HLA and Behçet's Disease in Northern Spain: Their Lack of Correlation with Arthritis Pattern

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Summary

We have studied the characteristics of arthritis present in 32 patients with Behçet's disease (BD), and how this arthritis is related to the HLA markers class I. 84% of the patients presented arthritis, the most common being mono-arthritis as the initial presentation, and oligoarthritis in subsequent episodes. In 63% of the cases, the development was in episodes of acute/subacute arthritis. We found statistically significant association between antigens B-5 and B-51, and the group with BD, with a relative risk of 3.89 and 4.71 respectively. The attempt to relate markers B-5, B-51 and B-27 to the presence of arthritis as well as to its manifestation and further development was not conclusive.

INTRODUCTION

Behçet's disease (BD) is peculiarly distributed in the world. Its high incidence in Japan and in ethnic groups in the Middle East, especially among the Turkish people and around the Mediterranean is well-known. Nevertheless it is rare among the British and North American people, black people and the American Indians (1-2). As for the symptoms presented by these patients, the frequency with which they present joint involvement is variable, between 26 and 100%, depending on the characteristics both of the study and of the group that conducts it (3-5).

Several histocompatibility antigens have been related to BD during these last years. Association of the disease with HLA B-5 is more frequent in Japanese and Arab patients and in those from the Mediterranean littoral. It has not appeared so often in North America or Northern Europe (6-9). More recently, B-51 has been associated with a higher risk of developing the disease (10), but there have been discrepancies regarding the association of clinical patterns with HLA antigens (11-12).

To evaluate whether this association exists in our country, we have studied these histocompatibility antigens in patients with BD, and also the possible relation of HLA with both the initial pattern and the evolution of arthritis.

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MATERIAL AND METHOD

We have studied joint involvement in 33 patients diagnosed for BD, following Mason and Barnes criteria (4), and establishing the diagnosis when the patients met with 3 major criteria, or else, 2 major and 2 minor. All but one fulfilled the ISG criteria (13). We made a distinction between the first manifestation of arthritis and subsequent episodes.

All the patients belonged to families living in our country for at least two previous generations. We based our study on clinical history, exploration, laboratory data and radiographs of the damaged joints.

Typing for HLA was performed in each of the cases of BD, using the standard lymphocyte microcytotoxicity assay (14). We compared the frequency of presentation with a control group of 230 persons from our community.

For the statistical analysis we used the epidemiology program (EPI-INFO) from the Epidemiology Program Office Center for Disease Control, Atlanta, GA 30333. Two-by-two tables for the comparison of the HLA types in patients and control group were used. The odds ratio was expressed in terms of relative risk (RR), within 95% of Cornfield confidence limits. The statistical significance of the RR was calculated by the Chi-squared test, applying Yates correction or Fisher's test (two-tailed) for each.

RESULTS

Of the 32 patients with BD, 27 (84%) presented arthritis. The characteristics of joint involvement are shown in Table I, indicating a distinction between the
Table I: Types of presentation of arthritis in 27 patients with BD

<table>
<thead>
<tr>
<th>Clinical Initial attack</th>
<th>Episodes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoarthritis</td>
<td>12 (44%) 6 (22%)</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>6 (22%) 13 (48%)</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>9 (33%) 6 (22%)</td>
</tr>
</tbody>
</table>

* 2 cases only presented one episode of arthritis.

Table II: Calculation of relative risk (RR) and statistical value for HLA in 27 patients with BD and arthritis

<table>
<thead>
<tr>
<th>HLA</th>
<th>h</th>
<th>H</th>
<th>k</th>
<th>K</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-5</td>
<td>14</td>
<td>47</td>
<td>13</td>
<td>183</td>
<td>4.19</td>
<td>0.001</td>
</tr>
<tr>
<td>B-51</td>
<td>10</td>
<td>26</td>
<td>17</td>
<td>204</td>
<td>4.62</td>
<td>0.001</td>
</tr>
<tr>
<td>B-27</td>
<td>4</td>
<td>14</td>
<td>23</td>
<td>216</td>
<td>2.68</td>
<td>0.1</td>
</tr>
<tr>
<td>B-12</td>
<td>7</td>
<td>58</td>
<td>20</td>
<td>172</td>
<td>1.04</td>
<td>0.8</td>
</tr>
<tr>
<td>B-5 + B-12</td>
<td>2</td>
<td>5</td>
<td>25</td>
<td>225</td>
<td>3.60</td>
<td>0.1</td>
</tr>
</tbody>
</table>

h - positive patients; k - negative patients; H - positive controls; K - negative controls

initial attack of arthritis and subsequent episodes. We want to point out that the first episode appeared mainly as monoarthritis (44%) but oligoarthritis was the most common presentation (48%) in successive episodes. Joint involvement appeared mainly in large joints, both in the initial attack and in subsequent episodes: arthritis in knees and ankles represents 69% of the initial attack. In two cases there was concomitant ankylosing spondylitis (AS) and BD, both with bilateral sacroiliitis.

Twenty-four cases (89%) showed episodes of arthritis, developing as intermittent, acute or subacute synovitis (63%) and chronic synovitis (37%). Eighty-four % of all the patients with BD presented 3 or more joint episodes in the course of their illness.

The clinical symptoms, which became more acute at the moment of the appearance of the arthritis episodes, were: fever (30%), erythema nodosum (8%), recurring aphthas (22%) and genital ulcers (12%).

With regard to the radiological study of the joints which presented arthritis, in 18 cases (67%) there were no radiological alterations. In the rest we found: 4 patients with soft tissue swelling, 2 with subchondral osteoporosis, 4 with erosions, 1 with periostitis while 2 cases presented symmetrical bilateral sacroiliitis.

The result of HLA typing on 27 patients with arthritis were: 14 cases (52%) with B-5, 10 (37%) with B-51, 4 (15%) with B-27 and 7 (26%) with B-12. We calculated the RR and statistical value for these antigens, (Table II). We observed that antigens B-5 and B-51 are more frequently carried by patients with BD, as compared to the general population. There are no significant differences, however, with regard to B-12, B-27 or the association of B-5 and B-12.

We related these markers to characteristics of arthritis in these patients, and we must point out that there is B-27 only in the cases of chronic synovitis and that B-51 does not appear in any of them. On the other hand, there was a high frequency of marker B-51 in the group that developed repeated episodes of acute synovitis. But the statistical analysis of these results was not significant in any markers in relation to joint evolution (Table III).

With regard to the symptoms which became more acute after the appearance of joint episodes, we only want to emphasize the presence of B-12 (44) in 50% of the patients who developed aphthous episodes together with joint involvement, although with no significant ratio for RR 1.43 (p<0.5).

We found no statistically estimable association between the first episodes of joint involvement, oligoarthritis or polyarthritis, and markers B-5, B-51 and B-27, or between these antigens and the different types of subsequent joint episodes (Table IV).

DISCUSSION

Our study showed that the frequency of arthritis in patients with BD was high, as compared to the frequency mentioned in most reports, which is usually around 50%. It is, however, similar to the frequency mentioned by different groups of rheumatologists who study BD, since in these cases arthritis is the main reason for the consultation.

The most frequent initial clinical manifestation was monoarthritis, but the follow-up showed that oligoarthritis was the most common in successive episodes. Mono-oligoarthritis is the most common type of joint involvement at the beginning of the illness (15-16), but Mason and Barnes find an average of 5.5 joints with arthritis per patients with BD (4). Other reports also consider polyarthritis as the most common presentation (17).

Arthritis is usually located in the large joints of the lower limbs, and this location represents 73% in our series; it is less frequently located in wrists and small joints of hands and feet (3,5,15). Involvement of the sacroiliac joints has produced controversy in BD: Dilsen finds that 20% of the patients with BD have ankylosing spondylitis, and 63% have radiological sacroiliitis (18); in another radiological study they reached 50% (19). Nowadays, however, it is generally admitted that there is an incidence of AS in patients with BD similar to that in the general population (20-23), in spite of the fact that, in our cases the prevalence of AS is identical to the one found by Kahan in France (24) namely 6.5%.

It usually occurred as intermittent, acute or subacute