HLA-B27 typing in the categorisation of uveitis in a HLA-B27 rich population

Minna Huhtinen, Anni Karma

Abstract

Aims—To determine whether HLA-B27 typing helps the clinician in the diagnostic examination of uveitis in a HLA-B27 rich population and also whether the clinical picture of HLA-B27 positive unilateral acute or recurrent anterior uveitis (AAU) is distinguishable from the idiopathic negative form.

Methods—During a 3-year period 220 consecutive patients with undetermined uveitis at onset were examined in the Helsinki University Eye Clinic. HLA-B27 antigen was tested for 88% of the patients. Other laboratory or x-ray examinations were performed on the basis of the anatomical classification of uveitis and the biomicroscopic features characteristic of uveitis associated systemic diseases.

Results—HLA-B27 antigen was found significantly more often in patients with anterior (71%) and acute/recurrent unilateral (79%) uveitis than in patients with intermediate, posterior panuveitis (7%), and chronic (7%) or bilateral (12%) forms. Of the 16 cases of HLA-B27 negative unilateral AAU, five showed biomicroscopic features representing uveitis entities. The remaining 11 cases did not differ in any respect from the cases of HLA-B27 positive unilateral AAU.

Conclusion—HLA-B27 antigen helps the clinician in the diagnostic examination of unilateral AAU. Positive test results serve as a clue to search for spondyloarthropathies, and negative results indicate the need to look for specific uveitis entities and other systemic diseases. The occurrence of HLA-B27 positivity in conjunction with uveitis entities other than unilateral AAU is of the same level or less than in the population of Finland in general.

Table 1  HLA-B27 antigen and the anatomical location of uveitis

<table>
<thead>
<tr>
<th>HLA-B27 antigen</th>
<th>Anterior (n=112)</th>
<th>Intermediate (n=36)</th>
<th>Posterior (n=31)</th>
<th>Panuveitis (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>75</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>30</td>
<td>33</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>34</td>
<td>15</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 2  HLA-B27 antigen and the duration and laterality of uveitis

<table>
<thead>
<tr>
<th>Classification</th>
<th>No of patients tested for HLA-B27/total no</th>
<th>No of HLA-B27 positive in tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/recurring unilateral</td>
<td>92/111</td>
<td>73 (79)</td>
</tr>
<tr>
<td>Acute/recurring bilateral</td>
<td>17/18</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Chronic unilateral</td>
<td>30/36</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Chronic bilateral</td>
<td>47/85</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>186/220</td>
<td>81 (44)</td>
</tr>
</tbody>
</table>

Table 3  General characteristics and biomicroscopic features of the unilateral cases of acute anterior uveitis

<table>
<thead>
<tr>
<th>General characteristics and biomicroscopic features</th>
<th>Idiopathic B27+ (n=63)</th>
<th>AS/SpA* B27+ (n=9)</th>
<th>Idiopathic B27− (n=11)</th>
<th>Other uveitis entity B27− (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at onset (years)</td>
<td>31</td>
<td>28</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Male/female</td>
<td>1:3.1</td>
<td>3:5:1</td>
<td>1:2.1</td>
<td>2:3</td>
</tr>
<tr>
<td>Recurrent (%)</td>
<td>49</td>
<td>78</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>Fibrin exudate (%)</td>
<td>43</td>
<td>56</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Hypopyon (%)</td>
<td>11</td>
<td>0</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Fatty keratic precipitates (%)</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Patchy/sectorial iris atrophy (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Persistent posterior synchiae (%)</td>
<td>22</td>
<td>22</td>
<td>18</td>
<td>40</td>
</tr>
</tbody>
</table>

*Ankylosing spondylitis (AS) or other seronegative spondyloarthropathy (SpA).

Results

A total of 220 patients (99 men and 121 women) had no established systemic disease known to be associated with uveitis entities when they entered this study. At the time of the first symptomatic uveitis attack the subjects' median age was 36 (range 9–91) years.

Seventy one per cent of the patients with anterior uveitis but only 7% of the patients with intermediate, posterior, or panuveitis were positive for HLA-B27 antigen ($\chi^2$, 1 df=76.24, p<0.0001) (Table 1). In addition, 79% of the patients with acute or recurrent unilateral disease, but only 7–12% of those with chronic and/or bilateral disease were HLA-B27 positive ($\chi^2$, 1 df=94.90, p<0.0001) (Table 2).

Of the patients with unilateral acute or recurrent anterior uveitis, 72 (82%) were HLA-B27 positive and 16 (18%) were HLA-B27 negative (Table 3). In the latter group, biomicroscopic specific features gave clues to distinct uveitis entities in five cases. Three patients had patchy or sectorial iris atrophy combined with fatty keratic precipitates suggestive of herpetic infections, one patient had sarcoid lung manifestations in the x-ray and histologically confirmed conjunctival granulomas, and one patient had a clinical picture consistent with Posner Schlossman uveitis.

Among the unilateral HLA-B27 positive AAU patients, ankylosing spondylitis was diagnosed in one man and one woman. In addition, undetermined spondyloarthropathy was detected in seven people.

The median age at the time of the first uveitis attack was significantly lower (30.5 versus 45 years) (Mann–Whitney U test, p=0.007) for the HLA-B27 positive unilateral AAU group (Fig 1) than for the group with HLA-B27 negative idiopathic unilateral AAU (Fig 2). The male to female ratio was 1:2:1 and 1:3:1 for the idiopathic HLA-B27 positive and negative groups, respectively (Table 3). The male dominance (3:5:1) was more evident among the patients with ankylosing spondylitis or spondyloarthropathy than among the idiopathic cases. However, in the age group of over 40 years, there was a tendency towards female dominance among the HLA-B27 positive unilateral AAU cases (Fig 1).

Patients with HLA-B27 positive unilateral AAU, especially when associated with ankylosing spondylitis or spondyloarthropathy, had a history of recurrent attacks more often than patients with idiopathic HLA-B27 negative unilateral AAU (Table 3). The presence of fibrin exudate was not observed to be more frequent in patients with idiopathic HLA-B27 positive unilateral AAU (43%) than in those with idiopathic HLA-B27 negative unilateral AAU.
**Table 4** Distribution of HLA-B27 antigen in uveitis entities or associated disorders

<table>
<thead>
<tr>
<th>Uveitis entity or associated disorder</th>
<th>No of patients tested for HLA-B27 total No (%)</th>
<th>No of HLA-B27 positive in total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic AAU* (unilateral)</td>
<td>74/74 (100)</td>
<td>63 (85)</td>
</tr>
<tr>
<td>AS/SpA‡</td>
<td>10/10 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Unknown</td>
<td>42/48 (88)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Infections‡</td>
<td>18/30 (60)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Other systemic disease§</td>
<td>8/14 (57)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Specific ocular entity§</td>
<td>3/44 (77)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>186/220 (85)</td>
<td>81 (44)</td>
</tr>
</tbody>
</table>

*AAU = acute anterior uveitis. †Ankylosing spondylitis (AS). ‡Undetermined spondyloarthropathy (SpA). §Sarcoidosis 12, chronic lymphatic leukaemia 1, lupus erythematosus disseminatus 1, Fuchs’ heterochromic iridocyclitis 12, pars planitis 9, white dot syndrome 8, idiopathic retinal vasculitis 8, Posner Schlossman syndrome 2, ischaemic uveitis 2, birdshot retinocchoroidopathy 2, infectious bilateral papillitis 1.

### Discussion

Our uveitis study population had a homogeneous demographic background. All the patients were white and were born in Finland. Although our clinic is a tertiary eye care centre, 30% of the patients are referred by general practitioners.

In published reports HLA-B27 has been examined in unilateral acute or recurrent anterior uveitis patients but in only some of the patients with bilateral or chronic uveitis or intermediate, posterior, or panuveitis. One might argue on the basis of the evidence that only AAU has a relation with HLA-B27 antigen. However, since we found no studies in the literature on this topic and HLA-B27 is common in our population, we wanted to determine the distribution of HLA-B27 antigen with respect to different uveitis entities. Furthermore, we were interested in whether the presence of HLA-B27 antigen helps to categorise uveitis when the clinical picture is not typical at onset. Unilateral AAU can begin insidiously, and affect one eye after another in a short period of time. However, it has sometimes been classified as bilateral. In addition the evaluation of the fundus is sometimes impossible in the beginning of iridocyclitis because of a reaction in the anterior vitreous.

In our series HLA-B27 existed significantly more often in cases of unilateral, acute recurrent, and anterior uveitis than in bilateral and/or chronic ones. In addition, HLA-B27 antigen was found significantly less frequently in relation to other uveitis entities and systemic diseases than in conjunction with unilateral AAU and spondyloarthropathies. The diagnosis of these disorders was based on duration, laterality, typical biomicroscopic features, and, in selected cases, some laboratory and ancillary tests. These findings suggest that the clinician does not benefit from HLA-B27 typing when uveitis is classified as bilateral and/or chronic or the inflammation is located in the posterior part of the eye. However, HLA-B27 positive AAU in connection with symptoms suspicious of spondyloarthropathy can sometimes develop into posterior or panuveitis. Rodriguez and colleagues described a series of patients with seronegative arthritic syndromes and HLA-B27 associated uveitis with severe, sight threatening, posterior segment ocular manifestations. There were five patients in our original series who were HLA-B27 positive and who also had spondyloarthropathy. Their inflammation began as acute anterior uveitis but during the course of the disease involved also posterior uveal tissues. We classified these cases as panuveitis. The systemic diseases and HLA-B27 positivity were diagnosed the patients entered our study; therefore we excluded them according to our study protocol. HLA-B27 typing can be recommended in posterior or panuveitis when associated with symptoms of spondyloarthropathies. Because patients with typical symptoms of iritis and unilateral acute anterior eye involvement have an 80% probability of being HLA-B27 positive in Finland, one could assume that HLA-B27 typing is not necessary at all in such cases. Power and
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sions are supported by the results of epidemiological studies. In addition to having their prognosis estimated, patients with idiopathic anterior uveitis. In contrast with the 24% to 90% reported earlier by other researchers, our series consisted strictly of patients with unilateral acute or recurrent anterior uveitis with no previous history of systemic diseases. There were 27 patients with spondyloarthropathy that had been diagnosed earlier in the excluded group, five of whom had posterior eye involvement. In addition, 34 of our 72 unilateral HLA-B27 positive AAU patients had their first attack when entering our study, and they may not have had time to develop the symptoms characteristic of ankylosing spondylitis. One might also argue that asymptomatic ankylosing spondylitis or undifferentiated spondyloarthropathy might have been diagnosed if all the patients had been referred to a rheumatologist and saccroiliac x rays had been taken. However, we believe that, in addition to exogenous factors, there must be other genetic markers besides HLA-B27 that predispose patients to ankylosing spondylitis or related spondyloarthropathies. These conclusions are supported by the results of epidemiological, family, and twin studies. The second most important reason for the HLA-B27 typing of unilateral AAU patients is its value to differential diagnosis. The lack of HLA-B27 antigen in a unilateral AAU patient may be a clue for the clinician to search for other specific uveitis entities and other systemic diseases. In our series five out of 16 HLA-B27 negative AAU cases involved distinct uveitis entities when examined carefully. The remaining 11 did not differ in clinical manifestation from the idiopathic B27 positive ones, although the sample size was too small for definite conclusions. This phenomenon has been observed also previously in four patients by Linssen and Meenken. Whether idiopathic unilateral HLA-B27 negative AAU is a specific uveitis entity is subject to debate. We conclude that HLA-B27 antigen is highly prevalent among patients with unilateral AAU. In uveitis entities affecting the posterior part of the eye or bilateral or chronic in nature, HLA-B27 was found rarely. The biomicroscopic features of HLA-B27 positive patients with or without spondyloarthropathies did not differ from idiopathic HLA-B27 negative ones.

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