The performance of different classification criteria in paediatric Behçet's disease

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ABSTRACT

Objective. *Behçet's disease (BD) is a variable vessel vasculitis. The most widely used classification criteria for adults is the International Behçet's Study Group (ISG) criteria. Recently, the paediatric BD (PEDBD) classification criteria has been developed for children. For disease activity, there are mainly two severity scores; the Iranian BD dynamic activity measure (IBDDAM) and BD current activity form (BDCAF). We tested the performances of PEDBD and ISG criteria and the correlation between severity scores and physician global assessment (PGA) in children with BD.*

Methods. *Thirty BD patients from Hacettepe University, Ankara, Turkey; 24 from Erciyes University, Kayseri, Turkey; and 14 BD patients from Rambam Medical Centre, Haifa, Israel were included. As controls, children with systemic lupus erythematosus, polyarteritis nodosa, and Crohn disease from Turkey and Israel were included. The sensitivity and specificity of the PEDBD and ISG criteria were evaluated based on the features of the patients before or at 16 years of age. The gold standard for the diagnosis of BD was based on expert opinion at each centre. Expert PGA (visual analogue scale between 0-10; where 0 indicates no disease activity), IBDDAM, and BDCAF were evaluated at the time of diagnosis and at last follow-up in all patients.*

Results. *Sixty-eight BD (disease onset≤16 years; 44.1% male) and 90 control patients were included. The sensitivity and specificity of PEDBD/ISG criteria were 73.5%/52.9% and 97.7%/100%, respectively. Thirty-two (47%) patients with BD failed to fulfill ISG criteria while almost all met PEDBD criteria. The median (interquartile range; IQR) IBDDAM and BDCAF scores at diagnosis were 6(4)/4(2); significantly decreased to 1(2)/1(2), respectively at latest follow-up (p<0.001 for both). The median (IQR) PGA score at diagnosis was 5(2); significantly decreased to 1(2) at latest follow-up (p<0.001). IBDDAM positively correlated with BDCAF (r=0.637; p<0.001). PGA positively correlated with BDCAF and IBDDAM (r=0.502; p<0.001 and r=0.624;p<0.001, respectively).*

Conclusion. *In our study, the PEDBD criteria showed better sensitivity than ISG criteria which is a big advantage for paediatric patients for early diagnosis. We also demonstrated that the severity scores were positively correlated with each other and PGA; thus may be used in clinical practice for paediatric BD patients.*

Introduction

Behçet's disease (BD) is a variable vessel vasculitis characterised by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions (1). Small vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur (1). It is unique among primary vasculitides affecting all sizes of vasculature in both the arterial and venous systems (2). BD is seen most frequently between the second and fourth decade (3, 4); however, increased awareness has led to increase in number of patients in childhood. Roughly, in 5-8% of BD patients, the disease onset is in childhood (3, 5). There are more than 15 sets of diagnostic/classification criteria for BD (6). The International Study Group (ISG) criteria set was presented in 1990 and 1992 (7, 8). According to the ISG criteria, to classify a patient as having BD, oral aphthosis was mandatory plus the

patient should have two of the following four features: genital aphthosis, skin manifestations (pseudofolliculitis, erythema nodosum), ophthalmological manifestations, and positive pathergy test. However, because of its low sensitivity, many BD patients were not classified as having BD according to the ISG criteria (9).

The ISG criteria set has never been validated in children. However, the disease characteristics may differ between children and adults. We were already aware that uveitis was less common and familial aggregation was more common in children with BD when compared to adult BD patients (10-13). In addition, although the first symptoms of BD may present at early ages, the disease is not complete before 16 years of age in more than 80% of patients (14).

Most recently, an international expert consensus group (the paediatric BD [PEDBD] group) has suggested new classification criteria for paediatric BD based on the widest cohort study in paediatric BD (15). The pathergy test was not included and oral aphthosis was not a mandatory criterion in the PEDBD criteria set. In addition, all symptom categories have the same weight. The patient is classified as having BD when he/she has three or more of the following criteria: oral aphthosis (≥3 attacks per year), genital aphthosis (typical with scars), skin involvement (necrotic folliculitis, acneiform lesions, erythema nodosum), neurologic involvement (except isolated headaches), ocular manifestations (anterior uveitis, posterior uveitis, retinal vasculitis), and vascular signs (venous thrombosis, arterial thrombosis, arterial aneurysms) (Supplementary Table I).

The scoring systems provide a systematic way of evaluating disease activity accurately in many diseases. There are mainly two scoring systems to evaluate BD activity; the Iranian BD dynamic activity measure (IBDDAM) (16) and BD current activity form (BDCAF) (17) both of which depend on clinical features. Currently, BD patients are treated according to the physician's judgement of disease activity which may be reflected by physician global assessment (PGA).

Table I. The characteristics of patients in Behçet's disease and control groups.

Characteristics, n (%)	BD* patients (n=68)	Control group patients (n=90)	*p*-value
Female	38 (55.9)	65 (72.2)	0.03
Oral aphthosis	68 (100)	38 (42.2)	<0.001
Genital aphthosis	49 (72.1)	2 (2.2)	<0.001
Skin involvement	34 (50)	37 (41.1)	0.26
Necrotic folliculitis	7 (10.3)	22 (24.4)	0.02
Erythema nodosum	21 (30.9)	2 (2.2)	<0.001
Acneiform lesions	7 (10.3)	0 (0)	0.002
Eye involvement	15 (22)	0 (0)	<0.001
Anterior uveitis	1 (1.5)	0 (0)	0.43
Posterior uveitis	2 (2.9)	0 (0)	0.18
Panuveitis	10 (14.7)	0 (0)	<0.001
Retinal vasculitis	2 (2.9)	0 (0)	0.18
Neurologic involvement	17 (25)	11 (12.2)	0.037
Vascular involvement	16 (23.5)	3 (3.3)	<0.001
Venous thrombosis	12 (17.6)	2 (2.2)	0.001
Arterial thrombosis	3 (4.4)	2 (2.2)	0.65
Arterial aneurysm	1 (1.5)	0 (0)	0.43
Pulmonary arterial aneurysm	1 (1.5)	0 (0)	0.43
Pathergy positivity	22/54 (40.7)	0/24 (0)	<0.001
Family history of BD	19 (27.9)	0 (0)	<0.001
BD according to the PEDBD* criteria (reference number 15)	50 (73.5)	2 (2.2)	<0.001

*BD: Behçet's disease; PEDBD: Paediatric Behçet's disease.

It is very important to have accurate classification criteria and valid outcome measures for paediatric BD in order to design better therapeutic interventional trials which will aid us in the management of BD in childhood. In this study, we aimed to test the performance of the PEDBD criteria compared to the ISG criteria in our paediatric BD patients by using data from our patients with systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), and Crohn disease (CD) as negative controls. Our secondary aim was to check the correlation between IBDDAM or BDCAF and expert PGA in the evaluation of disease activity in paediatric BD.

Patients and methods

Two centres from Turkey and one centre from Israel participated in this study. Thirty BD patients were enrolled at the Paediatric Rheumatology Unit of Hacettepe University, Ankara, Turkey; 24 BD patients were enrolled at the Paediatric Rheumatology Unit of Erciyes University, Kayseri, Turkey; and 14 BD patients were enrolled at Department of Paediatrics, Meyer Children's Hospital, Rambam Medical Centre, Haifa, Israel. The aforementioned departments are known referral centres for paediatric BD in their countries. None of these patients were included in the original cohort of PEDBD criteria study by Kone-Paut *et al*. (15). The symptom (first symptom reliable to BD) onset of all BD patients was at or before 16 years of age. The control group consisted of 67 patients admitted to the Hacettepe University, Ankara, Turkey and 23 patients admitted to the Rambam Medical Centre, Haifa, Israel. In the control group, there were patients with the following diagnoses: 66 SLE, 15 CD, and 9 PAN.

The gold standard for the diagnosis of BD was based on expert opinion at each centre (SO, BS, YBA). All three experts are experienced in BD and have been seeing BD patients for at least 10 years. Patient and control data were collected on standardised case report forms. Demographic features, treatment, items of different criteria sets, and outcome scores were evaluated. The sensitivity and specificity of the PEDBD and ISG criteria were evaluated based on the features of the patients before or at 16 years of age. Expert PGA (visual analogue scale between 0–10; where 0 indicates no disease activity), IBDDAM, and BDCAF were evaluated at the time of diagnosis

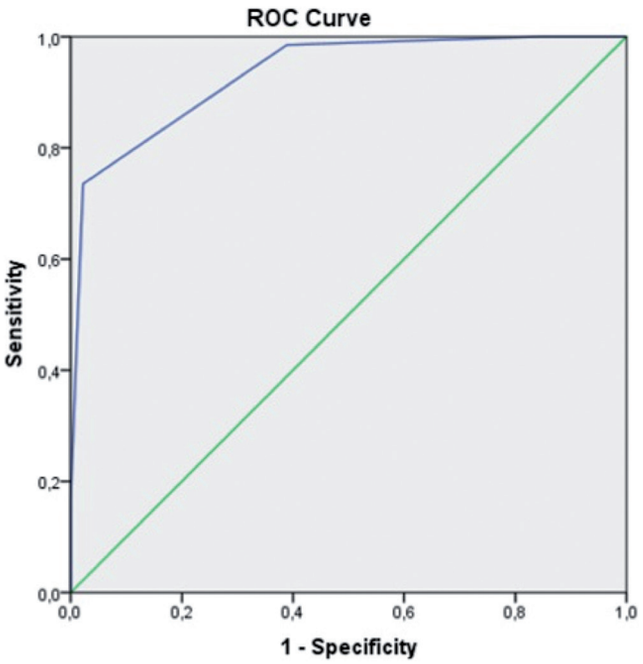

Fig. 1. Area under the receiver operating characteristic (ROC) curve for the paediatric Behçet's disease (PEDBD) classification criteria (15) in our study group.

Table II. Categories of patients according to the paediatric Behçet's disease (PEDBD) (15) and the International Study Group (ISG) (7, 8) criteria.

Criteria sets	BD patients (n=68)	Control patients (n=90)	Sensitivity	Specificity
BD* according to the PEDBD* criteria	50	2	73.5%	97.7%
Non-BD according to the PEDBD criteria	18	88		
BD according to the ISG* criteria	36	0	52.9%	100%
Non-BD according to the ISG criteria	32	90		

*BD: Behçet's disease; ISG: International Study Group; PEDBD: Paediatric Behçet's disease.

and at last follow-up in all patients and the correlations between these scores were checked.

The calculation of IBDDAM has been provided as supplementary material (Supplementary Table 2) and the calculation form for BDCAF is available in http://www.behcetdiseasesociety.org/.

Statistical analysis

The SPSS version 22.0 (SPSS, Inc., Chicago, Illinois) is used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogrov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using proportions, medians, and interquartile range (IQR) values as appropriate. Differences in proportions between groups were evaluated by the Chi-square test or Fisher's exact test where appropriate. The Mann-Whitney U test was used to compare the non-normally distributed continuous data between two groups. We used the Receiver Operating Characteristics (ROC) curve to demonstrate the sensitivity and specificity of the PEDBD classification criteria in our study group. While investigating the associations between non-normally distributed variables, the correlation coefficients and their significance were calculated using the Spearman test. A p-value <0.05 was considered as significant and confidence interval (CI) was 95%.

Results

Sixty-eight BD patients and 90 control patients were included in this study. Among BD patients, 44.1% were male. The median (IQR) age at symptom onset was 11 (5.1) years and the median time to diagnosis from symptom onset was 12 (31.5) months. The median (IQR) age at diagnosis was 13 (6) years for BD patients and 11 (6) years for control patients. The characteristics of patients in BD and control groups were summarised in Table I.

There was no significant difference except neurologic involvement between BD patients from Turkey and Israel with regards to the BD characteristics (Supplementary Table II). Neurologic involvement was more frequent in BD patients from Turkey than the ones from Israel (31.5% *vs*. 0%, respectively; p=0.015).

The area under the ROC curve for the PEDBD criteria was 0.933 (Fig. 1) which indicates a good discrimination (standard error 0.019; 95% CI 0.896-0.970). The sensitivity and specificity of the PEDBD criteria was 73.5% and 97.7%, respectively. The ISG criteria (7, 8) had a sensitivity of 52.9% and specificity of 100% (Table II). Thirty-two (47%) patients with BD failed to fulfill the ISG criteria. However, half of these patients met the PEDBD criteria. The characteristics of these patients who met PEDBD but not the ISG criteria are presented in Table III. Of note, 14 out of these 16 BD patients had either neurologic or vascular involvement.

Only two SLE patients were misclassified as having BD according to the PEDBD criteria.

As to the BD activity scores, the median (IQR) IBDDAM and BDCAF scores at diagnosis were 6 (4) and 4 (2) and significantly decreased to 1 (2) and 1 (2) respectively at the latest follow-up (p<0.001 for both). The median (IQR) PGA score at diagnosis was 5 (2) and significantly decreased to 1 (2) at the latest follow-up (p<0.001). The median (IQR) duration between the first and last visit was 36 (40.75) months.

IBDDAM had a strong positive correlation with BDCAF (r=0.637; p<0.001). PGA also had positive significant correlations with BDCAF and IBDDAM (r=0.502; p<0.001 and r=0.624; p<0.001, respectively).

Discussion

The present study is the first comparison of PEDBD and ISG criteria in paediatric BD, in two countries where the disease has a high prevalence. PED-

BD was developed and validated in a mainly European group, with the supplementation of Turkish patients. This is also the first study evaluating the existing activity scores in childhood BD patients. The PEDBD performed better and the outcome scores were valid in our paediatric cohort.

Most of the classification/diagnosis criteria sets for BD have been developed from studies on adult patients and none has been validated in children (6, 18). However, previous studies have shown that there were certain clinical differences between paediatric and adult patients. Karıncaoglu *et al*. compared the characteristics of the patients in the paediatric and the adult age group and reported that the most frequent initial symptom was oral ulcer for both groups; however, the neurological involvement and the gastrointestinal involvement in childhood were more frequent than in adulthood (11). The family history of BD was shown to be more frequent in paediatric cases suggesting a stronger genetic basis for the disease when presenting in young age (19, 20). In addition to these differences, in paediatric BD cases, it may take time for the patient to have the whole spectrum of symptoms of the disease. Treuder *et al*. revealed that the time interval between the initial symptom and the fulfillment of the BD diagnostic criteria was longer in childhood than adulthood (19). In the study by Nanthapisal *et al*., the median time to diagnosis was 3.74 years in paediatric BD cases (21). Kone-Paut *et al*. reported a mean delay of 3.7 years between the first symptom and BD suspicion (9). In our study, the median time to diagnosis from symptom onset was shorter (1 year). This was probably due to the increased awareness of BD at this site of the world. Another reason may be the definition of BD diagnosis according to the ISG criteria in previous studies.

The main differences of the PEDBD criteria from the ISG criteria are as follows: oral aphthosis is not a mandatory criterion and each criterion has equal weight; neurologic and vascular manifestations are included; pathergy test is not included. In our study, all of paediatric BD cases had oral aphthosis; however, previous studies have demonstrated BD patients without oral aphthosis (22). Thus, it is not a mandatory criterion anymore in the PEDBD criteria set. An international collaborative study reviewed 86 BD cases 21 of whom did not fulfill the ISG criteria although they had features suggestive of BD (13). Genital aphthosis, skin lesions, hypersensitivity, and uveitis were less frequent; whereas neurologic symptoms was more frequent in patients who did not fulfill the ISG criteria (13). In another study, expert paediatric rheumatologists investigated the clinical features of paediatric BD and found that almost half of the definitive or probable BD patients did not fulfill the ISG criteria (9). A revised set of criteria was also developed and revised in 2010 by adult rheumatologists and was called the International Criteria for BD (ICBD) (23-25). In our study, the sensitivity of PEDBD classification criteria was higher than the ISG criteria. The reason for this difference may be the inclusion of neurologic and vascular involvement in PEDBD criteria in contrast to the ISG criteria. Fourteen out of 16 BD patients who met PEDBD but not ISG criteria in our study had either neurologic or vascular involvement.

It is very important to evaluate disease activity with standard and objective methods. However, there is lack of validated and generally accepted outcome measures in BD (26). And there are major controversies on the use of outcome measures developed for similar conditions or developing BD-specific measures for each organ involvement (27). There are mainly two scoring systems for BD; IBDDAM (16) and BDCAF (17). In 2009, Shahram *et al*. performed a study to determine the concordance between IBDDAM or BDCAF and expert PGA in the evaluation of disease activity *changes* in BD patients with a mean (range) age of 34 (11-66) years (28). They demonstrated moderate agreement between IBDDAM/BDCAF and expert PGA with regard to the changes in disease activity. We have checked the correlation between IBDDAM or BDCAF and expert PGA in paediatric BD patients and found that there was moderate to strong positive correlation between IBDDAM/BDCAF and PGA. We suggest that these scoring systems and/or PGA could be used in our routine clinical practice while evaluating children with BD.

Table III. Behçet's disease (BD) patients who met the paediatric BD (PEDBD) classification criteria but not fulfilled the International Study Group (ISG) criteria (n=16).

Characteristics, n (%)	BD* patients who met PEDBD* but not ISG* criteria set (n=16)
Female	7 (43.8)
Age at symptom onset, years, median (IQR*)	13 (4.8)
Age at diagnosis, years, median (IQR)	13 (4.1)
Time from symptom onset to diagnosis, months, median (IQR)	12 (24)
Oral aphthosis	16 (100)
Genital aphthosis	8 (50)
Skin involvement	7 (43.8)
Necrotic folliculitis	1 (6.3)
Erythema nodosum	3 (18.8)
Acneiform lesions	1 (6.3)
Eye involvement	3 (18.8)
Anterior uveitis	0 (0)
Posterior uveitis	0 (0)
Panuveitis	3 (18.8)
Retinal vasculitis	0 (0)
Neurologic involvement	7 (43.8)
Vascular involvement	9 (56.3)
Venous thrombosis	7 (43.8)
Arterial thrombosis	2 (12.5)
Arterial aneurysm	1 (6.3)
Pulmonary arterial aneurysm	1 (6.3)
Pathergy positivity	1/12 (8.3)
Family history of BD	2 (12.5)

*BD: Behçet's disease; IQR: interquartile range; PEDBD: Paediatric Behçet's disease

Our study has certain limitations mainly based on its retrospective design. In addition, although previously the modifying effect of puberty was shown on clinical presentation of BD (13), we did not check the effect of puberty since this data was deficient in the files. However, we have the advantage of having patients from different centres.
In our study, the PEDBD criteria performed better than the ISG criteria with its higher sensitivity. The higher sensitivity of the PEDBD criteria set is a big advantage for paediatric patients since early diagnosis and timely treatment is very important. We have also demonstrated that expert PGA correlated well with BD outcome scores. Thus, we can use both the activity scores and PGA in the follow-up of children with BD. Larger multiethnic studies are needed to reinforce our data in paediatric BD.

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