanın 5'inde (%31,2) saptandı. Tedavi öncesinde, 34 hastanın 13'ünde (%38,2) en az bir serum immünoglobulin düzeyinde azalma görüldü (5 hastada IgG, 6 hastada IgM, 2 hastada IgA; tümü −2 SD altında); düşük IgG'si olan bir hastada COVID-19 sonrası MIS-C gelişti ve 6 ay boyunca intravenöz immünoglobulin tedavisi aldı. Lenfosit alt grubunda T, B ve/veya NK hücrelerinde azalma 30 hastanın 15'inde (%50) saptandı. Lenfosit alt grubu sayılarındaki değişiklikler ve/veya immünoglobulin düzeylerindeki azalmalar oral aftöz ülser ve gastrointestinal tutulumu olan hastalarda saptanırken, nörolojik veya vasküler tutulumu olan hastaların çoğunda immün testler normaldi. Kolşisin en sık reçete edilen ilaçtı (%90); bunu sistemik kortikosteroidler (%24) ve biyolojik ajanlar (%18) izledi. Otuz iki hastada (%64) klinik düzelme gözlendi ve üveit nedeniyle tedavi edilen 8 hastanın 5'inde biyolojik ajanlarla tam iyileşme sağlandı.

Sonuç: Çalışmamızda, özellikle gastrointestinal mukozal tutulumu ve oral ile genital aftöz ülserleri olan hastalarda antikor eksiklikleri ve lenfosit alt gruplarında değişiklikler gözlemledik. Bu bulgular, immünolojik değerlendirmenin Behçet hastalığı olan çocukların takibine katkı sağlayabileceğini düşündürmektedir; ancak tedaviyi yönlendirip yönlendiremeyeceğini belirlemek için kontrollü çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Behçet hastalığı; Çocuklar; İmmünoglobulinler; Lenfositler.

INTRODUCTION

Behçet's disease (BD) is a chronic, relapsing, multisystem vasculitis of unknown etiology, characterized by recurrent oral and genital ulcers and a wide range of manifestations that may involve the skin, eyes, joints, gastrointestinal tract, vascular system, and central nervous system[1]. It is recognized as a systemic vasculitis that can affect blood vessels of diverse sizes and types, impacting multiple organ systems. Although BD typically emerges between the second and fourth decades of life, approximately 15–20% of cases present during childhood[2,3].

Geographically, BD shows a predominant distribution along the historical Silk Road[4], where the highest prevalence is observed in Turkey (pooled estimate ~120 per 100,000), with progressively lower rates across the Middle East, Asia, and Europe[5]. Pediatric-onset BD, like its adult-onset counterpart, shows an equal sex distribution[6]. However, there are discernible differences in the frequency and severity of clinical findings between sexes, with males often experiencing a more severe disease course than females[2,3]. Severe uveitis and vascular complications are more prevalent in males, whereas females more frequently present with genital ulcers and erythema nodosum[3]. In pediatric BD, the full clinical phenotype often evolves over time, with manifestations emerging at variable intervals[3]. Notably, HLA-B51 confers the strongest genetic susceptibility to BD; the allele is carried by up to 60% of affected individuals, compared with approximately 10–20% of healthy controls[7].

Furthermore, BD shares pathogenic mechanisms reminiscent of autoimmune and autoinflammatory diseases and seronegative spondyloarthropathies[8]. In the immunopathogenesis of chronic inflammation in BD, both humoral and cellular immunity are involved, with contributions from Th1, Th2, and Th17 cytokines, as well as various chemokines, reflecting the complex nature of the disease[9].

Our study aimed to investigate the clinical manifestations, laboratory findings, and immunological characteristics of patients with BD, and to evaluate their treatment response.

METHODS

In this study, we recruited a cohort of 50 patients aged between 0 and 18 years who have been followed by the Department of Pediatric Rheumatology at Bursa Uludag University Faculty of Medicine, diagnosed with BD based on the diagnostic criteria established by the International Behçet's Disease and Pediatric Behçet's Disease (PEDBD) study group[10]. Because the study period (January 2011–2023) predates the 2016 publication of the PEDBD criteria, patients diagnosed before 2016 according to the International Study Group criteria[11] were subsequently re-screened retrospectively against the PEDBD criteria, and only those fulfilling the PEDBD criteria were included. Diagnostic delay was defined as the interval between the onset of the first Behçet's disease–related symptom and the establishment of the diagnosis. A retrospective analysis was performed on electronic medical records covering January 2011 to 2023, encompassing demographic data, clinical presentations, and laboratory and immunological profiles.

Serum immunoglobulin (IgG, IgA, and IgM) concentrations were interpreted using validated age-specific pediatric reference intervals derived from healthy children. In accordance with established clinical immunology practice, values below the age-adjusted lower reference limit (−2 standard deviations [SD]) were considered decreased[12]. Additionally lymphocyte subset analyses were evaluated using age-specific reference ranges derived from the healthy pediatric population, thereby ensuring age-appropriate interpretation of the immunological findings[13].

Lymphocyte subset analyses were available for 30 of the 50 patients. Patients without available pretreatment lymphocyte subset results, including those referred from other institutions, were excluded from this analysis. Consequently, lymphocyte subset analyses were performed using data from the 30 patients with available pretreatment results. At the time of diagnosis, serum immunoglobulin levels and lymphocyte subset analyses were performed before the initiation of corticosteroid or immunosuppressive therapy. Serum immunoglobulin levels were assessed as part of the routine clinical evaluation; however, only patients meeting the predefined study inclusion criteria were included in the final analysis. A key inclusion criterion was the absence of prior treatment that could potentially affect immunoglobulin levels. During the retrospective review covering the 12-year study period, patients with unverifiable treatment histories, uncertain prior treatment status due to referral from other centers, or incomplete immunological data were excluded. Consequently, immunoglobulin analyses were performed in 34 patients.

Lymphocyte subset analyses were available for 30 of the 50 patients. Patients without available pretreatment lymphocyte subset results, including those referred from other institutions, were excluded from this analysis. Consequently, lymphocyte subset analyses were performed using data from the 30 patients with available pretreatment results.

Neurological involvement was classified as parenchymal or non-parenchymal neuro-

Behçet's disease according to the international consensus recommendations.[14] Vascular involvement was defined as venous or arterial thrombosis or aneurysm at any site. Cerebral venous sinus thrombosis was classified as both non-parenchymal neurological and venous vascular involvement.

Clinical improvement was defined as regression of Behçet's disease-related clinical findings, absence of new organ involvement or disease flare, and no signs of active disease during follow-up. The median follow-up was 36 months (interquartile range 12–57).

Statistical Analysis

Continuous variables were assessed for normality with the Shapiro–Wilk test; normally distributed variables are presented as mean ± standard deviation and were compared with the Student's t-test, whereas non-normally distributed variables are presented as median (interquartile range, IQR) and were compared with the Mann–Whitney U test. For subgroup comparisons, exact p-values and effect sizes (rank-biserial correlation for the Mann–Whitney U test) are reported, and, given the small size of some subgroups, these results are interpreted with caution. Categorical variables were expressed as n (%), and Pearson's chi-square test or Fisher's exact test was used for independent variables. Analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA; released 2015), with the Type I error rate (α) set at 0.05. Ethical approval was obtained from the Bursa Uludag University Faculty of Medicine Medical Research Ethics Committee for the study (2022–11/23).

RESULTS

Our investigation comprised a cohort of 50 children with BD; 24 (48%) were male, and 26 (52%) were female. The mean age at the onset of initial symptoms was 9.02±4.71 years, whereas the average age at diagnosis was 11.12±4.24 years (10.75±4.55 for males and 12.35±3.65 for females), with an average diagnostic delay of 2.08 years.

In their medical backgrounds, five patients had asthma, two had epilepsy, and one had mastocytosis. Regarding family medical histories, BD was documented in 20 patients' families (40%), while Familial Mediterranean Fever (FMF) was the second most common rheumatological condition, affecting 11 patients' families (22%). As a clinical observation, oral aphthous ulcers were prevalent in 48 patients (96%), with an average frequency of 7.94±3.8 cases per year. Genital ulcers were present in 17 patients (34%), while signs of uveitis were noted in 9 (18%), comprising four cases of panuveitis, four of anterior uveitis, and one of posterior uveitis. Skin manifestations were present in 19 patients (38%), most commonly erythema nodosum.

Gastrointestinal involvement was identified in 17 patients (34%), while neurological involvement was observed in nine patients (18%), including six (12%) with parenchymal neuro-Behçet and three (6%) with non-parenchymal neuro-Behçet. Vascular involvement was identified in five patients (10%). Three patients were classified as having both neurological and vascular involvement. When the distribution of organ involvement was analyzed according to sex, vascular involvement was identified in five patients, four of whom were female. However, this difference did not reach statistical significance (Fisher's exact test, $p = 0.35$). Given the small number of patients with vascular involvement and the well-established male predominance of vascular and severe manifestations in Behçet disease reported in previous studies, this finding should be considered exploratory rather than indicative of a sex-specific association. No significant sex-based differences were observed for the other organ involvements. In our study, 29 (58%) patients had musculoskeletal system involvement, with arthritis/arthralgia co-occurring in 18 patients and arthralgia alone in 11 patients. Joint involvement was oligoarticular. The most commonly affected joints were the knee (n=8) and ankle (n=4), consistent with the literature. In others, involvement was observed in 3 patients at the wrist, two at the hip, and one at

the sacroiliac joint. In our study, one patient diagnosed with panuveitis underwent surgery due to secondary complicated cataract development.

Pathergy positivity was identified in only four patients. Clinical and laboratory findings were delineated in Table 1.

Table I: Clinical and general characteristics of patients

	n	%
Gender		
Male	24	48
Female	26	52
Parental consanguinity	5	10
Family History	20	40
Clinical Manifestations		
Oral Aphthous Ulceration	48	96
Genital Ulceration	17	34
Skin Manifestations	19	38
Uveitis	9	18
Panuveitis	4	8
Anterior uveitis	4	8
Posterior uveitis	1	2
Neurological Involvement	9	18
Vascular Involvement	5	10
Gastrointestinal System Involvement	17	34
Musculoskeletal System Involvement	29	58
Arthritis/Arthralgia	18	36
Arthralgia	11	22
Genitourinary		
Epididymo-orchitis	1	2
Associated Comorbidities		
Asthma	5	10
Epilepsy	2	4
Mastocytosis	1	2
Positive Pathergy Test	4	8
Laboratory Findings	median (IQR)	(n)
Hemogram		
Leukocytes (cells/μL) (normal range; 4170 - 10170)	7710 (6452–9278)	50
Lymphocytes (cells/μL) (normal range; 1360 - 3810)	2455 (2182–3188)	50
Neutrophil (cells/μL) (normal range; 1790 – 6860)	4080 (3098–5352)	50
Acute phase reactants		
Sedimentation (mm/h) (normal range; 2-20)	15 (5–29)	49
C-reactive protein (mg/L) (normal range; <5)	3.0 (2.0–4.0)	50
Serum amyloid A (mg/L) (normal range; 0-6.8)	6.0 (3.0–29.7)	47
Fibrinogen (mg/dl) (normal range; 180-350)	300 (244–414)	43
Systemic immune-inflammation index (SII) (platelet count × neutrophil count/lymphocyte count;$10^3/mm^3$)	430 (284–714)	50
HLA-B51 (n,%)	39	78
Positive ANA (n,%)	13	26
Treatment		
Colchicine	45	90
Steroids	12	24
Azathioprine	7	16
Methotrexate	4	8
Biological agents	9	18
Adalimumab	5	10
Infliximab	4	8

Laboratory analyses revealed that HLA-B51 was the most frequent allele, positive in 39 patients (78%). Other HLA-B alleles detected in the cohort included HLA-B35, HLA-B50, HLA-B27, HLA-B08, HLA-B15, HLA-B13, HLA-B40, HLA-B44, HLA-B52, HLA-B18, and HLA-B57, consistent with the individual HLA types reported in Tables 2 and 3. Antinuclear antibody (ANA) positivity was detected in 13 (26%) patients. Analysis of the MEFV gene was performed in 16 patients based on clinical indications (suspected familial Mediterranean fever or a compatible family history). In our study, mutations in the MEFV gene were found in 5 out of 16 patients (31.2%). Other genetic mutations identified in our study included MTHFR in 3 patients, Factor V Leiden in 2 patients, PAI-1 4G/5G in 2 patients, and Factor II, Factor III, and CARD14 genes in 1 patient.

Table II: Clinical and immunological evaluation of patients with low immunoglobulin level

Patient	Gender	Age (years)	Organ involvement	HLA type	Abnormal immunological findings	Treatment
1.	Male	11	Oral aphthae, Arthritis, Gastrointestinal system involvement	HLA-B51 HLA-B52	Low IgA Low NK cells Low switched memory B cells	Colchicine
2.	Female	15	Oral aphthae Uveitis, Erythema nodosum	HLA-B51	Low IgG Low CD8 cell	Colchicine Steroid
3.	Female	18	Oral aphthae, Arthritis, Gastrointestinal system involvement	HLA-B51	Low IgM High CD8 cells	Colchicine
4.	Female	10	Oral aphthae Arthralgia Erythema nodosum	HLA-B15 HLA-B51	Low IgG	Colchicine
5.	Female	11	Oral aphthae, Genital ulcer Gastrointestinal system involvement	HLA-B51	Low IgG Low NK cells High CD8 cells	Colchicine
6.	Male	18	Oral aphthae Arthritis Erythema nodosum	HLA-B14 HLA-B15	Low IgM High CD8 cells	Colchicine Methotrexate
7.	Male	16	Oral aphthae Arthritis Erythema nodosum	HLA-B13 HLA-B51	Low IgA Low Naive B cells	Colchicine
8.	Male	18	Oral aphthae, Arthritis, Gastrointestinal system involvement	HLA-B13 HLA-B51	Low IgG	Colchicine
9.	Male	7	Oral aphthae, Genital ulcer Erythema nodosum	HLA-B18 HLA-B57	Low IgM Low Naive B cells	Colchicine
10.	Female	14	Oral aphthae, Genital ulcer Erythema nodosum	HLA-B50 HLA-B51	Low IgM	Colchicine Steroid
11.	Female	17	Oral aphthae, Erythema nodosum Gastrointestinal system involvement	HLA-B51 (homozygous)	Low IgM	Colchicine
12.	Male	11	Uveitis, Vascular involvement, CNS involvement	HLA-B27 HLA-B44	Low IgM	Colchicine Methotrexate Adalimumab
13.	Female	15	Oral aphthae, Uveitis, CNS involvement	HLA-B50 HLA-B51	Low IgG Low CD4 cells	Colchicine Methotrexate Adalimumab Infliximab

Table III: Clinical and immunological evaluation of patients with vascular and neurological involvement

Patient	Gender	Age (year)	Organ involvement	HLA type	Abnormal immunological findings	Treatment
1.	Female	9	Oral aphthae, Genital ulcer Uveitis Thrombus in the bilateral transverse sigmoid sinus and jugular vein	HLA-B40 HLA-B51	Low switched memory B cells	Colchicine Infliximab Azathioprine Anticoagulant
2.	Female	11	Oral aphthae, Uveitis Thrombus in the left transverse sinus	HLA-B40 HLA-B51	-	Colchicine Steroid Azathioprine Anticoagulant
3.	Male	18	Oral aphthae, Genital ulcer Erythema nodosum Thrombus in the right atrium	HLA-B08 HLA-B51	-	Colchicine Steroid Azathioprine Anticoagulant
4.	Female	13	Oral aphthae, Genital ulcer Thrombophlebitis in the leg	HLA-B49 HLA-B51	-	Colchicine Anticoagulant
5.	Female	18	Oral aphthae, Genital ulcer Parenchymal involvement in left frontoparietal localization Pulmonary artery aneurysm	HLA-B08 HLA-B51	-	Colchicine Steroid Azathioprine
6.	Female	18	Oral aphthae, Gastrointestinal system involvement Ischemic contrast enhancement at the centrum semiovale level in bilateral cerebral hemispheres	HLA-B27 HLA-B51	-	Colchicine Steroid Azathioprine
7.	Male	13	Oral aphthae, Uveitis Erythema nodosum leptomeningeal involvement	HLA-B08 HLA-B51	-	Colchicine Steroid Azathioprine
8.	Male	18	Genital ulcer Uveitis (vision loss) CNS involvement		-	Colchicine Steroid Adalimumab
9.	Male	11	Uveitis Arthritis Papilledema (increased intracranial pressure)	HLA-B27 HLA-B44	Low IgM	Colchicine Methotrexate Adalimumab
10.	Female	16	Oral aphthae, Arthritis Parenchymal involvement (temporal signal change and edema); petrous apicitis	HLA-B50 HLA-B51	-	Colchicine
11.	Female	15	Oral aphthae, Uveitis CNS involvement (parenchymal involvement, dizziness, headache)	HLA-B50 HLA-B51	Low IgG Low CD4 cells Low switched memory B cells	Colchicine Methotrexate Adalimumab Infliximab

Before initiating immunosuppressive treatment, immunological assessment showed that 13 of 34 patients (38.2%) had a reduction in at least one serum immunoglobulin (Ig) level compared with age-matched reference values. Among these, values below −2 SD were detected for IgG in 5 patients, IgM in 6, and IgA in 2. One of the patients with low IgG developed multisystem inflammatory syndrome in children (MIS-C) following COVID-19 and received intravenous immunoglobulin (IVIG) for 6 months. The clinical features of patients with low immunoglobulin levels are presented in Table 2. When assessed by gender, no significant difference was observed in patients with low immunoglobulin levels ($p>0.05$).

Cellular pathologies were detected in the lymphocyte subset in 15 out of 30 patients

(50%). The specific subset abnormalities are summarized in Table 4. Because several patients had more than one abnormal subset, these counts sum to more than the 15 affected patients; for example, of the 6 patients with reduced natural killer (NK) cells, 2 had an isolated NK reduction and 4 had concurrent reductions in switched-memory B and CD8 cells. There was no significant change in the clinical findings of these patients compared to the others.

Table IV: Distribution of lymphocyte subset abnormalities among the 30 patients evaluated

Lymphocyte subset abnormality	n (of 30)
Reduced CD4 (< −2 SD)	2
Reduced CD8 (< −2 SD)	3
Reduced NK cells (< −2 SD)	6
Reduced naïve B cells (< −2 SD)	3
Reduced switched-memory B cells (< −2 SD)	2
Elevated CD8 (for age)	3
Patients with ≥1 abnormality	**15 (50%)**

Elevations in acute phase reactants such as erythrocyte sedimentation rate (ESR) (38%), C-reactive protein (CRP) (40.0%), fibrinogen (30.2%), and serum amyloid A (SAA) (53.2%) were observed during the laboratory manifestations. The systemic Immuno-Inflammation Index (SII), calculated by dividing neutrophils by lymphocytes and multiplying by platelet count, was also used to assess disease activity. The median SII was 430 (IQR 284–714) $\times 10^3/mm^3$. Applying the previously reported cut-off of $552\times 10^3/mm^3$,22 SII was elevated in 15 patients (30%).

No discrepancy was observed between the ages at diagnosis and onset of initial symptoms in patients with and without neurological involvement. Patients with neurological involvement (n = 9) had significantly higher systemic immune-inflammation index (SII) values than those without neurological involvement (median [IQR]: 518 [438–1127] vs. 420 [257–625], p = 0.034, r = 0.46). Leukocyte and neutrophil counts were also higher in the neurological involvement group (9.10 [7.82–13.53] vs. 7.39 [6.32–9.03] $\times 10^9$/L, p = 0.058, r = 0.41; and 5.23 [4.15–10.18] vs. 3.82 [3.06–5.18] $\times 10^9$/L, p = 0.065, r = 0.40, respectively), although these differences did not reach statistical significance. No significant differences were observed in lymphocyte count, C-reactive protein, or erythrocyte sedimentation rate between the two groups.

Another noteworthy issue was the detection of mutations in the Factor V Leiden gene in two patients, one male and one female, with neurological involvement.

Colchicine emerged as the most frequently prescribed medication for treatment (n = 45, 90%). In our study, 12 (24%) patients were treated with systemic steroids, and 9 (18%) patients were treated with biological agents. The treatments adapted according to patient presentations are detailed in Table 1. Throughout the follow-up period, clinical improvement was observed in 32 patients (64%). Twenty-nine of these patients received colchicine, and four received biological agent therapy. Of the nine patients with uveitis, eight received treatment (in one patient uveitis was mild and did not require systemic treatment), of whom five achieved complete recovery. Notably, only one patient required surgical intervention during treatment, necessitated by the development of a complicated cataract secondary to uveitis.

DISCUSSION

Behçet's disease is a systemic inflammatory condition characterized by features of both autoinflammation and vasculitis[15].

Although BD is largely sporadic, familial aggregation predominantly among first-degree relatives is well recognized and is significantly more frequent in pediatric-onset disease[3,15]. In a large two-centre cohort of 801 patients, a positive family history was significantly more common in pediatric than in adult BD[16]. In our study, 40% (n=20) of patients had a family

history of BD among their relatives, a higher proportion than reported in previous studies. Additionally, 5 patients (10%) were born to consanguineous parents. We also found that 14 patients (28%) had relatives with other rheumatological diseases, compared to 18% reported in a study from Türkiye[17].

Regardless of ethnic origin, the potent genetic risk factor for BD is the human leukocyte antigen (HLA) class I allele HLA-B5 and its suballele HLA-B51.[18] de Menthon et al. reported that individuals carrying the HLA-B5/B51 gene had a 5.78 times higher risk of developing BD[19]. Genital ulcers, ocular involvement, and skin manifestations are more common in HLA-B51-positive patients[18]. In our study, the rate of HLA-B51 positivity was high, at 78% of patients, with a nearly equal distribution between males and females (19 males, 20 females).

Behçet's disease and FMF share pathophysiological, epidemiological, and clinical features, and MEFV variants have been implicated in BD susceptibility; a meta-analysis confirmed that the M694V and M680I mutations are significantly associated with BD, particularly in Turkish patients[20]. Consistent with this, MEFV gene mutations were identified in 5 of the 16 patients (31.2%) who underwent genetic testing in our cohort, supporting a contributory role of MEFV variants in pediatric BD.

Among the five patients with MEFV variants, four had gastrointestinal involvement and two had mucocutaneous involvement, with one patient exhibiting both manifestations. The central nervous system manifestations of BD, also known as neuro-Behçet's disease (NBD), have been reported in 2.2%–50% of adults and 3.6%–59.6% of children[1,3]. Unlike adult patients, most children with NBD present with non-parenchymal diseases, most commonly cerebral venous thrombosis[3]. In our study, neurological involvement was observed in 14% of patients, with cerebral venous thrombosis detected in three of them.

BD lacks characteristic or pathognomonic laboratory findings. But inflammatory laboratory markers, such as CRP, ESR, and ferritin, may increase with increased disease activity[21]. Serum amyloid A levels have been interpreted as an indicator of major organ involvement and recurrence of ocular disease in BD[22]. Consistent with the literature, our study also showed increased CRP and ESR levels during disease activation. Serum amyloid A levels were high in 25/47 (53.2%) patients, with the highest frequency observed in patients with neurological (71.4%) and mucocutaneous involvement (63.1%).

A bidirectional interaction in which T cells drive neutrophil hyperactivation and activated neutrophils in turn stimulate T cells is considered a key contributor to the vasculitic pathogenesis of BD, with neutrophil hyperactivity playing a central role in tissue damage[9,23].

Tanacan et al. reported that the SII value in the active BD group was significantly higher than in the inactive BD group. Additionally, a cut-off value of $552\times10^3/mm^3$ for SII was determined, demonstrating relatively high sensitivity and specificity[24]. In our study, elevated SII levels were detected in 15 patients (30%).

Hasan et al. demonstrated a significant correlation between the decrease in the number of NK cells in peripheral blood and the increase in disease activity in BD[25]. In our study, oral aphthae and gastrointestinal involvement were present in a few patients with low NK cell counts; given the small numbers, this observation is hypothesis-generating. Overall, low NK cell counts were found in 20% of the 30 tested patients (6/30), while none had elevated levels. Two patients presented with isolated NK cell deficiency, whereas four had concurrent reductions in CD8 cells, switched memory B

cells, and NK cells. It has been proposed that modulation of NK-cell activity may influence disease manifestations in BD[26]. However, our data cannot establish such a relationship, which remains a hypothesis to be tested in controlled studies.

Serum immunoglobulin findings in BD are heterogeneous: while a polyclonal increase, particularly in IgA, has been reported in active disease[27], Scully et al. found mean serum IgG, IgM, IgD, and IgE levels comparable to controls, with only IgA elevated[28]. In contrast, van der Houwen et al. observed reduced serum immunoglobulin levels (IgG, IgA, or IgM) in 3 of 36 patients (8%), with normal levels in the majority[29]. In our cohort, the level of at least one of the serum immunoglobulins was low in 13 of 34 patients (38.2%) compared to their age group. A patient with low IgG was started on IV immunoglobulin therapy due to MIS-C developing after COVID-19 infection, and this treatment was continued for 6 months. IgM was reduced (below −2 SD) in 6 patients and IgA in 2.

Immunoglobulin abnormalities have also been reported in other pediatric rheumatological diseases. In a study of pediatric systemic lupus erythematosus (SLE) patients, hypogammaglobulinemia was detected in 6 out of 86 patients (7%) included in the analysis[30]. Similarly, immunoglobulin disorders in juvenile idiopathic arthritis have been investigated more extensively, with IgA deficiency reported in 8.3% of patients in a case-control study of 83 patients[31]. In contrast, in our Behçet's disease cohort, 13 out of 34 patients (38.2%) showed a deficiency in at least one serum immunoglobulin isotype; 5 (14.7%) had IgG, 6 (17.6%) had IgM, and 2 (5.9%) had IgA levels below the age-appropriate reference range. However, this high rate should not be interpreted as an indicator of the true prevalence. Since our study was conducted in a tertiary pediatric immunology and rheumatology center that also housed an immunodeficiency unit, referral bias may have contributed to these findings. Therefore, these results should not be considered prevalence estimates but rather descriptive and hypothesis-generating findings that can serve as the basis for larger, multicenter, and systematic screening-based studies in the future.

The primary goal in the treatment of BD is to suppress inflammation in order to prevent organ damage and disease flares. Systemic corticosteroids are recommended for oral or genital lesions unresponsive to topical therapy, as well as for cutaneous lesions resistant to colchicine[32]. In our study, systemic steroid treatment was administered to 12 (24%) patients. Combination therapy with systemic steroids was administered to 6 patients with azathioprine, three patients with adalimumab, one patient with methotrexate, and one patient with infliximab. Colchicine is an anti-inflammatory medication that inhibits neutrophil migration and is the first-line therapy for preventing mucocutaneous lesions[33]. In our study, 90% of patients used colchicine, consistent with previously reported studies.[10]

Evaluating antibody and cellular changes in the immune system at diagnosis and during treatment may help to identify cellular and humoral immune defects that could occur in the future when administering immunosuppressive therapy.

In pediatric BD, anti-TNF agents are recommended for use in cases where conventional treatments fail to control the disease or in situations of intolerance or allergic reactions to conventional agents.[32] In our study, nine patients were treated with biological agents, including adalimumab in five and infliximab in four. In our study, the frequency of anti-TNF use was found to be 18%, which is similar to a study conducted in pediatric BD

patients in the United Kingdom[34]. Biological agents were used in 3 patients for uveitis, 3 for neurological and articular involvement, 2 for gastrointestinal involvement, and 1 for vascular involvement.

Although all patients with vascular involvement in our cohort were female, this observation was based on only five patients and did not reach statistical significance using Fisher's exact test ($p = 0.0502$). This contrasts with the well-recognized male predominance of vascular and severe manifestations of Behçet's disease[2,3,23]. Therefore, it should be interpreted as an exploratory, hypothesis-generating observation rather than evidence of a true sex-specific association, and requires confirmation in larger cohorts.

This study has several limitations. First, it is a retrospective, single-center study. In addition, owing to the relative rarity of pediatric Behçet disease and the retrospective design, immunoglobulin levels and lymphocyte subsets were not assessed systematically in the entire cohort but only in selected patient subgroups (34/50 and 30/50, respectively). Immunological evaluations were performed at the time of diagnosis, during the active phase of the disease, and before the initiation of immunosuppressive therapy. Although active inflammation may have influenced some of the immunological parameters assessed, the primary objective of our study was not to determine the absolute effect of inflammation, but rather to evaluate whether adaptive immune response profiles differ according to patterns of organ involvement under comparable levels of inflammatory activity. Nevertheless, given the limited sample size of several clinical subgroups, these findings should be interpreted as descriptive and hypothesis-generating, and require confirmation in larger prospective studies. Consequently, the reported frequencies may be influenced by selection bias and should not be directly compared with population-based prevalence estimates. Furthermore, several subgroup analyses were based on small sample sizes, limiting statistical power and precluding definitive conclusions. Therefore, our immunological findings should be interpreted as descriptive and hypothesis-generating rather than confirmatory, and their disease specificity should be validated in appropriately designed controlled studies. Nevertheless, our findings may offer preliminary insights that could inform the design of future multicenter, prospective, controlled studies evaluating the prevalence, clinical relevance, and potential prognostic significance of immunological abnormalities in pediatric Behçet disease.

CONCLUSION

Behçet disease may involve alterations in the adaptive immune system in addition to innate immune dysregulation. In the present study, we evaluated both humoral (immunoglobulins) and cellular (lymphocyte subsets) components of adaptive immunity in a pediatric BD cohort. Antibody deficiency and/or reduced lymphocyte subsets were more frequently observed in patients with oral and genital ulcers and gastrointestinal involvement. However, these observations were based on small patient subgroups and should therefore be interpreted as descriptive, hypothesis-generating findings rather than established associations. Although our results suggest that immunological abnormalities may be present in a subset of children with BD, their clinical significance remains uncertain. Further prospective, controlled studies are needed to validate these findings and to determine whether immunological assessment has a role in the clinical evaluation and management of pediatric Behçet disease.

Authors' Contributions

All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by YK, ZK, and SSK.

The first draft of the manuscript was written by YK and SSK, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Committee Approval: Ethical approval was obtained from the Bursa Uludag University Faculty of Medicine Medical Research Ethics Committee for the study (2022–11/23).

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