Acute Anterior Uveitis and HLA-B27 Subtypes

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The tissue antigen HLA-B27 is found in 50% of Dutch acute anterior uveitis (AAU) patients. The prevalence of HLA-B27 in the normal population is only 8%. However, only approximately 1% of HLA-B27+ individuals will develop AAU. Therefore, it is possible that the disease is associated with a particular B27 subtype. We typed lymphocytes of 36 B27+ AAU patients, of which 20 also had ankylosing spondylitis, for three serologically defined B27 subtypes (B27 W, B27 K and B27 non W/non K). These subtypes were normally associated with AAU. The subtype frequencies in the patients suffering from both AAU and AS also showed no preference for a certain subtype. Subtype-specific characteristics of the primary structure of the various B27 subtype molecules therefore cannot be responsible for the disease association. Invest Ophthalmol Vis Sci 29:1137–1140, 1988

The association between acute anterior uveitis (AAU) and HLA-B27 is generally accepted.1 In the normal Dutch population HLA-B27 is found in 8%; in the patients the prevalence is increased to about 50%. About half of these B27+ AAU patients develop ankylosing spondylitis (AS).2 In a recent study we found that AAU occurs in about 10% of the B27+ relatives of B27+ AAU patients compared to only 1% of B27+ healthy individuals.3 Therefore we postulated that besides HLA-B27, other genetic factors play a role in the pathogenesis of AAU. It is also possible that not HLA-B27 in general but one of its subtypes is preferentially associated with AAU.

These HLA-B27 subtypes vary only in two to four amino acids. The B27 subtypes can be determined by using human allo-activated cytotoxic T-lymphocytes,4 isoelectric focusing,5 monoclonal antibodies,6 antiviral responses7 and even human allo-antisera.8 These subtypes were given different numbers and letters by distinct authors. The subtypes W, K, C and D are probably identical to the types 1, 2, 3 and 4, respectively, but other names have been used.9,10

In the current study we therefore investigated whether the association between AAU and HLA-B27 is confined to one or some of the subtypes.

Materials and Methods

Patients with AAU from the departments of ophthalmology of three universities (University of Amsterdam, Erasmus University at Rotterdam and Free University at Amsterdam) were typed for HLA-B27.2 AAU was diagnosed, as described by Rothova et al, as an iridocyclitis or iritis with a duration of less than 3 months.11 Patients in whom the inflammation became chronic were excluded from the study. The patients were all examined for ankylosing spondylitis and related arthropathies by one of us (AL), using the New York criteria.12 Finally, the lymphocytes of 36 patients were available to perform HLA-B27 subtyping. A group of 70 healthy, unrelated Dutch individuals, mostly blood donors, served as controls. Informed human consent was obtained prior to undertaking the study.

Subtyping was performed in a complement dependent lymphocytotoxicity assay in microtiter plates using allo-antisera recognizing the subtypes W, K and the complex non W/non K.

Statistical analysis was performed by Chi square test, using Yate's correction for small numbers.

Results

The results of HLA-B27 subtyping of 36 B27+ AAU patients, with or without AS, are presented in Table 1. The frequencies of the W, K and non W/non K subtypes in the patient groups did not differ significantly from the frequencies in the control group. P-values for W, K and non W/non K for all AAU patients as compared to controls were 0.9, 0.65 and 0.20, respectively. Two patients who were positive for
Table 1. Frequencies of HLA-B27 and the subtypes B27 W, B27 K and B27 non W/non K in patients with acute anterior uveitis (AAU) whether or not occurring with ankylosing spondylitis (AS)

<table>
<thead>
<tr>
<th></th>
<th><em>AAU</em> total</th>
<th><em>AAU</em> AS+</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number studied</td>
<td>36</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>B27 W</td>
<td>33</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>%</td>
<td>92%</td>
<td>85%</td>
<td>90%</td>
</tr>
<tr>
<td>B27 K</td>
<td>1</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>%</td>
<td>3%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>non W/non K</td>
<td>16</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

the non W/non K serum, and presumably carried the C/D subtype, were of oriental origin. In orientals 50% of HLA-B27 subtypes are C/D.13

Therefore, neither AAU in general, nor AAU in conjunction with AS, were preferentially associated with a subtype of HLA-B27.

Discussion

The fact that AAU showed no association with one of the B27 subtypes was not surprising. Breur et al already found that in ankylosing spondylitis (AS) no single B27 subtype was increased. AAU, AS, Reiter's syndrome and other reactive arthritides probably form a pathogenic entity, the so-called "B27-associated diseases".3 If these diseases are associated with HLA-B27, but not preferentially with one of its subtypes, a structure in the class I molecule shared between the subtypes, but different from other class I molecules, probably plays a role in the pathogenesis.

Comparing the protein structure of HLA-B27 with the structures of other class I antigens of the B locus reveals strong conservation. For instance, HLA-B27, HLA-B7 and HLA-B40 have an α1 domain which is completely identical for all three. However, several residues are unique for B27 and thereby important in disease association (Fig. 1). The amino acids at positions 67, 70 and 97 varied between B27 on the one hand and other HLA-B molecules on the other. Two were in the α1 domain, located in the highly polymorphic region (62-83), the other one was in the α2 domain.

Comparison with HLA-A and HLA-C molecules revealed that amino acid 97 was an asparagin in HLA-A28, HLA-Aw68 and HLA-B27. Hence, the only difference between HLA-B27 and other class I antigens was that HLA-B27 always had a cysteine at position 67 and a lysine at 70, in contrast to all other human class I antigens sequenced so far. These B27-specific amino acid differences, contributing a free sulfhydryl group and a net positive charge, respectively, are in the middle of the highly variable region and could be of importance in HLA-B27 immunological function and disease association.24 As long as

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the three-dimensional structure of HLA molecules and especially HLA-B27 remains unelucidated, attempts to predict class I antigen interaction patterns will be highly speculative.

The negative results of the present study underline the need for further studies of the genetic factor(s) which, in addition to HLA-B27, play a role in the pathogenesis of AAU.
Key words: acute anterior uveitis, ankylosing spondylitis, HLA-B27 (subtypes), HLA disease association

Acknowledgments

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References