Objective: to make Pediatricians aware of the fact that they must investigate Behcet’s disease while performing differential diagnosis of recurrent aphthous stomatitis, even though it is a vasculitis of rare occurrence in early life.

Methods: between June 1996 and December 2000, we retrospectively evaluated seven patients of our Pediatric Rheumatology Unit. Demographic, clinical, and laboratory data as well as data regarding treatment and follow-up were presented.

Results: five out of seven patients were female (71.4%), four were non-Caucasian (57.1%), the mean age at onset was 8 years and 11 months (variation of 6 months to 13 years and 8 months), the mean period until diagnosis was 2 years and 3 months (variation of 2 months to 8 years) and the mean follow-up period was 4 years and 2 months (three patients without follow-up). The major criteria of diagnosis were: oral ulcers in seven patients (100%), genital ulcers in three patients (42.8%), ophthalmic alterations in four patients (57.1%) cutaneous vasculitis in one patient (14.2%) and positive pathergy test in one patient (14.2%). The minor criteria were: arthralgia/arthritis in five patients (71.4%), family history in two patients (28.5%), and sagittal sinus thrombosis in one patient (14.2%). The initial symptoms included recurrent aphthous stomatitis (more than three painful aphthous ulcers episodes in the period of 1 year), genital ulcers, arthralgia, fever and weight loss. The laboratory findings were: mild anemia in 1/6 patients, ESR>25 in 3/6 patients, increased serum gammaglobulin level in 2/4 patients, B5 histocompatibility antigen in 2/7 patients. The treatment included corticosteroids for 5/7 patients (4 oral, 1 intravenous and one local use), thalidomide for 4/7 patients, colchicine for 2/7 patients and dapsone for 1/7 patient. The outcome was favorable in 4/6, and 3/6 patients presented relapse.

Conclusion: our results confirm the importance of considering the diagnosis of Behcet’s disease in patients with recurrent oral and genital ulcers.

Introduction

Hulusi Behcet described a triple-symptom complex of recurrent aphthous ulcers, genital ulcers, and iritis in 1937.1 Behcet’s disease is a rare, chronic, recurrent, and multisystemic vasculitis in children.2
Some studies report an incidence of 1/20,000 in children. The mean age at diagnosis is ±10 years, regardless of gender. The etiology is unknown; however, some causes are suggested: viral infection and exposure to organophosphorated compounds. Immunological alterations, such as cellular immunity disorders, presence of immunocomplexes and complement activation have been described.

More specific diagnostic criteria were proposed by the International Study Group for Behcet’s Disease in 1989. Major criteria include: oral ulcers, genital ulcers, ocular injuries, skin lesions, and pathergy test. Minor criteria consisted of arthritis, cardiovascular injury, thrombophlebitis, neurological disorders, gastrointestinal injury, and family history. The diagnosis should include 3 major criteria or 2 major criteria plus 2 minor criteria.

Oral ulcers are the most frequent symptom, affecting between 88 and 100% of patients. Genital ulcers usually appear at the pubertal stage and can be seen on the penis, scrotum, vulva and vagina. Skin involvement occurs during the progression of the disease in 70 to 93% of patients. The pathognomonic skin lesion resulting from Behcet’s disease is the intracutaneous response to the trauma, which is called pathergy test, and occurs in 22 to 84% of patients. Both the anterior eye segment (iritis) and the posterior eye segment (chorioretinitis, optic papillitis, retinal thrombophlebitis, arthritis) are involved. Ophthalmic involvement is not common in children; according to the literature, it is present in 28 to 68% of the children, and is associated with the presence of HLA-B5.

The involvement of the joints is characterized by arthritis/arthralgia (usually on the knees), which may be oligoarticular or polyarticular. Normally, there are no sequelae. Vascular involvement includes arteries and veins, and is present in 35% of the cases. The involvement of the central nervous system has been described in approximately 18% of the patients, and is considered the most severe manifestation of the disease. Gastrointestinal involvement is characterized by esophageal ulcers and anal lesions, abdominal pain, gastritis, diarrhea, hepatomegaly, and splenomegaly. Other complications include: nephrotic syndrome, amyloidosis, focal segmental glomerulonephritis, epidermitis, urethritis, recurrent cystitis, myocarditis, pericarditis, and myocardial infarction.

Lab exams may be useful for following up the activity of the disease and establishing the differential diagnosis. The increased level of gammaglobulin is a predictor of better ocular prognosis. The assay for autoantibodies is negative. The HLA-B5 is present in 50 to 84% of the cases.

Several forms of treatment have been proved effective. Systemic corticosteroids and, occasionally, topical ointments and eyewash, immunosuppressive therapy, nonhormonal anti-inflammatory drugs, colchicine and thalidomide are among the therapeutic options. The disease evolves in outbreaks and remission at intervals that may comprise months or even years. Mortality occurs in 3% of the children due to vascular complications.

Our objective was to assess the clinical and epidemiological characteristics, the treatment and the development of children and adolescents with Behcet’s disease who were assisted at our department.

Patients and methods

The medical records of seven patients assisted at the Outpatient Clinic of Pediatric Rheumatology (UNIFESP-EPM) were retrospectively evaluated between June 1996 and December 2000. The inclusion criteria were: 1) children and adolescents diagnosed with Behcet’s disease by two independent pediatric rheumatologists; 2) patients with complete medical records available for data collection. All patients were submitted to a structured interview and in-depth physical examination at the time of the study. The following subsidiary exams were carried out: hemogram, inflammatory activity tests, protein electrophoresis, renal function, antinuclear antibodies by indirect immunofluorescence, HLA-B5 by microlymphocytotoxicity, and urine sedimentation. The medical records were revised by two investigators who analyzed the epidemiological, clinical, laboratory, evolution, and treatment data. The present study was approved by the Ethics Committee.

Results

Table 1 shows the epidemiological characteristics of patients with Behcet’s disease. Five of seven patients were female (71.4%), four were non-Caucasian (57.1%), with mean age at onset of the disease of 8 years and 11 months, mean time before diagnosis of 2 years and 3 months and mean evolution time of 4 years and 2 months (3 patients were not followed up).

Table 2 shows the clinical characteristics, family history, laboratory results, treatment and evolution of patients. The major diagnostic criteria were: oral ulcers in 7 patients (100%), genital ulcers in 3 patients (42.8%), ophthalmologic alterations in 4 patients (57.1%), cutaneous vasculitis in 1 patient (14.2%) and positive pathergy test in 1 patient (14.2%). The minor diagnostic criteria were arthralgia/arthritis in 5 patients (71.4%) and family history in 2 patients (28.5%). We observed sagittal sinus thrombosis in 1 patient (14.2%). All patients had oral ulcers at the initial phase of the disease.

Anemia was present in 1/6 patients (16.6%), ESR>25 in 3/6 patients (50%) and hypergammaglobulinemia in 2/4 patients (50%). The HLA-B5 was positive in only 2/7 patients (28.5%). Leukocyte and platelet count results were normal. Renal function was normal in all patients. No
Table 1 - Epidemiological characteristics of patients with Behcet’s disease (n=7)

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
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<td>M</td>
</tr>
<tr>
<td>Race</td>
<td>NC</td>
<td>NC</td>
<td>C</td>
<td>NC</td>
<td>C</td>
<td>C</td>
<td>NC</td>
</tr>
<tr>
<td>Onset age</td>
<td>4y 7m</td>
<td>4y</td>
<td>12y 10m</td>
<td>9y</td>
<td>6m</td>
<td>13y 8m</td>
<td>12y 5m</td>
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<tr>
<td>Time before diagnosis</td>
<td>4m</td>
<td>8y</td>
<td>2m</td>
<td>3y</td>
<td>2m</td>
<td>11m</td>
<td></td>
</tr>
<tr>
<td>Evolution time</td>
<td>2y 10m</td>
<td>8y 8m</td>
<td>1y</td>
<td>4y 9m</td>
<td>9y 8m</td>
<td>8 m</td>
<td>1y 4m</td>
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</table>

M = male; F = female; NC = non-Caucasian; C = Caucasian; y = years; m = months

Table 2 - Clinical characteristics, family history, laboratory results, treatment and evolution of patients with Behcet’s disease (n=7)

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
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<td>yes</td>
<td>yes</td>
<td>yes</td>
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<td>uveitis/ conjunctivitis</td>
<td>no</td>
<td>glaucoma</td>
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<td>Arthralgia/ arthritis</td>
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<td>no</td>
<td>yes</td>
<td>yes</td>
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<td>yes</td>
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<td>NR</td>
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<td>yes</td>
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<td>no</td>
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<tr>
<td>Y &gt;1.6</td>
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<td>NR</td>
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<td>yes</td>
<td>no</td>
<td>yes</td>
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<td>no</td>
<td>yes</td>
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<td>CE OA thalidomide</td>
<td>CE OA dapsone colchicine</td>
<td>CE OA eye drops</td>
<td>thalidomide colchicine</td>
<td>CE OA dapsone</td>
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<tr>
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<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
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<tr>
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<td>NE</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

yes = present; no = absent; - = decrease; Hb = hemoglobin; BSR = blood sedimentation rate; Y = gammaglobulin; HLA B5 = histocompatibility antigen-B5; CE = corticosteroid; OA = oral administration; IA = intravenous administration; NE = nonevaluated

One child (patient 6) had glaucoma as a result of ophthalmic involvement and muscle weakness as neurological sequela. No patient died.

Discussion

Behcet’s disease is not a familial entity to pediatricians, due to its low incidence and nonrecognition, since specific symptoms/signs sometimes appear at a later time. This patient had hematuria and/or proteinuria. None of the patients was positive for antinuclear antibodies. The treatment consisted of corticosteroids in 5/7 patients (71.4%), (oral administration in 4, IV in 1, and topic in 1), thalidomide in 4/7 patients (57.1%), colchicine in 2/7 patients (28.5%) and dapsone in 1/7 patients (14.2%). Treatment response was satisfactory in 4/6 (66.6%) patients. The disease was recurrent in 3/6 (50%) patients.
should not be forgotten in the case of children who have recurrent oral ulcers (more than 3 episodes a year), associated with other nonspecific clinical manifestations. The incidence of Behcet’s disease is low, except in some Mediterranean countries, such as Israel and Turkey. 2,10,12

Although no gender-specific predominance has been found in the literature, female patients were predominantly affected by the disease (5:2) in our study.

The mean age for disease onset in our patients was 8 years and 11 months, which is in agreement with other studies. 2-4,9,17 However, Behcet’s disease was reported in infants, 4 as was the case of our youngest patient (6 months old at diagnosis). We found out that early diagnosis was usually made in patients with more intense symptoms at the beginning of the disease, with bipolar ulcers (patient 3) and cerebral thrombosis (patient 6). The mean time for the appearance of symptoms until diagnosis was 2 years and 3 months, which is lower than that described in the literature (5 years). 4,10

All of our patients had recurrent oral ulcers as initial symptom, with an incidence rate similar to that described in the literature. 8-10 However, genital ulcers occurred at the onset of the disease in only 3 (42.8%) patients. This type of ulcer is less frequent than oral ulcers, and is usually present when Behcet’s disease appears during puberty. This hinders diagnosis at early ages, since bipolar ulcers are highly indicative of the disease. Ophthalmologic disorders were present in 57% of the cases. We know that ophthalmologic complications are more common in childhood, predominantly in males, and are associated with HLA. 14-16,18 We did not observe that possibly due to our population’s characteristics. One of our female patients had glaucoma, but the HLA-B5 was negative.

Skin involvement was present in only one patient; this is different from the information obtained from other reports (92%). 3,9,11,12 This might result from shorter evolution time presented by our patients. According to the literature, the frequency of the pathergy test varies a lot (from 22 to 84%). 2,4,10,12 Only one patient had positive pathergy test results (14.2%).

The only vascular disorder was saggital sinus thrombosis, although thrombophlebitis is mostly frequent. 11

Only 4 patients met the necessary criteria for the diagnosis of Behcet’s disease during the evolution of the disease (patients 1, 3, 5 and 6), indicating that the incomplete presentation of the disease is frequent. 3 Patients 2 and 4 had two major criteria and one minor criterion, while patient 7 had one major and one minor criterion.

Lab exams are not specific and help with the follow-up of disease evolution in few cases. The presence of hypergammaglobulinemia was described as the best prognostic factor for ophthalmic involvement. 18 Although we carried out this exam in only 4 patients, the results we obtained confirm the findings reported in the literature. In other words, 2 patients who had hypergammaglobulinemia did not show this kind of involvement, while the 2 patients with normal gammaglobulin had ophthalmic involvement. The frequency of HLA B5 occurred in only 2 patients (28%), a low frequency if compared with other studies (50 to 84%). 2,17 this may happen due to the characteristics of our population.

The treatment with oral corticosteroids is used in the acute phase of the disease in most patients. In milder cases, corticosteroids are not necessary, as with 3 of our patients. Thalidomide and colchicine were used according to patients’ clinical symptoms.

The efficacy of the treatment was assessed in 6/7 patients. The treatment was efficient in 66% of the cases. The frequency of recurrence was 50%, which is in agreement with the literature. 3

Since Behcet’s disease is not so frequent and its initial symptoms are nonspecific, it may not be recognized by pediatricians. Recurrent oral ulcers at any time during childhood and adolescence should be regarded as possible diagnosis of the disease.

References


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