Disease activity and outcomes in juvenile Behçet's disease: 10 years' experience of a single centre

D. Gezgin Yıldırım[1], S.A. Bakkaloğlu[1], M. Hasanreisoğlu[2], N. Buyan[1]

[1]*Department of Paediatric Rheumatology, Gazi University Faculty of Medicine, Ankara;* [2]*Department of Ophthalmology, Gazi University Faculty of Medicine, Ankara, Turkey.*

Deniz Gezgin Yıldırım, MD
Sevcan A. Bakkaloğlu, MD
Murat Hasanreisoğlu, MD
Necla Buyan, MD

Please address correspondence to:
Deniz Gezgin Yıldırım,
Paediatric Rheumatology Department,
Gazi University Medical Faculty,
06560 Ankara (Yenimahalle), Turkey.
E-mail: gezgindeniz@gmail.com

Received on August 23, 2020; accepted in revised form on November 9, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 127): S105-S111.

Key words: juvenile Behçet's disease, outcome, paediatric rheumatology, event-free survival

Competing interests: none declared.

ABSTRACT

Objective. *The aims of this study were to investigate the development of new events (new clinical signs related to Behçet's disease) and to evaluate outcomes in juvenile Behçet's disease (jBD) patients over a 10-year follow-up.*

Methods. *We included 57 patients diagnosed with jBD according to the International Behçet's Study Group (ISG) criteria and/or the International Criteria for BD (ICBD) and/or Paediatric BD (PEDBD) group criteria, followed-up between 2008 and 2018. Any new organ system involvement during follow-up was defined as an event in event-free survival analysis.*

Results. *The patients' female/male ratio was 33/24. The most prevalent clinical feature was recurrent oral aphthosis (100%), followed by musculoskeletal symptoms (63%), genital ulcers (56%), ocular manifestations (47%) and cutaneous manifestations (46%). Vascular, neurological, gastrointestinal and genitourinary manifestations were observed in 4-17% of the patients. Fifty-four (95%) cases fulfilled the ICBD, while 31 (54%) and 34 (60%) fulfilled ISG and PEDBD criteria, respectively. The median Iranian Behçet's disease dynamic activity measure (IBDDAM) score at diagnosis was 5 (range: 3–14) and decreased to 1 (range: 0–6) at the last visit. One to three events occurred in 21 (37%) cases. One fifth (19%) of these events were severe. The event-free survival rate was 95% at one year, 70% at three years and 50% at eight years.*

Conclusion. *This study shows that with effective treatment, jBD has favourable outcome and a remarkable event-free survival. Underdiagnosed cases according to ISG and PEDBD criteria could be diagnosed using the ICBD.*

Introduction

Behçet's disease (BD) is a multisystemic inflammatory disorder characterised by recurrent episodes with oral aphthous lesions, genital ulcers and ocular, cutaneous, gastrointestinal, neurological, articular and vascular manifestations (1-3). The disease is most commonly seen along the ancient 'Silk Road', including East Asia and the Mediterranean Basin (3-5). Human leukocyte antigen-B51 (*HLA-B51)* allele is known to be the strongest associated genetic susceptibility factor for BD (5). Diagnosis is based on sets of clinical criteria, the first of which was established by the International Behçet's Study Group (ISG), with 85% sensitivity and 96% specificity (6). Subsequently, the International Criteria for Behçet's Disease (ICBD) were established, with 94.8% sensitivity and 90.5% specificity (7). A set of clinical criteria specifically for children was recently proposed by the Paediatric BD group (PEDBD) with higher sensitivity (91.7%) but lower specificity (42.9%) compared to the ISG criteria (8, 9). Symptoms of BD usually begin at the age of 30–40, but can also be seen in childhood (10). BD in childhood is usually seen as an incomplete form and therefore these patients should be closely monitored for new clinical findings (8). The definite clinical picture of BD may take years after the occurrence of the initial symptoms, which may even be even longer in childhood BD. The symptoms of BD often occur with a recurrent episodic course (3). Treatment of BD, including colchicine, corticosteroids, immunosuppressants and biological therapies, varies according to the severity of the recurrent attacks and involvement of organ systems (11). Although BD is relatively common in Turkey (3, 5, 12), data on juvenile BD (jBD) are scarce

(13, 14). Therefore, the primary aim of this study was to investigate the rates of development of new events (new clinical signs related to BD) and event-free survival in jBD patients over a 10-year follow-up. The secondary aims were to evaluate the demographic and clinical features, laboratory findings, treatment choices, treatment efficacy and outcomes of jBD and the rates for the fulfilment of different classification criteria sets for jBD patients.

Patients and methods

Patient selection

We enrolled 57 jBD patients who fulfilled at least one diagnostic criteria for BD (based on expert physicians' clinical diagnosis as the gold standard), including the ISG criteria and/or the ICBD and/or PEDBD criteria; the patients were younger than 16 years of age and were followed up for at least one year in our clinic. Incomplete cases were excluded from the study. The medical records of the patients who were followed up in the Department of Paediatric Rheumatology of Gazi University between 2008 and 2018 were retrospectively evaluated. The patients' characteristics were recorded, including age, gender, region of origin in Turkey, family history, age at onset of jBD symptoms, age at diagnosis, disease duration, initial symptoms, symptom evolution over time and concomitant diseases, such as enthesitis-related arthritis (ERA) and familial Mediterranean fever (FMF), laboratory findings, including *HLA-B51* status, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and treatments. Organ involvement was identified with imaging methods, endoscopy, ophthalmological examination and/or biopsy studies. The clinical and laboratory findings at the time of diagnosis were analysed. Elevated ESR was defined as higher than 20 mm/h, while elevated CRP was defined as higher than 5 mg/L. *HLA-B27* antigen positivity in ERA cases and *Mediterranean fever gene* (*MEFV*) mutation results in FMF cases were also recorded. *HLA-B51* and *HLA-B27* antigens were detected by flow cytometry method. The *MEFV* gene was evaluated using direct sequencing of the Polimerase Chain Reaction amplified fragments.

The patients were followed up at three-month intervals in our clinic. Patients also underwent a detailed ophthalmological examination twice a year. At follow-up, the patients underwent a detailed physical examination, and systemic disease activity was measured using the Iranian Behçet's disease dynamic activity measure (IBDDAM) (15). New BD-associated clinical findings were considered new events. Among them, genital ulcers, skin findings, erythema nodosum, folliculitis, gastrointestinal manifestations and arthritis were considered mild events, while uveitis, vascular thrombosis-aneurysm formation and neurological signs were considered severe events. The medical files of patients were retrospectively evaluated in terms of whether they experienced a new event related to BD at the third, sixth, ninth month and at annual follow-ups. Event-free survival for new events was calculated accordingly.

The mandatory ISG criteria are oral aphthous lesions recurring more than three times a year and two of the following: genital ulcers, uveitis, skin lesions and pathergy positivity (6). According to the ICBD scoring system, oral aphthosis, genital aphthosis and ocular lesions are assigned 2 points each, and skin lesions, vascular manifestations and neurological manifestations are assigned 1 point. A total score of ≥4 points indicates BD (7). The PEDBD criteria include six items: oral aphthosis, genital aphthosis, skin involvement, ocular involvement and neurological and vascular manifestations. Three or more items are sufficient for the diagnosis of BD in children (8).

Statistical analysis

Statistical analyses were evaluated by using SPSS, v. 3. Descriptive values were specified as ''number'' and ''percent''. Variables were defined as mean + standard deviation (SD) or median (minimum-maximum) according to the distribution of the data. Normality of the distribution of continuous variables were determined by using Kolmogorov-Smirnov test. The differences between two independent groups were compared by using Independent Sample *t*-test for normally distributed variables or Mann-Whitney U-test for non-normally distributed ones. A comparison of the categorical variables was done using a chi-square test. Estimates of sensitivity for the ISG and ICBD and PEDBD criteria were calculated using the formula: sensitivity=TP/(TP+FN); (true positive (TP); false negative (FN), using physician diagnosis of BD as gold standard for the purposes of this retrospective study). Event-free survival rates were assessed by using Kaplan-Meier analysis. $p<0.05$ was considered to be statistically significant.

Ethics

This study was approved by the Gazi University Medical Faculty Ethics Board (28.01.2019/78) and was conducted in accordance of the Declaration of Helsinki.

Results

The patients' general characteristics

The patients' ages ranged from 9 to 25 years. The female/male ratio was 33/24. The median age at the onset of symptoms/complaints was 10 years (range: 5–16 years), while the median age at diagnosis was 12 years (range: 5-16 years); therefore, the median lag in diagnosis was two years (range: 0-6 years). The median follow-up duration was four years (range: 1–10 years). The patients' demographic characteristics and clinical and laboratory findings are summarised in Table I.

Eighteen (31%) patients had a positive family history of BD. Additionally, four (7%) had concomitant FMF and two (3%) had ERA. *M694V* homozygous mutations were detected in two of the FMF patients, and heterozygous mutations were detected in the other two. All patients with ERA had *HLA-B27* antigen positivity. *HLA-B51* antigen was positive in 33 (58%) patients.

Clinical features

The most common clinical symptom was recurrent oral aphthosis (n=57, 100%), followed by musculoskeletal symptoms (n=36, 63%), genital ulcers (n=32, 56%), ocular symptoms (n=27,

Table I. Demographic, clinical and laboratory findings of juvenile Behçet's disease patients.

	n (%)	median (min-max)
Demographic variables		
Total	57 (100%)	
Female/ Male	33 (58%)/24 (42%)	
Age at disease onset (years)		10 (5-16)
Age at diagnosis (years)		12 (5-16)
Lag time in diagnosis (years)		2 (0-6)
Age at study time (years)		16 (9-25)
Disease duration (years)		4 (1-10)
Family history of BD	20 (35%)	
Clinical manifestations		
Oral aphthous lesions	57 (100%)	
Genital ulcers	32 (56%)	
Pseudofolliculitis	20 (35%)	
Erythema nodosum	8 (14%)	
Pathergy positivity	11 (19%)	
Eye involvement	27 (47%)	
Anterior uveitis	10 (17%)	
Posterior uveitis	10 (17%)	
Panuveitis	5 (9%)	
Optic neuritis	2 (4%)	
Vascular BD	10 (17%)	
Cardiac thrombus	1 (2%)	
Neuro-BD	5 (9%)	
Parenchymal	1 (2%)	
Non-parenchymal	4 (7%)	
Gastrointestinal	5 (9%)	
Musculoskeletal	36 (63%)	
Arthralgia	18 (31%)	
Arthtritis	18 (31%)	
Epididymitis	2 (4%)	
Laboratory variables		
HLA–B51 positivity	33 (58%)	
CRP (mg/L)		4 (0.1-98)
ESR (mm/H)		18 (4-103)

BD: Behçet's disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HLA: human leukocyte antigen.

47%), cutaneous findings (n=26, 46%), vascular symptoms (n=10, 17%), neurological manifestations (n=5, 9%), gastrointestinal manifestations (n=5, 9%) and epididymitis (n=2, 4%). Eleven (19%) patients tested positive for pathergy. Headache was the most frequent symptom in neuro-jBD. One (2%) patient had parenchymal-type neuro-jBD, whereas four patients had vascular-type neuro-jBD, including one with transvers and three with dural sinus thrombosis. The main gastrointestinal symptoms were abdominal pain and diarrhoea. Three patients had ulcers in the terminal ileum, and two had multiple ulcers in the intestinal mucosa. One patient who was receiving aggressive immunosuppressive therapy due to pulmonary artery aneurysm and thrombosis presented with epididymitis in the fifth year of treatment.

Table II. Retrospective application of the ISG, ICBD and PEDBD criteria at last follow-up of the cohort.

	n (%)
ISG	31 (54%)
ICBD	54 (95%)
PEDBD	34 (60%)
ISG + ICBD	31 (54%)
ISG + PEDBD	27 (47%)
ICBD + PEDBD	31 (54%)
ISG + ICBD + PEDBD	27 (47%)

ISG: International Behçet's Study Group; ICBD: International Criteria for Behçet's Disease; PEDBD: Paediatric Behçet's Disease group.

Inflammatory eye involvement was identified in 27 (47%) patients. In all but one of these patients, diagnosis of jBD was preceded by diagnosis of uveitis. One patient (mentioned above) developed panuveitis while receiving treatment for neuro-jBD. Among patients with uveitis, one had parenchymal neuro-jBD, one had transverse sinus thrombosis, two had gastrointestinal involvement, one had pulmonary artery aneurysm and two had deep vein thrombosis.

Diagnostic criteria

A comparison of the three diagnostic criteria in terms of sensitivity showed that 31 (54%) cases fulfilled ISG criteria, 54 (95%) fulfilled the ICBD, and 34 (60%) fulfilled PEDBD criteria. The proportions of patients fulfilling the BD diagnostic criteria are shown in Table II and Fig. 1.

Treatment

The treatment choices are summarised in Fig. 2. Treatment was tailored to each patient according to clinical signs and organ involvement. All patients were prescribed colchicine. Diarrhoea and elevated liver enzymes were the main adverse effects of colchicine in two patients, in both of whom they were resolved with dose reduction. Corticosteroid therapy (intravenous and/or oral) was administered to 29 (51%) patients during activation periods of the disease. Indications included aggressive mucosal aphthous lesions, genital ulcers, uveitis and other organ involvements. Immunosuppressive therapies, including azathioprine (AZA; n=19, 33%), cyclosporine (CSA; n=12, 21%), cyclophosphamide (CYC; n=3, 5%), and mycophenolate mofetil (MMF; n=1, 2%), were used as steroid-sparing agents. In cases of life-threatening events, intravenous pulse CYC was the most preferred therapy, followed by AZA as maintenance therapy. CSA treatment with or without AZA and biological therapies (anti-tumour necrosis factor agents), including etanercept (ETC; n=2, 4%), adalimumab (ADA; n=2, 4%) and infliximab (INF; n=5, 9%) were prescribed to patients with eye involvement. Interferon alpha was preferred in one (2%) patient with posterior uveitis and concomitant hepatitis B infection. Leukopenia due to immunosuppressant and/or biological therapies was observed in two cases, gastrointestinal intolerance in one and elevation of liver enzymes in three

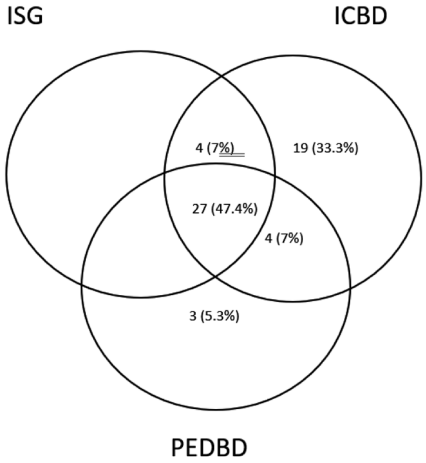

Fig. 1. Sensitivity rates between ISG, ICBD and PEDBD diagnostic criteria[a] of the cohort.
ISG: International Behçet's Study Group; ICBD: International Criteria for Behçet's Disease; PEDBD: Paediatric Behçet's Disease group.

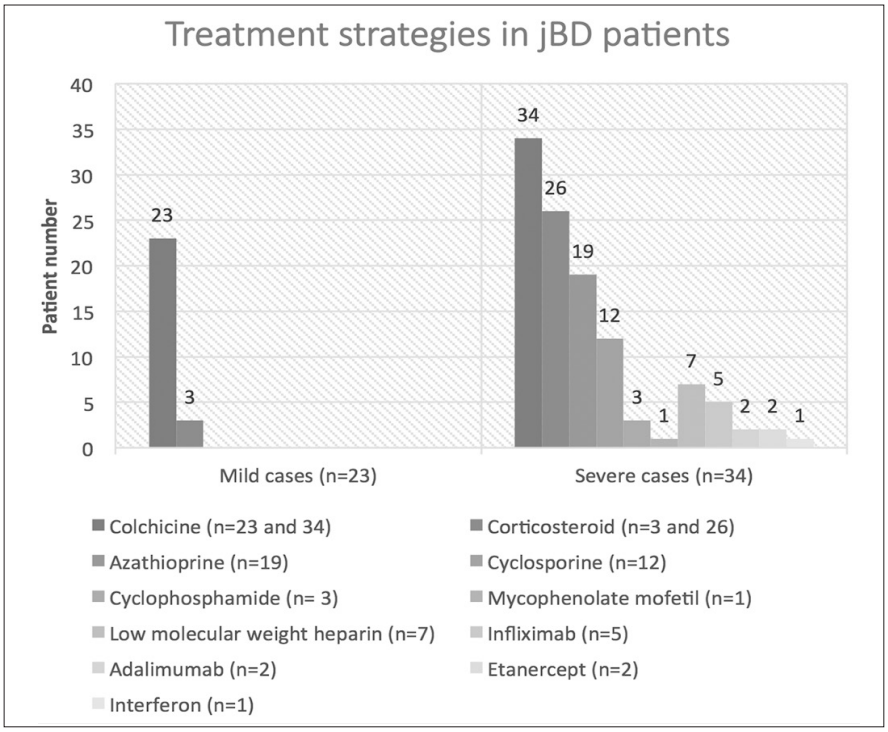

Fig. 2. Summary of treatment strategies in juvenile Behçet's disease cohort.

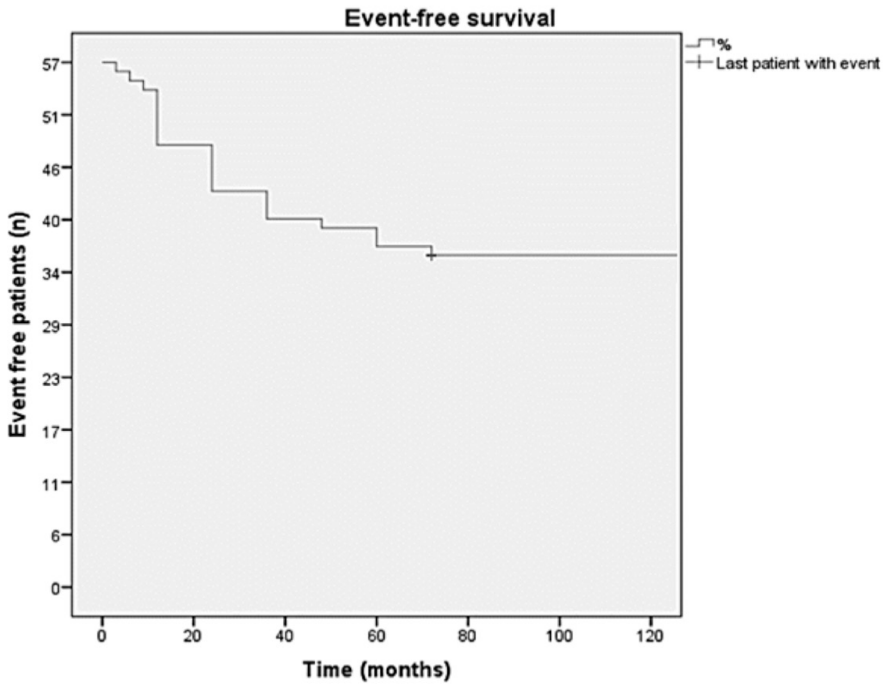

Fig. 3. Overall event-free survival rate for development of new events in patients with juvenile Behçet's disease.

patients. Of the five patients receiving INF, one had multiple aneurysms and thrombosis in the pulmonary artery, one had iliac and caval vein thrombosis, one had neuro-jBD and panuveitis, one had posterior uveitis and one had retinitis. Additionally, ADA was used in two patients for optic neuritis refractory to corticosteroids, AZA and CSA. ETC was prescribed in two patients, one with mucocutaneous lesions with an aggressive course and one with uncontrolled ERA. Low molecular weight heparin (n=7, 12.3%) was prescribed to seven (12.3%) patients with vascular thrombosis in addition to immunosuppressive treatment.

Outcomes

The rate of occurrence of new events over 120 months despite therapy is shown in Fig. 3. One to three events occurred in 21 (37%) cases in the course of 120 months. Severe events occurred in 4 of the 21 cases (19%), while mild events occurred in 17 (81%). The event-free survival rate for development of new events was 95% at one year, 70% at three years, 65% at five years and 50% at eight years. The median IBDDAM score was 5 (range: 3-14) at diagnosis and decreased to 1 (range: 0–6) on the last visit.

Discussion

In this study, clinical findings, system involvements, *HLA-B51* status, family history, disease activity, treatment responses and outcomes were evaluated in a large cohort of jBD patients representing a 10-year experience of a single centre. The results showed favourable outcomes. It is of note that most previous studies on jBD did not include disease activity or outcome data.

In large cohorts of jBD patients from different ethnic populations, the female to male ratios range from 0.47 to 1.49 (Table III). Previous studies had reported variable sex distribution, with

Table III. Comparison of the demographic and clinical data of the patients in the present study and the other large juvenile Behçet's disease cohorts.

	Number of patients	Female/ Male ratio	Median age of onset (years)	Family history for BD (%)	Oral aphtous (%)	Genital ulcers (%)	Cutaneous lesions (%)	Pathergy positivity (%)	Eye involvement (%)	Neuro-BD (%)	Vascular BD (%)	GI-BD (%)
Present report (Ankara, Turkey)	57	1.37	10	35	100	56	46	19	47	9	17	9
Atmaca *et al*. (16) (Ankara, Turkey)	110	1.6	11.6	12.3	100	82.7	76	45.5	30.9	3.6	3.6	NA
Karincaoglu *et al*. (13) (Multicentre, Turkey)	83	1.25	12.3	19	100	82	NA	37	35	7.2	9.6	4.8
Koné-Paut *et al*. (14) (International)	86	1	8.4	16	97.2	60.4	93	63.2	60.4	36	16.2	14
Sungur *et al*. (17) (Ankara, Turkey)	62	0.9	NA	42	100	55	NA	47	NA	13	5	NA
Hamzaoui *et al*. (18) (Tunisia)	81	0.47	16.1	NA	100	76.5	88.9	55.7	44.4	22.2	32.1	NA
Kim *et al*. (19) (Korea)	40	1.49	NA	NA	100	82.5	72.5	17.5	27.5	2.5	NA	5
Nanthapisal *et al*. (20) (UK)	46	1.11	4.8	NA	97.8	74	32.6	60	8.7	32.6	6.5	58.7
Galizzi *et al*. (21) (Italy)	110	0.76	8.3	NA	94.5	33.6	39.6	14.5	43.6	30.9	1.8	42.7
Shahram *et al*. (23) (Iran)	204	0.98	10.5	9.9	91.7	42.2	51.5	57	66.2	4.9	6.4	5.9

BD: Behçet's disease; GI: gastrointestinal; NA: not available.

female predominance in Asian populations and male predominance in Middle Eastern and Mediterranean countries (13, 14, 16-21, 23). In our study, jBD was more common in girls (the female to male ratio was 1.37). Previous studies have reported varying median ages of disease onset between countries: 16.1 years in Tunisia, 4.8 years in the United Kingdom and 8.3 in Italy (18, 20, 21). In two previous studies in Turkey, the median ages of disease onset were slightly later than in our cohort: 11.6 and 12.3 years (13, 16). This study is the first to document a lag of two years between onset and diagnosis, which can have a significant impact on the disease outcome.

The rate of recurrent oral ulcers, one of the most common symptoms in BD, was 100% in our cohort, which is higher than those reported by other studies (14, 20, 21, 23). In contrast, the rate of genital ulcers, the third most common clinical sign in our cohort, is slightly lower than in other cohorts (13, 14, 16, 18, 19, 20), as are the rates of skin lesions and gastrointestinal manifestations (14, 16, 18-21, 23). Vascular jBD was more prevalent in our study than in other studies (13, 14, 16, 17, 20, 21, 23), except in Hamazoui *et al.'s* study (18). Similarly, eye involvement was more common than in other cohorts (13, 16, 18-21). The rate of pathergy test positivity in our cohort was 19%, which is quite lower than in other studies (14, 18, 20, 23), including Turkish series (37-47%) (13, 16, 17), except one study from Italy (21). *HLA-B51* positivity, on the other hand, was 56% in our cohort, which is consistent with other studies (21).

Family history plays an important role in the diagnosis of this rare autoinflammatory vasculitic disease and is more pronounced in pediatric than in adult studies (14, 22). In large Turkish cohorts, it ranges from 12% to 42% (12, 16, 17). However, there is no proven genetic transmission. We found a positive family history rate of 35%, which can be considered high. Hence, we speculated that having a family member with BD increases awareness of the disease's symptoms and makes patients refer to rheumatology clinics while still in the early phase of the disease. One possible reason for delayed diagnosis can be the broad spectrum of diseases resembling BD. During differential diagnosis, periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA), hyperimmunoglobulin D syndrome (HIDS) and A20 haploinsufficiency (HA20) must be kept in mind, as aphthous lesions and fever are the cornerstone clinical findings in all these diseases (24). Therefore, due to the similarities, some PFAPA and HIDS patients could be misdiagnosed with BD or vice versa in adulthood (25).

Oral aphthosis recurring more than three times per year is the mandatory criterion according to the ISG. The lack of vascular and neurological involvements may cause difficulty in making diagnosis of BD especially in children. On the other hand, some jBD patients show typical vascular and/or neurological signs without oral aphthous lesions. The main differences between ISG and ICBD are that both criteria are not evaluated with equal points and oral aphthae is not a mandatory criterion. Another important modification in ICBD is the addition of vascular and neurological manifestations to the criteria. Both criteria were developed for adult patients, while PEDBD was developed to diagnose pediatric BD cases. Removal of recurrent oral aphthosis as a mandatory criterion and addition of vascular and neurological symptoms to PEDBD criteria may be necessary for preventing missed cases in children as a rare subgroup of BD. Additionally, the PEDBD group did not include pathergy test positivity as a criterion for juvenile BD (3). In line with this, only one-fifth of our patients tested positive for pathergy. In this study, the sensivity of ISG criteria was 54%, ICBD was 95%, and PEDBD criteria was 60%. In line with our study, Batu et al. reported a higher sensitivity in PEDBD compared to ISG criteria for diagnosis of jBD. While they did not evaluate the sensitiviy of ICBD (9), we found highest sensitivity in ICBD. These results show that most patients were fulfilled ICBD criteria and diagnosed as complete jBD cases, while some of them

were defined as incomplete cases according to ISG and PEDBD criteria. This may result in delayed diagnosis in some patients and effect of successful treatment. Incomplete cases according to ISG and PEDBD criteria could be diagnosed using the ICBD. Considering that all the patients in our cohort had a probable diagnosis of jBD over a 10-year follow-up, the sensitivity of the PEDBD and ISG criteria was lower to diagnose cases, which may cause considerable harm to the patients.

Currently, there is not a standard treatment guideline for jBD. Treatment is based on suppression of the inflammatory phases of the disease with corticosteroids, immunosuppressants and biological agents (11). Despite the treatment efforts, BD can be associated with high morbidity and mortality (26). Measuring disease activity is a useful tool for evaluating the effectiveness of the treatment and predicting the long-term damage caused by the disease (15). Using the IBDDAM, we found that the treatment regimens were highly effective in suppressing disease activity.

This is the first study to report findings regarding the occurrence of new events in the follow-up of jBD patients. Severe events occurred in 7% and mild events occurred in 30% of our patients despite colchicine therapy during a 10-year follow-up. We speculate that the prevalence of severe events is low in patients on colchicine therapy. Also, the event-free survival rate was remarkably high at one year, and half of the patients never experienced even mild events over 10 years.

This study analysed not only clinical and laboratory manifestations but also patterns of disease activity and outcomes in a Turkish jBD population in a tertiary referral centre. A major limitation of this study is its retrospective design. Its small sample size is another limitation in terms of not only sensitivity/specificity but also survival analysis. Moreover, as we did not include initially suspected but unconfirmed cases, we were unable to evaluate the specificity of the three sets of classification criteria. ICBD and PEDBD criteria are relatively new, so we have retrospectively performed these classification criteria to the patients based on expert physician's clinical diagnosis, this may be another limitation of the study. Comprehensive studies evaluating these criteria in large cohort and a large number of control groups, are needed.

Conclusion

This study shows that jBD has favourable outcome, with lower IBDDAM scores and high event-free survival rates, suggesting satisfactory treatment responses. Juvenile BD patients may have spontaneous remissions, and these patients should be followed-up closely for the development of new symptoms related to BD. The observed frequent familial occurrence with a younger age at diagnosis is possibly due to increased awareness of the disease among family members. However, a significant delay in diagnosis was still observed, partly due to limitations of the available diagnostic criteria. Although incomplete cases according to ISG and PEDBD criteria could be diagnosed using the ICBD, this issue warrants further studies. Early diagnosis, appropriate treatment and systematic monitoring of patients are important for reducing jBD-related morbidity and mortality.

Acknowledgements

The authors thank FMF patients and their caregivers for participating in this study.

References

1. SAKANE T, TAKENO M, SUZUKI N, INABA G: Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
2. OZEN S: Pediatric onset Behçet disease. *Curr Opin Rheumatol* 2010; 22: 585-9.
3. YILDIZ M, KOKER O, ADROVIC A, SAHIN S, BARUT K, KASAPCOPUR O: Pediatric Behçet's disease - clinical aspects and current concepts. *Eur J Rheumatol* 2019; 7 (Suppl 1): 1-10.
4. COHEN L: Etiology, pathogenesis and classification of aphthous stomatitis and Behçet's syndrome. *J Oral Pathol* 1978; 7: 347-52.
5. VERITY DH, MARR JE, OHNO S, WALLACE GR, STANFORD MR: Behçet's disease, the Silk Road and HLA-B51: historical and geographical perspectives. *Tissue Antigens* 1999; 54: 213-20.
6. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
7. INTERNATIONAL TEAM FOR THE REVISION OF THE INTERNATIONAL CRITERIA FOR BEHÇET'S DISEASE (ITR-ICBD): The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; 28: 338-47.
8. KONÉ-PAUT I, SHAHRAM F, DARCE-BELLO M *et al*.: Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis* 2016; 75: 958-64.
9. BATU ED, SONMEZ HE, SOZERI B *et al*.: The performance of different classification criteria in paediatric Behçet's disease. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S119-23.
10. GURLER A, BOYVAT A, TURSEN U: Clinical manifestations of Behçet's disease: an analysis of 2147 patients. *Yonsei Med J* 1997; 38: 423-7.
11. HATEMI G, CHRISTENSEN R, BANG D *et al*.: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77: 808-18.
12. CIRKINOGLU MS, DEMIR S, BILGINER Y, OZEN S: Behçet's disease in children: single-center experience. *Turk Pediatri Ars* 2019; 54: 179-84.
13. KARINCAOGLU Y, BORLU M, TOKER SC *et al*.: Demographic and clinical properties of juvenile-onset Behçet's disease: A controlled multicenter study. *J Am Acad Dermatol* 2008; 58: 579-84.
14. KONÉ-PAUT I, YURDAKUL S, BAHABRI SA *et al*.: Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. *J Pediatr* 1998; 132: 721-5.
15. DAVATCHI F, AKBARIAN M, SHAHRAM F, TEBBI M, CHAMS C, CHAMS H: Iran Behçet's disease dynamic activity measure. Abstracts of the XIIth European congress of rheumatology. *Hungarian Rheumatol* 1991; 32: 134.
16. ATMACA L, BOYVAT A, YALCINDAG FN, ATMACA-SONMEZ P, GURLER A: Behçet disease in children. *Ocul Immunol Inflamm* 2011; 19: 103-7.
17. SUNGUR GK, HAZIROLAN D, YALVAC I *et al*.: Clinical and demographic evaluation of Behçet disease among different paediatric age groups. *Br J Ophthalmol* 2009; 93: 83-7.
18. HAMZAOUI A, JAZIRI F, BEN SALEM T *et al*.: Comparison of clinical features of Behçet disease according to age in a Tunisian cohort. *Acta Med Iran* 2014; 52: 748-51.
19. KIM DK, CHANG SN, BANG D, LEE ES, LEE S: Clinical analysis of 40 cases of childhood-onset Behçet's disease. *Pediatr Dermatol* 1994; 11: 95-101.
20. NANTHAPISAL S, KLEIN NJ, AMBROSE N, ELEFTHERIOU D, BROGAN PA: Paediatric Behçet's disease: a UK tertiary centre experience. *Clin Rheumatol* 2016; 35: 2509-16.
21. GALIZZI R, PIDONE C, CANTARINI L *et al*.: A national cohort study on pediatric Behçet's disease: cross-sectional data from an Italian registry. *Pediatr Rheumatol Online J* 2017; 15: 84.
22. TREUDLER R, ORFANOS CE, ZOUBOULIS CC: Twenty-eight cases of juvenile-onset Adamantiades-Behçet disease in Germany. *Dermatology* 1999; 199: 15-9.

23. SHAHRAM F, NADJI A, AKHLAGHI M *et al*.: Paediatric Behçet's disease in Iran: report of 204 cases. *Clin Exp Rheumatol* 2018; 36 (Suppl. 115): S135-40.
24. AESCHLIMANN FA, LAXER RM: Haploinsufficiency of A20 and other paediatric inflammatory disorders with mucosal involvement. *Curr Opin Rheumatol* 2018; 30: 506-13.
25. BERTEAU F, ROUVIERE B, DELLUC A *et al*.: Autosomic dominant familial Behçet disease and haploinsufficiency A20: A review of the literature. *Autoimmun Rev* 2018; 17: 809-15.
26. ALPSOY E: Behçet's disease: A comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. *J Dermatol* 2016; 43: 620-32.