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Performance of diagnostic criteria in pediatric Behçet's disease

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Abstract

Behçet's disease is an inflammatory vasculitic disease of unknown etiology characterized by recurrent oral and genital ulcers, ocular findings, and multiple organ involvement. Mucocutaneous findings are the most common symptoms. The most used diagnostic criteria are International Criteria for BD (ICBD), International Study Group (ISG) criteria and pediatric Behçet's disease criteria (PEDBD). Although diagnostic criteria have been defined, the diagnosis is still difficult due to clinical findings developed in pediatric patients. The aim of this study was to evaluate the clinical findings, phenotype characteristics, sensitivity and specificity of diagnostic criteria, and the course of pediatric Behçet's disease (BD). We evaluated retrospectively the files of 67 (29 M/38 F) patients diagnosed with BD according to expert opinion. The patients were reclassified according to ISG, ICBD, and PEDBD criteria. The control group consisted of a total of 69 patients with BD-mimicking diseases or presenting at least one major BD sign followed at the same center. Sensitivity and specificity were evaluated for the criteria. The mean age of diagnosis was 13.38 ± 3.2 years. There were oral aphthous ulcers in 98.5%, genital ulcers in 68.7%, skin lesions in 31.3%, vascular involvement in 17.9%, neurological involvement in 11.9%, positive pathergy test in 33.8%, and positive HLA-B51 in 57.1% of patients. The sensitivity of ICBD, ISG and PEDBD criteria was 88.1, 43.3, and 37.3%, respectively. The specificity of ICBD, ISG, and PEDBD criteria was 100%. Diagnosis of BD in childhood is still difficult. ICBD criteria have the highest sensitivity among the diagnostic criteria. These criteria can also be used in childhood.

Keywords Pediatric Behçet's disease · Diagnostic criteria · Sensitivity · Specificity

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Introduction

Behçet's disease (BD) is an inflammatory vasculitic disease of unknown etiology by characterized oral aphthous ulcers (OAU), genital ulcers, ocular, vascular, central nervous system, and pulmonary system involvement [1]. Although the age of onset is more common in the 2nd and 3rd decades, it is seen in 4–26% of children before the age of 16 [2, 3]. Clinical symptoms vary widely according to geographic region, gender, and ethnicity [4, 5]. The prevalence among adults varies by geographic region. It is estimated at 10–15 per 100,000 in countries along the Silk Road [6–8]. There are limited data on prevalence/incidence in children [8].

Early diagnosis of the disease is important in increasing the quality of life and decreasing mortality and morbidity. Therefore, many diagnostic criteria have been defined in adults [9]. Until recently, these criteria were also used in pediatric BD. The most used diagnostic criteria are the International Criteria for BD (ICBD) and the International Study Group (ISG) criteria [10, 11]. Recently, diagnostic criteria

have been defined in pediatric disease, called pediatric BD criteria (PEDBD) [12]. The items used in these diagnostic sets are the most common findings in BD. Oral aphthous ulcers, genital ulcers, skin, and ocular lesions are common items in all three criteria. However, there are vascular and neurological manifestations in ICBD and PEDBD criteria. The scores in the ICBD criteria were determined according to the frequency of clinical findings. OAU, genital ulcer, and ocular lesions are more common in adults. Therefore, it is 2 points in scoring. However, the frequency of clinical findings in pediatric patients is not fully known. In PEDBD criteria, each item scores 1 point.

Despite the presence of diagnostic criteria, the diagnosis of pediatric BD is still difficult due to atypical findings and the heterogeneity of the disease. Although diagnostic criteria help diagnosis, most patients do not fulfill these criteria at the onset of the disease.

The aim of this study was to evaluate the clinical features, phenotype characteristics, and course of pediatric BD. In addition, it was aimed to compare the sensitivity and specificity of PEDBD, ICBD, and ISG criteria in pediatric BD.

Methods

We retrospectively evaluated the files of 67 patients diagnosed with pediatric BD between 2010 and 2019 in our center. Age, gender, clinical characteristics, and laboratory data of the patients were recorded. Major organ involvement was defined as eye, vessels, nervous system, and gastrointestinal system. Vascular manifestations including venous thrombosis, superficial thrombophlebitis, and aneurysm were confirmed by doppler ultrasonography or angiography. Eye examination was evaluated by an ophthalmologist.

The patients were reclassified according to ISG, ICBD, and PEDBD criteria. According to ISG criteria, OAU are mandatory for BD and the patient should have at least two of the genital ulcers, ocular, and skin findings (erythema nodosum, pseudofolliculitis) and a positive pathergy test [10]. Vascular (arterial thrombosis, large vein thrombosis, superficial phlebitis) and neurological (except isolated headaches) symptoms were added to the ICBD criteria, which was revised in 2010. Oral aphthous ulcers, genital ulcer, and ocular findings (uveitis, retinal vasculitis) were determined as two points and the others as single points. The Pathergy test was optional, but an extra score was made. Four points or more are diagnostic for BD [11]. In the PEDBD criteria, all findings have the same weight. Three or more of the following criteria are required in PEDBD: OAU, genital ulcer, ocular, skin lesions (erythema nodosum, necrotic folliculitis, acneiform lesions), neurological and vascular (venous thrombosis, arterial thrombosis, arterial aneurysm) symptoms. Pathergy test is not scored [12]. We evaluated sensitivity and specificity for the criteria. The sets of criteria were summarized in Fig. 1.

The control group consisted of a total of 69 patients with BD-mimicking diseases or presenting at least one major BD sign followed at the same center including 31 patients with

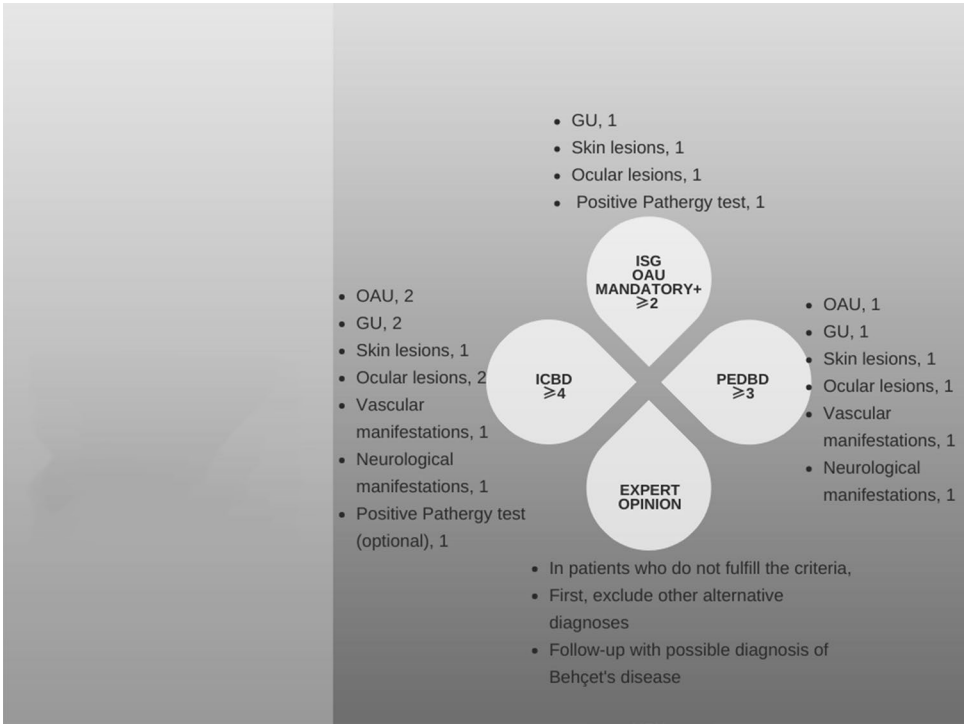


Fig. 1 The diagnostic criteria in pediatric Behçet's disease. *OAU* Oral aphthous ulcers, *GU* Genital ulcer, *ICBD* International Criteria for BD, *ISG* International Behçet's Study Group, *PEDBD* Pediatric Behçet's disease criteria

periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome, 37 systemic lupus erythematosus patients. Table 1 was summarized the clinical features of the control group.

Ethics committee approval was received for this study, from the scientific and ethics committee of our hospital (approval number: E1/891/20202; approval date: February 7, 2020).

Statistical analysis

The values were analyzed using Statistical Package for social sciences (SPSS) software version 22. Kolmogorov–Simirnov/Shapiro–Wilk's test was used to determine whether the data distributed normally or non-normally. Quantitative variables were calculated as mean, ranges (minimum–maximum) or percentage. The sensitivity and specificity values were given as a percentage. Fisher's exact test was used to compare the categorical variables. Differences between the continuous variables were compared using the nonparametric Mann–Whitney–U test for independent samples. *P* value less than 0.05 was considered significant.

Results

Demographic and clinical manifestations

There were 67 patients with pediatric BD (29 M/38 F). The mean age of onset of symptoms was 11.09 ± 3.43 (2.5–17) years and, the mean age of diagnosis was 13.38 ± 3.2 (3–18) years. Twenty-nine (43.3%) patients had BD in their family history. The mean follow-up time was 4.23 years (2–10).

All patients had recurrent OAU except one patient, and the mean frequency of OAU was 9.66 ± 6.23 (0–24) per year. There were genital ulcers in 46 (68.7%), papulopustular lesions in 13 (19.4%), and erythema nodosum in five (7.5%) patients. Six (9%) patients had fever at the onset of the disease. Nine (13.4%) patients had arthritis and there was no difference by gender. Table 1 summarizes the demographic and clinical characteristics of the patients. There was no significant difference between gender and genital ulcer, eye involvement, joint involvement, and skin manifestations ($p = 0.12$, $p = 0.67$, $p = 0.23$, $p = 0.27$, respectively). There was no relationship between age at diagnosis and neurological, vascular, and ocular lesions ($p = 0.23$, $p = 0.70$, $p = 0.33$, respectively).

During the follow-up period, 48 patients had normal ocular examination, 14 (20.8%) had uveitis, and 5 (7.5%) had papillary edema. Ocular lesions were significantly less in patients with genital ulcers ($p = 0.018$). There was a significantly relationship between ocular lesions and neurological involvement ($p = 0.009$), but not with other clinical findings.

Thrombosis developed at different sites in 12 (17.9%) patients and 81.8% of the patients with thrombosis had positive thrombophilia factors (such as MTHFR 1298, PAI, factor V Leiden mutation). Vascular involvement was significantly higher in males ($p = 0.007$) and was less common in patients with genital ulcer ($p = 0.028$). There was no relationship between other clinical findings and vascular involvement.

Table 1 The clinical features of the BD and control group

Symptoms	BD	Control group		*p*
		SLE	PFAPA	
Age at diagnosis, mean ± SD (years)	11.9 ± 3.43	11.9 ± 2.84	4.9 ± 2.62	–
Male/Female	29/38	6/31	16/15	–
OAU, *n* (%)	66 (98.5%)	5 (13.5%)	17 (53.1%)	0
Genital ulcer, *n* (%)	46 (68.7%)	0	0	0
Ocular lesions, *n* (%)	14 (20.8%)	0	0	0
Skin lesions (erythema nodosum, necrotic folliculitis, acneiform lesions), *n* (%)	21 (31.3%)	0	0	0
Vascular manifestations, *n* (%)	12 (17.9%)	0	0	0
Neurological manifestations, *n* (%)	8 (11.9%)	10 (27%)	0	0
Positive Pathergy test, *n* (%)	20/59 (33.8%)	–	–	
Arthritis, *n* (%)	9 (13.4%)	0	0	0
Positive HLA-B51, *n* (%)	32/56 (57.1%)	–	–	
Fever, *n* (%)	6 (9%)	14 (37.8%)	30 (93.7%)	
Positive ANA	–	31 (83.8%)	–	
Positive Anti dsDNA, *n* (%)	–	26 (70.3%)	–	

BD Behçet's Disease, *SLE* Systemic Lupus Erythematosus, *PFAPA* Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome, *OAU* Oral aphthosis ulcers, *ANA* Anti nuclear antibody

Eight of the pediatric BD (11.9%) were identified with neuro-BD (NBD). Four of these patients had parenchymal involvement. The most common neurological symptom was headache and was significantly more common in females ($p=0.014$). Four patients developed pseudotumor cerebri syndrome, and two developed weakness.

Pathergy test was performed in 59 patients and positivity was found in 20 (33.8%). There was no phenotypic difference between those who had negative and positive pathergy test ($p=0.26$). There was no difference in the presence of clinical findings according to the pathergy test, but papulopustular lesions were significantly more common in the positive pathergy test ($p=0.025$).

HLA-B51 gene was performed in 56 patients and positivity was detected in 32 (57.1%). There was no relationship between HLA-B51 gene and BD phenotypes and clinical findings ($p=0.20$).

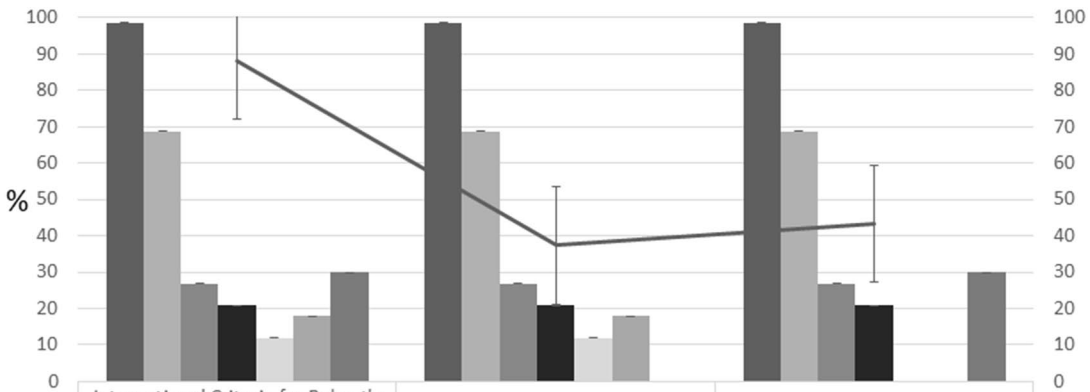
Diagnostic criteria

Twenty-nine (43.2%) fulfilled the ISG criteria, 59 (88.1%) ICBD, and 24 (35.8%) PEDBD criteria. Sensitivity of ICBD, ISG, and PEDBD criteria was 88.1, 43.3, and 37.3%, respectively. The sensitivity of PEDBD criteria was found to be 46.7%, including the pathergy test. Thirty (44.7%) patients were diagnosed with only OAU and genital ulcer according to ICBD criteria and these patients could not be diagnosed according to PEDBD and ISG criteria. The specificity of ICBD, ISG, and PEDBD criteria was 100%. None of the patients in the control group were diagnosed as BD. There were at most two criteria in these patients. However, clinical and laboratory findings were available to exclude BD. The percentage distribution of clinical findings was summarized in Fig. 2. Also, sensitivity was defined as the Y-axis for all three sets of criteria.

Discussion

As is known, there are no specific laboratory, imaging, and histopathological findings in BD, and diagnosis is based on clinical symptoms and expert opinion [4]. It may be difficult to diagnose BD in children because clinical findings do not occur simultaneously. Therefore, sensitive diagnostic criteria are required for the diagnosis. In this study, we evaluated the performance of diagnostic criteria in pediatric BD. We especially registered the sensitivity in the PEDBD, ISG, and ICBD criteria of 37.3, 43.3, and 88.1%, respectively. We observed a minimal increase in the sensitivity of PEDBD criteria, including the pathergy test. We also found the high specificity of all three sets of criteria.

There are important differences between three diagnostic criteria. OAU is a mandatory item, and two of the other items (genital ulcer, ocular involvement, skin lesions and positive pathergy test) should be included in ISG criteria. The sensitivity and specificity of this criteria are 85 and



	International Criteria for Behçet's Disease	Pediatric Behçet's Disease	International Study Group
Oral aphthous ulcers	98,5	98,5	98,5
Genital ulcers	68,7	68,7	68,7
Skin lesions	26,8	26,8	26,8
Ocular manifestations	20,8	20,8	20,8
Neurological manifestations	11,9	11,9	
Vascular manifestations	17,9	17,9	
Positive pathergy test	29,9		29,9
sensitivity	88,1	37,3	43,3

Fig. 2 Distribution of clinical findings by diagnostic criteria

95%, respectively [10]. In our study, sensitivity of ISG criteria was found 43.3%. We think it is rational to attribute the difference in sensitivity to the development of clinical findings of pediatric BD in different time periods. As is known, the time to diagnosis in children is between 2 and 5 years, and children with oral/genital ulcers require a long follow-up period [4, 13]. Although 98% of our patients have OAU which is mandatory for the ISG criteria at the time of diagnosis, two criteria that should be in addition to OAU have not been determined yet. Moreover, there is no item for neurological or vascular manifestations that may determine the prognosis for BD in the ISG criteria. Neurological involvement was detected in 11.9% and vascular involvement in 17.9% of our patients. Patients with vascular or neurological involvement could not fulfill the ISG criteria even if they had mandatory item (i.e., OUA) together with one of the other items (genital ulcers, ocular, and skin findings and a positive pathergy test).

Criteria including all clinical findings and phenotypic differences of BD will be helpful in diagnosis. Recently, ICBD criteria including neurological and vascular involvement have been defined [11]. This classification, scored according to the presence of clinical findings, is defined for adult BD. OAU are not mandatory criteria in this classification and there is scoring for each criterion. Its sensitivity is higher, especially with the addition of neurological and vascular involvement. The pathergy test is not mandatory, but its positivity can be evaluated as 1 point [11]. In our study, we found the sensitivity of the ICBD criteria to be 88.1%. We think that OAU, genital ulcer, and ocular events having two points in ICBD criteria and the presence of these three criteria in most of our patients increase the sensitivity. Neurological and vascular involvement not included in the ISG criteria but in ICBD causes the difference in sensitivity between the criteria.

In 2015, PEDBD criteria were defined with a large cohort [12]. OAU are not mandatory item in PEDBD criteria and neurological and vascular involvement criteria have been added. Since the frequency of clinical findings in pediatric BD is not known exactly, the scoring of each item in PEDBD criteria is the same. Pathergy test is not included in the criteria. The PEDBD consensus found that the presence of the pathergy test had no effect on the performance of the criteria. The sensitivity of the PEDBD criteria was 91.7%, and the specificity was 42.9% without the pathergy test [12]. However, sensitivity has been reported between 45.5 and 73.5% in the literature [14, 15]. Maldini et al. reported that without the pathergy test, the sensitivity of most of the diagnostic criteria decreased by 1.9–35% [16]. Increased sensitivity was observed when the pathergy test was included in our study (46.7%). The sensitivity of PEDBD criteria was found to be lower in our study than other studies. It can be explained by the fact that most of our patients have only two criteria. In our study, OAU and genital ulcers were 98.5% and 68.7%, respectively, and were the most common symptoms. Whereas patients must have three or more items to fulfill the PEDBD criteria. However, these patients can be followed up as possible BD after other autoimmune and autoinflammatory diseases are excluded.

In our study, there was a significant difference between the sensitivity in ICBD and PEDBD. The most important difference between ICBD and PEDBD is the scoring of the criteria. The same weight given to the criteria may be the reason for the low sensitivity of the PEDBD criteria.

The prevalence of HLA-B51 is more common in BD than the healthy population. Although HLA-B51 has no place in the diagnosis, it is known that it has a genetic contribution to the disease [17]. It suggests that genetic factors play an important role in the pathogenesis of the disease due to familial clustering. In most studies, HLA-B51 positivity was reported at over 60% [18]. HLA-B51 positivity was in about half of our patients. No relationship was detected between HLA-B51 and BD phenotypes in our study. Although HLA-B51 is not among the diagnostic criteria, it may help the clinician in identifying the patient to be followed up with possible BD, even in patients who do not fulfill the diagnostic criteria regardless of the BD phenotype.

The main limitation of our study is primarily its retrospective design. The other limitation was the relatively small number of patients. Although BD is not common in the pediatric period, larger patient groups and prospective studies are required.

In conclusion, our study suggested that the sensitivity of the PEDBD criteria is lower than the other two diagnostic criteria. It has also showed that pathergy testing may be useful in the diagnosis of pediatric BD in some patients. More sensitive diagnostic criteria are required. Expert opinion is still the gold standard in diagnosis.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval Ethics committee approval was received for this study, from the scientific and ethics committee of our hospital (approval number: E1/891/20202; approval date: February 7, 2020).

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