HLA-B27 associated rheumatologic diseases in Indonesia
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Chapter 1

Introduction and
Aims of this thesis
Chapter 1

Introduction

B27 associated diseases

Twenty five years ago the first reports about the association between ankylosing spondylitis (AS) and HLA-B27 appeared [1,2]. About 90% of patients with AS were found at that time to be HLA-B27 positive. This disease association was observed in many different racial populations [3]. Also reactive arthritis (ReA) including Reiter’s syndrome was shown to be associated with HLA-B27 [4]. All these diseases are now grouped together and extended with less severe rheumatoid diseases under the term spondyloarthropathy (SpA). SpA is a group of rheumatic diseases in which clinical features like enthesitis, dactylitis, peripheral arthritis, sacroiliitis, inflammatory back pain are occasionally accompanied by extra-articular manifestations as acute anterior uveitis (AAU) and aorta insufficiency. The European Spondyloarthropathy Study Group (ESSG) has proposed preliminary classification criteria with the specific intention of encompassing the wider clinical spectrum, including patients with so called undifferentiated spondyloarthropathy (table 1) [5].

Table 1

Criteria for SpA as proposed by the ESSG [5]

<table>
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<tr>
<th>Inflammatory spinal pain or Synovitis / Asymmetrical arthritis predominantly in the lower limbs</th>
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<td>and one or more the following:</td>
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<td>Positive family history</td>
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<td>Psoriasis</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Urethritis, cervicitis or acute diarrhoea, one month before arthritis</td>
</tr>
<tr>
<td>Enthesopathy (pain at insertion of achilles tendon / plantar fascia)</td>
</tr>
<tr>
<td>Buttock pain alternating between right and left gluteal areas</td>
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<tr>
<td>Sacroiliitis (bilateral grade 2-4 or unilateral grade 3-4 ; according to X-ray grading)</td>
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</table>

AAU is an acute, severe, mostly unilateral inflammation of the iris and ciliary body with a duration of less than three months [6]. The anterior chamber contains fibrin and cells. The visual acuity is often temporarily decreased. Also AAU shows a strong association with HLA-B27. One third of the SpA patients has from time to time attacks of AAU. Because these attacks are very painful and frightening, most SpA patients with AAU will consult an ophthalmologist on their own. Reversely ophthalmologists should refer their HLA-B27 positive patients with AAU to a rheumatologist, since in half of these patients some form of SpA can be found [7].

Juvenile chronic arthritis (JCA) in HLA-B27 positive boys might be considered as the juvenile form of AS [8]. Usually these patients develop later an adult AS.

Since the above mentioned diseases show a great clinical and familial overlap, they are lumped together under term “B27 associated diseases” [9].

Psoriatic spondyloarthropathy and arthropathy associated with inflammatory bowel diseases like Crohn’s disease or ulcerative colitis are also associated with HLA-B27, but to much lower degree
and should therefore not be mentioned as one of the “B27 associated diseases” [9]. ReA were already known to be correlated with enterobacterial infections due to Salmonella, Shigella, Yersinia, Campylobacter or Chlamydia trachomatis. Approximately one third of the patients with ReA are comprised of Reiter’s syndrome. Dr. Hans Reiter in 1916 described a syndrome with a triad of symptoms consisting of arthritis, urethritis and conjunctivitis which subsequently came to known by his name [10].

In inflammatory bowel diseases associated with arthritis, endotoxinemia can occur during the dysenteric prodromes associated with ReA. These mucocutaneous rashes can even lead to ulceration. Laboratory tests revealed positive C-reactive protein, high blood sedimentation rate and a rising titre of antibodies against Salmonella typhimurium in many patients with ReA, so that sometimes the diagnosis of typhoid fever was made, although clinical features of typhoid were absent. Those positive reactions are possibly false positive, due to increased gammaglobulin levels in the presence of bacterial infections with Salmonella, Shigella or Yersinia. Structures of these bacteria have been found to persist for long periods in blood cells of patients with ReA. They also have been detected in synovial fluid cells and in the synovial membrane [11,12]. Some investigators found an increased frequency of raised titres of antibodies against Klebsiella pneumoniae in patients with active AS [13]. Granfors suggested that HLA-B27 positive persons are less capable of killing the intracellularly living bacteria and they might accumulate in the joints, thus triggering arthritis [14].

**HLA-B27**

HLA-B27 is just one out of a great many molecules which are determined by genes of the class I of the major histocompatibility complex (MHC). The genes of the MHC region have an enormous number of alleles. B27 is just one of the about hundred alleles of the B locus. The alleles are mutually exclusive, thus per haplotype only one gene on the B locus comes to expression. Each person therefore shows two HLA-B types, unless he is homozygous.

The class I molecules consist of two chains of a polymorphic glycoprotein. The α or heavy chain is encoded in the MHC region on the short arm of chromosome 6. This α-chain is non-covalently linked to a β or light chain, which is a non-HLA-encoded, non-polymorphic protein, called β2-microglobulin. The entire HLA molecule is anchored to the cell membrane by the heavy chain. The α-chain contains three extracellular segments (α1, α2 and α3-domains) of approximately 90 amino acid residues each, a short hydrophobic transmembrane part of about 25 amino acid residues and an intracellular part of about 30 amino acid residues at the cytoplasmic carboxyl terminal end (fig 1) [15].

The three-dimensional X-ray crystallographic structure revealed that the α1 and α2-domains of class I molecules interact to build a platform made of eight β-pleated sheets supporting two parallel strands of α-helices. The groove between the two α-helices can bind antigenic peptides in an unique way (fig 1). On the bottom of this antigenic peptide binding cleft at least six different pockets have been identified. These pockets fix corresponding amino acid residues of antigenic peptides [16].

Actually HLA-B27 is an obsolete term from the days that HLA typing was mainly performed by serological methods. Now it is known that twelve subtypes of HLA-B27 (HLA-B*2701 - HLA-B*2712) can be distinguished. These subtypes show only minor mutual differences, but since these are situated in the antigenic peptide binding groove, they are probably of importance for their function
Chapter 1

Figure 1 Schematic representation of the three-dimensional structure of an HLA class I molecule. Side view (A), top view (B). Adapted from ref. [15]. In the top view the amino acid residues 114 and 116 are marked. Residue 114 is unique for HLA-B*2706 and 116 for HLA-B*2709 if compared with the other HLA-B27 subtypes.

as antigen presenting molecule [17]. Most of the HLA-B27 subtypes are associated with SpA. The present thesis will learn that the subtype B*2706, however, is not associated with SpA. Also HLA-B*2709 is probably not associated with this disease. The only unique amino acid residues for the negatively associated subtypes are aspartic acid at position 114 of B*2706 and histidine at position 116 of B*2709 (fig 1) [18].

Nearly all nucleated cells express HLA class I molecules on their surface. Their function is to present antigenic peptides to the receptors on cytotoxic (CD8+) T lymphocytes (CTL) and natural killer (NK) cells.

Crossreactivity between bacteria and HLA-B27

Some authors reported cross reactions between HLA-B27 and Gram-negative bacteria [19]. Schimmbeck et al. using a computer analysis showed a structural homology of six amino acids of Klebsiella reductase and HLA-B27 (table 2) [20]. They found a sequence homology between six consecutive amino acids (Gln-Thr-Asp-Arg-Glu-Asp) on the positions 72-77 of the α1 domain of the
Table 2.
Comparison of partial amino acid sequences of HLA-B*2705, *Klebsiella pneumoniae* nitrogenase reductase and *Shigella flexneri* plasmid

<table>
<thead>
<tr>
<th></th>
<th>71</th>
<th>77</th>
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<tbody>
<tr>
<td><strong>B*2705</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ala</td>
<td>Gln</td>
<td>Thr</td>
</tr>
<tr>
<td>A</td>
<td>Q</td>
<td>Thr</td>
</tr>
<tr>
<td>187</td>
<td>193</td>
<td></td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong> nitrogenase reductase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>Q</td>
<td>Thr</td>
</tr>
<tr>
<td>A</td>
<td>Q</td>
<td>Thr</td>
</tr>
<tr>
<td>188</td>
<td>193</td>
<td></td>
</tr>
<tr>
<td><strong>Shigella flexneri</strong> plasmid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Q</td>
<td>Thr</td>
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<tr>
<td>188</td>
<td>193</td>
<td></td>
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</tbody>
</table>

most prevalent B27 subtype (B27.1 now renamed B*2705) and six residues (188-193) on a *Klebsiella pneumoniae* protein called nitrogenase reductase. The observed short sequence homology is only with B*2705, although most subtypes such as B*2704 have an equivalent susceptibility to AS. Results of studies of sera from patients with SpA for antibody reactivity with a synthetic oligopeptide containing the six amino acids homologous region have been quite variable [21]. Moreover, it is highly unlikely that nitrogenase reductase plays a pathogenic role in AS, because this enzyme is used for nitrogen fixation and its gene is expressed only when the bacteria are in nitrogen-free media which is a highly unlikely environment in the human host. Ringrose recently studied the literature of these and other studies concerning the clinical significance of crossreactivity between bacteria and HLA-B27 [22]. The conclusion was that there is no evident proof that SpA is an autoimmune disease due to crossreactivity between bacteria and HLA-B27.

*Indonesia*

Indonesia is the world’s largest island nation. Situated in the Southeastern Asian equatorial area it stretches 5000 kilometres from east to west and 2000 kilometres from north to south. Of the 6000 inhabited islands, Java is the most densely populated, since 60% of the 200 million inhabitants live here. The capital, Jakarta, has 10 million inhabitants. The majority of the people are of the Malaysian race. The largest non-Malaysian race group is formed by the 4 million Chinese. Other minority races are Arabs, Indians and Caucasians [23].

Since Indonesia in 1945 became independent, the government promoted education and health care. More than 60% of the adults can now read and write, while almost all children now receive an elementary school education.

Although the health care improved considerably, gastro-enteritis, respiratory infections including tuberculosis, skin and eye diseases and in some areas malaria are affecting a great part of the population. The unequal spreading of physicians over the country renders a physician : patient ratio of less than 1 : 3,000 in some urban areas, to over 1 : 50,000 in remote rural districts. The overall ratio is 1 : 10,000. In 1969 community health centres or Pusat kesehatan masyarakat (Puskesmas) were raised in all districts of the country and later in various subdistricts of Java. Each community health centre serves about 50,000 people on Java and Madura and far more on the other islands. This care is extended by a referral system to district hospitals. These hospitals are staffed by medical specialists. There are at the moment only 27 rheumatologists in Indonesia. Nine of them are practising
in Jakarta, 11 in other cities in Java and 7 in the rest of Indonesia. In Jakarta one rheumatologist serves one million people. Outside of Jakarta one rheumatologist has to cover the needs of two to five million inhabitants [24].

Primary health care is almost free, costing about US$ 0.10 per visit, including three days supply of medicines. The national health insurance covers only the government civil servants, the army forces and their families. Private health insurance has started since the last decade.

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Aims of the present thesis

It was already known for a long time that SpA is far more common in ethnic Chinese living in Indonesia than in native Indonesians. When the association between HLA-B27 and SpA became known, it was thought that HLA-B27 would occur more frequently in Chinese than in native Indonesians. Muslichan, however, found HLA-B27 in 11% of native Indonesians, while Chinese in China showed HLA-B27 only between 2 and 6% [25,26]. We therefore assessed the prevalence of HLA-B27 among patients with SpA of ethnic Indonesian and of Chinese descent and among healthy Chinese and native Indonesians. In chapter 2 the results are presented. These show that HLA-B27 is twice as frequent in native Indonesians as in Chinese Indonesians. The native Indonesian SpA patients showed a frequency of HLA-B27 which was somewhat lower than the frequency among the healthy native Indonesian controls. This would mean that native Indonesians would be the only population in the world where SpA was not found to be associated with HLA-B27.

As soon as it was possible to examine whether differences of the HLA-B27 subtype distribution might explain this strange phenomenon, this was studied. In chapter 3 the results are given. It is shown that most healthy HLA-B27 positive native Indonesians had a subtype which never occurred in SpA patients. The HLA-B27 positive Chinese Indonesians on the contrary, had mostly another subtype which was frequently seen in SpA patients.

It seemed that the subtype which was so frequently seen in native Indonesians protected against the development of SpA. In chapter 4, however, we described two families in which both the supposed protective subtype and the disease associated subtype occurred. Some family members, which were heterozygous for both subtypes, had SpA. The supposed protective subtype was thus not protective at all.

Of course Chinese and native Indonesians differ in far more aspects than just their HLA-B27 subtype. We therefore decided to study whether the clinical features of the distinct forms of SpA in these two races showed differences. The results as presented in chapter 5 revealed, however, that the clinical picture of the diseases showed no mutual differences.

Finally we thought it wise to reach the rheumatologists in Southeast Asia a hand in explaining them how to approach patients of the Chinese versus the Malaysian race if they visit a rheumatological (out ward) clinic with symptoms which resemble SpA. These suggestions are presented in chapter 6.

Chapter 7 contains a summary of these findings.