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Paediatric Behçet's Disease: Data From A Single Center Experience in Turkey

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Abstract

Behçet's disease (BD) is a multisystemic inflammatory disease with unknown etiology. It is characterized by recurrent oral and genital ulcerations, uveitis, and skin lesions, various musculoskeletal, gastrointestinal, central nervous system, and vascular manifestations. The aim of this study was to analyse the demographic characteristics and clinical features, treatment in Turkish paediatric BD from a single center experience. The records of 36 patients with BD who were diagnosed according to the International Study Group criteria between January 2017 and January 2019 in the department of paediatric rheumatology, were retrospectively reviewed. Data on demographic, clinical features and therapy were collected. A total of 36 (19 male) patients were included in this study. Mean age at disease onset was 9.36±4.45 years and mean age at diagnosis 13.99±2.83 years. The frequencies of signs/symptoms were: recurrent oral aphtosis 100%, genital ulcers 80.6%, musculoskeletal 30.6%, ocular 16.7%, neurological 11.1% and vascular involvement 11.1%, gastrointestinal 2.8%. Colchicine and corticosteroids were the main treatments. In this single-center retrospective study, we analyzed the data of paediatric BD and their treatment from a single center in Turkey. The presented small series and the literature review suggest that paediatric BD is a heterogeneous disease with varied clinical manifestations.

Keywords: Juvenile, Behçet syndrome, oral ulcer

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Introduction

Behçet's disease (BD) is a systemic auto-inflammatory disease affecting all sized vessels and is therefore classified as a variable vasculitis. It has unknown origin that was first demonstrated by a Turkish dermatologist, Dr Hulusi Behçet in 1937.[1] It is commonly seen in the region of the 'Silk Road', which also includes our country. It is well known that it may affects many organ and/or systems such as central nervous system, musculoskeletal system, and gastrointestinal system, and it is characterized by ocular and cutaneous findings, as well as recurring oral and genital ulcers.[2] BD generally presents in the second to fourth decades of life and although the incidence of paediatric onset is rare.[3,4] But it is rising in children gradually due to awareness. Unfortunately, there is no pathognomonic test to make the correct diagnosis, which is based on clinical criteria. The mostly wide criteria used are those developed by an international study in 1990 called the International Behçet's Study Group (ISG) with 85% sensitivity and 96% specificity.[5,6] Recently, the Paediatric BD group (PEDBD) has developed a new set of criteria for the diagnosis of BD in children.[2] This PEDBD criteria has higher sensitivity (91.7%), but lower specificity (42.9%) when compared to ISG.[7] There are limited data regarding treatment and outcomes of paediatric patients with BD especially in Turkey. The primary aim of this study was to collect information on demographic and clinical features from paediatric patients with BD in a single center and compare them with the reports from the literatüre.

Highlights

- Behçet's disease is characterized by recurrent oral and genital ulcerations, uveitis, and skin lesions, various musculoskeletal, gastrointestinal, central nervous system, and vascular manifestations.
- The main treatment in mucocutaneous involvement is colchicine, and in organ and system involvement, treatment varies according to the site of involvement.

Material and Method

The files of patients who had been seen in our outpatient department (during routine follow-up visits) between January 2017 and January 2019 were retrospectively evaluated. Demographic, clinical and laboratory data of patients were collected from the patients' files and hospital database. An information form was completed about demographic features (sex, age at onset, age at diagnosis), ethnicity, family history, follow-up time, clinical manifestations (mucocutaneous, musculoskeletal, ocular, gastrointestinal, vascular, neurological manifestations), the presence of human leucocyte antigen (HLA)- B51 positivity and treatment.

Behçet's disease was diagnosed according to the ISG criteria.[5,6] The parents gave their written informed consents prior to the present study, which was approved by our hospital ethics committee. The study was carried out with the permission of Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital Clinical Research Ethics Committee (Date: 04.03.2021, Decision No: E-21/03-121). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients were excluded from the study if no approval from their families to participate in the study. Disease onset after the age of 16 was considered a reason for exclusion. Patients who had no clear diagnosis of BD were excluded.

Statistical Package for Social Sciences (SPSS) (version 22.0; Chicago, IL, USA) was utilized for statistical analysis. According to the determination of distribution tests, continuous variables were summarized as mean and standard deviation (SD) and as median and minimum-maximum where appropriate. Clinical and demographic characteristics were summarized by mean and standard deviation for continuous variables and count and percent for categorical variables.

Results

The study group comprised 36 paediatric Behçet's disease with a mean age of 16.61±3.10 years. Mean age at onset was 9.36±4.45 years and mean age at diagnosis 13.99±2.83 years. There was a mean of approximately 4 years between the initial manifestation and diagnosis. All patients were Turkish except one patient (from Syria). The ratio of male to female in the study was 1.11 (female: 17, male:19). The time between the development of uveitis and the diagnosis of Behçet disease was 6 years for this patient. Among all pateints, the most frequent of sign/symptom was recurrent oral aphtosis with 100%. The patients' demographic characteristics and clinical findings are summarised in **Table 1**. Ocular involvement occurred in 6 patients: 2 (33.3%) as anterior uveitis, 2 (33.3%) posterior uveitis, 2 (33.3%) bilateral panuveitis.

Among 4 patients (11.1%) who were found to have vascular involvement in the follow-up, one had arterial involvement, three had venous involvement. Venous involvement occurred in 6 site in 3 patients, including cerebral venous thrombosis (one patient had sagittal venous thrombosis and transverse sinus thrombosis, one patient had right iliac vein thrombosis and left femoral vein thrombosis, one patient had sagittal venous thrombosis and right femoral vein thrombosis). The patient with arterial involvement had thrombosis in the percheron artery. Among four patients who were found to have central nervous system (CNS) involvement, one had parenchymal involvement, and three had non-parenchymal involvement. In the patient with parenchymal involvement had other clinical findings for seven years. He was admitted with a history of walking disability. He had parenchymal and spinal cord involvement at MR images compatible with BD. Two patients with non-parenchymal involvement were admitted with headache as the initial neurological symptom. They revealed benign intracranial hypertension. Two of them had cerebral venous sinus thrombosis. The other patient with non-parenchymal involvement was presented with fever, occult onset of blurry vision, which progressed to vision loss, and consciousness. He had percheron artery thrombosis.

Table 1
Clinical features of paediatric BD in the literature

	Çirkinoğlu 2019 (Turkey)	Hu 2019 (Taiwan)	Shahram 2018 (Iran)	Gallizzi 2017 (Italy)	Yıldırım 2020 (Turkey)	Tekin Ekici 2021 (Turkey)	Batu 2020 (Turkey)	Present Study
Total number	34	55	204	110	57	72	165	36
Male/female ratio	1,1	0,6	1,02	1,3	0,72	0,8	0,91	1,1
Mean age at onset	11.1	11	10.5	8.3	10	11	11	9.3
Recurrent oral aphtosis (%)	97	100	91.7	94.5	100	100	100	100
Genital ulcers (%)	62	69.1	42.2	33.6	56	68.1	64.8	80.6
Pseudofoliculitis/Pustular lesions (%)	82	36.4	43.1	39.6	35	19.4	26.8	38.9
Erythema nodosum (%)	N/A	N/A	10.3	N/A	14	9.7	19.4	25
Vascular manifestations (%)	32	1.8	6.4	10	17	18.1	11.5	11.1
Pathergy test positivity (%)	50	N/A	57	14.5	19	28.8	27.3	33.3
Ocular manifestations (%)	35	27.3	66.2	43.6	47	20.8	13.3	16.7
CNS* involvement (%)	18	3.6	4.9	30.9	9	15.3	15.8	11.1
Gastrointestinal involvement (%)	5.8	N/A	N/A	42.7	9	20.8	12.1	2.8
Joint involvement (%)	38	27.3	30.9	N/A	31	36.1	44.8	27.7
Positive family history for BD (%)	N/A	N/A	N/A	12	31	41.7	29.1	41.7

* CNS: central nervous system * N/A, not available

Gastrointestinal system (GIS) involvement developed in one patient (ulcerated lesions in the terminal ileum). No case pulmonary artery aneurism and heart involvement developed in our cohort. Pathergy test was positive in 12 (33.3%) of cases in which it was performed (25/36). Table summarises the clinical phenotype of our paediatric cohort compared to other paediatric series.

Median frequency oral aphtosis was 24 (4-120) /year in before colchicine and 3.5 (0-12) /year in after colchicine. Median frequency genital ulcer was 1 (0-5) /year in before colchicine and 0 (0-2) /year in after colchicine. All patients had significant benefit from colchicine for oral aphtosis and genital ulcers. Only azathioprine was received in 2 patients because of colchicine-resistant aphthosis lesions. There were familial cases in 41,7% of our patients. Two of them were first-degree relatives, others were second-degree relatives. HLA-B51 testing was performed in 12 patients and was present in 7 (58.3%). Most of our patients (77.7%) had increased acute phase reactants (erythrocyte sedimentation rate and C-reactive protein). Mean ESR values at the time of diagnosis was 28 mm/hour (15-98) and mean CRP values at the time of diagnosis was 27 mg/L (6-75). Genetic testing for Familial Mediterranean Fever (FMF) was performed in 9/36 patients because of recurrent fever and abdominal pain. Results were negative in 6 cases and the other 3 patients had heterozygous mutations. M694V heterozygous mutations were detected in two of them, and M680I heterozygous mutation was detected the other patient. These mutations didn't change the treatments. All patients received topical steroid therapy (for ocular and/or oral aphthous lesions) and colchicine. Immunosuppressants recevied in 16 patients (44.4%) with the following drugs: 9 azathioprine, 4 cyclophosphamide, 2 methotrexate, 1 sulphasalazine. Anti-tumor necrosis factor-alpha (anti TNF-α) was used in 2 patients (adalimumab). The patient who was found to have GIS involvement (ulcerated lesions in the terminal ileum) were treated with sulphasalazine and adalimumab. The other patient using adalimumab had chronic arthritis in the right knee. Anticoagulant treatment was given additionally to patients who had vascular involvement. Four patients who had have central nervous system (CNS) involvement were treated with cyclophosphamide in addition to high-dose intravenous steroid treatment. Non Steroidal Anti-Inflammatory Drugs (NSAIDs) were used in 20 cases for arthritis and arthralgia. The follow-up of all patients who were evaluated in the study is still continuing.

Discussion

In this single-center retrospective study, we analyzed the data of paediatric BD and their treatment from a single center in Turkey and compared our findings to those of other paediatric studies (**Table 1**). BD is less frequent in childhood. In the literature, there are few data on paediatric BD in Turkey, mostly limited to adult data. The mean age of disease onset was 9.3 years in our study, similary to most of the studies. A reported as 8.3 years in a multi-center study conducted from Italy by Galizzi et al. in which 110 paediatric patients with BD were evaluated.[8] Atmaca et al and Çirkinoğlu et al showed in their cohort average age at onset was 11.6 and 11.1, respectively.[9,10] But in some studies it has been shown to present extremely very earlier.[11,12] The reason for this is not known exactly. In our study, we noted a diagnostic delay of 4 years, similar to in previous studies.[8,12] In the literature, adult and paediatric studies have reported that the mean delay is two or four years.[12,13] Nanthapisal et al noted a significant diagnostic delay up to 13.5 years in their cohort. They commented that the disease is not well known in the world.[11]

The male/female ratio was 1,1 in our cohort and was consistent with the literature. Shahram et al was reported as 1,02 in their stduy.[14] Male predominance seems to be slightly more common in children like adults studies.

Most of studies showed that recurrent oral aphtosis was the most frequent clinical manifestation (**Table 1**). Our cohort demonstrated that recurrent oral aphtosis is the most common symptom. Similar to that of adults, the most common initial manifestation of BD in children is oral ulcers: 97.3% in our study, and 100% and 75% in others.[12-14]

The second most common clinical finding in our patients was genital ulcer (80.6%) similarly Hu et al. and Nanthapisal et al. studies.[11,12] Galizzi et al showed that in 110 pediatric patients with BD, the second most common clinical finding was reported to be ophthalmologic involvement.[8] Another study from Turkey the second most common cause for presentation was cutaneous lesions (82%).[10] Interestingly, only 16.7 % of the children had ocular involvement in our series, this contrasts with the high frequency of 30-35 % reported in other Turkish studies[9,10] and 43.6 % in Italian children.[8]

Pathergy test positivity has been reported to be very different, especially in children.[8-10] We found a positivity of 33.3%.

We observed 41,7% of our patients had a positive family history for BD. This rate seems to be higher than the literature. Galizzi et al. showed that this rate to be 12%.[8] Also Koné-Paut et al. found familial cases in 15% of children.[15] This may be due to the frequent occurrence of BD in Turkey.

Although HLA-B51 may be positive in healthy people, it is known that highlier positive in patients with BD than in healthy people.[16] HLA-B51 testing was performed in 12 patients and was present in 7 (58.3%).

Ocular involvement has a wide range (8-66%) in the literatüre.[11-14] Ocular involvement occurred in 6 patients (16.7%) in our study. Two of them had bilateral panuveitis. In the literature, it is reported that panuveitis is the most common ocular involvement in BD. Similarly Atmaca et al showed that panuveitis in 13 eyes (23.6%).[9] Similar to our observation, a retrospective study of 86 paediatric BD cases by Kone-Paut et al reported that panuveitis in 28% patients.[15] In a study from Italy, ocular involvement is the second manifestation in their cohort (43.6%).[8] Shahram et al reported ocular lesions were more frequent (66.2%) compared to other reports.[14] This difference could be due to patients with different ethnic backgrounds in different countries.

Gastrointestinal system involvement rates reported in studies from Italy and United Kingdom has been reported 42-58% that seems to be higher rate especially according to studies reported from Turkey.[8-11] Prevalence of GIS involvement changes signifcantly across diferent ethnicities, being much more common in the Far East.[17-23] The frequency was as high as 50% in a Japanese cohort and 1% in a study in Turkey.[17-23] In the children as was the case in adult studies of GIS involvement is less common in Turkey.[10,19]

Consistent with the literatüre vascular involvement developed in 11.1% of the our patients. In our series, the patients who had vascular involvement, but did not have pulmonary involvement, were treated with heparin infusion or subcutaneous enoxaparin and warfarin. There were no complications or side effects.

In BD, there is no definite recommendations for the treatment of pediatric patients. Treatment is usually based on adult studies and according to the severity of organ involvement. The systemic treatments more commonly used were colchicine and corticosteroids, followed by immunosuppressants. All our patients received colchicine as monotherapy, presented by recurrent oral aphtosis, genital ulcer and skin lesions. All patients had significant benefit from colchicine for oral aphtosis and genital ulcers. Only azathioprine was received in 2 patients because of colchicine-resistant oral aphthosis lesions. Two patients received biologic therapy. Pulmonary artery aneurism wasn't found in our cohort. No patient died.

There are some limitations to our study. Retrospective study and limited number of patients may be considered as our limitations.

Conclusion

Our data showed a slightly male predominance in juvenile Behçet disease. The clinical spectrum of our cohort in this study was similar to that of other reports; however, genital ulcers were noticed to occur more frequently; while vascular, gastrointestinal and neurologic involvement was seen rarely in our series. Demographic and clinical features of paediatric BD may vary according to geographical region, gender and ethnicity. We hope that this study will contribute to the epidemiologic data of paediatric BD which may exhibit different clinical and demographic features in different parts of the world.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital Clinical Research Ethics Committee (Date: 04.03.2021, Decision No: E-21/03-121).

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