Paediatric Behçet's disease in Iran: report of 204 cases

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ABSTRACT

Objectives. *This study proposed to report the characteristics of paediatric Behçet's disease (PED-BD) in a cohort of patients from Iran's registry and compare them with different reports throughout the world.*

Methods. *From a cohort of 7504 Iranian patients with Behçet's disease those diagnosed before the age of 16 years were included in this study. Data were collected on a standard protocol comprising 105 items, including demographic features, type of presentation, and different clinical and laboratory findings.*

Results. *PED-BD was seen in 2.7% of patients. The male/female ratio was 1.02/1, and the mean age at onset was 10.5±3.4. Positive familial history was present in 9.9%. As a first manifestation, oral aphthosis was the most frequent (75%) followed by ocular lesions in 19.1%. The prevalence rates of various manifestations were as follows: oral aphthosis: 91.7%; genital ulcer: 42.2%; skin: 51.5% (pseudofolliculitis: 43.1%, erythema nodosum: 10.3%); ocular lesions: 66.2% (anterior uveitis 52%, posterior uveitis 58.3%, retinal vasculitis 39.7%); articular manifestations: 30.9%; neurological involvement: 4.9%; vascular involvement: 6.4% (venous 4.9%, arterial 2.5%); gastrointestinal manifestations: 5.9%; epididymo-orchitis: 8.7% (boys); high ESR (≥20): 50.8%; abnormal urine: 14.1%; positive pathergy test: 57%; HLA-B5/51: 48.7%. ICBD criteria have the highest sensitivity for the classification of PED-BD patients in Iran (91.7%).*

Conclusion. *The clinical spectrum of PED-BD in Iran in this study was similar to that of other reports; however, genital ulcers, skin lesions (notably erythema nodosum), and gastrointestinal involvement were noticed to occur less frequently, while ocular lesions were more frequent and more severe compared to other reports.*

Introduction

Behçet's disease (BD) is a chronic multi-system vasculitis (1). It was recently reclassified as a variable type, due to affecting vessels of all sizes (2). Its clinical picture is dominated by recurrent oral and genital ulcers, skin manifestations, and ocular lesions. Other manifestations are related to the involvement of joints, large vessels, the nervous system, and the gastrointestinal (GI) tract.

Disease onset is usually in the third or fourth decade of life (1); however, a growing number of reports on childhood BD has appeared over the last few years (3, 4). Concerning incidence and prevalence, there is no published data in children, but they comprise 3 to 24% of total patients with BD in different reports (5-7).

The definition of childhood BD differs among these reports. It is based on either the full disease expression and diagnosis in childhood (7-15) or the onset of initial disease symptoms in childhood (16-18). Due to varying delays in the appearance of BD symptoms, even if initially manifested before the age of 16 years, its diagnosis may be delayed to adulthood. Hence, a definition of childhood BD based on the onset of the first symptom prior to the age of 16 years may actually include a significant number of adult patients (5, 18). Paediatric BD (PED-BD), according to today's accepted terminology, includes patients with both disease onset and diagnosis before 16 years of age (5, 19-21) and should be distinguished from juvenile onset BD in which only the disease onset is before 16 years of age (19, 20).

A significant controversy exists regarding the characteristics of the disease reported in children. The clinical presentation of BD is heterogeneous and may vary based on gender, ethnicity,

country of residence, and age at onset (3, 5, 8, 22).

Herein, the characteristics of PED-BD in a considerable number of patients from Iran's BD registry are reported and compared with different reports throughout the world.

Patients and methods

Study setting

This study was done retrospectively on a cohort of patients diagnosed as BD and registered at the Rheumatology Research Center in Tehran University of Medical Sciences during the past 40 years (between 1975 and the end of 2016).

Case definition and selection

All patients in whom BD was fully manifested and diagnosed before the age of 16 years were assigned as PED-BD. Those diagnosed in adulthood, even with disease onset and/or completion before the age of 16 years, were excluded from the study as they did not meet the latest definition of PED-BD (5, 19-21). All patients were followed in a multidisciplinary clinic by the same team of physicians comprising rheumatologists, ophthalmologists, and dermatologists. Patients were seen by affiliated neurologists and gastroenterologists when necessary. The diagnosis of BD was made by the clinical judgment of the experienced specialist (mainly rheumatologist, or dermatologist and ophthalmologist) based on the clinical picture of the disease and not only by any specific classification/diagnosis criteria. The diagnosis was double-checked by either the first author (FS) or FD before the patient was entered into the BD registry. However, nearly all cases were classified by at least one of the major sets of diagnostic criteria (22-27).

Data collection

A computerised data sheet of 105 items, including demographic, clinical, and laboratory items, was systematically used to collect different characteristics of the disease in each patient, and the data was fed into an electronic database. Patients were followed up once every 1 to 6 months based on the severity of the disease, and the database was updated after each visit. The data used for analysis comprised a summation of all manifestations which had ever occurred for a given patient. Demographic information included gender, age at disease onset, age at diagnosis, date of the first and last visit, and family history for BD and oral aphthosis (OA). Clinical characteristics included type of presentation and different clinical manifestations of the disease, such as OA; genital ulcer (GU); skin lesions including pseudofolliculitis/acneiform lesions, erythema nodosum (EN), or other lesions; ocular involvement including uveitis and retinal vasculitis (RV); joint manifestations (arthralgia, arthritis, axial involvement); vascular involvement including superficial and deep venous thrombosis (DVT), arterial aneurysm and thrombosis; headache; neurological involvement including central (parenchymal, cerebral vascular thrombosis, recurrent meningoencephalitis) and peripheral lesions; GI involvement; epididymo-orchitis; pulmonary and cardiac involvement. Laboratory tests included complete blood cells and platelet counts, erythrocyte sedimentation rate (ESR), urinalysis, human leukocyte antigen (HLA) typing (for B5, B51, and B27), and pathergy skin test.

Definitions

Age of disease onset was defined as the age at onset of the first BD symptom. Delay in diagnosis or referral was defined as the time between the first manifestation and the first visit. Disease duration was calculated as the time interval between disease onset and the last visit of the patient to the clinic.

Statistical analysis

The number, percentage, and confidence intervals at 95% (CI) were calculated for categorical variables. The mean and the standard deviation (SD) were calculated for continuous items. Either the independent *t*-test or the Mann-Whitney U-test was used to compare the quantitative variables, and the chi-square test was used to compare qualitative or categorical variables. A *p*-value of less than 0.05 was considered statistically significant. Data was analysed using SPSS software version 18 (SPSS Inc., Chicago, IL, USA).

Ethical approval

The study protocol was approved by the Research Committee of Rheumatology Research Centre and the Ethics Committee of Tehran University of Medical Sciences. The study was conducted in accordance with the Code of Ethics of the World Medical Association (Helsinki Declaration of 1975/83) for experiments involving humans and Good Clinical Practice guidelines.

Results

In a cohort of 7504 BD patients, PED-BD was seen in 204 (2.7%, CI:0.4).

Demographic data

One hundred and three patients in this study were male (50.5%, CI: 7.1). The male-to-female ratio was 1.02/1. The age at onset of disease ranged between 1 to 16 years with a mean of 10.5 years (SD: 3.4, CI: 0.5). The mean disease duration was 8.8 years (SD: 7.7), and the mean follow-up time was 5.6 years (SD: 7.3). The mean referral delay was 3.2 years (SD: 2.7) after the first manifestation.

A positive familial history for BD was present in 9.9% (CI: 5.3) of patients, mostly (58.3%, CI: 27.9) in their first-degree relatives (parents or siblings). In 46.3% (CI: 8.9) of patients a positive familial history of OA was also present, 87.5% (CI: 8.6) of which was in first-degree relatives.

Disease presentation

As the first manifestation, OA was the most frequent, presenting in 75% (CI: 5.9) of cases. GU was present in 7.4% (CI: 3.6) of patients, mostly accompanied by OA. Only in 6 cases (2.9%, CI: 2.3) was it seen alone with no other symptom. Ocular lesions were the first presentation of the disease in 39 patients (19.1%, CI: 5.4), uveitis in 37, RV in 1, and both (panophthalmitis) in 1. Joint involvement and the other signs (mostly skin lesions) each in 10 patients (4.9%, CI: 3) were the other initial manifestations of the disease.

Major manifestations

Mucous membrane involvement, either oral or genital, was present in 92.2% (CI: 3.7) of patients. OA was the most

frequent symptom, seen in 91.7% (CI: 3.8) of patients. GU was seen in 42.2% (CI: 6.8) of patients. Only in 2 cases it remained the unique mucosal lesion of the disease, while in the remaining it was associated with OA.

Skin lesions were present in 51.5% (CI: 6.9) of patients, pseudofolliculitis in 43.1% (CI: 6.8), and EN in 10.3% (CI: 4.2) of cases. These two lesions are classified as a major sign in most existing diagnostic criteria (22-27). Other skin lesions were not so frequent (8.3%, CI: 3.8). They included a wide range of non-specific lesions such as non-inflammatory subcutaneous nodules, Sweet syndrome, Behcet's cellulitis, pyoderma gangrenosum, and vasculitis. Among them, only skin aphthosis was highly suggestive of the disease.

Ocular lesions were seen in 66.2% (CI: 6.5) of the studied patients, anterior uveitis (AU) in 52% (CI: 6.9), posterior uveitis (PU) in 58.3% (CI: 6.8), and RV in 39.7% (CI: 6.7). The classic ocular lesion in BD, panophthalmitis involving all 3 parts, was seen in 29.4% (CI: 6.2) of patients. Panuveitis was present in 17.2% (CI: 5.2). Isolated involvements of each segment were infrequent. Cataract was seen in 27.5% (CI: 6.1) and conjunctivitis in 5.9% (CI: 3.2) of patients.

Minor manifestations

Joint involvement was seen in 30.9% (CI: 6.3) of patients. Inflammatory arthralgia without clinically evident swelling was reported by 17.2% (CI: 5.2) of patients. The most frequent form of arthritis was asymmetric oligoarthritis (usually involving large lower limb joints), seen in 8.8% (CI: 3.9). Monoarthritis, mainly involving the knee joints, was seen in 7.4% (CI: 3.6) of patients. Ankylosing spondylitis developed only in 2 patients (1%, CI: 1.4) during their follow-up.

Neurological manifestations were seen only in 4.9% (CI: 3) of cases, and most of them were due to central nervous system (CNS) involvement (4.4%, CI: 2.8). Only one of the studied patients had cerebral venous thrombosis (in both transverse and sagittal sinuses); 3 others had recurrent meningoencephalitis, and the remaining 5 had parenchymal involvement (two with convulsions). Peripheral nervous system lesions were present only in one patient. Headache was reported by 4.9% (CI: 3) and included cases that could not be attributed to the CNS or ocular involvement.

Large vessel involvement was seen in 13 patients (6.4%, CI: 3.4). Venous involvement was more than arterial (10 vs. 5), including lower limb DVT in 7 and superficial phlebitis in 4 patients (one with DVT, one with visceral vein thrombosis, and 2 isolated). Arterial aneurysm occurred in 4 patients and arterial thrombosis in one patient. Two patients showed both arterial aneurysm and DVT.

GI manifestations were uncommon with an overall prevalence of 5.9% (CI: 3.2). Diarrhea was seen in 3.4% (CI: 2.5), abdominal pain mimicking an acute surgical abdomen in 2% (CI: 1.9), rectal bleeding in 1.5% (CI: 1.7), non-specific dyspepsia in 1% (CI: 1.4), and peptic ulcer disease in 0.5% (CI: 1) of patients.

Epididymo-orchitis was seen in 8.7% (CI: 5.4) of the boys. No cases presented with hepatosplenomegaly, pulmonary, or renal involvement in this study. Pericarditis was seen in only one case. In 4 patients (2%, CI: 1.9), an overlap or association with another autoimmune or collagen vascular disease was present.

Laboratory findings

ESR was normal during the disease course in most patients (49.2%, CI: 7.4). It was between 20 and 49 in 34.2% (CI: 6.8) and between 50 and 100 in 16.1% (CI: 5.3) of cases. Only in one patient ESR>100 was seen.

Urinary abnormalities were detected in 14.1% (CI: 5) of patients. Hematuria was seen in 6% (CI: 3.4), proteinuria in 1.6% (CI: 1.8), and leukocyturia in 10.3% (CI: 4.4). They were transient in all cases, and no urinary casts were detected. Therefore, no kidney biopsy was needed.

Pathergy test was positive in 57% (CI: 6.9), HLA B5/51 in 48.7% (CI: 7), and HLA B27 in 13.4% (CI: 4.9) of patients. Typing for HLA B5 was done for 195 patients, but only in 57 of them was HLA B51 included as well, and it was positive in 22.8% (CI: 10.9).

Gender differences

There was no statistically significant gender difference in the rate of positive familial history for BD (11.5% *vs.* 8.3%, p=0.78) or demographic features of the disease (Table I). Comparison of clinical data showed a higher prevalence of GU, both at disease onset and during the disease course in girls (11.9% *vs.* 2.9% with p<0.007, and 53.5% *vs.* 31.1% with p<0.002, respectively). Abnormal urine was detected more in girls (9.7% *vs.* 18.7% with p<0.05), mainly due to a higher prevalence of leukocyturia in them (4.3% *vs.* 16.5% with p<0.004). On the other hand, there were higher prevalence rates of EN (16.5% *vs.* 4% with p<0.007) and ocular lesions (78.6% *vs.* 53.5% with p<0.0002) in boys. Both PU and RV were significantly higher in boys (69.9% *vs.* 46.5% with p<0.0008, and 52.4% *vs.* 28.7% with p<0.0002 respectively). Monoarthritis was the only type showing statistically significant higher prevalence in males (12.6% *vs.* 2% with p<0.009), while the higher prevalence of joint involvement as a whole was not significant (p=0.12). There were no significant differences in other manifestations (Table II).

Table I. Sex difference in demographic features of paediatric Behçet's disease.

	Boys		Girls		
Item	Mean	SD*	Mean	SD*	*p*-value
Age at onset	10.4	3.4	10.6	3.4	0.68
Disease duration	9.5	7.8	8	7.5	0.17
Follow-up time	6.3	7.6	4.9	6.9	0.17
Referral delay	3.2	2.6	3.1	2.7	0.79

*SD: standard deviation.

Table II. Sex difference in clinical characteristics of paediatric Behçet's disease.

Item	Boys		Girls		*p*-value
	No	%	No	%	
Total	103	100	101	100	
Presenting manifestations					
Oral ulcer	74	71.8	79	78.2	0.29
Genital ulcer	3	2.9	12	11.9	<0.007
Ocular lesions	22	21.4	17	16.8	0.41
Joint manifestations	8	7.8	2	2	0.11
Others	5	4.9	5	5	0.72
Clinical manifestations					
Oral ulcer	96	93.2	91	90.1	0.58
Genital ulcer	32	31.1	54	53.5	<0.002
Skin lesions	56	54.4	49	48.5	0.40
Pseudofolliculitis	44	42.7	44	43.6	0.90
Erythema nodosum	17	16.5	4	4	<0.007
Ocular lesions	81	78.6	54	53.5	<0.0002
Anterior uveitis	60	58.3	46	45.5	0.07
Posterior uveitis	72	69.9	47	46.5	<0.0008
Retinal vasculitis	54	52.4	27	26.7	<0.0002
Joint manifestations	37	35.9	26	25.7	0.12
Vascular involvement	10	9.7	3	3	0.09
Neurological involvement	8	7.8	2	2	0.11
Gastrointestinal involvement	5	4.9	7	6.9	0.35
Laboratory findings					
Positive pathergy test	56/102	54.9	58/98	59.2	0.54
High ESR*	43/94	45.7	52/93	55.9	0.16
Positive HLA-B5/51	52/99	52.5	43/96	44.8	0.28
Positive HLA-B27	12/93	12.9	13/93	14	0.83
Abnormal urine	9/93	9.7	17/91	18.7	<0.05

*ESR: erythrocyte sedimentation rate.

Diagnosis/classification criteria

The most sensitive diagnostic criteria in the studied patients were the revised international criteria for Behçet's disease (ICBD) (27) which classified 187 patients with a sensitivity of 97.1% (CI: 3.7). The sensitivity of the International Study Group (ISG) criteria (23) was 68.6% (CI: 6.3) by classifying 140 patients. Consensus classification criteria for PED-BD (14) were able to classify only 98 of the patients in the current study with a sensitivity of 48% (CI: 6.9).

Discussion

Since the publication of the first article on BD presenting in a child by Mundy and Miller in 1978 (28), several reports on clinical characteristics of paediatric onset of BD have appeared throughout the world (5, 7-11, 16, 17, 19-21, 29-31). However, they are mostly limited to case reports or small case series. This study reports the clinical features of PED-BD patients from an endemic area for BD. This is the largest cohort reported to date, with an acceptably long follow-up time and disease duration (mean of 5.6 and 8.8 years, respectively).

As the comparison of national studies requires the use of adjusted diagnostic and age criteria, only those studies that had included patients with both disease onset and diagnosis before the age of 16 years were accepted for comparison in the current study (15).

Despite the high prevalence of BD in Iran (32), the frequency of the paediatric disease was low (2.7%) and comparable to that in other countries (16, 17, 33, 34). While predominance in both boys and girls has been reported in different series (Table III), no gender predominance was seen in the studied cohort. This was the same as reported in multicentre studies (14, 29). The mean age of onset (first BD symptom) was 10.5 years in the studied patients, which is within the reported range (6.9 to 13 years) in previous reports (Table III). A characteristically high positive familial history was seen in the paediatric BD patients of this study (nearly 10%), in concordance with the higher familial aggregation that had been found in the paediatric group (34).

In general, the clinical spectrum of disease in the studied cohort was similar to that of other reports; however, the prevalence rates of certain manifestations were varied. In this study, less GU, less skin involvement (notably EN), and less GI involvement were noticed, while ocular involvement was more frequent and more severe compared to other reports (Table III).

OA was the presenting symptom in 75% of cases and was the most common sign seen in 92% of PED-BD patients. GU was observed in 42%, less than all other reports (Table III) except a report from Israel (16). Fewer skin lesions with a significantly lower prevalence of EN (10%) were seen in this study compared to previous reports on PED-BD. This was not true for pseudofolliculitis which was seen within a frequency range comparable to that reported by others (Table III). The occurrence and severity of ocular lesions was higher in Iranian PED-BD patients. Ocular involvement was seen in two thirds of the patients in this cohort, with a higher rate of posterior segment involvement (PU in 64% and RV in 40%). It was reported in 19% of cases as the first manifestation. The typical pictures of oculo-Behçet such as panuveitis and panophthalmitis (combined anterior and posterior segment intraocular inflammation with RV) were seen in 17% and 29% of patients, respectively.

The frequency of almost all minor manifestations of the disease in the current paediatric cohort was interestingly in the lower range of what had been reported previously (Table III). This is in accordance with the BD features in Iranian adult patients (6, 35, 36).

With regards to laboratory findings, ESR was normal in near half of the studied patients (49%), pathergy tests were positive in 57%, and HLA-B5/B51 was positive in 49% of cases, although none of them are considered mandatory for the diagnosis of BD.

These different findings in the current study might be attributed mainly to ethnicity and geographic variation in

Table III. Comparison of different reports on paediatric Behçet's disease patients in the world.

	Iran 2017	PEDBD 2015[14]	International 1998[8]	Turkey 2011[12]	Israel 1999[9]	Japan 1997[7]	Korea 1994[16]	Taiwan 2013[13]	Tunis 2016[15]	France 2002[11]	**UK 2016**[31]	Germany 1999[17]	Greece 1999[10]
Number	204	156	65	110	19	31	40	20	38	55	**46**	28	18
M/F ratio	1.02	1.00	1.03	0.59	1.37	0.82	0.67	1.00	1.71	0.89	**0.92**	1.08	2.00
Age at onset*	10.5	7.8	8.4	11.6	6.9	8.9	10.9	13	12.8	7.5	**4.9**		10.3
Familial	9.9	24.4	15.4	12.3		3.2	22.5	5	7.9	14.5	**17**	25	
Oral ulcer	91.7	100	96.9	100	100	100	100	100	100	100	**97.8**	100	100
Genital ulcer	42.2	55.1	69.2	82.7	31.6	58.1	82.5	70	71	79	**73.9**	82	67
Skin	51.5	66.7	92.3	76	89.5	54.8	72.5	65	76.3		**23.9**	89	
Pseudofolliculitis	43.1	43	53.8	39	42.1	38.7	50			38	**15.2**	70	50
Erythema Nodosum	10.3	22.7	39.6	37.3	36.8	32.3	42.5			26	**4.3**	46	44
Positive pathergy	57		80	45.5	41.2	59.1	17.5		70.4		**60**	38	22
Ocular	66.2	45.5	61.5	30.9	47.4	25.8	27.5	20	50		**4.3**	48	67
Anterior uveitis	52	30.1	35.4		42.1						**4.3**		
Posterior uveitis	58.3	28	36.9		10.5						**0**		
Uveitis	63.7		44.6		47.4	16.1		15	47.4	36	**4.3**		
Retinal vasculitis	39.7	16.7	23.1		5.3	6.5			26.3	24	**0**		
Articular	30.9	41	46.2	22.7	78.9	54.8	27.5	30		17	**47.8**	57	61
Vascular	6.4	14.7	15.4	3.6	10.5	6.5	5	0	21.1	21	**6.5**	25	11
Neurological	4.4	59.6[¥]	15.4	3.6	26.3	16.1	2.5	5	21.1		**8.7**	21.4	17
Headache	5.4		21.5		36.8					35	**23.9**		
Gastrointestinal	5.9	29.5	13.8		36.8	54.8	5	50		40	**56.5**	17.9	11

*Mean/median (year); [¥] including headache.

disease expression. However, different gender ratio and age of disease onset might influence this heterogeneity in the clinical spectrum (3, 8).

Regarding the gender difference (Table II) and in accordance with previous reports, GU (both at disease onset and during disease course) was significantly associated with the female gender in the studied PED-BD cohort (5, 12, 14, 30, 34). Male patients showed a higher prevalence of ocular lesions ($p<0.0002$), with a higher frequency of severe forms such as PU ($p<0.0008$), RV ($p<0.0002$), and panophthalmitis ($p<0.02$). Series specifically addressing the eye involvement of childhood BD had revealed a nearly twofold prevalence of males (3, 14, 18, 34, 37). Cutaneous symptoms as a whole were reported more in males (14), while EN symptoms were more frequently seen in females (3, 5, 8, 38). No gender difference in the prevalence of cutaneous involvement was seen in the studied patients, and interestingly, EN was seen more in males. This was also true for joint manifestations, showing no gender difference but a higher monoarthritis rate in males ($p<0.009$). Although both higher vascular and neurological involvement rates had been reported in males (3, 5, 8, 14, 38), no gender predilection for them was seen in Iranian patients with PED-BD.

The new classification criteria for children with BD, proposed recently by an international expert consensus (14), were checked in Iranian PED-BD patients. This was the first time these criteria had been validated in a national PED-BD cohort. The relatively low sensitivity of this classification criteria (48%) in the current paediatric cohort may mainly be attributed to the ignorance of the pathergy test as a diagnostic criterion. Adding pathergy test to the criteria, either as another skin lesion or as an individual criterion, could increase its sensitivity in the studied patients (66.7% and 73%, respectively). In a previous study, the current authors demonstrated that, without positive pathergy test as a criterion for BD diagnosis, the sensitivity of other classification criteria is also decreased (39). Despite the fact that none of the existing diagnosis criteria for BD was made specifically for children, the ICBD criteria showed a high sensitivity of 97% in the current patients (27). However, in concordance with the result on an international PED-BD cohort (14), the performance of ISG criteria (23) was not so good in Iranian patients.

The main strength of the present study is that it is the largest PED-BD cohort reported to date from a single national registry, including cases with long follow-up times and disease duration. The diagnosis of BD was made based on the clinical picture of the disease and the clinical judgment of experienced rheumatologists of the group and not on just any specific diagnostic/classification criteria. As Iran's national registry for BD is well recognised by most Iranian physicians with different specialties, nearly all patients diagnosed as having BD throughout the country are sent to our unit for confirmation of the diagnosis and further evaluation. Therefore, our data could reflect the real picture of the disease in Iran, with the least possible referral bias regarding disease severity (mild, moderate, or severe forms) and subspecialties of the authors (rheumatology, dermatology, ophthalmology, etc.).

The current study certainly had the limitations associated with its retrospective nature, such as overlooked subtle symptoms due to incomplete recorded files, and so on. It was also limited by all the confounding factors associated with any series of patients with a rare disease like underpowered comparisons for rare manifestations.

Conclusion

The clinical spectrum of disease in Iranian patients with PED-BD was similar to that of other reports characterised by the high prevalence of positive familial history. However, less GU, less skin involvement (notably EN), and less GI involvement was noticed in this study, while ocular involvement was more frequent and more severe compared to other reports. This study had a different gender variation with higher GU and abnormal urine (leukocyturia) in girls and higher prevalence of EN, ocular lesions, and arthritis (mono) in boys. Regarding diagnosis, this study demonstrated the relatively low sensitivity of new the consensus classification criteria for PED-BD in our paediatric cohort due to the ignorance of the pathergy test as a diagnostic criterion in it. The ICBD criteria showed the highest sensitivity in our patients, while the performance of ISG criteria was not so good.

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