

Original Article

Pediatric-onset Behçet Disease in Bahrain: Report of Nine Cases and Literature Review

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Abstract

Background: This report studies the clinical features of Behçet disease (BD) in children and compares our results with other international studies.

Methods: We retrospectively reviewed patient data that included the clinical picture, HLA typing, and treatment in BD cases.

Results: This study reviewed data from a total of nine children with BD. Median age at presentation was seven years, with a male to female ratio of 2:1. There was one patient who had Down's syndrome. Oral ulcers were present in all children, while genital ulcers were present in only 66% of cases. Skin manifestation was seen in 88% and uveitis in 55%. There was evidence of gastrointestinal (55%), neurological (55%), and musculoskeletal manifestations (77%). HLA B5 was positive in 66% of cases and 55% had positive family histories. Apart from gastrointestinal symptoms, our results were comparable with other studies.

Conclusion: Awareness of BD symptoms in the pediatric age group is crucial for early diagnosis and treatment. The coexistence of BD and Down's syndrome needs further genetic study, which may link these two major disorders.

Keywords: Bahrain, Behçet disease, children

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Introduction

Behçet disease (BD) is a chronic multi-systematic inflammatory disease of unknown origin.¹ An International Study Group has proposed criteria for diagnosing BD that requires the presence of recurrent oral ulcers plus two of the following symptoms in the absence of other systemic diseases: recurrent genital ulcerations, eye lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, papulopustular lesions, or acneiform nodules), or a positive pathergy test.² Pediatric onset BD has been reported in the literature as an uncommon disease that presents before the age of 16 years and has a distinct clinical presentation of recurrent abdominal pain and episodes of fever.³ While the clinical feature of BD in children in many studies is reported to be similar to adults, other authors have concluded more neurologic and gastrointestinal involvement in juvenile-onset BD. However, the frequency of familial cases is significantly higher in the pediatric group.^{4,5}

We reviewed nine cases of children with BD who were followed in the Pediatric Rheumatology Clinic between 2002–2010. Our results were compared with pediatric-onset BD in other international studies. This review also included HLA typing and basic treatment for BD children.

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Patients and Methods

We reviewed the files of patients who were below 16 years of age and suspected to have BD. These patients were followed in the Pediatric Rheumatology Clinic at Salmaniya Medical Complex (SMC) from 2002–2010. SMC is a tertiary hospital that includes the Pediatric Department which consists of 200 beds and pediatric clinics. Biographic data, age at presentation and time spent for the patients to be diagnosed with BD was included. Duration of disease, clinical pictures at presentation, and other involved systems were registered. Endoscopy findings and neurological investigations were reviewed.

Family history of BD and HLA typing were obtained. HLA studies were performed by the microlymphotoxicity method according to Tersaki.⁶ Treatment and the use of biological therapy were reviewed.

Diagnosis of BD was based on the International Study Group Criteria for Diagnosis of BD as the presence of recurrent oral ulceration at least three times/year and two of the following symptoms: recurrent genital ulceration, eye lesions, cutaneous lesions, or a positive pathergy test in the absence of other clinical explanations.²

Z-test was used to test the difference in clinical data values between the study population and other studies. *P* was considered significant if less than 0.5.

Results

A total of ten patients were diagnosed with BD. With the exception of one case, the remainder fulfilled the criteria for the diagnosis of BD.² All patients who were natives of Bahrain were below

Table 1. Clinical data of nine children with Behçet disease (BD).

Pt. no	AP (y)	AD (y)	TD (m)	DD (Y)	Sex	Oral ulcers	Genital ulcers	Skin	Uveitis	Other systems	FH	HLA type
1	5	6	11	8	M	+	+	-	+	GI, MSK, kidney, hair loss.	+	A11,B52(5),B45,Bw4
2	10	12	20	4	M	+	-	+	+	GI, CNS, MSK	-	A11,A26,B51,B70,Cw4-Cw6,Bw4-Bw6
3	7	7	5	4	M	+	+	+(PT)	+	GI, CNS, MSK	+	A1,A23,Bw4,Bw6,Cw4
4	6	6	6	1	F	+	-	+	+	-	+	A1,B73
5	6	6	5	1	M	+	+	+	-	GI, MSK	+	A2,A74,B51 (5),B35
6	12	12	4	1	F	+	-	+	+	Hair loss	+	A2,A19,B51 (5),Cw4-Cw6,Bw4-Bw6
7	11	15	48	6	M	+	-	+(PT)	+	CNS, MSK, lungs	-	A2,A29 (9),B49 (21),Bw4-Bw6,Cw2-Cw7
8	3	9	60	3	F	+	+	+(PT)	+	Down's syndrome	-	A11,A31,B51 (5),B70,Bw4-Bw6,Cw
9	13	15	24	7	M	+	+	+(PT)	-	CNS, lungs	-	A2,A32 (19),B52 (5),B78,Bw4-Bw6,Cw7

AP = age at presentation; AD = age at diagnosis; TD = time to diagnosis; DD = duration of disease; PT = pathergy test; FH = family history.

16 years of age at the time of diagnosis. Age at presentation ranged from 3 to 13 years with a median of 7 years (Table 1). The male to female ratio was 2:1 and the time to reach a diagnosis ranged from 4 to 60 months, with a median of 11 months. Duration of disease ranged from one to eight years (median: four years).

Five (55%) patients had family histories of BD. Two patients, a boy who presented at age six and his niece who also presented at age six (cases 1 and 4) were positive for a family history of BD in the boy's mother and grandmother. Two other patients were a boy who presented at the age of 6 and his sister who presented at the age of 12 (cases 5 and 6) with BD. Another boy's father had a history of BD (case 3).

Case 8, a 13-year-old girl with Down's syndrome and no cardiac complications presented with recurrent mouth ulcers that were diagnosed as herpetic stomatitis at age of three years. At age six she was seen by an ophthalmologist for red eyes which turned out to be posterior uveitis. She was referred to a Rheumatology Clinic at age nine for complaints of arthritis and skin lesions, where she was diagnosed with BD.

A total of six out of nine (66%) patients had the HLA B5 allele. Among those, four had HLA B51 and two had HLA B52.

Table 2 shows the results of this study. One patient presented with recurrent conjunctivitis. One who only had recurrent abdominal pain underwent an endoscopy, which revealed nodules in the pre-antral area. Microscopically there was inflammation in the gastric mucosa while the intestinal biopsy revealed non-specific inflammation and foci of minimal hemorrhage in the lamina propria.

Table 2. Study results.

Patient's data	Results
No. of patients	9
Age, years (median)	3–13 (7)
M:F ratio	2:1
Oral ulcers	9 (100%)
Genital ulcers	5 (55%)
Skin lesions	8 (88%)
Uveitis	7 (77%)
Gastrointestinal manifestations	5 (55%)
Neurological manifestations	4 (44%)
Arthralgia/arthritis	7 (77%)
HLA B5	6 (66%)
Positive family history	5 (55%)

Two patients with meningoencephalitis had cognitive impairment that primarily involved memory function, which led to learning disabilities. Apart from a patient with seizure disorder, those with neurological symptoms had no changes in their EEG or brain images.

Two patients had bronchial asthma. One case had an abnormal urine analysis, which showed pyuria and hematuria, but his renal function was normal. Renal biopsy was recommended but refused by the family.

Patients with oral ulcers, skin manifestations and uveitis were treated with local treatment, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, or methotrexate. Patients with refractory arthritis required biological treatment with anti-tumor necrosis factor-alpha (anti-TNF- α ; Etanercept) which resulted in significant improvement. Colchicine was administered to two patients with oral and genital ulcers, arthritis, and recurrent abdominal pain.

Discussion

BD is a multi-systemic vasculitic disease. Pediatric onset is defined as presentation with BD below the age of 16 years, whereas juvenile onset BD is presentation after 16 years of age with symptoms that started before age 16.³

A growing number of studies have been published on BD in this age group. However, the diagnosis of BD was frequently reported to be late in the absence of the clinical trial of oral or genital lesions, and eye manifestations.⁷ Similarly, in our study the delay in diagnosing BD ranged from 4 months to 6 years.

Familial aggregation of BD was found to be significantly higher in the pediatric group compared to the non-pediatric group.⁸ Among the nine studied pediatric cases, five (55%) had first degree relatives with BD, which supported the hypothesis of a genetic component in the pathogenesis of BD as postulated by others.⁹

In the current study the presence of HLA B5 allele, either B51 or B52, was 66.7%, which was similar to that reported in the adult Bahraini population with BD. In that study the incidence of HLA B5 in the Bahraini population was estimated to be 23%, which

Table 3. A comparison between patient data in our study and other studies.

	Current study	Karıncaoglu, et al. ⁵	Borlu, et al. ⁴	Laghamri, et al. ¹⁵	Bahabri, et al. ¹⁶
No	9	10	17	13	12
Age, years (median)	7	4	—	13.9	11.5
M:F ratio	2:1	4:6	12:5	10:3	1.4:1
Oral ulcers	100%	100%	100%	100%	100%
Genital ulcers	55%	60%	94%	76%	91%
Skin lesions	88%	90%	64%	7.6%	83%
Uveitis	77%	50%	24%	76%	50%
Gasrointestinal	55%	50%	12%	7.6%	0%
Joints	77%	60%	76%	30.7%	75%
Positive family history	55%	0%	45%	30.7%	—

had been calculated from a total of 425 healthy Bahraini kidney transplant donors. The reported relative risk for developing BD in those who were HLA B5-positive compared to the general Bahraini population was reported to be 6.35.¹⁰

Headache is the most common neurological symptom in BD of which migraine has been reported as the most common type followed by tension headache. However, patients with BD in our study who complained of headaches and no neurological symptoms were not considered to have neuro-BD, which was in accordance with previous studies.^{11,12} Cognitive impairment that involved memory function was frequently observed among 26 patients with BD without overt neurological involvement.¹³ In our study we reported two patients that had memory defects and difficulty learning, which could be attributed to meningoencephalitis during their infancy rather than disease activity or steroid therapy.

Data such as oral ulcers, genital ulcers and uveitis from our study were comparable with other studies (Table 3). There were familial cases of BD (55%) in our study whereas a study by Kari et al. revealed no familial BD (P value = 0.007).¹⁴

In our study, there were more skin lesions (88% vs. 7.6%), gastrointestinal symptoms (55% vs. 7.6%), and arthritis (77% vs. 30.7%) compared with Moroccan children with P values of 0.001, 0.014 and 0.033, respectively.¹⁵

Compared to the Borlu et al. study, we reported more gastrointestinal manifestations (55%) compared to their study (12%) with a P value of 0.019 while no cases with gastrointestinal symptoms were observed among Saudi children (P = 0.003).^{4,16}

We detected only one case with Down's syndrome and BD in the literature.¹⁷ This patient was a girl who presented with recurrent mouth ulcers followed by uveitis, skin lesions and arthritis with a duration of two to three years between each symptom. Similarly, our patients developed sequences of BD symptoms that occurred every two to three years. An association between Down's syndrome and vasculitis has been reported.¹⁸ In addition, the rare association of Down's syndrome and mannose-binding lectin deficiency (MBL) with IgG2 deficiency and cutaneous vacuities has been observed. In this case there was a prothrombin mutation and deep venous thrombosis (DVT).¹⁹ MBL deficiency has also been reported with vasculitis, in particular ANCA associated small vessel vasculitis and vasculitis in BD.^{20,21}

Because of the classic triad of BD symptoms and HLA B5 in this patient and no recurrent infections or DVT episodes, no more investigations for the patient were undertaken.

Conclusion

BD has diverse clinical presentations therefore awareness of its clinical manifestations is important for early diagnosis and disease management. The coexistence of BD and Down's syndrome

needs additional genetic analysis to link the two major diseases.

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