

Topical Reviews

An overview of current research and practice in rheumatic disease



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Seronegative Spondyloarthropathies

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CLINICAL FEATURES AND CLASSIFICATION OF SPONDYLOARTHROPATHIES

- The seronegative spondyloarthritides comprise a group of diseases sharing key clinical features and an association with HLA-B27
- Recent studies propose an early and important role for enthesitis (inflammation at the insertion of tendon or ligament into bone)
- Possession of HLA-B27 is important in the pathogenesis, severity and chronicity of spondyloarthritis
- New treatments including anti-TNF α therapy and bisphosphonates are promising but need further evaluation

The concept of spondyloarthropathy introduced by Moll and Wright (1) is based on mainly clinical findings. Several inflammatory arthritides have common features which include familial clustering, association with HLA-B27, predominant axial and peripheral asymmetrical joint involvement, enthesitis, extra-articular signs and negative rheumatoid factor. Although active debate remains about which conditions should be classified as seronegative spondyloarthropathies, we will here concentrate on those conditions, shown in Table 1, whose association with HLA-B27 suggests a common or related aetiology. At present, specific diagnostic criteria for all conditions are not widely accepted, as opposed to classification criteria for use in trials such as those of the European Spondyloarthropathy Study Group (2). The combined prevalence of spondyloarthropathy in the general population is estimated to be approximately 1%, comparable to that of rheumatoid arthritis.

TABLE 1. HLA-B27-associated spondyloarthritides

Disease	HLA-B27 frequency % (approximate)
Ankylosing spondylitis	96%
Undifferentiated spondyloarthropathy	70%
Reactive arthritis	30-70%
Colitis-associated spondyloarthritis	33-75%
Psoriatic spondyloarthritis	40-50%
Juvenile enthesitis-related arthritis	70%
Iritis	50%
Cardiac conduction defects with aortic incompetence	Up to 88%

INTRODUCTION

In this review, we will discuss the clinical features and diagnosis of seronegative spondyloarthritis, before highlighting recent advances in our understanding of the aetiology and treatment of these conditions.

Ankylosing spondylitis (AS) is the commonest of the spondyloarthritides, with a prevalence of 0.2-0.86% in adult Caucasian populations and a male preponderance. Diagnosis, which is frequently delayed for several years after presentation of symptoms, usually involves the finding of inflammatory back pain and limitation of spinal movement in multiple planes together with radiological evidence of sacroiliitis. Ninety-six percent of patients are HLA-B27-positive (3). The utility of HLA-B27 testing depends on the pretest probability of disease. It is not a useful screening test because it is present in 6-9% of the UK Caucasian population. A group of patients with **undifferentiated spondyloarthropathy** - typically an oligoarticular asymmetrical arthritis of the lower limbs - is also recognized.

Acute **reactive arthritis (ReA)** is by no means always a benign self-limiting condition; there is progression to a chronic spondyloarthropathy in approximately 15-30% of cases (4). Recurrent attacks are more common in patients with chlamydia-triggered ReA. Chronicity of ReA can in part be predicted by the presence of hip or heel pain, high ESR, positive family history and HLA-B27-positivity (4).

Both **oligoarthritis and sacroiliitis associated with psoriasis and inflammatory bowel disease** are HLA-B27-associated. Inflammatory gastrointestinal lesions, demonstrated by ileocolonoscopy, are commonly found, even in asymptomatic patients with all forms of spondyloarthropathy (5). Their presence varies between 20% and 70%. Interestingly, 6% of patients with spondyloarthropathy but without clinical evidence of inflammatory colitis at the time of diagnosis will subsequently develop inflammatory bowel disease. There appears to be a temporal relationship between activity of colitis and Type 1 oligoarthritis (6). The link between gut inflammation and arthropathy has also been demonstrated in animal models such as HLA-B27 transgenic rats (see below).

Spondyloarthropathies are responsible for a number of children with juvenile idiopathic arthritis (JIA). In the past, the majority of these were labelled as pauciarticular arthritis. More recently, a World Health Organisation/International League Against Rheumatism report (7) proposed a classification for JIA based on clinical patterns, including seven different subtypes. The **enthesitis-related arthritis** subtype is identified by criteria, shown in Table 2, closely related to classifications of adult spondyloarthropathy, but reflecting the lower incidence of sacroiliitis in children. However, long-term follow-up of children with enthesitis-related arthritis indicates that over half of those with no evidence of sacroiliitis at diagnosis will go on to develop sacroiliac inflammation (8).

TABLE 2. ILAR task force criteria for juvenile enthesitis-related arthritis

Arthritis and enthesitis
OR
Arthritis and at least one of the following:
sacroiliac joint tenderness
inflammatory spinal pain
HLA-B27
positive family history of at least one of:
(a) anterior uveitis
(b) spondyloarthropathy confirmed by a rheumatologist
(c) inflammatory bowel disease

Eye inflammation, especially **uveitis**, is a prominent extra-articular feature of spondyloarthropathies. Indeed, uveitis may precede the onset of arthropathy. Uveitis associated with AS and Reiter's syndrome is usually a unilateral acute anterior uveitis (AAU) with a high tendency to recur, sometimes in the contralateral eye. Uveitis associated with inflammatory bowel disease, psoriasis and undifferentiated spondyloarthropathy may be less characteristic in its presentation, with a higher tendency to posterior uveitis, bilateral involvement and chronicity. Half of all patients with any form of anterior uveitis are HLA-B27-positive and over half of the B27-positive patients have a spondyloarthropathy. All HLA-B27-positive patients with AAU should therefore be referred for rheumatological assessment. Because attacks of AAU are extremely painful, the majority of spondyloarthropathy patients with AAU will refer themselves for urgent ophthalmological care. It is our practice to inform all HLA-B27-positive patients with spondyloarthropathy about the possibility of developing iritis and the need for immediate treatment.

Cardiac manifestations are seen in spondyloarthropathies, particularly associated with AS. These include aortitis causing aortic insufficiency, myocarditis causing conduction disturbances and myocardial fibrosis causing abnormalities of left ventricular relaxation. Atrioventricular block has been found to be frequently associated with spondyloarthropathy in Scandinavian countries. Conduction system disorders in spondyloarthropathy tend to occur intermittently. They can affect HLA-B27-positive patients even in the absence of symptomatic arthritis (9). In one study 88% of male patients with severe conduction disturbance and aortic incompetence were HLA-B27-positive (10). A prolonged QT interval may indicate a higher risk of occult ventricular arrhythmias in AS (11).

There is still some debate on the inclusion or otherwise of other inflammatory disorders. Both Whipple's disease and Behçet's syndrome were suggested as spondyloarthropathies by Moll and colleagues (1), but are now generally felt to be separate disease entities. This delineation is related to lack of familial clustering,

poor association with HLA-B27 and less apparent homogeneity of clinical features. Approximately half of the patients with SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) satisfy the criteria for spondyloarthropathy (12). However the association with HLA-B27 is either weak or absent, indicating that SAPHO probably differs in its pathogenesis.

PATHOGENESIS OF SERONEGATIVE SPONDYLOARTHROPATHY

Genetic studies in ankylosing spondylitis and spondyloarthritis

Family and twin studies have shown that predisposition to AS is largely genetically determined, with heritability in excess of 90% (13), suggesting that any environmental trigger must be ubiquitous. Genome screening using polymorphic markers spaced across the human genome has confirmed the contribution of the HLA region and of HLA-B27 on chromosome 6, but suggested that at least four further genetic sites make significant contributions to disease (14). Some of these may be common to other polygenic diseases such as inflammatory bowel disease. Candidate gene studies may also be useful in the spondyloarthropathies. Indeed, Brown and colleagues have recently confirmed the association of a cytochrome Cyp2D6 polymorphism with AS (15). Extension of genetic studies through multinational collaboration raises the tantalizing possibility that further associations with specific genes will be identified and confirmed.

Evidence for an inflammatory aetiology of the spondyloarthritides

A number of recent studies have provided indirect evidence that the spondyloarthropathies have an immune-mediated pathogenesis. Patients with reactive arthritis have expanded populations of activated T-lymphocytes in their blood and synovial fluid (16-18). Biopsies of inflamed sacroiliac joints show evidence of increased expression of pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF α) (19), and disease appears to improve dramatically with anti-TNF α treatment (see below).

What is the role of HLA-B27?

The human leukocyte antigen (HLA) class I allele HLA-B27 is strongly associated with spondyloarthritis, with an odds ratio of 171, (95% confidence interval 135 to 218) (3). Despite extensive studies, the pathogenic role of HLA-B27 remains unknown. Numerous theories have been proposed to explain the association, reviewed in reference 20. We favour those theories invoking mechanisms related to the natural immunological function of HLA-B27. The principle natural function of HLA-B27 is to complex with beta 2 microglobulin

(β 2m), forming a structure that can then bind short antigenic peptides, derived for example from infectious agents within cells. These complexes then travel to the cell surface where they can be specifically recognized by cytotoxic T-lymphocytes which then kill the infected cell. The role of HLA-B27 in spondyloarthropathy may well involve this process of antigen presentation. Direct evidence for a role of HLA-B27 in disease pathogenesis comes from studies of rats made transgenic for HLA-B27, which develop a multisystem disease resembling human spondyloarthritis (21). Studies of HLA-B27-transgenic mice suggest that HLA-B27 heavy chains alone may be able to cause disease, since expression of HLA-B27 heavy chains together with β 2m and peptide at the cell surface is not necessary for causing disease (22). Interestingly, it has recently been shown that HLA-B27 heavy chains can form stable homodimers lacking β 2m (23), and it is possible that such an aberrant form of the B27 molecule could be involved in disease pathogenesis (**Figure 1**). Possible mechanisms would include recognition of an aberrant HLA-B27 dimer structure by antibodies, T- or natural killer cells. This finding suggests novel approaches to studying disease pathogenesis.

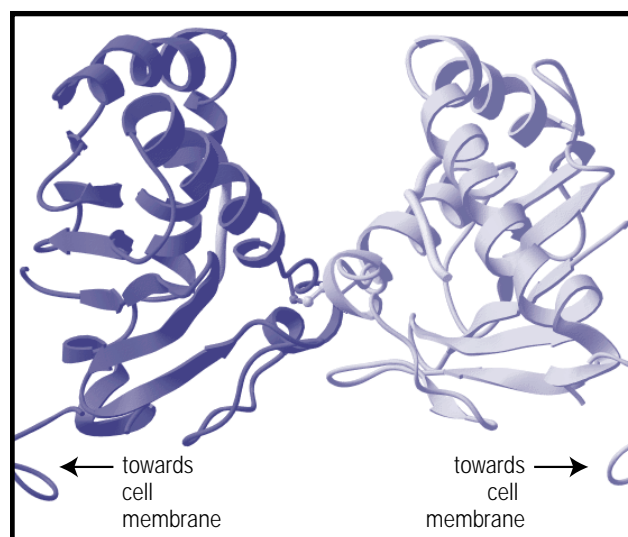


FIGURE 1. A molecular model of an aberrant form of the B27 molecule, showing how a stable homodimer can be formed from HLA-B27 heavy chains. Heavy chains are shown in ribbon format (one in dark blue and one in light blue). The heavy chains are joined by a disulphide bond through positions cysteine 67. The α 1 and α 2 domains only are shown.

Lessons from the tissue distribution of spondyloarthritis: a key early role for enthesitis?

Enthesitis - inflammation at the insertion of tendon or ligament into bone - is a frequent feature in many forms of spondyloarthropathy and may involve synovial joints, cartilaginous joints and syndesomes as well as extra-articular entheses. In psoriatic arthritis, fat-suppressed T2-weighted magnetic resonance images (MRI) show peri-entheseal inflammation and bone marrow oedema at entheseal insertions (24). These

findings have led to the hypothesis that synovitis in psoriatic arthritis (and perhaps spondyloarthropathy in general) is secondary to enthesal inflammation, in contrast to the primary synovitis of rheumatoid arthritis (25). Enthesitis in the spondyloarthropathies most frequently involves the lower limbs, perhaps related to the greater bulk or physical stress on entheses at these sites. It has recently been suggested that the striking tissue distribution of the spondyloarthropathies may relate to tissue-specific modulation of immune responses towards fibrosis rather than lysis at sites subject to stress, such as the spine, lung apices, aorta and uveal tract (26).

Infection and spondyloarthropathy: lessons from HIV infection

The clear association of bacterial infection with reactive arthritis suggests a pathogenic link between spondyloarthritis and infection. Both bacterial products and T- cells responding to arthritis-associated bacteria can be detected in inflamed joints (27). Patients with AS also have increased antibody responses. These findings, which do not prove a pathogenic mechanism, were discussed at a recent workshop on reactive arthritis and are reviewed by Sieper and colleagues (28).

Until the advent of HIV infection in the 1980s, spondyloarthropathy was considered rare in Africa. There has however been a recent dramatic increase in the African frequency of spondyloarthropathy in association with HIV infection (29,30). In Lusaku, Zambia, the prevalence of spondyloarthropathy is 180 per 100,000 in HIV-positive individuals versus 15 per 100,000 in the absence of HIV. The majority of patients diagnosed with spondyloarthropathies are HIV positive (psoriatic arthritis 92%, ReA 87%, and undifferentiated spondyloarthropathy 98%) (29, 30).

What does this association tell us about the pathogenesis of spondyloarthropathies? HIV infection causes both non-specific immune stimulation and alteration in the ratio and function of CD4 and CD8 T-lymphocytes. In particular CD4 T-cells are depleted. This suggests that either loss of CD4 T-cells or a relative increase in CD8 T-cells might be important in spondyloarthropathy. An alternative but less probable explanation is that co-infection with a separate urogenital trigger (or even HIV itself) might have a direct aetiological role in spondyloarthropathy.

RECENT ADVANCES IN THE TREATMENT OF SPONDYLOARTHROPATHIES

Many patients with spondyloarthropathy and mild disease respond well to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy including physiotherapy, regular exercises and hydrotherapy (31). Persistent oligoarthritis is often

improved by intra-articular steroid injections. CT- or X-ray guided corticosteroid injection of sacroiliac joints has been shown to lead to an improvement in symptoms, often lasting many months, and to reduce bone marrow oedema on MRI. Enthesitis may also respond to local steroid injections although great caution should be exercised injecting in or near the insertion of the Achilles tendon in view of the risks of tendon rupture. Spondyloarthropathy patients with severe peripheral joint disease commonly require treatment with a combination of NSAIDs and disease-modifying anti-rheumatic drugs (DMARDs). The DMARDs used in the treatment of spondyloarthropathy largely overlap with those used in rheumatoid arthritis.

Efficacy of conventional disease-modifying drugs (DMARDS)

Sulphasalazine has been shown to be of benefit in double-blind randomized controlled trials for the peripheral arthritis of spondyloarthropathy, but has no proven benefit on axial pathology (32, 33). Recently, uncontrolled studies have shown comparable improvement in clinical, physical and laboratory measures with mesalazine (34, 35). It will be important to confirm these findings in randomized controlled trials, because mesalazine offers the advantage over sulphasalazine of not causing oligospermia. Methotrexate (36) and azathioprine may also be beneficial, and there have been recent studies using intravenous loading doses of azathioprine to decrease its initial response time (37). This includes beneficial effects on stiffness, function, pain, active joint counts, enthesitis and ESR/CRP, but no effect on axial flexibility.

Novel treatments for spondyloarthritis

Anti-TNF α therapy Tumour necrosis factor alpha (TNF α) is a pro-inflammatory cytokine thought to play an important role in the joint inflammation of inflammatory arthritis. TNF α -blocking agents have been shown to be highly effective in rheumatoid arthritis and Crohn's disease. Preliminary observations of TNF α blockade in both psoriatic arthritis and AS have been highly encouraging. The TNF α inhibitor etanercept has been shown to improve both the skin and joints of patients with psoriatic arthritis in a 12-week randomised double-blind placebo-controlled trial (38). Open-label phase 1 clinical trials of the anti-TNF α monoclonal antibody infliximab have found rapid improvement, not only of peripheral arthritis but also of axial symptoms and function in AS (39, 40). Interestingly, preliminary reports suggest that thalidomide, a drug which is known to have anti-TNF α activity, may also be efficacious in AS (41).

Bisphosphonates Recent interest has also focussed on the use of bisphosphonates in the treatment of spondyloarthritis (42). The benefits may relate more to their anti-inflammatory effects rather than effects on

bone resorption. Randomized clinical trials are now underway. In parallel with this work there is increasing interest in the incidence of osteoporosis in spondyloarthritides. In one ankylosing spondylitis study, 86% of patients had osteoporosis or osteopenia in the proximal femur (43). Osteoporosis is more likely in those with active disease (44). In later disease bone mass loss is best evaluated in the femur because of the presence of paravertebral calcification and ossification in the lumbar spine. In view of these findings we believe corticosteroids should be used with caution in AS.

Antibiotic treatment in reactive arthritis

Antibiotics have been shown not to improve the duration or progression of enteropathic ReA (45). However, prolonged treatment with tetracyclines such as limecycline may be effective in the treatment of chlamydia-induced ReA (46). Bardin and colleagues also showed a reduction of post-chlamydia reactive arthritis relapses from 37% to 10% with the use of erythromycin or tetracycline (47).

CONCLUSIONS

There have been significant recent advances in our understanding of the pathogenesis of the spondyloarthropathies. The substantial and multigenic genetic contribution to ankylosing spondylitis is now well appreciated. We have a greater understanding of the immunological processes underlying disease and of possible new ways in which HLA-B27 might cause disease and treatment. There is renewed interest in enthesitis as an important diagnostic and pathogenic process. Equally exciting are therapeutic developments including anti-TNF therapy and perhaps the use of bisphosphonates. These hold great promise but their efficacy in placebo-controlled trials and long-term safety need further evaluation.

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