ABSTRACT. Objective. To describe the characteristics of a group of pediatric patients with Behçet’s disease (BD) who presented at least 1 episode of thrombosis during their disease course.

Methods. We made a retrospective chart review of the clinical, biological, and radiological data of children with BD who presented at least 1 episode of either arterial or venous thrombosis. Data were extracted from both an international pediatric Behçet cohort and files referred from 7 French centers.

Results. Twenty-one patients were included. Diagnosis of BD was based on the criteria of the International Study Group for BD. Main locations for thrombosis were the cerebral sinuses, in 11 patients (52.4%); and lower limbs, in 9 patients (40.9%). Recurrent episodes were observed in 4 patients (21%). Thrombophilia measurements were normal in 14 patients out of 21, while anticoagulant antibodies were positive in 4 patients, and 2 out of 21 had protein C deficiency. One patient had lupus anticoagulant. All patients were treated with colchicine. Corticosteroids were also added for variable periods in 13 patients. Five patients out of 21 were treated with anticoagulants (heparin, then anti-vitamin K) and 3 with antiplatelets (acetylsalicylic acid).

Conclusion. Thromboses are a serious complication of BD and may occur early in the disease course. The presence of thrombophilic markers could increase the risk of thrombosis in BD, but the size of our population does not allow any conclusion. An international cohort (PED-BD) is currently in place and will allow study of such cases longitudinally, as well as assessment of the elements that correlate with an increased risk of thrombosis in children with BD. (First Release Nov 15 2010; J Rheumatol 2011;387–90; doi:10.3899/jrheum.100257)

Key Indexing Terms:

BEHÇET’S DISEASE CHILDREN THROMBOSIS THROMBOPHILIA

Behçet’s disease (BD) is a relapsing systemic vasculitis first described in 1937 by Hulusi Behçet, a Turkish dermatologist1. The prevalence of the disease is highest in Japan and in Mediterranean countries. Its multifactorial etiology combines abnormalities of both the innate and the adaptive immunity, leading to dysregulation of various proinflammatory cytokines2. At the genetic level, BD has been associated with the histocompatibility antigen HLA-B5101 3. The involvement of microbial antigens in the disease remains a plausible hypothesis. The diagnosis relies on the clinical basis, and the classification established in 1990 by the International Study Group for Behçet’s Disease (ISBD) is still the most commonly used even if it is not validated in pediatric patients4. The classical triad of BD combines uveitis, oral and genital aphthosis, and numerous systemic events including vasculitis, which occurs in 10% of cases. Thromboses occur in 50% of cases and could be caused by the association of abnormal procoagulant and anticoagulant factors, as well as by endothelial injury 5,6,7,8.

In France, the overall prevalence of BD is about 7.1 per 100,000 inhabitants, with differences by ethnicity9. The epidemiology of pediatric BD is difficult to assess because of conflicting definitions, but the number of identified cases is increasing10,11,12. Familial forms are more frequent in children. Embolism is very unusual. Arterial involvement occurs in 2% to 10% of cases. The symptoms of the disease described in children are the same as those in adults, and include severe thromboses in 6.6% to 38.4% of patients, according to some studies13,14,15,16,17.

We therefore sought to describe the characteristics of thrombosis in pediatric BD, and to find a possible link with thrombophilia. In adults, the respective roles of antithrombin III, protein C and S deficiency 18,19,20, factor V Leiden mutation, and prothrombin mutation are controversial5,21.

MATERIALS AND METHODS

We retrospectively analyzed clinical, biological, and radiological data of children diagnosed with BD between May 1, 1990, and January 1, 2009,
RESULTS
Twenty-one patients were included in our study (18 male, 3 female) with a 6:1 male-female ratio. They came from a population of 237 children, including 100 children from the PED-BD cohort and 137 patients from the 7 French centers, with a male-female ratio close to 1:3.1. In our study, 10 patients (47.6%) were Europeans while 6 were Turkish. Median age at the diagnosis of BD was 9.2 years (range 6–15 yrs). Mean time between the first symptoms of BD and the first episode of thrombosis was 22.8 months (range 0–96 mo). BD was not yet diagnosed at the time of thrombosis in 7 patients out of 18 in whom it was performed (38.9%). The disease course was complicated by short stature linked to treatments and delayed puberty in 3 patients, and arthritis in 2 patients. Two patients had aneurysms (1 of the aorta and the other of the mesenteric artery). One patient had persistent urinary disorders (dysuria). There was 1 death, a 13-year-old boy who, 4 years after diagnosis, died from complications of thrombosis of the mesenteric vein.

Treatment carried out after the first thrombosis episode consisted of colchicine in all patients and corticosteroids in 13 patients (61.9%). Six patients were treated with azathioprine (28.6%). One of these subsequently received cyclophosphamide and mycophenolate mofetil, another was treated with cyclosporine A. One patient received methotrexate. Five patients out of the 21 (23.8%) were treated with anticoagulants (heparin and subsequently warfarin) and 3 (14.3%) with antiplatelets (low-dose acetylsalicylic acid). Three cases of recurrent thromboses were observed (all with warfarin) among the 5 patients treated with anticoagulants (4 with warfarin and 1 with tinzaparin sodium).

Thrombophilia laboratory examinations revealed 1 patient with lupus anticoagulant, 4 with positive anticardiolipin antibodies (3 medium and 1 low titer; 19%), and 2 patients with partial protein C deficiency; no family history of thrombosis was present in any patient.

One patient had a heterozygous variant of MTHFR. One patient was heterozygous and another was homozygous for the M694V mutation of the MEFV gene (11.8% of 17 patients were carriers of the mutation).

DISCUSSION
In our study, the male-female ratio was 6:1, much higher than the ratio in the 237-patient cohort, which was close to those reported in literature.9,10,12 However, being male is associated with severe forms of BD.23,24 Ten patients (47.6%) were Western Europeans whereas 6 were Turkish.

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Table 1. Distribution of thromboses in 21 patients.

<table>
<thead>
<tr>
<th>Location</th>
<th>No. Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous</td>
<td></td>
</tr>
<tr>
<td>Cerebral</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Lateral sinus</td>
<td>7 (33.3)</td>
</tr>
<tr>
<td>Longitudinal sinus</td>
<td>4 (19.1)</td>
</tr>
<tr>
<td>Vena cava</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Sural</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Iliofemoral</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Saphenous</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Central vein of the retina</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Jugular</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Arterial</td>
<td></td>
</tr>
<tr>
<td>Central retinal artery</td>
<td>1 (4.8)</td>
</tr>
</tbody>
</table>
a cohort of 661 patients. Time to diagnosis of 17.6 months was close to that of the first occurrence of thrombosis of 22.8 months. This suggests a short time to treat patients before the onset of thrombotic complications. Incidentally, diagnosis was not made before first episode of thrombosis despite a long evolution of BD in 14 patients. The thromboses found in our study were venous (except for one of the central artery of retina) and occurred principally in large veins. The main location was the cerebral venous sinuses. In patients without BD, the principal location is the lower limbs.

A significant number of patients were treated with anticoagulants (23.8%) or antiplatelets (14.3%). Three of them had anticardiolipin antibodies, 1 had lupus anticoagulant, and 1 was immobilized because of sequelae of the first episode of thrombosis. This therapeutic approach, which is supported by some publications on cerebral thrombophlebitis, is challenged by other studies, which suggest that anticoagulants, in contrast to immunosuppressants, are ineffective in BD-related thromboses. Our study corroborates these data, because 3 patients out of 5 had other episodes of thrombosis despite anticoagulation. Only 1 study describes 7 cases of thromboses treated with anticoagulants with no relapses after more than 18 months, but it was associated with corticosteroids and either azathioprine or cyclophosphamide.

Anticardiolipin antibodies were found in 4 patients out of 21. This result does not suggest that the presence of these antibodies is a risk factor for thrombosis in BD, because they are common (40%) in adults with BD, whether they have thrombosis or not. Two patients (9.5%) had moderate protein C deficiency. This rate is clearly higher than the proportion in the general population. Protein C deficiency is a known risk factor for thrombosis, but the small size of our population did not allow us to draw any conclusions.

Another interesting finding was identification of the M694V mutation of MEFV gene in 2 patients, one of whom was homozygous. Mutations of MEFV gene are known to be more frequent in BD (2.6% for M694V) than in the general European population. These studies implicate MEFV as a disease-modifying gene. Certain studies have even suggested that it is a risk factor for vasculitis and thrombosis in BD. Our results do not allow any conclusion because of the lack of systematic research and the small number of carriers in our population.

This is the largest cohort of children with BD-associated thrombosis. We found only a few case reports describing mostly cerebral venous thrombosis or other locations, and 1 cohort study of 7 patients.

Thromboses are a major clinical characteristic of BD, although they are not part of the international classification criteria. Our study suggests that both protein C deficiency and M694V mutation in the MEFV gene can be additional risk factors for thromboses in pediatric BD. However, we cannot conclude that, because of the lack of a comparison group, in addition to the small number of patients. Our study also highlights the long time to diagnosis in BD. Moreover, in 14 patients, diagnosis was made only after this serious complication had occurred. The great disparity of treatments...
used in these patients shows the lack of consensus for therapy in children with BD-associated thromboses.

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