HLA-B27 associated rheumatologic diseases in Indonesia

Mardjuadi, A.

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Chapter 2

Higher relative risk of spondyloarthropathies among B27 positive Indonesian Chinese than native Indonesians
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Higher Relative Risk of Spondyloarthropathies Among B27 Positive Indonesian Chinese than Native Indonesians

ACHMAD R. NASUTION, ADMIWIRAWAN MARDJUADI, NYOMAN G. SURYADHANA, RIZASJAH DAUD, and SOENARDI MUSLICHAN

Abstract. We assessed the prevalence of HLA-B27 among ethnic Indonesian and Indonesian Chinese patients with ankylosing spondylitis (AS) or related spondyloarthropathies, and also among healthy controls. HLA-B27 was found in 23 (62.2%) of 37 Chinese patients and 4% of 176 Chinese healthy controls (p < 0.001). In contrast, only 2 (8.3%) of 24 native Indonesian patients and 13 (9%) of 145 healthy controls were HLA-B27+, indicating the lack of association of HLA-B27 with spondyloarthropathies in native Indonesians. These findings also suggest that HLA-B27 Chinese Indonesians carry a greater relative risk of developing AS and related spondyloarthropathies than native Indonesians, although the prevalence of HLA-B27 in the general population is more than 2 times higher in native Indonesians. (J Rheumatol 1992;20:988-90)

Key Indexing Terms: SPONDYLOARTHOGRAPHIES HLA-B27 INDONESIANS CHINESE

Genetic factors play an important role in the pathogenesis of rheumatic disorders such as ankylosing spondylitis (AS) and related spondyloarthropathies. These diseases are strongly associated with the genetic marker HLA-B27. The prevalence of HLA-B27 varies among different ethnic groups. For example, in Caucasian populations HLA-B27 prevalence varies between 6 and 14%, while 50% of Haida Indians in Canada carry the B27 gene. In populations studied so far, the prevalence of AS roughly parallels the prevalence of B27. In addition to HLA-B27, other genetic markers might play a role in susceptibility to these diseases. Among HLA-B27+ Caucasian individuals the HLA-B locus allele Bw60 has been shown to increase the risk of developing AS by a factor of ~3.

In our clinical experience AS and related spondyloarthropathies are much more common in ethnic Chinese living in Indonesia compared to native Indonesians. Our purpose was to see whether the difference in disease occurrence was accompanied by a difference in the prevalence of HLA-B27 among patients and healthy individuals in these 2 ethnic groups in Indonesia. Our view is that B27+ Chinese Indonesians have a higher relative risk of developing AS and related spondyloarthropathies than native Indonesians, although the prevalence of B27 is more than 2 times higher in the latter group.

From the Department of Medicine, Division of Rheumatology and Department of Pediatrics, Division of Hematology, University of Indonesia, Jakarta, Indonesia.

A.R. Nasution, MD, Associate Professor, Head; A. Mardjuadi, MD, MSc, Visiting Rheumatologist; N.G. Suryadhana, MSc, Immunologist; R. Daud, MD, Clinical Epidemiologist, Division of Rheumatology; S. Muslichan, MD, PhD, Associate Professor, Division of Hematology.

Address reprint requests to Dr. A.R. Nasution, RSCM Hospital, Division of Rheumatology, Department of Medicine, FKUI, Jalan P. Diponegoro 71, Jakarta Pusat, Indonesia.


MATERIALS AND METHODS

Controls. Three hundred twenty-one healthy individuals of both sexes were selected randomly from several locations in Jakarta: 29.2% were schoolchildren, 19.5% hospital employees, 11.5% mineral water factory workers; 39.0% were healthy individuals who came for a medical checkup. In total 145 native Indonesians and 176 Chinese patients of Chinese origin were included as controls (Table 1). It has been estimated that 10-11% of people living in Jakarta are of Chinese descent, whereas this figure for the whole population of Indonesia is estimated at about 4%.

Patients. We studied 61 patients of all ages known to have AS and related spondyloarthropathies; 37 patients were of Chinese ethnic origin and 24 native Indonesians. A total of 30 patients attended a private rheumatology clinic, whereas the others visited the rheumatology clinic of the University of Indonesia in Jakarta. The patients had not been specifically referred to us by practising physicians. Table 2 summarizes the diagnoses and demographic data.

The diagnosis of AS was based on the modified New York criteria. The 10 patients with juvenile onset were all rheumatoid factor (RF) negative and the onset of symptoms was at age 16 or younger. Six of the 7 patients with juvenile onset of Chinese origin had both thoracic and inflammatory low back pain, whereas the single HLA-B27+ Chinese patient with juvenile onset had thoracic pain, enthesitis around the heel and a swollen knee joint. This patient met criteria for seronegative enthesopathy and arthropathy (SEA) syndrome. The 3 patients with juvenile onset had thoracic, inflammatory low back and shoulder pain. Therefore, all 10 patients can be regarded as having juvenile AS or SEA syndrome. Recognition of SEA syndrome may help to identify children with the prodromal manifestations of spondyloarthropathy.

Table 1. Demographic data on Chinese and native Indonesian controls

<table>
<thead>
<tr>
<th></th>
<th>Chinese</th>
<th>Native</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>176</td>
<td>145</td>
</tr>
<tr>
<td>% Males</td>
<td>48.9</td>
<td>51.0</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>27.6</td>
<td>34.7</td>
</tr>
<tr>
<td>Range (yrs)</td>
<td>11-82</td>
<td>15-76</td>
</tr>
<tr>
<td>Number HLA-B27+ (%)</td>
<td>7 (4.0)</td>
<td>13 (9.0)</td>
</tr>
</tbody>
</table>
While only one amino acid (lysine in Position 70) is how this clinical impression was reflected in the distribution to our understanding of the etiology of AS and spondyloarthropathy. If it can be shown that some B27 subtypes among patients and healthy controls in the 2 ethnic groups.

The numbers of patients with AS and related spondyloarthropathies in our study are rather small. Certainly, larger sample sizes in cross sectional studies would be needed to more reliably assess for both ethnic groups the strength of association between HLA-B27 and spondyloarthropathies. Nonetheless, our descriptive study supports the view that B27+ Indonesian Chinese have a higher risk of developing spondyloarthropathies compared to B27+ native Indonesians.

Our findings could be the result of either some differences in exposure to environmental factors, or due to differences in genetic susceptibility. For example it is possible that native B27+ Indonesians carry a B27 subtype that relatively protects them from developing AS or spondyloarthropathy, similar to B27+ individuals living in Gambia, West Africa. In contrast, B27+ Chinese Indonesians might possess a B27 subtype that confers higher susceptibility to these diseases. There is reason to further explore this susceptibility.

There are at least 7 different molecular subtypes of HLA-B27. While only one amino acid (lysine in Position 70) is unique to HLA-B27 among all the HLA class I specificities, the subtypes of HLA-B27 show multiple polymorphisms at other sites of the molecule. The most common subtypes of HLA-B27 have all been implicated in disease predisposition. A recent study suggests, however, that one particular subtype, HLA-B*2703, which is the predominant subtype of HLA-B27 in Gambia, West Africa, is not associated with spondyloarthropathy in black Africans. This subtype differs from the common Caucasian HLA-B27 subtypes in its recognition by cytotoxic T cells. It has been suggested that a lack of association of HLA-B*2703 with AS and related spondyloarthropathies may account in part for the rarity of this condition in black African populations.

Differences among populations in the prevalence of other genetic factors might contribute to the difference in the prevalence of AS and related spondyloarthropathies. For example among Caucasians, those relatives of B27+ patients with AS who were both B27+ and BW60+ were 3 times more likely to develop AS compared to the relatives who were B27+ but lacked BW60. The gene frequency of BW60 in China was 10.57 based upon HLA-typing of 172 random haplotypes, whereas in Indonesia BW60 was only found in 2.8% of the 93 haplotypes studied so far (I. Schreuder, Dept. of Immunohematology, Leiden, the Netherlands—personal communication). Therefore, when comparing the risk for B27 positives across populations, appropriate consideration should be given not only to differences in the frequency of B27 subtypes among patients and controls, but also to the prevalence of other B locus alleles as well as non-HLA genetic differences. Such studies may make an important contribution to our understanding of the etiology of AS and spondyloarthropathy. If it can be shown that some B27 sub-

### Table 2. Spondyloarthropathies among Chinese and native patients

<table>
<thead>
<tr>
<th></th>
<th>Chinese Indonesians</th>
<th>Native Indonesians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Male (female ratio)</td>
<td>23.1</td>
<td>16.56</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>38.3</td>
<td>33.8</td>
</tr>
<tr>
<td>Range (yrs)</td>
<td>16-54</td>
<td>16-58</td>
</tr>
<tr>
<td>Diagnosis (number HLA-B27+)</td>
<td>16 (9)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>AS</td>
<td>10 (7)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>SEA syndrome</td>
<td>6 (3)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Reiter's syndrome</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Undifferentiated spondyloarthropathy (BASE syndrome)</td>
<td>14 (3)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Total number (number HLA-B27+)</td>
<td>37 (23)</td>
<td>24 (2)</td>
</tr>
</tbody>
</table>

Five patients had psoriatic arthritis; all showed radiographic sacroiliac changes. None had RF. Two of the native patients also had enthesitis. With the exception of 1 native patient, all 5 showed involvement of distal interphalangeal finger joints together with psoriatic nail lesions.

Reiter's syndrome was seen in 5 patients. They had symmetric oligoarthritis with at least one extrarticular manifestation.

In total 28 patients were diagnosed with undifferentiated spondyloarthropathy or with B27, arthritis, sacroiliitis and extrarticular manifestations (BASE syndrome) as recently proposed. All of these patients had inflammatory spinal pain for at least 3-6 months. RF was not found in any, their pain was relieved by exercise, but not by rest; they showed slight decreases in thoracic chest expansion and also some limitation of lumbar movement. The 5 patients with BASE syndrome (3 Chinese and 2 native) had HLA-B27+ and oligoarthritis of large joints. Acute anterior uveitis was seen in 1 native and 2 Chinese patients with BASE syndrome.

HLA typing. Owing to financial constraints, full HLA-class I or class II typing could not be done. Only the HLA-B27 specificity was determined.

### RESULTS

**Controls.** HLA-B27 was found in 7 (4.2%) of 176 healthy Chinese Indonesians and in 13 (9.0%) of 145 native Indonesians (Table 1). Fisher's exact test revealed a significantly higher prevalence of HLA-B27 among native Indonesians compared to the Chinese ethnic group (p = 0.027) The 4% prevalence of HLA-B27 in the Chinese Indonesians is quite similar to the 4.4% prevalence observed in Mainland China. The prevalence of HLA-B27 in native Indonesians, 9% in our study, is comparable to the 11.1% reported by Muslichan.

**Patients.** The frequency of B27 among the patients is shown for both ethnic groups (Table 2).

### DISCUSSION

In our opinion, the clinical impression of a striking difference in the prevalence of AS and spondyloarthropathies among the Chinese Indonesian vs native Indonesians is unlikely to be explained by any difference in access to the Indonesian health care system. Our intention was to examine how this clinical impression was reflected in the distribution of HLA-B27 among patients and healthy controls in the 2 ethnic groups.

The numbers of patients with AS and related spondyloarthropathies in our study are rather small. Certainly, larger sample sizes in cross-sectional studies would be needed to more reliably assess for both ethnic groups the strength of association between HLA-B27 and spondyloarthropathies. Nonetheless, our descriptive study supports the view that B27+ Indonesian Chinese have a higher risk of developing spondyloarthropathies compared to B27+ native Indonesians.

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types are not associated with an increased susceptibility to AS, then this would strongly support the arthritogenic peptide model of disease pathogenesis rather than the altered self or molecular mimicry model. In conclusion, B27+ Indonesians of Chinese origin seem to have a higher risk of developing spondyloarthropathy than B27+ Indonesian native individuals, although the prevalence of B27 is much lower among Indonesians of Chinese descent than among native Indonesians. These findings raise the possibility of a preferential association of AS and spondyloarthropathy with B27 subtypes. Further studies should include subtyping of B27 and also pay attention to differences in the prevalence of other genetic and nongenetic (environmental) risks.

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