Chapter 2

Overview of ankylosing spondylitis

The concept and classification of spondyloarthritis

The term ‘spondyloarthritis’ (SpA) comprises AS, reactive arthritis, arthritis/spondylitis associated with psoriasis, and arthritis/spondylitis associated with inflammatory bowel disease (IBD). There is considerable overlap between the single subsets (Figure 2.1). The main link between each is the association with the human leukocyte antigen (HLA)-B27, the same pattern of peripheral joint involvement with an asymmetrical, often pauciarticular, arthritis, predominantly of the lower limbs, and the possible occurrence of sacroiliitis, spondylitis, enthesitis, dactylitis and uveitis. All SpA subsets can evolve into AS, especially in those patients who are positive for HLA-B27. The SpA subsets can also be split into patients with predominantly axial and predominantly peripheral SpA (Figure 2.2), with an overlap between the two parts in about 20–40% of cases. Through use of such a classification the presence or absence of evidence for a preceding gastrointestinal or urogenital infection, psoriasis or IBD is recorded but does not result in a different classification. The term ‘predominant axial SpA’ covers patients with classic AS and those with non-radiographic axial SpA [4]. The latter group of patients would not have radiographic sacroiliitis according to the modified New York criteria, but would normally have evidence of active inflammation as shown by magnetic resonance imaging (MRI) or other means (discussed in more detail in Chapter 5).

The concept of ‘seronegative spondarthritides’, now known as ‘spondyloarthritides’, was first introduced in 1974 by Moll and Wright from Leeds. ‘Seronegative’ stands here for rheumatoid factor negative. Subsequently, both the European Spondyloarthropathy Study Group (ESSG) classification criteria and the Amor criteria (from the French rheumatologist Bernard Amor) tried to define the whole spectrum of SpA [5, 6]. It was thanks to the ESSG criteria that in 1991 the SpA group was first split into predominantly axial and peripheral subsets. Figure 2.3 shows the current ESSG classification criteria for spondyloarthritis. Most recently the Assessment in SpondyloArthritis international Society (ASAS) has proposed new classification criteria on axial spondyloarthritis, a term that is used throughout this book [7].
Epidemiology of ankylosing spondylitis

AS is a disease that starts normally in the third decade of life, with about 80% of patients developing the first symptoms before the age of 30 and less than 5% of patients being older than 45 at the start of the disease. Up to 20% of patients are even younger than 20 years when they experience their first symptoms (Figure 2.4) [8]. Patients who are positive for HLA-B27 are about 10 years younger than HLA-B27-negative patients when the disease starts [9].

Figure 2.1 The concept of spondyloarthritides.

Figure 2.2 Axial and peripheral spondyloarthritides. IBD, inflammatory bowel disease; SpA, spondyloarthritis. Data from Rudwaleit et al. [4].
ESSG classification criteria for spondyloarthropathy

<table>
<thead>
<tr>
<th>Inflammatory back pain</th>
<th>or</th>
<th>Synovitis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>• asymmetrical or</td>
</tr>
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<td></td>
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<td>• predominantly in the lower limbs</td>
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plus one of the following:

- alternating buttock pain
- sacroiliitis
- heel pain (enthesitis)
- positive family history
- psoriasis
- Crohn’s disease, ulcerative colitis
- urethritis / acute diarrhea in the preceding 4 weeks

Figure 2.3 ESSG classification criteria for spondyloarthropathy. ESSG, European Spondyloarthropathy Study Group. Data from Dougados et al. [5].

Age at first symptoms and at first diagnosis in patients with AS

Figure 2.4 Age at first symptoms and at first diagnosis in patients with AS. AS, ankylosing spondylitis. Reproduced with permission from Feldtkeller et al [8].
Men are slightly more affected than are women, with a ratio of about 2:1. However, women develop chronic radiographic changes of the sacroiliac joints and the spine later than men, a possible explanation for the frequent under-diagnosis of AS in women in the past, resulting in a much higher male:female ratio than currently accepted [9].

There is a clear correlation between the prevalence of HLA-B27 and the prevalence of AS in a given population: the higher the HLA-B27 prevalence the higher the AS prevalence. HLA-B27 is present throughout the world with a wide ethnic and geographical variation. It is most prevalent in northern countries and some tribes (Figure 2.5). Overall, estimations about the prevalence of AS

<table>
<thead>
<tr>
<th>Country</th>
<th>AS prevalence</th>
<th>HLA-B27 prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>US*</td>
<td>1.0–1.5%</td>
<td>8%</td>
</tr>
<tr>
<td>The Netherlands†</td>
<td>0.1%</td>
<td>8%</td>
</tr>
<tr>
<td>Germany‡</td>
<td>0.55%</td>
<td>9%</td>
</tr>
<tr>
<td>Norway§</td>
<td>1.1–1.4%</td>
<td>14%</td>
</tr>
<tr>
<td>Haida Indians¶</td>
<td>6.1%</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Data from Calin et al. [10]; †Data from van der Linden et al. [11]; ‡Data from Braun et al. [12]; §Data from Gran et al. [13]; ¶Data from Gofton et al. [14].

**Figure 2.5 Prevalence of AS.** AS, ankylosing spondylitis; HLA, human leukocyte antigen. *Data from Calin et al. [10]; †Data from van der Linden et al. [11]; ‡Data from Braun et al. [12]; §Data from Gran et al. [13]; ¶Data from Gofton et al. [14].

**Figure 2.6 Prevalence of spondyloarthritides and rheumatoid arthritis.**
*Data from Saraux et al. [15] and Guillemin et al. [16]; †Data from Adomaviciute et al. [17]; ‡Helmick et al. [18].
are between 0.1% and 1.4%, with most of these data coming from Europe. In western and mid-Europe a prevalence of 0.3–0.5% for AS and of 1–2% for the whole SpA group is likely. Recent studies from France, the USA and Lithuania indicate that SpA is at least as common as rheumatoid arthritis (Figure 2.6), which makes AS and SpA one of the most important chronic inflammatory rheumatic diseases [15–19].

HLA-B27 is positive in 90–95% of AS patients and in about 80–90% of patients with non-radiographic axial SpA. This percentage goes down to about 60% in AS patients who also have psoriasis or IBD. In predominant peripheral SpA, less than 50% of patients are positive for HLA-B27.

Aetiopathogenesis of ankylosing spondylitis

A major breakthrough in the research on the pathogenesis of AS and related SpA was the reported strong association of the disease with HLA-B27 in 1973 [20]. However, intensive research over more than three decades has not clarified the functional role of the HLA-B27 molecule in the pathogenic process. In the centre of the discussion about pathogenesis of SpA is the interaction between bacteria and HLA-B27, as a result of known triggering bacteria in reactive arthritis (after preceding bacterial infections of the urogenital or gastrointestinal tract) and the association with IBD; in the latter the immune system can interact with local gut bacteria because of a damaged mucosa [21]. Between 10% and 50% of HLA-B27-positive patients with reactive arthritis or IBD develop AS over the years, supporting a central role for such an interaction between bacteria and HLA-B27 in its pathogenesis. Although in most AS patients no bacterial exposure can be detected, subclinical bacterial infection or gut inflammation would be a possibility in these patients.

Many recent MRI studies and older pathological investigations suggest that the primary target of the immune response is at the cartilage/bone interface, including the insertion of tendon and ligaments at the bone (enthesis) [22]. Such an immunopathology would most probably differ from rheumatoid arthritis, in which inflammation occurs primarily in the synovium. We have recently provided further evidence for this hypothesis, showing that the presence of mononuclear cell infiltrates and osteoclasts depends on the presence of cartilage on the joint surface in AS patients (Figure 2.7) [23]. However, there is currently no evidence that bacteria or bacterial antigens persist in the cartilage or close to the cartilage of spine and joints. Thus, there have been speculations that bacteria might trigger an autoimmune response against cartilage-derived antigens such as proteoglycan or collagen, possibly mediated somehow through HLA-B27, although this hypothesis has not yet been proved. A third
and necessary triggering component could be microtrauma(s) of cartilage/bone because weight-bearing parts of the skeleton are almost exclusively affected in AS.

In addition to inflammation, AS is also characterized by new bone formation, with the possible consequence of bone fusion, most frequently found in the axial skeleton in the form of syndesmophytes. For a long time there has been a question over how inflammation and new bone formation are coupled in AS, whether AS is a disease of excessive new bone formation or whether this is only part of a physiological repair mechanism. Figure 2.8 shows a likely sequence of events: first inflammation causes an osteitis, followed by erosive structural damage of bone and cartilage, which are filled up with (fibrous) repair tissue, with a final step in which this repair tissue is subsequently ossified. If this is true, new bone formation would not occur without previous erosive damage from inflammation [24–26]. Further research is necessary to clarify the pathogenesis of AS and the characteristic interaction between inflammation and new bone formation.

Figure 2.7 Osteoclasts infiltrate at the bone–cartilage interface in patients with AS hip arthritis. AS, ankylosing spondylitis. Osteoclasts are shown in red (arrows). From Appel et al. [25].
Genetics of ankylosing spondylitis

Susceptibility to AS has been estimated to be genetically determined in more than 90% of cases, and it has been suggested that, as a result, there might not be a single factor, such as one bacterium, but ubiquitous environmental factors, (eg, many different bacteria) [27]. By far the strongest genetic association is with HLA-B27, and more than 30 HLA-B27 subtypes have been described to date. Some of them, such as HLA-B*2706 and HLA-B*2709, are either not associated, or less associated, with the disease, suggesting that minor molecular differences between the molecules might be the key to a better understanding of the pathogenesis. Although differentiation of HLA-B27 subtypes is of research interest, it has no clinical value and should therefore not be applied in daily clinical practice.
Most recently two new genetic loci have been shown to be associated with AS: interleukin receptor IL-23R, which is involved in the Th-17 (T-helper cell 17) pathway of chronic immune responses, and ARTS-1 (endoplasmic reticulum aminopeptidase 1), an enzyme that is relevant for the processing of peptides in the cytoplasm [28]. The relative contribution of these genes to the susceptibility to AS can be compared by using the population-attributable risk fraction statistic, which is 90% for HLA-B27, 26% for ARTS-1 and 9% for IL-23 [28]. Other factors such as HLA-B60, IL-1A and CYP2D6 (cytochrome P450 2D6) have been described as affecting the risk of developing AS, although this is not completely clear.

Only about 5% of HLA-B27-positive individuals develop AS. The average risk of developing AS in a first-degree relative (children or sibling) of an AS patient is about 8%, although only 1% or less of second- and third-degree relatives are affected. The risk can be better estimated when the HLA-B27 status is known: about 12% in HLA-B27-positive first-degree relatives, but less than 1% in HLA-B27-negative relatives (Figure 2.9) [29].

<table>
<thead>
<tr>
<th>HLA-B27 status</th>
<th>Risk (%)</th>
</tr>
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<tbody>
<tr>
<td>Negative</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 2.9 Risk of developing AS in a first-degree relative. AS, ankylosing spondylitis; HLA, human leukocyte antigen. Data from Brown et al. [29].
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