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ORIGINAL ARTICLE

Pediatric Behçet's disease: Experience of a single tertiary center

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ABSTRACT

Objectives: The aim of this study was to examine the clinical and phenotypic features of pediatric Behçet's disease (PEDBD) in our clinic and present the rates of fulfilling the diagnostic criteria.

Patients and methods: Thirty-four patients (20 males, 14 females; mean age: 16.0±2.1 years; range, 10 to 18 years) diagnosed with PEDBD between January 2010 and December 2019 were retrospectively evaluated. Patients were reclassified according to 1990 International Study Group (ISG) criteria, 2014 International Criteria for Behçet's Disease (ICBD), and PEDBD criteria.

Results: The mean age at diagnosis was 12.6±3.1 years, the median diagnosis delay time was 12.0 (range, 4.5 to 27.0) months, and the mean age at symptom onset was 10.8±2.9 years. The mean follow-up period was 31.9±20.9 months. Oral aphthous ulcer was observed in 33 (97.1%), genital ulcer in 16 (47.0%), ocular involvement in 15 (44.1%), skin lesion in 11 (32.3%), joint involvement in nine (26.4%), both vascular and neurological involvement in six (17.6%) patients. The pathergy test was positive in 11 (37.8%) patients, and human leukocyte antigen (HLA)-B51 was positive in 11 (78.5%) of 14 patients. The rates of patients meeting the criteria for ISG, ICBD, and PEDBD were 52.9%, 82.4%, and 50.0%, respectively.

Conclusion: Pathergy and HLA-B51 can be used as supportive findings in patients who do not meet the diagnostic criteria. However, expert opinion is still the gold standard in diagnosis.

Keywords: Diagnostic criteria, HLA-B51, pathergy, Pediatric Behçet's disease.

Behçet's disease (BD) is a multisystemic chronic inflammatory disease characterized by recurrent oral aphthae, genital ulcers, and skin, eye, joint, gastrointestinal, and central nervous system involvement. Behçet's disease is a variable vessel vasculitis affecting all sizes of vasculature in both the arterial and venous systems.[1] It most commonly starts in the second and third decades. However, the disease is also complete in childhood in around 2.5 to 4.5% of cases in recent cohorts.[1-3]

Clinical symptoms vary greatly by geographic region, sex, and ethnicity. The prevalence among adults varies by geographic region. Its incidence is estimated to be 10 to 15 per 100,000 individuals in countries on the Silk Road, but data on prevalence/incidence in children are limited.[4]

Despite the existence of diagnostic criteria, the diagnosis of pediatric BD (PEDBD) is still difficult due to atypical findings and heterogeneity of the disease. Although diagnostic criteria aid diagnosis, most patients do not meet these criteria at the onset of the disease.[5] There is also no accepted standard guideline for its treatment. The aim of this study was to examine the clinical and phenotypic features of PEDBD in our clinic and to present the rates of meeting the PEDBD criteria, 1990 International Study Group (ISG) criteria,

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and 2014 International Criteria for Behçet's Disease (ICBD).

PATIENTS AND METHODS

Thirty-four patients (20 males, 14 females; mean age: mean age: 16.0±2.1 years; range, 10 to 18 years) diagnosed with PEDBD at the Dokuz Eylül University, Pediatric Rheumatology Outpatient Clinic between January 2010 and December 2019 were retrospectively evaluated. Patients' age, sex, clinical characteristics, and laboratory data were recorded. Major organ involvement was classified as eye, vascular, nervous system, and musculoskeletal system. The rates of meeting the diagnostic criteria based on the patients' findings were evaluated.

Patients were reclassified according to the ISG, ICBD, and PEDBD criteria. According to the ISG criteria, the presence of an oral aphthous ulcer is mandatory, while the presence of at least two of the other criteria, genital ulcer, ocular and skin findings (erythema nodosum and pseudofolliculitis), and pathergy test positivity, are required for the diagnosis of BD.[6] Vascular symptoms, such as arterial thrombosis, large vein thrombosis, superficial phlebitis, and neurological symptoms, except for isolated headaches, are added to the ICBD, revised in 2010. Oral aphthae, genital ulcers, and ocular findings (uveitis and retinal vasculitis) are designated 2 points, whereas the others 1 point. An extra point is given for the pathergy test. Four or more points are diagnostic for BD.[7] All findings have the same weight in the PEDBD criteria. Three or more of the following criteria are required in PEDBD: oral aphthous ulcer, genital ulcer, ocular or skin lesions (erythema nodosum, necrotic folliculitis, and acneiform lesions), and neurological or vascular (venous thrombosis, arterial thrombosis, and arterial aneurysm) symptoms. The pathergy test is not scored within these clinical criteria.[8]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as median (min-max) and mean ± standard deviation (SD) for continuous variables and as number and percentage for categorical variables. The Shapiro-Wilk test was used to analyze the distribution of the data. A p value of <0.05 was considered statistically significant.

RESULTS

The mean age at diagnosis was 12.6±3.1 years, median diagnosis delay time was 12.0 (range, 4.5 to 27.0) months, and the mean age at symptom onset was 10.8±2.9 years. The mean follow-up period of the patients was 31.9±20.9 months. Thirty-three (97.1%) patients had an oral aphthous ulcer, 16 (47.0%) had a genital ulcer, 15 (44.1%) had ocular lesions, 11 (32.3%) had skin lesion, nine (26.4%) had joint involvement, six (17.6%) had vascular involvement, and six (17.6%) had neurological involvement. Skin findings were acneiform lesions in eight (23.5%) and erythema nodosum in three (8.8%). Ocular lesions were uveitis in 10 (29.4%), macular edema in four (11.7%), and retinitis in one (2.9%). Vascular lesions were cerebral vein thrombosis in three (8.8%), lower extremity deep vein thrombosis in two (5.8%), and pulmonary and intracardiac thrombosis in one (2.9%). Demographic, clinical, and laboratory findings are shown in Table 1. Neurological pathologies included four (11.7%) patients with nonparenchymal cerebral venous thrombosis and two (5.9%) patients with encephalopathic course and parenchymal lesions due to parenchymal involvement. Multiple sclerosis was clinically and radiologically ruled out in patients with parenchymal lesions. These patients performed lumbar puncture, and no oligoclonal band was observed in the cerebrospinal fluid examination. The clinical findings, cerebrospinal fluid examination, and radiological evaluation were inconsistent for other neurological disorders, such as acute disseminated encephalomyelitis, infectious encephalitis, central nervous system vasculitis. Only six patients with vascular thrombosis were investigated for thrombophilia. Heterozygous mutation in the PAI-1 gene was found in one and heterozygous mutation in the MTHFR gene in another. Other four patients exhibited no thrombophilia disorders, such as thrombophilia gene, protein C or S deficiency, and anti-phospholipid antibody positivity. The pathergy test was positive in 11 (37.8%) patients,

and human leukocyte antigen (HLA)-B51 was positive in 11 of 14 (78.5%) patients in whom HLA-B51 concentrations were measured. Systemic lupus erythematosus and other autoimmune diseases were ruled out in three patients who were antinuclear antibody positive. The patients did not have other clinical (e.g., malar rash, sclerodactyly, Gottron's papule, and myositis) and laboratory (e.g., anti-dsDNA [anti-double-stranded deoxyribonucleic acid] positivity, ENA [extractable nuclear antigens] positivity, and low complement proteins) findings of systemic

Table 1. Demographic, clinical, and laboratory characteristics of PEDBD patients

	n	%	Mean±SD	Median	IQR
Sex					
Male	20				
Female	14				
Age at diagnosis (year)			12.6±3.1		
Age at symptom onset (year)			10.8±2.9		2.5-15.5
Diagnosis delay time (month)			21.3±24.7		4.5-96
Follow up time (month)			31.9±20.9		4-104
Oral aphthae	33	97.1			
Genital ulcers	16	47.0			
Ocular lesions	15	44.1			
Uveitis	10	29.4			
Macular edema	4	11.7			
Retinitis	1	2.9			
Skin lesions	11	32.3			
Acneiform lesions	8	23.5			
Erythema nodosum	3	8.8			
Joint involvement	9	26.4			
Vascular findings	6	17.6			
Cerebral vein thrombosis	3	8.8			
Deep vein thrombosis	2	5.9			
Pulmonary and intracardiac thrombosis	1	2.9			
Neurological findings	6	17.6			
Paranchimal	4	11.7			
Nonparenchimal	2	5.9			
Family history	9	26.4			
BDCAF first visit			3.0±1.0		
BDCAF last visit			1.0±0.8		
Hemoglobin (g/dL)			12.5±1.4		
Leukocyte ($\times10^3$)/mm^3			8.7±3.2		
Thrombocyte ($\times10^3$)/mm^3			310.7±125.9		
C-reactive protein (mg/dL)				6.80	3.02-21.02
Erythrocyte sedimentation rate				21	7-41
Positive pathergy test	11	32.3			
Positive human leukocyte antigen-B51	11/14	78.5			
Antinuclear antibody positivity	3/16	18.7			
Positive thrombophilic factor	3/6	50.0			

PEDBD: Pediatric Behçet's disease; SD: Standard deviation; IQR: Interquartile range; BDCAF: Behçet's Disease Current Activity Form.

lupus erythematosus, dermatomyositis, and scleroderma. Bone marrow examination of a patient with BD and thrombocytopenia revealed myelodysplastic syndrome (MDS), and molecular genetic examination revealed trisomy 8. The patient had a high risk of developing leukemia due to concomitant MDS and trisomy 8 and underwent allogeneic hematopoietic stem cell transplantation (HSCT). In the six-month follow-up post-HSCT, the patient's clinical findings improved, and oral and genital ulcers did not recur.

Treatment regimens of the patients are as follows: colchicine in 88.2%, corticosteroids in 38.2%, azathioprine in 32.4%, nonsteroidal anti-inflammatory drugs in 14.7%, adalimumab in 14.7%, antithrombotic agents in 14.7%, methotrexate in 2.9%, and cyclosporine in 2.9%.

The patients were reevaluated for BD according to the ISG, ICBD, and PEDBD criteria, and 52.9%, 82.4%, and 50.0% met the requirements, respectively.

DISCUSSION

Pediatric BD is a rare vasculitis that can progress with complications. Recognition of the disease, early detection of complications, and effective treatment are crucial for disease prognosis. Children with risk factors, such as recurrent oral aphthae and family history, should be carefully followed since diagnostic findings emerge in the process. Minor aphthae, major aphthae, or herpetiform ulcerations observed by the physician or patient and recurring at least three times in a 12-month period should be considered possible Behçet's disease. Painful nonscarring oral aphthae are characterized by a sharp circular shape with erythematous borders and usually appear on the tongue or in the oropharyngeal and buccal mucosa.[9]

In studies conducted with PEDBD patients, female predominance was found in Asian populations and male predominance in Middle Eastern and Mediterranean populations.[2,8,10-16] The data in our study were collected from the western part of Türkiye, and there was a male predominance (female to male ratio [F/M]: 0.7). However, other Turkish studies report different rates (F/M: 0.92-1.37).[11-15] In studies from other countries, the F/M ranges between 0.77 and 1.01.[2,8,10,13,16] According to the results, there is no significant trend in terms of sex in PEDBD. Table 2 presents the clinical and demographic data of our study and other cohorts.

In our study, the mean age of symptom onset was 10.8±2.9 years. In the literature, the age of symptom onset was reported between 9.1 and 11 years in the Turkish series, while it was reported between 4.8 and 11.2 years in other countries.[2,8,10-16] The mean age at diagnosis in our study was 12.5±3.0 years. In other series, the age at diagnosis was reported to be between 12 and 14 years in Türkiye and between 3.7 and 13.9 years in other countries.[2,8,10-16] While the symptoms usually start at the end of the primary school period, the age of diagnosis shifts to adolescence. Delay in diagnosis may be due to delayed onset of diagnostic symptoms or difficulty in diagnosing atypical patients.

There is no gene that has been linked to BD, but family history is a supportive finding in the diagnosis. In our study, family history was found in 26.4% of patients. In other Turkish studies, family history was reported in 19 to 43.3% of cases.[11-15] In other countries, this rate varies between 9 and 24.4%.[2,8,9,12] A genetic risk factor that increases the development of BD 5.78 times is HLA-B51 positivity.[9] In our study, the HLA-B51 test was positive in 11 (78.3%) of the 14 patients that were tested. While this rate was reported between 46.2 and 68.3% in studies from Türkiye, it was between 48.7 and 56.8% in studies conducted in other countries.[2,8,10-15] The healthy population can also exhibit HLA-B51 positivity without any clinical findings. Although HLA-B51 is not among the diagnostic criteria, it can help clinicians to identify patients that need to be followed up with a possible diagnosis of BD, even if they do not meet the diagnostic criteria, regardless of the BD phenotype.

In this study, the most common clinical findings were oral aphthous ulcers (97.1%), followed by genital ulcers (47.0%) and eye (44.1%) and skin (32.3%) findings. Recurrent oral ulceration was the most common symptom in all studies, but the distribution of other findings was variable.[2,8,10-16] However, PEDBD may rarely present without

Table 2. Comparison with other studies on PEDBD patient

	Our study	Tekin et al.[14]	Kone-Paut et al.[8]	Shahram et al.[2]	Karıncaoğlu et al.[11]	Çirkinoğlu et al.[15]	Nanthapisal et al.[16]	Galizzi et al.[10]	Gezgin et al.[12]	Butbut et al. Israel data[13]	Butbut et al. Turkish data[13]
Number	34	72	156	204	83	34	46	110	57	40	165
Sex Male Female	0.7	1.25	1.01	0.98	1.25	0.88	1.09	0.77	1.37	0.7	0.92
Symptom onset age	10.8±2.9	11 (2-16)	7.8±4.3	10.5±3.4	9.1±3.2	11.2±3.3	4.8 (0.04-15.7)	8.3±4.1	10 (5-16)	11.2 (1-15.9)	11 (4-16)
Age at diagnosis	12.5±3.0	14 (2-16)	13.9±3.8	-	12.3±3.5	16.5±4.1	3.7 (0.25-13.4)	11.3±3.9	12 (5-16)	12.7 (4-15.9)	13 (4-15.9
Oral ulcer (%)	97.1	100	100	91.7	100	97.0	97.8	94.5	100	97.5	100
Genital ulcer (%)	47.0	68.1	55.1	42.2	81.9	62.0	73.9	33.6	56	67.5	64.8
Ocular finding (%)	44.1	20.8	45.5	66.2	34.9	35.0	8.7	43.6	47	17.5	13.3
Skin finding (%)	32.3	34.7	66.6	51.5	51.8	82.0	23.9	39.6	46	22.5	55.2
Neurologic (%)	17.6	15.3	59.6	4.4	7.2	17.6	28.3	30.9	9	10.0	15.8
Vascular (%)	17.6	18.1	14.7	6.4	7.2	32.0	6.5	1.8	17	7.5	11.5
Joint (%)	26.4	36.1	41.0	30.9	39.8	38.0	21.7	42.7	63	35.0	44.8
Pathergy (%)	32.3	27.8	44.7	57.0	37.3	50.0	60	14.5	19	23.1	27.3
HLA-B51 (%)	78.5	48.6	-	48.7	-	50.0	-	56.8	58	46.2	68.3
Family history (%)	26.4	41.7	24.4	9	19	15.0	17	12	35	15.0	29.1

PEDBD: Pediatric Behçet's disease; HLA: Human leukocyte antigen.

oral ulcerations.[2,4,10,13] Patients without oral aphthous ulcers can be diagnosed according to the PEDBD criteria and ICBD. However, since an oral aphthous ulcer is a mandatory finding according to the ISG criteria, patients cannot be diagnosed if this finding is not present. While oral and genital ulcerations have been equally reported in several studies, some studies have observed that genital ulceration is less common in children than in adults.[9,16] Most studies, however, still report genital ulceration as having the second or third frequency in PEDBD.[2,8,10-16]

Skin findings were reported in 31.3 to 55.2% of the Turkish population and between 22.5 and 66.6% in other countries. In our series, the skin findings were observed in 32.3% of patients. Mucocutaneous manifestations occur in the early stages of BD, and it is difficult to diagnose without these symptoms. Skin lesions are a more common finding in adult BD patients than in pediatric patients.[9]

Eye involvement was reported at a rate of 13.3 to 47.0% in series from Türkiye and 8.7 to 66.2% in publications from other countries.[2,8,10-16] In this study, eye involvement was found in 44.1% of patients. Ocular involvement in PEDBD was reported as the second most common symptom in Iranian and Italian studies.[2,10] It was evaluated as the third most common symptom in this study and another Turkish study.[12] The most significant cause of morbidity in BD is eye involvement. Early diagnosis and treatment are essential to prevent eye damage.

Vascular and neurological pathologies are rare but severe manifestations encountered in PEDBD. According to the literature, the rate of vascular involvement accompanying PEDBD ranges from 1.8 to 18.1%.[2,8,10-16] In our study, the rate of vascular involvement was 17.6%, which was consistent with the literature. Vascular involvement was observed as dural sinus, jugular, pulmonary, cardiac, and femoral vein thrombosis. However, vascular involvement is observed at a higher rate in adult-onset BD.[9,17]

In our series, the rate of patients with neurological involvement was 17.6%. In other Turkish studies, this rate was between 7.2 and 15.8%.[11-15] According to the data reported from other countries, neurological involvement ranges from 4.4 to 59.6%.[2,8,10,12,13,16] In our study, two of the six patients with neurological involvement had parenchymal involvement, while the others had thrombosis only in the cerebral veins. Demyelinating central nervous system diseases, such as multiple sclerosis, were excluded in patients with parenchymal involvement.

In the present study, joint involvement was detected in 26.4% of patients. Joint involvement has been reported between 13.4 and 63.0% in other studies.[2,8,10-16] Arthritis observed in PEDBD is nonerosive, asymmetrical, and nondeforming, mostly affecting medium and large joints.[14]

Immunosuppressive therapy may be required to suppress inflammation and prevent end-organ damage in BD. However, treatment guidelines for PEDBD have not been developed. The treatment plan is mostly made according to the experience in adult BD patients. In this study, colchicine (88.2%) was given to patients with mucocutaneous signs. The most commonly used immunosuppressive agents are corticosteroids (38.2%) and azathioprine (32.4%). These agents are often preferred as the first line of treatment in patients with ocular, neurological, and vascular involvement. Cyclosporine and cyclophosphamide are less commonly used agents. Anti-tumor necrosis factor (TNF) agents (14.7%) have recently become more frequently used in severe cases that do not respond to other agents. Three patients with uveitis did not respond to azathioprine and corticosteroid treatment, and an anti-TNF agent (subcutaneous 40 mg adalimumab every two weeks) was started for them. One patient with pulmonary and intracardiac thrombosis did not improve with high-dose cyclophosphamide and corticosteroids, and this patient went into remission after adalimumab. A patient with optic neuritis and sinus vein thrombosis who did not respond to previous treatment improved with adalimumab. The immunosuppressive/anti-inflammatory treatments received by the patients and their indications are given in Table 3.

Similarly, in the literature, colchicine was the most commonly used drug, while corticosteroids and azathioprine cyclophosphamide were other frequently preferred medications.[2,8,10-16]

Table 3. Immunosuppressive/anti-inflammatory treatments received by PEDBD patients and their indications

			Mucocutaneous		Ocular		Joint		Neurologic		Vascular	
Medication	n	%	n	%	n	%	n	%	n	%	n	%
Colchicine	30	88.2	30	88.2								
Corticosteroid	13	38.2			7	20.5			5	14.7	5	14.7
Azatioprin	11	32.4	1	2.9	5	14.7			6	17.6	5	14.7
NSAIDs	5	14.7					5	14.7				
Adalimumab	5	14.7			3	8.8			1	2.9	1	2.9
Antithrombotic	5	14.7									5	14.7
Methotrexate	4	11.8			2	5.8	2	5.8				
Cyclosporine	1	2.9							1	2.9		
Cyclophosphamide	1	2.9									1	2.9

PEDBD: Pediatric Behçet's disease; NSAIDs: Non-steroidal anti-inflammatory drugs.

Anti-TNF agents have been used to a lesser extent in patients with ocular and gastrointestinal involvement.[14]

Vascular involvement and thrombosis in BD result from inflammation and endothelial damage. Therefore, it may be necessary to administer antithrombotic drugs together with immunosuppressive and anti-inflammatory therapy. In addition, in the BD Treatment Recommendations Guideline published by Hatemi et al.,[18] there is no definite consensus about the use of anticoagulants in vascular involvement. According to their report, treatment with anticoagulants and immunosuppressives compared with immunosuppressives alone did not provide a significant benefit in preventing relapses. An exception to the use of anticoagulants in BD could be represented by cerebral vein thrombosis.[19] In a recent study, 108 subjects with central venous sinus thrombosis were initially treated with pulsed steroids and low-molecular-weight heparin; afterward, this therapy was replaced with warfarin.[20] Warfarin alone was also an effective maintenance treatment. Low molecular weight heparin, warfarin, and acetylsalicylic acid were used as antithrombotic agents in our cases with vascular and nonparenchymal neurologic involvement with thrombosis (14.7%).

Myelodysplastic syndrome was detected in a 12-year-old female with BD and thrombocytopenia, and molecular genetic examination revealed trisomy 8. This patient had received colchicine for oral and genital lesions before, but there was no adequate response. The patient had a high risk of developing leukemia due to concomitance of MDS and trisomy 8 and underwent allogeneic

Table 4. The rate of meeting the criteria of patients according to the BD diagnosis criteria systems

Diagnostic criteria systems	Our study (%)	Kurt et al.[4] (%)	Butbul et al.[13] Turkish data (%)	Butbut et al.[13] Israeli data (%)
ISG	52.9	43.3	47.9	17.5
ICBD	82.4	88.1	72.7	75
PEDBD	50.0	37.3	54.5	20.0
PEDBD/pathergy*	58.8	46.7	-	-

BD: Behçet's disease; ISG: International Study Group; ICBD: International Criteria for Behçet's Disease PEDBD: Pediatric Criteria for Behçet's Disease * Rates when pathergy positivity are included in the PEDBD criteria.

HSCT. In the six-month follow-up after HSCT, her clinical findings improved, and oral and genital ulcers did not recur. The cooccurrence of MDS with trisomy 8 and Behçet-like disease was recently demonstrated. Immune dysregulation and altered T-cell hemostasis play an important role in the pathogenesis of Behçet-like diseases and MDS with trisomy 8.[21,22] A 30-year-old female with refractory gastrointestinal BD and trisomy 8 MDS underwent a successful myeloablative allogeneic HSCT resulting in complete resolution of both BD and MDS.[23] Our patient was the youngest case with trisomy 8-associated MDS and Behçet-like disease in the literature, and both disease findings improved after HSCT.

The rates of patients meeting the criteria for ISG, ICBD, and PEDBD were 52.9%, 82.4%, and 50.0%, respectively. Kurt et al.[4] evaluated the sensitivity and specificity of these three criteria. While they found the specificity rates of the three diagnostic methods as 100%, the sensitivity rates were 43.3%, 88.1%, and 37.3% for ISG, ICBD, and PEDBD, respectively. When they included pathergy positivity in the PEDBD criteria, they found the sensitivity to be 46.7%. In present study, when pathergy added to PEDBD rates increased to 58.8%. Butbul et al.[13] reported these rates as 17.5%, 75.0%, and 20.0% in the Israeli series and as 47.9%, 72.7%, and 54.5% in the Turkish cohort for ISG, ICBD, and PEDBD, respectively. The comparison of the rates of meeting the criteria of the patients according to the BD diagnostic criteria systems with the other series is presented in Table 4.

The main limitation of our study is its retrospective design. Another limitation was the relatively small number of patients. Although BD is not common in pediatric patients, larger prospective studies are needed.

In conclusion, we presented the clinical and demographic characteristics of PEDBD patients from Türkiye, where BD has a high prevalence. In our study, HLA-B51 positivity was 78.5%. Ocular, neurologic, and vascular involvements are the major causes of morbidity. Since there is no standard treatment, adult experiences are used for treatment modalities. Biological agents should be considered as a treatment option in major morbidities, such as uveitis, vascular involvement, and neurological involvement, and patients unresponsive to conventional treatment. There is no perfect diagnostic evaluation system among the diagnostic criteria. The fulfilling rates of the PEDBD criteria are found to be lower than the other two diagnostic criteria. Patients who do not have oral aphthous ulcers or who do not have typical clinical findings may be skipped. The diagnostic method in which clinical findings are scored will facilitate the identification of these patients. Pathergy and HLA-B51 can be used as supportive findings in patients who do not meet the diagnostic criteria. An expert opinion is still the gold standard in the diagnosis of BD.

Ethics Committee Approval: The study protocol was approved by the local Non-Interventional Research Ethics Committee (approval date/no 2022/06-19). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study conception and design: C.A., R.İ., R.T., B.M., Ş.E.Ü.; Data collection: C.A., R.İ., R.T.; Analysis and interpretation of results: C.A., B.M., Ş.E.Ü.; Draft manuscript preparation: C.A., R.İ., R.T., B.M., Ş.E.Ü.; All authors reviewed the results and approved the final version of the manuscript.

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