Overview of axial spondyloarthritis

The concept and classification of spondyloarthritis

The term “spondyloarthritis” (SpA) comprises ankylosing spondylitis (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).

Figure 2.1 The concept of spondyloarthritides.
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 [1]. 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 (axSpA)” covers patients with classic AS and those with nonradiographic axSpA (nr-axSpA) [1]. 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 spondyloarthritis”, now known as “spondyloarthritides”, was first introduced in 1974 by Moll and Wright from Leeds. “Seronegative” stands here for the absence of rheumatoid factor. 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 [2,3]. It was thanks to the ESSG criteria that in 1991 the SpA group was

<table>
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<tr>
<th>Predominant axial and peripheral spondyloarthritides</th>
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<tr>
<td>Early nonradiographic axSpA</td>
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<tr>
<td>Ankylosing spondylitis</td>
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<tr>
<td>Predominant axSpA</td>
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<td>Predominant peripheral axSpA</td>
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**Figure 2.2** Predominant axial and peripheral spondyloarthritides. axSpA, axial spondyloarthritis; IBD, inflammatory bowel disease; SpA, spondyloarthritis. Adapted from Rudwaleit et al [1].
first split into predominantly axial and peripheral subsets. Figure 2.3 shows the current ESSG classification criteria for spondyloarthritis [2]. Most recently the Assessment in SpondyloArthritis international Society (ASAS) has proposed new classification criteria on axSpA, a term that is used throughout this book [4].

**Epidemiology of axial spondyloarthritis**

AxSpa 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) [5]. Patients who are positive for HLA-B27 are about 10 years younger than HLA-B27-negative patients when the disease starts [6].

Men with AS are slightly more affected than are women, with a ratio of about 2:1, but women are equally affected compared to men in the nr-axSpA stage. Indeed, women generally develop chronic radiographic changes of the sacroiliac joints and the spine later than men, a possible explanation for the frequent underdiagnosis of AS in women in the past, resulting in a much higher male:female ratio than currently accepted [6].

<table>
<thead>
<tr>
<th>European Spondyloarthropathy Study Group classification criteria for spondyloarthropathy</th>
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<tr>
<td><strong>Inflammatory back pain</strong> or <strong>Synovitis</strong></td>
</tr>
<tr>
<td><strong>or</strong></td>
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<tr>
<td><strong>asymmetrical or</strong></td>
</tr>
<tr>
<td><strong>predominantly in the lower limbs</strong></td>
</tr>
<tr>
<td><strong>plus one of the following:</strong></td>
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<tr>
<td>alternating buttock pain</td>
</tr>
<tr>
<td>sacroiliitis</td>
</tr>
<tr>
<td>heel pain (enthesitis)</td>
</tr>
<tr>
<td>positive family history</td>
</tr>
<tr>
<td>psoriasis</td>
</tr>
<tr>
<td>Crohn’s disease, ulcerative colitis</td>
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<td>urethritis/acute diarrhea in the preceding 4 weeks</td>
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*Figure 2.3 European Spondyloarthropathy Study Group classification criteria for spondyloarthropathy.* Reproduced with permission from © John Wiley and Sons 2013, Dougados et al [2]. All Rights Reserved.
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) [7–11]. Overall, estimations about the prevalence of AS 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 [12–16]. A study from the USA reported an overall prevalence of axSpA of about 1% [17]. However, a major limitation of this study was the lack of information on sacroiliac joint imaging and HLA–B27 status of the patients.
HLA-B27 is positive in 90–95% of patients with AS and in about 80–90% of patients with nr-axSpA. This percentage goes down to about 60% in patients with AS who also have psoriasis or IBD. In predominant peripheral SpA, less than 50% of patients are positive for HLA-B27.

Attempts have been made to estimate the ratio between patients with AS (radiographic axSpA) and nr-axSpA when a diagnosis of axSpA is first made by a rheumatologist. Nr-axSpA has been found in between 25% and 50% of patients with axSpA [18]. This proportion is higher when concentrating on patients with shorter symptom durations [19].
Etiopathogenesis of axial spondyloarthritis

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. The center of the discussion on the pathogenesis of SpA has long been 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. These findings have supported a central role for an interaction between bacteria and HLA-B27 in the pathogenesis; however, in the majority of patients with AS, no bacterial exposure can be detected, but subclinical bacterial infections or gut inflammation may be a possibility.

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 patients with AS (Figure 2.7) [23,24]. 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 axSpA. An elevated expression of the cytokines interleukin (IL)-17 [25] and IL-23 [26] have been found
In the subchondral bone marrow of patients with AS and these cytokines have more recently gained much interest as potential treatment targets (see Chapter 6). Furthermore, IL-23 has been found to play a crucial role in the pathogenesis of enthesitis in an animal model with features resembling SpA [27].

In addition to inflammation, axSpA 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 with (fibrous) repair tissue, with a final step in
which this repair tissue is subsequently ossified [24]. If this is true, new bone formation would not occur without previous erosive damage from inflammation [24,28,29]. Interestingly, the previously mentioned animal model of SpA IL-23 could trigger inflammation via IL-17 stimulation but also osteoblast activation through IL-22 activation [27]. Further research is necessary to clarify the pathogenesis of axSpA and the characteristic interaction between inflammation and new bone formation.

**Prognostic parameters in axial spondyloarthritis for radiographic progression**

In general, AS is a slowly progressing disease. In patients with a mean disease duration of about 20 years, syndesmophytes of the spine were
detectable only in about 60% [30]. A growth of syndesmophytes is normally visible on radiographs only over a follow-up period of at least 2 years. However, there is a subgroup of still ill-defined patients who suffer from a more rapid progression. An older retrospective study reported the presence of hip arthritis, elevated erythrocyte sedimentation rate, young age at onset, poor response to nonsteroidal anti-inflammatory drug treatment, and extraspinal manifestations as predictors of a more severe course [31]. The presence of syndesmophytes at baseline seems to be the best predictor for the development of more syndesmophytes [30]. More recently, elevated C-reactive protein was identified as the only relevant parameter predicting progression from nr-axSpA to AS over 2 years [32] and also as a relevant parameter, besides baseline syndesmophytes and smoking, to predict further progression of radiographic damage of the spine [33].

More studies are needed to get a better idea of prognostic factors, which is also crucial for identifying patients who are in need of early, more aggressive therapy.

**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) [34]. By far the strongest genetic association is with HLA-B27, and more than 100 HLA-B27 subtypes have been described to date. Some of them, such as HLA-B*2706 and HLA-B*2709, do not seem to be 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: IL-23 receptor (IL-23R), which is involved in the T-helper cell 17 (Th-17) pathway of chronic immune responses, and endoplasmic reticulum aminopeptidase-1 (ERAP-1), an enzyme that is relevant for the processing of peptides in the cytoplasm [35]. Quite interestingly,
an ERAP-1 association has only been found in HLA-B27-positive patients with AS [36], suggesting that ERAP-1 and HLA-B27 might be linked via peptide presentation. The relative contribution of these genes to the susceptibility to AS can be compared by using the population-attributable risk fraction statistic, which is 30–50% for HLA-B27, 26% for ERAP-1, and 9% for IL-23 [35]. Other factors, such as HLA-B60, IL-1A and cytochrome P450 2D6 (CYP2D6), have been described as affecting the risk of developing AS, although this is not completely clear.

On the other hand, 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 a patient with AS 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) [37].

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<tr>
<th>HLA-B27 status</th>
<th>Risk (%)</th>
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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>
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Figure 2.9 Risk of developing ankylosing spondylitis in a first-degree relative. HLA, human leukocyte antigen. Adapted from Brown et al [37].

References


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