HLA-B27 associated rheumatologic diseases in Indonesia
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Chapter 5

Clinical Features of Spondyloarthropathy in Chinese and native Indonesians
Clinical Features of Spondyloarthropathy in Chinese and native Indonesians

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Running headline: Spondyloarthropathy in Chinese and native Indonesians

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Abstract:
The prevalence of spondyloarthropathy (SpA) in Chinese Indonesians is much higher than in native Indonesians. This is due to HLA-B27 subtype differences. In the present study we re-examined the clinical features of SpA in Indonesia, to see whether besides the HLA-B27 subtypes differences, other factors are of influence on the frequency of SpA. Seventy two patients with SpA were re-examined. The patients came from two clinics for rheumatic diseases. The overall entry ratio Chinese : native was 1 : 2. Ankylosing spondylitis (AS) was more frequent among the Chinese (n=32, 94% B27 positive) than among the native Indonesians (n=5, 40% B27 positive). HLA-B27 subtyping was performed on 22 of the 37 HLA-B27 positive AS patients. Twenty Chinese were positive for B*2704, 2 native Indonesians were B*2705. The clinical features of AS and reactive arthritis (ReA) showed no differences between the two populations and were equal to the clinical descriptions in other parts of the world. In conclusion, it can be stated that in spite of the HLA-B27 subtype differences the clinical features of SpA in Chinese and native Indonesians are fully comparable.

Keywords: Spondyloarthropathy; Ankylosing Spondylitis; HLA-B27; Subtypes of HLA-B27, Epidemiology, Indonesia, Chinese.
Introduction
The spondyloarthropathies (SpA) are HLA-B27 associated inflammatory rheumatic diseases affecting mainly the axial and sacroiliac joints, but peripheral joints are also frequently involved. Extraarticular manifestations include acute anterior uveitis (AAU), dilatation of the aorta and cardiac conduction disturbances. Ankylosing spondylitis (AS) and reactive arthritis (ReA), including Reiter’s syndrome, are in Indonesia the most common diseases in the group of (SpA). Psoriatic arthritis, arthropathies associated with inflammatory bowel diseases and the so-called undifferentiated spondyloarthropathies also belong to SpA, but the association with HLA-B27 is much weaker [1,2].

The etiology of SpA is not known, but genetic factors such as HLA-B27 seem to play a pathogenetic role. Actually HLA-B27 does not exist. We now distinguish twelve subtypes of HLA-B27 (B*2701-B*2712). The prevalence of the HLA-B27 subtypes differs among the distinct populations of the world [3,4]. Two of our previous studies revealed a great difference in susceptibility between native Indonesians and Chinese living in Indonesia [5,6]. The HLA-B27 positive native Indonesians are mostly HLA B*2706 positive. Up to now no Indonesian with this subtype had SpA. The HLA-B27 positive Chinese, however, are mostly HLA-B*2704 positive. These Chinese Indonesians are susceptible for SpA [6].

In the present study we re-examined the clinical features, the radiographic pictures and laboratory findings of all our patients with SpA to see whether there are other differences between native Indonesians and ChineseIndonesians than the HLA-B27 subtype distribution. By this retrospective study we also had the chance to evaluate three multicase families with SpA.

Material and Methods
Seventy two patients (64 males and 8 females) fulfilling the ESSG criteria for SpA were studied [7]. The patients were followed in a rheumatology clinic in Jakarta during the period 1987 until 1997. The overall population visiting this clinic concerns about 60 % Chinese and 40 % native Indonesians. We also studied the staff of a factory with over 4000 employees. All employees from this factory had to visit a health centre if they have rheumatic complaints. Any further investigation took place in the rheumatology clinic. These patients were for 90 % native Indonesians and for only 10 % Chinese. The number of the patients visiting the rheumatology clinic and the factory health centre is about equal. The overall entry ratio of Chinese versus native Indonesians is thus about 1 : 2. It should be kept in mind that the distinction between Chinese and native Indonesians was only based on superficial judgment of physical characteristics and especially on the own declaration of the patient.

Information on a history of gastroenteritis, urethritis, skin or eye disease and also the family history was noted according to a fixed protocol. Physical examinations included measurement of chest expansion, finger to floor distance and the Schober test. Radiography of spine and sacro-iliac joints were performed. Laboratory investigations consisted of haemoglobin, leucocyte differentiation, blood sedimentation rate, C-reactive protein and rheumatoid factor determination.

In addition HLA-B27 was determined using the lymphocytotoxic microtest. HLA-B27 subtyping was performed in the Central Laboratorium of the Blood Transfusion Service (CLB) in Amsterdam by the polymerase chain reaction (PCR) in combination with specific oligonucleotide probes (SSO’s) to analyze the polymorphisms in exon 2 and 3 of HLA-27 [6].
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Results
Fifty eight Chinese SpA patients and 14 native Indonesians were studied. Of the 72 SpA patients 28 (20 Chinese, 8 native Indonesians) had ReA. The symptoms developed after a gastro-intestinal or urogenital infection while the arthritis, usually a mono- or oligoarthritis in the lower limbs, had a duration of more than 3 months. Five ReA patients (3 males, 2 females) had also signs of conjunctivitis and urethritis besides an oligoarthritis. These five patients were considered as having Reiter's syndrome. The other 44 patients, consisting of 38 Chinese and 6 native Indonesians, fulfilled the modified New York criteria for AS [8]. The race and sex distribution of the patients is given in table 1. The male : female ratio was 4.5 : 1.

Table 1:
Disease, race and sex distribution of the patients with spondyloarthropathy studied

<table>
<thead>
<tr>
<th>disease</th>
<th>Chinese Indonesians</th>
<th>native Indonesians</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>AS</td>
<td>32</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>ReA</td>
<td>14</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>total</td>
<td>46</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Onset of AS between 16 and 25 years of age was observed in 80% of both the Chinese and native Indonesian AS patients. The duration of the disease was mostly over 10 years at the time of the study. The severity of the AS was equal for men and women. The spinal mobility was severely decreased. Pain, stiffness and bilateral sacroiliitis were the prominent features at the moment of the study. In most cases thoracal, sternal and low back pain were noted as the main complaints. Most of these AS patients had a bamboo spine appearance, with stiffness in the cervical, thoracal or lumbal region and a sacro-iliitis grade III or IV. The thorax expansion, finger to floor distance and Schober test were clearly limited. Peripheral arthritis and enthesopathy as initial symptoms were only found in one third of the cases. One third of the patients suffered of unilateral-bilateral involvement of the hips.

The clinical features of AS of the Chinese patients did not differ from those of the native Indonesians (table 2). Both groups showed advanced disease with restriction of chest expansion and

Table 2.
Articular manifestations of 44 patients with ankylosing spondylitis

<table>
<thead>
<tr>
<th>race</th>
<th>number</th>
<th>peripheral arthritis</th>
<th>enthesopathy</th>
<th>cervical spondylitis</th>
<th>thoracal spondylitis</th>
<th>lumbal spondylitis</th>
<th>bilateral sacroiliitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>38</td>
<td>28%</td>
<td>11%</td>
<td>83%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>native</td>
<td>6</td>
<td>22%</td>
<td>11%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
spinal mobility. Four patients (3 Chinese males, 1 female native Indonesian) had a completely ankylosed spine with a loss of the lumbar lordosis and the development of a thoracic kyphosis. AAU had been present in 6 (15%) of the patients with AS. The uveitis affected 5 Chinese (4 males, 1 female) and 1 female native patient. Systemic corticosteroids had been given with remarkable improvement.

HLA-B27 typing could be performed on the cells of 37 AS patients. Of the 32 Chinese AS patients 30 (94%) were HLA-B27 positive, in contrast to only 2 of the 5 native Indonesian AS patients. From the 32 HLA-B27 positive patients with AS, 22 patients were subtyped. All 20 Chinese AS patients were of the HLA-B*2704 subtype, while the two native Indonesian AS patients which were subtyped were both HLA-B*2705.

Figure 1. Father (81 years, HLA-B*2704) and son (42 years, HLA-B*2704/HLA-B*2705) of Chinese origin, both having severe ankylosing spondylitis. Photo published with permission of the patients.
Nine patients had one or more first degree relatives with SpA (fig 1). Of three of these nine patients, the relatives could be interviewed and physically and radiographically examined, while also an HLA-B27 (sub)typing could be performed. Two probands, both HLA-B*2704 positive Cinese AS patients, had each one HLA-B*2704 positive relative with AS. The family of the third proband showed three relatives with SpA. This family of mixed Chinese/native Indonesian origin was discussed in a previous article [9]. All five affected relatives of these three families were positive for HLA-B*2704 or HLA-B*2705. The HLA-B*2704 relatives were of Chinese origin. The native Indonesian relatives with SpA were HLA-B*2705.

Five patients with SpA were HLA-B27 negative. Two were of Chinese origin. One of them had psoriatic SpA. The other three were native Indonesians. One of these had an inflammatory bowel disease. None of the five HLA-B27 negative patients had a relative with SpA.

Discussion

The present study shows that the clinical features of AS, frequency of peripheral joint involvement and the age of onset of complaints were almost similar for the Chinese and native Indonesian patients. These features were also not different from those observed in other parts of the world [10,11,12,13,14,15].

The finding of 44 patients with the diagnosis classical AS in this study seems important for the epidemiology of rheumatic diseases, since in a previous epidemiologic survey among 5854 persons for rheumatic diseases in the northern part of Central Java, involving rural and urban areas, not a single case of AS was observed [16]. This might be due to the fact that this study was mainly confined to native Indonesians, since they observed less than 0.5% Chinese Indonesians. The present study is consistent with the study of Deesomchok and Tumrasvin from Thailand concerning 61 cases of SpA [17]. They collected the patients over a 6 year period and found no unusual features in the clinical expression or pattern of the SpA. Koh and Boey from Singapore studied the clinical features of 150 AS patients (147 Chinese and 3 non Chinese) with a male : female ratio of 7 : 1 [16]. Uveitis was found in 17% of the cases. They also described the classical features of AS in their patients.

European studies report that thoraco-sternal and low back pain are mostly the initial articular manifestations [10,11,12]. Similar findings were noted in the present study. For three male patients the disease started at the age of 16 years with a pauciarticular onset, later developing into a classical AS. A similar course of the disease was already reported in a previous study by Dequeker and Mardjuadi [19].

ReA is not uncommon, both in Chinese and native Indonesians. ReA patients generally have asymmetric oligoarthritis of the large joints of the lower extremity after gastro-intestinal or urogenital infection. The clinical features of ReA in Indonesia are similar to those described in other countries. However, it is interesting to note that some of our ReA patients developed arthritis after the diagnosis of so called "typhoid fever". Although the clinical features of typhoid were limited, the serology showed high titres of antibodies against Salmonella typhimurium.

AAU was noted in 15% of cases. This is in accordance with reports from other parts of the world [20]. Other extra-articular features were confined to one patient having a cardiac conduction abnormality.

In the present study the dominance of Chinese over native Indonesian patients with ratio 4 to 1 is important, since the entry ratio of Chinese : native was only 1 : 2. The present results confirm those
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of our previous study concerning the association between HLA B27 and SpA in Indonesia [5]. We found that HLA-B27 positive Chinese have a higher risk to acquire AS or SpA than native Indonesians. Later we found that healthy HLA-B27 positive native Indonesians are almost always positive for the HLA B*2706 subtype [6]. This subtype is not associated with SpA. Chinese, however, mostly have the HLA-B*2704 subtype. This subtype is firmly associated with SpA [6]. This explains why Chinese show more frequently SpA than native Indonesians. It might be an important finding for elucidating the possible role of HLA-B*2704 in the pathogenesis, since HLA-B*2704 and HLA-B*2706 differ in only two amino acids from each other [3,4,6].

The observed dominance of males over females in a ratio of 4.5:1 was about equal to that in previous studies [21,22]. Male and female patients with AS showed about the same severity of the disease. This is in accordance with the observation by Kidd et al. [23].

In the present study only a few HLA-B27 negative SpA patients were observed. It is not astonishing that these were mostly native Indonesians and that some of them had psoriasis or inflammatory bowel disease.

In conclusion it can be stated that the clinical features of AS and related SpA among Chinese and native Indonesians differ not much and are equal to those reported in other population studies. A pathogenetic role of HLA-B*2704 is supposed, while HLA-B*2706 is not associated with SpA.

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