HLA-B27 associated rheumatologic diseases in Indonesia

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Chapter 6

Spondyloarthropathies in Southeast Asia
Abstract

Objectives. The HLA-B27 associated spondyloarthropathies (SpA) and particularly ankylosing spondylitis (AS), were thought to occur in low frequencies in Southeast Asia. HLA-B27 subtype studies in this part of the world revealed that HLA-B*2704, which is associated with SpA, is mainly present in Chinese, while HLA-B*2706, not being associated with SpA, is mainly seen in Malayans. For rheumatologists working in this area and thus dealing with both Chinese and Malayan patients, it is important to be aware of these B27 subtype differences. They should learn how to deal with HLA-B27 typing and subtyping and how to interpret the results.

Epidemiology. Recent studies revealed that SpA is indeed rare in countries mainly inhabited by people of the Malayan race, like Thailand, Malaysia, Indonesia and the Philippines, but frequent in countries mainly inhabited by people from Chinese descent, like Singapore.

HLA-B27 subtypes. Studies in Indonesia showed that although most HLA-B27 positive native Indonesians have the B*2706 subtype, which is not associated with SpA, this subtype does not protect against this disease if they are also positive for B*2704, B*2705, or B*2707.

Conclusions. Especially for patients of mixed Chinese-Malayan origin, a proper handling of the new knowledge is of importance. If HLA-B27 (sub)typing is not possible, Malayan patients should be asked if they have Chinese or Caucasian ancestors. Especially patients with SpA who are HLA-B*2702, B*2704, B*2705 or B*2707, should refrain from local alternative drugs which often contain corticosteroids.

Epidemiology of SpA

Although Southeast Asia spreads from China to New Zealand, this article will be confined to the countries between Thailand and Papua New Guinea. Even in this limited area, people of many races are assembled. For the study of SpA it is important to know that more than 450 years ago many Chinese migrated from the south of the Chinese mainland to the Southeast Asian lands, peninsulas and islands. Now 40% of the inhabitants of Malaysia, 90% of the Singaporeans and 5% of the inhabitants of Indonesia are of Chinese origin, while many Chinese live in the Philippines and Papua New Guinea.

The epidemiological studies of SpA in Southeast Asia are the following: In Thailand Deesomchok and Tumrasvin [1] studied 61 patients with SpA. These included 46 cases of AS, 8 of Reiter's syndrome and 7 of psoriatic SpA. Uveitis was noted in 11% of these patients. HLA-B27 was present in 91% and the male : female ratio was 5 : 1. In Malaysia Veerapen et al. [2] observed AS in 0.1%
of 474 Chinese inhabitants. But among 1267 native Malaysians they found not a single case of AS. In Singapore Koh and Boey [3] studied the clinical features of 150 patients with AS. Uveitis was observed in 17% of the patients. The male : female ratio was 7 : 1. In Indonesia Darmawan et al. [2,4] performed a study on rheumatic diseases in 4683 rural and 1071 urban people living in the northern part of Central Java. They found not a single case of AS or related diseases. This is astonishing since in a regular rheumatology practice in Jakarta we observe generally twice as much patients with AS as with rheumatoid arthritis (RA). This ratio is thus completely the reverse from the AS : RA ratio which is observed in Europe. In the Philippines Manahan et al. [2,5] found not one SpA patient among 1685 persons of all ages in a rural area. Also Wigley et al. [6] observing a remote village area in the Philippines did not detect any case of AS or related disease. In Papua New Guinea Richens et al. [7] observed 138 patients with reactive arthritis (ReA), all being HLA-B27 positive. It is striking that no patients with AS were seen. The study was performed in the highlands and the northern coast, but Lloyd et al. [8] had the same experience at the southern coast, while Pile et al. [9] confirmed the earlier observations performed in the highlands. In China the prevalence of ankylosing spondylitis (AS) of 0.3% is comparable to that in Europe, even although the HLA-B27 frequency of about 5% is somewhat lower [2,10-13].

Most of the mentioned studies suggest that in Southeast Asia SpA is mainly observed among the Chinese while native Malayans are rarely affected by this group of diseases. In this light it is of importance to be aware of the infiltration of Chinese in the native population, even if this took place a long time ago.

In Caucasians HLA-B27/HLA-B60 heterozygous individuals have about three times more frequently SpA than HLA-B27 positive, but HLA-B60 negative persons. HLA-B60 is the most common HLA-B type in Han Chinese. The suggestion that HLA-60 might be less frequently present in people of the Malayan race and therefore responsible for the low prevalence of SpA was therefore solid. Lan, however, showed that the HLA-B60 frequency among Chinese SpA patients and healthy controls was equal [14].

**HLA-B27 subtypes**

The prevalence of HLA-B27 in this area of the world shows no great differences. Khan in his latest review mentions frequencies between 5 and 12% [13]. The only prevalence which is significantly higher, is that of some isolated populations in Papua New Guinean highlanders which reach even 50%.

Among HLA-B27 now 12 subtypes can be distinguished (HLA-B*2701 to HLA-B*2712) [15]. These subtypes differ from each other by only a few amino acids in the groove which binds antigenic peptides to be presented to the T cell receptors on cytotoxic T cells (CTL) and natural killer (NK) cells.

Studies in Thailand, Singapore and Indonesia showed that of the subtypes which occur in Southeast Asia, HLA-B*2704, B*2705 and B*2707 are positively associated with SpA, while on the contrary no patients with the subtype B*2706 were seen (table 1) [19].

Our studies in Indonesia revealed that although the prevalence of HLA-B27 is somewhat higher in the native Indonesians (4.5%) than in Indonesian citizens of Chinese descent (1.3%), the prevalence of SpA is at least four times higher in the latter part of the population than in native Indonesians [18,20]. It was found that HLA-B27 positive Chinese Indonesians are mostly of the B*2704 subtype
Table 1

HLA-B27 subtypes in HLA-B27 positive SpA-patients and controls in Southeast Asia

<table>
<thead>
<tr>
<th>subtype</th>
<th>Thailand [16]</th>
<th>Singapore [17]</th>
<th>Indonesia [18]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>patients</td>
<td>controls</td>
<td>patients</td>
</tr>
<tr>
<td>B*2704</td>
<td>41</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>B*2705</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>B*2706</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>B*2707</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>17</td>
<td>50</td>
</tr>
</tbody>
</table>

and therefore susceptible to SpA. The HLA-B27 positive native Indonesians, however, are mostly of the HLA-B*2706 subtype. Among such individuals no SpA was observed, unless they are heterozygous HLA-B*2704/HLA-B*2706 as we showed recently [21].

This indicates that HLA-B*2706 does not protect against SpA in the presence of a disease associated subtype. In this study we also observed that HLA-B*2708 is probably comparable to HLA-B*2706 since it was also not present in SpA patients unless these had HLA-B*2704 on the other haplotype. It is therefore possible that HLA-B*2708 is also not associated with SpA. If this is true, and if HLA-B*2708 occurs not so rarely in Southeast Asia, B*2708 typing might be of the same clinical importance as the typing of B*2706. A problem in this respect is, that serological HLA-B27 typing can not be used as a screening method, since the classical serological typing methods type HLA-B*2708 as HLA-B7 and not as HLA-B27.

Clinical features of SpA

Since it is possible that the mentioned HLA-B27 subtype differences between Chinese and native Indonesians are not the only reason for the fact that SpA is nearly absent among the native Indonesians but frequently observed among the people of Chinese origin, we recently studied whether the clinical picture of the patients with these genetical background differences also differ in other aspects. It was found that all the clinical features of SpA i.e. the severity of the disease, the sex distribution, the age of onset and the extra articular phenomena were not only equal between these two kinds of populations, but also equal to the clinical picture described in other parts of the world [20]. The only difference might be that in Southeast Asia patients were often presented in a late phase of the disease, showing bamboo spine lesions. Diagnostic problems are especially acquainted in the early stages of the disease, since the disease usually starts with an atypical oligoarthritis resembling a viral or bacterial arthritis (e.g. tuberculous arthritis).

Consequences for the daily practise

The rheumatologist operating in Southeast Asia who is confronted with patients with diseases resembling SpA, should, besides the normal rheumatological examination, pay attention to the racial
descent of the patient. Native Thai, Malaysian, Indonesian or Philippine patients should be asked whether they have Chinese or Caucasian ancestors. HLA-B27 typing is only a partial help, since it gives no information about the subtypes which are so relevant in this part of the world. If possible the HLA-B27 positive patients should be subtyped for HLA-B*2706. A positive result should lead to the search for other diseases than SpA.

HLA-B27 typing cost about 40 USA dollars, while HLA-B27 subtyping is often not performed locally. If for financial and/or practical reasons HLA (sub)typing can not be performed, the taking of racial history becomes even more important.

Racial history and HLA-B27 (sub)types are of importance to come to a proper diagnosis. Patients with AS who are positive for HLA-B*2702, B*2704, B*2705 or B*2707 should certainly not be treated with local alternative drugs which often contain high concentrations of corticosteroids, analgesics and butazolidine. The AS patients should mostly be treated with physiotherapy, which tries to save thoracic and lumbar mobility and to prevent deformations. Instructions have to be given of the best sleeping posture, i.e. with a straight back and certainly not curled up on one side. Deep-breathing exercises and refraining from smoking will help to maintain a good chest expansion. For medication we suggest indomethacin or diclofenac as first line drugs. This lowers the pain and stiffness and thus promotes the participation at sustained programs of exercise and physical therapy. Sulphasalazine is the drug of choice for the severe cases, certainly if peripheral joints are involved.

For the HLA-B*2706 and probably B*2708 positive patients the therapeutic rules can be less strict. Patients with ReA should of course be treated with antibiotics if the bacterial infection is still active.

References
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