Clinical and demographic evaluation of Behçet disease among different paediatric age groups

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ABSTRACT

Aim: The aim of the study is to describe the demographic and clinical features of Behçet disease (BD) in paediatric patients.

Methods: The study included 62 patients who presented to the Department of Ophthalmology at Ankara Education and Research Hospital, Ankara, Turkey and diagnosed as having BD. These patients were placed into three age groups based on the age at the time of BD presentation: group 1, birth to 10 years old; group 2, 11–15 years old; group 3, 16–20 years old. Among these three age groups, the objective was to identify the ocular and extraocular clinical findings and complications of BD, and to uncover the role of gender, if exists, in the aetiology of the disease.

Results: The findings indicated that gender played no significant role in the aetiology of BD. In group 1, a family history of BD was more prevalent, and the most common ocular finding was bilateral anterior uveitis. The most frequent form of ocular involvement in groups 2 and 3 was bilateral panuveitis with retinal vasculitis and retinitis. The majority of disease complications were glaucoma, maculopathy and cataract formation.

Conclusion: Patient age appeared to define the type of ocular involvement in BD. While anterior uveitis was the most frequent ocular finding in BD patients younger than 10 years, panuveitis was the most frequent in patients older than 10 years. As a family history of BD was more frequent among patients younger than 10 years, family screening for BD is considered critical for early and accurate diagnosis of BD, as well as for the control of its complications.

Behçet disease (BD) is a chronic, multisystem disorder characterised by oral aphthae, genital aphthous ulcers, arthritis, cutaneous lesions and ocular, gastrointestinal and neurological manifestations[1 2]. BD is named after Hulusi Behçet, a Turkish dermatologist, who first reported it in 1937. His diagnostic criteria included the classical triad of recurrent oral aphthous ulcers, genital ulcers and hypopyon uveitis.[2] Besides neurological symptoms, other clinical manifestations may include vascular, gastrointestinal, renal and cardiopulmonary signs and symptoms. BD onset peaks in the third decade but can also occur in childhood or in older people.[3 4]

Several recent studies have examined the childhood onset of BD.[5 6] Diagnosis of the disease in childhood is made based either on its classical full expression or its initial symptoms.[5 6] The incidence of paediatric BD is reported to be 0.5–2.2% in countries in which the disease is uncommon.[7 8] Furthermore, it has been reported that the mean age of onset is 7–10 years and that it is more prevalent among males.[2 9] The occurrence of uveitis in BD differs among children. Soylu *et al* reported that 11% of children that suffered from uveitis also presented with BD.[10] The rate of ocular involvement greatly varies, ranging from 24% to 80% in childhood BD series.[2 11]

In the present study, we collected and assessed the clinical notes and medical records for 62 children diagnosed as having childhood-onset BD. Our goal was to describe the demographic and clinical features of the disease and its complications, as well as to discuss our treatments and the visual results obtained in these patients.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 62 patients that presented to the Ankara Education and Research Hospital, Ophthalmology Department Uveitis-Behçet Service, Ankara, Turkey between 1990 and 2005. All the patients were diagnosed as having childhood-onset BD. Inclusion criteria for the present study were the fulfillment of the classification criteria of the International Study Group for BD[12] and onset of disease $\leqslant$16 years of age. The locally appointed ethics committee approved review of the medical records for the purpose of the present study, and informed consent was obtained from the patients or their relatives.

We followed our BD patients (Caucasians of Turkish origin) in our Uveitis–Behçet Service for 15 years. They were informed about the familial tendency of the disease, and their first-degree relatives were called to our service for BD screening; most of the patients' relatives were diagnosed as having BD during this screening.

The medical records that were reviewed included reports from the patients' primary ophthalmologists, paediatricians, dermatologists and rheumatologists. Moreover, a complete ocular examination was performed for each patient during each visit, including best-corrected visual acuity using a Snellen chart, biomicroscopy, tonometry and ophthalmoscopy. In addition, to complete ocular examination, fundus fluorescein angiography was also performed in selected patients when necessary to visualise the retina and the choroid. Routine laboratory examinations, consisting of a complete blood count, erythrocyte sedimentation rate, chest radiograph, serum biochemical analysis and urinanalysis, were conducted for each patient. Furthermore, pathergy test, HLA typing, antinuclear antibody, skin tuberculin test and toxoplasma serology were performed as required.

Some studies examined age-related findings regarding childhood-onset BD; therefore, to assess

Table 1 Initial manifestations of Behçet disease

Initial manifestations	Group 1 n = 8	Group 2 n = 21	Group 3 n = 33	Total n = 62 (%)
Oral ulcer	4	20	27	51 (82.2)
Genital ulcer	–	–	1	1 (1.6)
Uveitis	4	1	4	9 (14.5)
Skin	–	–	–	–
Neurological involvement	–	–	1	1 (1.6)

the clinical and demographic features of paediatric BD according to age, we divided our 62 patients into three age groups based on age at the time of BD presentation: Group 1, birth to 10 years old; group 2, 11–15 years old; group 3, 16–20 years old.

We then sought to (1) describe the initial symptoms, clinical ocular features, and ocular complications of BD, (2) determine the rate of loss of potential visual acuity, (3) uncover the role of gender, if it exists, in the aetiology of the disease and (4) discuss the results of systemic treatment.

Statistical analysis

Data analysis was performed using SPSS for Windows v.11.5 (SPSS, Chicago). Descriptive statistics were expressed as median (minimum–maximum) for continuous variables. Categorical variables were tested using χ^2 or Fisher exact tests, as appropriate. Within-group comparisons of vision were analysed using the Wilcoxon signed rank test. A p value <0.05 was considered statistically significant.

RESULTS

Among the 62 patients, 33 were male (53.2%), and 29 were female (46.8%). Groups 1, 2 and 3 contained 8, 21 and 33 patients each, respectively. The female-to-male ratio was 3:5 in group 1, 11:10 in group 2 and 15:18 in group 3. There were no significant differences in the incidence of BD between the gender and age groups ($p = 0.753$). The mean length of follow-up for all the patients was 4.2 (SD 4.3) years (range 1–15 years). The mean follow-up was 5 years (range 1–8 years) in group 1, 3.3 years (range 1–15 years) in group 2 and 6 years (range 1–15 years) in group 3. Initial manifestations of BD in the study patients are shown in table 1. The most frequent initial manifestations of BD were oral ulcer (82.2%) and uveitis (14.5%).

The distribution of demographic and extraocular features at the end of the follow-up period, according to group, is illustrated in table 2. Among the initial features, oral ulcer (82.2%) and uveitis (14.5%) were the most frequent manifestations.

A retrospective review of the patients' medical records showed that a family history of BD was more prevalent among the patients in group 1 than among those in groups 2 and 3 ($p<0.001$). All of the patients had oral ulcers at the end of the follow-up period. Among the groups, genital ulcers were observed significantly more frequently in group 3 ($p = 0.016$). We did not observe any major differences between the groups with regard to the presentation of oral ulcers, pathergy positivity, arthritis, papulopustular lesions or the incidence of erythema nodosum. Moreover, nine patients (14.5%) developed uveitis as the initial symptom of the BD, in addition to extraocular findings. On the whole, 50/62 patients (80.7%) developed uveitis by the end of the follow-up period (seven patients (87.5%) in group 1, 17 patients (81%) in group 2 and 26 patients (78.8%) in group 3). This observation indicated that there were no noteworthy differences in the development of uveitis between the groups ($p = 0.844$). The overall mean age at onset of uveitis was 13.8 (3.8) years (range 3–20 years) (5.6 years (range 3–7 years) in group 1, 13.1 years (range 11–15 years) in group 2, and 16.5 years (range 13–20 years) in group 3). Interestingly, none of the patients in groups 2 or 3 had the onset of uveitis $\leqslant 10$ years of age. Furthermore, the time interval between presentation to our Uveitis–Behçet Department and onset of uveitis was 8.6 months (range 4 months to 2 years) in group 1, 6.4 months (range 6 months to 1 year) in group 2 and 1.6 years (range 8 months to 4 years) in group 3. Of the 50 patients who suffered from uveitis, 44 (88%) developed bilateral disease (six patients (75%) in group 1, 13 patients (61.9%) in group 2 and 25 patients (75.6%) in group 3).

The distribution of uveitis types and ocular findings among the groups are presented in table 3. Anterior uveitis was the most common form of uveitis in group 1, with a considerably higher prevalence ($p<0.001$) than noted in groups 2 and 3. In contrast, panuveitis was the most frequent type of uveitis in groups 2 and 3, with a notably higher frequency ($p = 0.005$) than that observed in group 1. Additionally, intermediate uveitis was the least common form of uveitis in all three groups and was only identified in four patients in group 2. We also noted markedly higher incidences of retinal vasculitis ($p = 0.007$) and retinitis ($p<0.001$) in group 3, as compared with groups 1 and 2. The occurrence of papillitis was appreciably higher in group 2 than in groups 1 and 3 ($p = 0.004$). Similar to

Table 2 Distribution of demographic and extraocular features

	Group 1 n = 8 (%)	Group 2 n = 21 (%)	Group 3 n = 33 (%)	Total n = 62 (%)	p Value
Familial	8 (100)	6 (28.6)*	12 (36.4)*	26 (41.9)	<0.001
HLA B5	3 (37.5)	4 (19.0)	9 (27.3)	16 (25.8)	0.574
Pathergy positivity	6 (75.0)	9 (42.9)	14 (42.4)	29 (46.8)	0.220
Oral ulcer	8 (100)	21 (100)	33 (100)	62 (100)	–
Uveitis	7 (87.5)	17 (81)	26 (78.8)	50 (80.7)	0.844
Genital ulcer	1 (12.5)	11 (52.4)	22 (66.7)*	34 (54.8)	0.016
Arthritis	4 (50)	10 (47.6)	12 (36.4)	26 (41.9)	0.633
Papulopustular lesions	2 (25)	5 (23.8)	13 (39.4)	20 (32.3)	0.439
Erythema nodosum	–	5 (23.8)	11 (33.3)	16 (25.8)	0.149
Neuro-Behçet	–	3 (14.3)	5 (15.2)	8 (12.9)	0.303
Thrombophlebitis	–	1 (4.8)	2 (6.1)	3 (4.8)	0.640
Pulmonary involvement	–	–	1 (3.0)	1 (1.6)	0.528

*The difference between group 1 was statistically significant ($p<0.05$).

Table 3 Distribution of uveitis types and ocular findings

	Group 1 n = 13 eyes (%)	Group 2 n = 30 eyes (%)	Group 3 n = 51 eyes (%)	Total n = 94 eyes (%)	p Value
Anterior uveitis	11 (85)	6 (20)*	14 (27.5)*	31 (33)	< 0.001
Panuveitis	2 (15)	20 (67)*	37 (72.5)*	59 (63)	0.005
Intermediate uveitis	–	4 (13)†	–	4 (4)	0.016
Total	13	30	51	94	
Hypopyon	–	2 (6.7)	8 (15.7)	10 (10.6)	0.095
Retinal vasculitis	–	2 (6.7)	15 (29.4)‡	17 (18.1)	0.007
Retinitis	–	6 (20)	24 (47.1)‡	30 (31.9)	<0.001
Papillitis	–	15 (50)	14 (27.5)	29 (30.9)	0.004
Macular oedema	–	9 (30)*	20 (39.2)*	29 (30.9)	0.024

*The difference between group 1 was statistically significant (p<0.05).
†The difference between group 3 was statistically significant (p<0.05).
‡The difference between group 1 and 2 was statistically significant (p<0.05).

panuveitis, the incidence of macular oedema was higher in groups 2 and 3 than in group 1 (p = 0.024).

Ocular complications recorded during the follow-up period are presented in table 4. The most common complications were the formation of cataract, glaucoma and maculopathy. No significant differences were observed between the groups when the incidences of cataract and maculopathy were compared. The incidence of secondary glaucoma was markedly higher in group 3 than in groups 1 and 2 (p = 0.016). In addition, the formation of band keratopathy in group 1 was distinctly higher in comparison with groups 2 and 3 (p = 0.017).

Medical treatment protocols received by the patients are shown in table 5. The treatment regimens included ciclosporin, azathiopurine and colchicine, administered individually or in combination.

The initial visual acuity (measured during the initial visit) and potential visual acuity (the best visual acuity measured after treatment of active inflammation at the beginning of follow-up) are presented in table 6. Note that the potential visual acuity was >0.5 in 92.3% (n = 12) of the eyes in group 1, in 93.3% (n = 28) of the eyes in group 2 and in 90.2% (n = 46) of the eyes in group 3.

The rate of loss of potential visual acuity between the first and last visit (according to the loss of lines on the Snellen chart) is summarised in table 7. Although the loss in potential visual acuity during the follow-up period was not statistically significant among the groups (p = 0.17), the number of patients who had a visual acuity <0.6 was higher in group 3.

DISCUSSION

The common presenting features of childhood Behçet disease include uveitis, recurrent oral ulcers[11 14–17] and a family history of Behçet disease with a male predominance.[5 10 11 14 19 20]

Although there are numerous studies describing the effects of childhood Behçet disease on specific organs in the body, none of them have examined age as a factor of importance in the characterisation of BD-related symptoms. Previous studies have characterised paediatric BD-related findings, including the mean age at disease onset, male:female ratio, family history, oral and genital ulcers and formation of uveitis, erythema nodosum, papulopustules and thrombophlebitis, in addition to joint symptoms, neurological involvement and a positive pathergy test. Borlu *et al*[2], in a series of 17 paediatric patients with BD, reported that the mean age of onset was 7 years (range 4–16 years), the male:female ratio was 12:5, and 45% of the patients had a family history of BD. They also report that all 17 patients had oral ulcers, 94% had genital ulcers, 76% had a positive pathergy test and joint symptoms, and 24% had uveitis.

Similar to our observation, a retrospective study of 86 paediatric BD cases by Koné-Paut *et al*[21] reported that BD affected both genders equally, indicating the absence of or an insignificant role of gender in the prevalence and aetiology of the disease. The conflict between these studies and others[2 7] that report a male predominance might simply be due to the mean age and number of patients studied. Moreover, the mean age at onset of uveitis in the present study is comparable with the findings of Tugal-Tutkun *et al*[9] and Borlu *et al*,[2] suggesting consistency in the appearance of BD-related uveitis. Although

Table 4 Ocular complications

	Group 1 n = 13 (eyes) (%)	Group 2 n = 30 (eyes) (%)	Group 3 n = 51 (eyes) (%)	Total n = 94 (eyes) (%)	p Value
Band keratopathy	2 (15.4)*	–	–	2 (2.1)	0.017
Posterior synechia	4 (30.8)	1 (3.3)†	5 (9.8)	10 (10.6)	0.046
Cataract	2 (15.4)	5 (16.7)	12 (23.5)	19 (20.2)	0.681
Glaucoma	1 (7.7)	4 (13.3)	19 (37.3)‡	24 (25.5)	0.016
Maculopathy	1 (7.7)	6 (20.0)	14 (27.5)	21 (22.3)	0.291
Retinal tear	1 (7.7)	1 (3.3)	2 (3.9)	4 (4.3)	0.823
Optic atrophy	1 (7.7)	2 (6.7)	1 (2.0)	4 (4.3)	0.474
Phthisis bulbi	–	–	1 (2.0)	1 (1.1)	0.540
Disc neovascularisation	–	–	1 (2.0)	1 (1.1)	0.540
Exudative detachment	–	–	1 (2.0)	1 (1.1)	0.540
Branch retinal vein occlusion	–	1 (3.3)	7 (13.7)	8 (8.5)	0.076

*The difference between group 3 was statistically significant (p<0.05).
†The difference between group 1 was statistically significant (p<0.05).
‡The difference between group 1 and group 2 was statistically significant (p<0.05).

Table 5 Medical treatment protocols

	Group 1 n = 8 (%)	Group 2 n = 21 (%)	Group 3 n = 33 (%)	Total n = 62 (%)	p Value
Csa	1 (7.7)	7 (23.3)	6 (23.5)	14 (21.3)	0.435
Azo	–	1 (3.3)	–	1 (5.3)	0.324
Col	1 (7.7)	3 (10.0)	8 (25.5)	12 (18.1)	0.125
Csa + Azo	–	–	3 (5.9)	3 (3.2)	0.153
Csa + Col	–	–	2 (3.9)	2 (2.1)	0.289
Csa + Col + Azo	–	–	1 (2.0)	1 (1.1)	0.540
Cyclophosphamide	–	–	1 (2.0)	1 (1.1)	0.540
Total immunosuppression	2 (15.4)	11 (36.7)	21 (41.2)	34 (36.2)	0.224

Azo, azothioprine; Col, colchicine; Csa, ciclosporin.

Table 6 Visual acuity

	Group 1 n = 13 (eyes)		Group 2 n = 30 (eyes)		Group 3 n = 51 (eyes)	
	IVA	PVA	IVA	PVA	IVA	PVA
No light perception	1	1	1	1	–	1
Light perception or hand movements	–	–	1	1	1	1
Count fingers	–	–	–	–	6	1
0.1–0.5	–	–	5	–	3	2
0.6–1.0	12	12	23	28	41	46

IVA, initial visual acuity; PVA, potential visual acuity.

Table 7 Rate of loss of potential visual acuity

Rate of loss of potential visual acuity	Group 1 n = 13 (eyes)	Group 2 n = 30 (eyes)	Group 3 n = 51 (eyes)	Total n = 94 (eyes)
1–5 lines	–	3	4	7
6–10 lines	–	2	3	5
Count fingers	–	–	–	–
Light perception or hand movements	–	–	–	–
No light perception	–	1	–	1
Same or improved visual acuity	13	24	44	81

the incidence of BD-related uveitis increases as BD progresses, its initial prevalence was not higher in the present study or in other published reports:[7] therefore, paediatricians should consider the lower frequency of BD-related uveitis in the diagnosis of childhood-onset BD. Additionally, panuveitis, the most common form of uveitis, also seems to appear with a greater frequency after age 10. We observed in the present study that, as with uveitis, the panuveitis prevalence rate was lower among those aged <10 years.

We also found that ocular and extraocular findings, similar to the literature, started to appear mostly after the age of 10 years.[5 7 11] More importantly, we noted that the most common ocular finding was anterior uveitis, in addition to a pronounced history of BD in family members aged between birth and 10 years. Similar to adults, bilateral panuveitis with retinal vasculitis and retinitis was the most frequent form of ocular involvement in this study's 11–20-year-old patients.

The diagnosis of paediatric onset BD could be made more difficult due to the low frequency of ocular involvement in birth-to-10-year-old patients, whereas the high frequency of BD family history among birth-to-10-year-old patients might facilitate diagnosis. Indeed, in the present study, we observed that most of the relatives of the patients were BD-positive.

The most common complications observed in the present study, akin to earlier studies,[7] were secondary glaucoma, maculopathy and cataract formation. Glaucoma and cataract were probably due to the ordinary use of long-term corticosteroids. There were no differences between the age groups in terms of the incidence of complications or treatment results. Treatment was often challenging because of the high rate of complications associated with the use of immunosuppressive drugs. Moreover, our patients' responses to drugs were variable.

In conclusion, a retrospective analysis of the medical records of a large sample of paediatric BD patients did not show a male predominance of the disease. A high correlation between paediatric BD and a family history of BD before the age of 10 years appears to be a critical finding, suggesting that genetic factors coding for an altered immune system trigger the early onset of the disease. Furthermore, we observed that the most common ocular finding was anterior uveitis in those younger than 10 years and panuveitis in those older than 10 years. Our observations also suggest that family screening for BD is crucial for the early diagnosis and prevention of complications of BD in patients younger than age 10 years.

Competing interests: None.

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REFERENCES

1. **Yazici H,** Yurdakul S, Hamuryudan V. Behçet's syndrome. *Curr Opin Rheumatol* 1999;**11**:53–7.
2. **Borlu M,** Uksal U, Ferahbas A, *et al*. Clinical features of Behçet's disease in children. *Int J Dermatol* 2006;**45**:713–16.
3. **Zierhut M,** Saal J, Pleyer U, *et al*. Behçet's disease: epidemiology and eye manifestations in German and Mediterranean patients. *German J Ophthalmol* 1995;**4**:246–51.
4. **Yazici H,** Tuzun Y, Pazarli H, *et al*. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. *Ann Rheum Dis* 1984;**43**:783–9.
5. **Pivetti-Pezzi P,** Accorinti M, Abdulaziz MA, *et al*. Behçet's disease in children. *Jpn J Ophthalmol* 1995;**39**:309–14.
6. **Fujikawa S,** Suemitsu T. Behçet's disease in children: a nationwide retrospective survey in Japan. *Acta Paediatr Jpn* 1997;**39**:285–9.
7. **Kanski JJ,** Shun-Shin GA. Systemic uveitis syndromes in childhood: an analysis of 340 cases. *Ophthalmology* 1984;**91**:1247–52.
8. **Pivetti-Pezzi P.** Uveitis in children. *Eur J Ophthalmol* 1996; **6**:293–8.
9. **Tugal-Tutkun I,** Urgancioglu M. Childhood onset uveitis in Behçet's disease; a descriptive study of 36 cases. *Am J Ophthalmol* 2003:**136**:1114–19.
10. **Soylu M,** Ozdemir G, Anli A. Pediatric uveitis in Southern Turkey. *Ocul Immunol Inflamm* 1997;**5**:197–202.
11. **Eldem B,** Onur C, Ozen S. Clinical features of pediatric Behçet's disease. *J Pediatr Ophthalmol Strabismus* 1998;**35**:159–61.
12. **International Study Group for Behçet's Disease**. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;**335**:1078–80.
13. **Kari JA,** Shah V, Dillon MJ. Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology* 2001;**40**:933–8.
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. **Treudler R,** Orfanos CE, Zouboulis ChC. Twenty-eight cases of juvenile-onset Adamantiades–Behçet's disease in Germany. *Dermatology* 1999;**199**:15–19.
16. **Sarica R,** Azizlerli G, Kose A, *et al*. Juvenile Behçet's disease among 1784 Turkish Behçet's patients. *Int J Dermatol* 1996;**35**:109–11.
17. **Kim DK,** Chang SN, Bang D, *et al*. Clinical analysis of 40 cases of childhood-onset Behçet's diease. *Pediatr Dermatol* 1994;**11**:95–101.
18. **Krause I,** Uziel Y, Guedj D, *et al*. Mode of presentation and multisystem involvement in Behçet's disease: the influence of sex and age of disease onset. *J Rheumatol* 1998;**25**:1566–9.
19. **Krause I,** Uziel Y, Guedj D, *et al*. Childhood Behçet's disease: clinical features and comparison with adult-onset disease. *Rheumatology* 1999;**38**:457–62.
20. **Koné-Paut I,** Gorchakoff-Molinas A, Weschler B, *et al*. Paediatric Behçet's disease in France. *Ann Rheum Dis* 2002;**61**:655–6.
21. **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.

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