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Childhood Behçet’s disease: clinical features and comparison with adult-onset disease

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Abstract

Objective. To study the clinical spectrum of Behçet’s disease (BD) in childhood, in comparison to adult-onset disease.

Methods. Nineteen children, who fulfilled disease criteria up to the age of 16 yr, were studied. The results were compared to those of 34 adult patients with BD. An activity index and severity score were calculated for both study groups.

Results. The mean age of disease onset was 6.9 ± 3.9 yr, similar ages of onset were found in males and females. The clinical spectrum of childhood BD resembled that of adult disease; however, the prevalence of certain manifestations was different between children and adults. Children with BD had significantly less genital ulcers, less vascular thromboses and more non-specific gastrointestinal symptoms, as well as central nervous system involvement and arthralgia. A relatively high prevalence of uveitis was found in childhood BD. The activity index and severity score were significantly lower in children than in adults.

Conclusion. Our results point to a similar systemic expression of BD in children and adults; however, the disease seems to run a less severe course in children.

Key words: Behçet’s disease, Child, Adult, Clinical spectrum, Severity.

Behçet’s disease (BD) is a multisystem disease characterized by recurrent oral and genital ulcers, relapsing uveitis, and mucocutaneous, articular, neurological, urogenital, vascular, intestinal and pulmonary manifestations [1]. Although the usual onset of the disease is after puberty, and between the second and fourth decades [2, 3], there has been an increased awareness of patients with an onset before puberty [4–15]. Nevertheless, most of the reports deal with small numbers of patients, and even fewer studies compare the expression of childhood and adult-onset BD [8, 11, 14, 15]. Furthermore, the majority of the studies on childhood BD defined it according to the time of onset of the disease, i.e. if the first disease manifestation appeared up to the age of 16 yr. Since BD is characterized by exacerbations and remissions, and affects many organ systems, with varying delays in the appearance of symptoms, many years can pass between the onset of the first disease manifestation and the rise of full disease expression [5, 6, 16]. Therefore, the diagnosis of BD, even if initially manifested before the age of 16 yr, may be delayed to adulthood. Hence, a definition of childhood BD which is based on the onset of the first symptom prior to the age of 16 yr may actually include a significant number of adult patients. The aim of our study was to evaluate the clinical spectrum in patients in whom the disease was fully manifested and diagnosed during childhood, and to compare the expression of childhood BD with the adult disease.

Patients and methods

Patients with BD from several medical centres in Israel were studied. BD was defined according to the International Study Group criteria [17] as follows: recurrent oral ulcers plus two of the major features of the disease: recurrent genital ulcers, uveitis, typical skin lesions (erythema nodosum, folliculitis, papulopustular rash) or positive pathergy test (performed by an intradermal 21 gauge needle puncture on the skin of the forearm, with injection of one drop of sterile normal...
Table 1. Severity of Behcet’s disease

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Oral aphthosis</td>
<td>Arthritis</td>
<td>Posterior/pan uveitis</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>Deep vein thrombosis of the legs</td>
<td>Arterial thrombosis or aneurysms</td>
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<tr>
<td>Typical skin lesions (erythema nodosum, papulopustular lesions, folliculitis, leukocytoclastic vasculitis)</td>
<td>Anterior uveitis</td>
<td>Major vein (vena cava, hepatic) thrombosis</td>
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<tr>
<td>Arthralgia</td>
<td>Gastrointestinal bleeding</td>
<td>Neuro-Behcet</td>
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<td>Recurrent headaches</td>
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<td>Bowel perforation</td>
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<tr>
<td>Epididymitis</td>
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<tr>
<td>Mild gastrointestinal symptoms (chronic diarrhoea, chronic recurrent colicky abdominal pain)</td>
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<tr>
<td>Pleuritic pains</td>
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<td>Superficial vein thrombosis</td>
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Activity index was calculated according to the method presented by Yazici et al. [19] and Fresko et al. [20], as the numerical sum of clinical features listed in Table 2.

Statistical analysis was performed employing Student’s t-test for mean values and χ² for table analysis.

Results

Nineteen patients with juvenile BD were studied, 11 males and eight females. All the patients were Israelis. The clinical manifestations of childhood BD were compared to a group of 34 Israeli patients with adult-onset BD (Table 3). The mean age of disease onset was 6.9 ± 3.9 (range 2–16) yr, similar ages of onset were found in males (6.8 ± 3.2 yr) and females (7.2 ± 5.1 yr).

The age group distribution of disease onset in children is presented in Fig. 1, most cases of childhood BD appeared before the age of 8 yr. The time interval between childhood first disease manifestation and the evolution of the full disease complex was 3.9 ± 3.5 yr (range: a few months to 12 yr). The mean disease duration was greater in adults than in childhood BD (12.9 ± 7.4 yr vs 9.6 ± 4.9 yr; P < 0.05). The mean follow-up times were 4.9 ± 2.2 yr in children and...
6.4 ± 3.5 yr in adults (P < 0.05). There were no cases of mortality in our study population.

Clinical manifestations of juvenile BD

Major clinical manifestations. Per definition, all patients had recurrent oral ulcers. Oral aphthosis was the most common initial disease manifestation: 16 out of 19 children (84.2%) presented first with recurrent aphthous stomatitis. Genital ulcers appeared in six children (31.6%). Similar rates of genital ulcers were observed in males and females. Children with genital ulcers had a tendency for higher age at disease onset than children without them (8.6 ± 3.7 vs 6.4 ± 3.2 yr; P = 0.11). Major eye involvement occurred in nine children (47.4%), similarly in males and females. Ocular manifestations included anterior (seven patients), posterior (one patient) or pan (one patient) uveitis. One patient had posterior uveitis as well as retinal vasculitis. Three patients suffered decreased vision, one of them to blindness, despite treatment with corticosteroids, azathioprine and cyclophosphamide. Typical skin lesions occurred in 17 patients (89.5%), 10 boys and seven girls. Skin manifestations included erythema nodosum (seven patients (36.8%), five boys and two girls) and/or folliculitis (eight patients, equally in males and females), and/or papulopustular rash (four patients, equally in males and females). One patient had leucocytoclastic vasculitis of the skin. A positive pathergy test was found at a similar rate in males and females, totalling seven out of 17 children (41.2%).

Minor clinical manifestations. Similar rates of all minor disease manifestations were found in males and females. Joint disease was the most frequent minor expression (78.9%). Nine patients (47.4%) had recurrent arthralgia, six patients (31.6%) had arthritis. The joint disease was usually of the pauci-articular pattern, mainly of the knees, ankles and hip joints. Non-specific gastrointestinal (GI) symptoms occurred in seven patients (36.8%). The symptoms were mild, usually manifested as repeated abdominal pain and/or diarrhoea, which was not bloody. There were no events of GI bleeding nor bowel perforation; GI endoscopy was not performed. None of the patients was suspected of having FMF, which was also not reported in close family members. Pleuropulmonary manifestations appeared in one patient, in the form of recurrent pleuritis. Frequent headaches were reported by seven children (36.8%). Other expressions of neuro-Behçet were diagnosed in another five children (26.3%), manifested as pseudotumour cerebri in two patients; both of them underwent brain CT and EEG, which were normal, one of the patients was further evaluated by MRI, which was normal. Two patients had meningoencephalitis, in which the cerebrospinal fluid examination showed pleocytosis, mainly lymphocyte, with normal protein and glucose content. The EEG was within the normal range in one patient, and showed slow diffuse disturbances in the other. One patient had psychiatric disturbances, manifested by severe anxiety and personality changes. Vascular involvement, in the form of deep or superficial vein thrombosis of the lower limbs, was found in two children. There were no cases of major vein (vena cava or hepatic vein) thrombosis, nor cases of arterial involvement. A positive family history of oral aphthosis was reported in seven children (36.8%).

Comparison of clinical manifestations in juvenile vs adult BD

Major disease manifestations. All patients had recurrent oral ulcers. The frequency of other major manifestations in children and adults is presented in Fig. 2. Similar rates were found in children and adults regarding uveitis, typical skin lesions and a positive pathergy test. Similar rates of decreased vision were observed in children and adults who had major eye involvement (3.9 vs 5/18, respectively). In contrast, genital ulcers were significantly more common in adults than in children (30/34 vs 6/19; P < 0.01).

Minor disease manifestations. Similar prevalences were found in children and adults concerning overall joint disease, vascular involvement and recurrent headaches (Fig. 3). Children with BD had a tendency toward more non-specific GI symptoms (36.8% vs 11.7%; P = 0.04), central nervous system (CNS) involvement other than headaches (26.3% vs 5.8%; P = 0.08) and arthralgia (47.4% vs 17.6%; P = 0.02) than adults. The children also had a lower rate of vascular thrombosis than adults (10.5% vs 26.5%); the difference was not statistically significant. Previous studies have demonstrated a high frequency of oral ulcers among family members of patients with BD [21, 22]. We found similar rates of familial aphthosis (recurrent aphthous stomatitis in a close family member) in children and adults.

Severity score and activity index. These were significantly lower in children with BD compared with adults [6.05 ± 2.20 vs 7.18 ± 2.49 (P < 0.05) and 3.58 ± 1.93 vs 5.24 ± 2.31 (P < 0.005), respectively].

Fig. 2. Major clinical manifestations in children and adults with BD.
In the current study, we present the clinical spectrum of a series of patients with childhood BD. The peak age of onset in our patients was between 1 and 8 yr old, with similar ages of onset in males and females. Previous studies on adult BD patients [15, 19] have reported on earlier appearance of the disease in male patients. Our findings of similar ages of onset in males and females may be explained by the narrower range of ages of onset in children (up to 16 yr) than in adults. The male:female ratio of childhood BD in our study was 1.4:1, which is in accordance with previous reports on juvenile-onset BD, demonstrating a male:female ratio ranging between 1.1–1.4:1 [5–7, 13].

Overall we found the clinical spectrum of childhood BD to resemble that of adult disease; however, the prevalence of certain manifestations was different between children and adults. Children with BD had significantly less genital ulcers than adults, and had more mild GI symptoms, as well as CNS involvement and arthralgia. Previous studies on juvenile-onset BD reported a high percentage of genital involvement [4, 5, 7]. Those studies, however, included a high percentage of adult patients, hence their results may not necessarily reflect the true incidence of genital ulcers in children with BD. In contrast, Shafaei et al. [11, 14] reported on significantly less genital ulcers in children with BD compared to adults. The finding in our study, of a higher mean age in children with than in children without genital ulcers, implies that the incidence of genital ulcers might increase with age. GI complaints are common in adults with BD, especially in Japan, but are rare in the Mediterranean countries [23]. GI involvement in BD was also reported in children [24, 25]. Colicky abdominal pain and diarrhoea, which can be bloody, are the main symptoms. The basic pathology is the development of mucosal ulcers. The higher rate of GI symptoms in children compared to adults, as found in our study, may to some extent be attributed to a higher incidence of abdominal pain and diarrhoea in children than adults. Nevertheless, taking the chronic nature of the GI manifestations in our BD children, the findings may represent a true tendency in our area toward higher GI involvement, albeit mild, in children compared with adults. Indeed, some previous studies estimated the prevalence of GI symptoms in juvenile BD to be as high as 40% [4, 8], which is similar to our findings (36.8%), although other studies reported much lower rates of GI disease [5, 7]. CNS involvement is potentially the most serious manifestation of BD, and may cause pseudotumour cerebi, brain-stem involvement, neuropsychiatric symptoms and meningoencephalitis [26]. Significant cerebral involvement has been reported in ~25% of children with BD [4, 8–10], which is in accordance with our findings (26.3%). It seems from our study that neuro-Behçet might be more common in children than in adults. In contrast, Shafaei et al. [14] found similar rates of CNS involvement in children and adults in Iran. The different findings in our study might be attributed to geographic variation in disease expression [13]. We found other clinical manifestations of the disease to occur at similar rates in adults and children. Of note is the relatively high prevalence (47%) of uveitis in our series. Most of the early studies on juvenile-onset BD have reported a low prevalence of ocular involvement, ranging from 14 to 27% [4–6, 8, 9, 12], which is far below the prevalence in adult patients [23]. In contrast, Bahabri et al. [7] and Kone-Paut et al. [13] have reported a 44–55% prevalence of major eye involvement in juvenile-onset BD, which is similar to our findings. These differences might be the result of the different diagnostic criteria used in the studies. Our findings imply that, in contrast to earlier reports, the frequency of ocular involvement in BD might be similar in children and adults. Furthermore, a significant rate of ocular morbidity was found in our children with BD, which is similar to the rate observed in our adult patients (3/9 vs 5/18, respectively). Venous thrombosis was found in only two of our children (10.5%), one had superficial and the other deep vein thrombosis. The low rate of vascular involvement in juvenile BD is compatible with most previous reports, ranging from 0 to 15% [10, 11, 13, 14]. The relative rate of certain disease manifestations in our children was different from those in some of the previously reported series on childhood BD (e.g. relatively high rates of uveitis and mild GI symptoms, and lower rate of genital ulcers). Those differences might be the result of different expression of BD in various geographical areas [23], compared to our patients who were all Israelis. Indeed, in the study of Kone-Paut et al. [13], which compared the expression of childhood BD in four different countries, significant geographical variation was found. Patients from France and Saudi Arabia had significantly more neurological and GI complications, whereas patients from Turkey had more frequent cutaneous manifestations.

At present, there is no standardized and reliable method for measuring the severity of BD [27]. Since
there are no laboratory markers that correlate well with clinical findings in BD, our assessment relied solely on clinical features. We used a scale in which we gave relative weights to the whole spectrum of clinical manifestations in BD, according to expected outcome and potential morbidity and mortality (Table 1) [18]. In previous studies, it has been suggested that BD runs a more severe course in young men [19, 28, 29], but only a few formal studies on this aspect of the syndrome have been performed. Yazici et al. [19] stated that male sex and younger age at disease onset (≤25 yr) were associated with more severe disease. They further extended their results, reporting on increased mortality in young male patients with BD, the cause of which was unknown [29]. Dilsen et al. [30] found a higher prevalence of vital organ involvement in male patients, and in patients with age at onset of ≤25 yr. Those studies, however, were carried out in adult patients. To the best of our knowledge, the severity of BD during childhood has not yet been studied. In our study, we found the severity score to be significantly lower in children compared with adults. This finding may seem peculiar, since the expression of BD in children and adults was basically similar. Nevertheless, as a group, adults with BD had increased involvement of organ systems which have the potential for increased morbidity, such as vascular complications, and arthritis rather than arthralgia (Figs 1 and 2). We further assessed our patients according to the method introduced by Yazici et al. [19] and Fresko et al. [20], for the determination of total activity index in BD, based on disease activity in selected organ systems. We found that children had a significantly lower activity index compared with adults. Part of this difference may be explained by the lower disease duration and follow-up times in our childhood BD group than in the adult patients, yet, it seems that BD in our area runs a less severe course in children than in adults, at least during childhood and early adulthood. A prospective study with a large number of patients and objective physical and laboratory variables of disease activity is needed to establish the present results.

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References