Axial spondyloarthritis

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Abstract

The prevalence of axial spondyloarthritis (AxSpA) is approximately 1% of the general population. Ankylosing spondylitis (AS) affects 0.2—0.5% of the northern European population, the prevalence varying with the prevalence of HLA-B27. AS affects men three times more often than women, but AxSpA (without X-ray changes) affects men and women equally. Symptoms usually begin in the third decade of life with inflammatory back pain. The key pathological element is enthesitis, though the main diagnostic feature is sacroiliitis. Approximately one-third of patients develop peripheral lesions including lower limb oligoarthritis, heel enthesitis, iritis, inflammatory bowel disease and psoriasis. Vertebral osteoporosis is not uncommon and cardiovascular disease and renal impairment may complicate severe AS. The diagnosis of AxSpA can be made on the basis of imaging (X-ray or MRI) or on clinical features alone.

The cause(s) of AS remain unknown. Genetic factors, including HLA-B27 and the interleukin-23 receptor, confer susceptibility to AS but environmental precipitating factors have not been identified. Treatment involves the maintenance of spinal movement and comfort through exercise supported, where necessary, by analgesia and anti-inflammatory treatment. Disease-modifying anti-rheumatoid drugs are not effective for spinal disease, but TNF-α inhibitor drugs provide dramatic improvements in symptoms, function and quality of life.

Keywords Ankylosing spondylitis; axial spondyloarthritis; biologic therapy; diagnostic criteria; enthesitis; treatment

What's new?

- The spectrum of axial spondyloarthritis ranging from non-radiographic disease to severe ankylosing spondylitis is now well recognized
- Enthesitis and osteitis, both of which are demonstrable on MRI, are the key pathological lesions representing active disease. Emerging evidence supports early recognition and treatment to improve long-term outcomes
- A variety of patient- and physician-reported disease activity scoring systems exist; these include the ASDAS, which provides useful gradations of disease activity, although this is not yet widely used
- Genome-wide association studies have identified multiple genetic loci that contribute to the development of AS in addition to HLA-B27, notably ERAP-1 and IL-23r
- A novel population of IL-23-dependent entheseal T cells have been identified which may be central to aetiology
- TNF-α inhibitor drugs are the mainstay of treatment of severe AS. A number of new agents, notably apremilast (PDE inhibitor) and secukinumab (anti-IL17) are currently in clinical trials

Introduction

Axial spondyloarthritis (AxSpA) is an aseptic inflammatory condition primarily affecting fibrous and synovial joints in the spine, producing pain and progressive spinal stiffness. When radiographic changes at the sacroiliac joints are present, the term ankylosing spondylitis (AS) is used. It is a life-long condition of adults that substantially impairs life quality and work capacity, and may shorten life.

AxSpA is a member of the spondyloarthritis (SpA) family, whose members share similar clinicopathological features and genetic predisposition, notably an association with the HLA-B27 gene. Other members of this group are psoriatic arthritis, reactive arthritis and enteropathic arthritis. Undifferentiated forms of SpA also occur in both children and adults, though involvement of the spine tends not to occur until late teenage years.

The prevalence of AxSpA varies in different populations, according to the background prevalence of HLA-B27, being higher in some circumpolar regions and lower in some black African populations.

The prevalence of AxSpA in the US has been defined at 1.0% to 1.4% and AS at 0.52% to 0.55%.[1]

Aetiology

AxSpA is likely to result from the interaction of environmental and genetic factors. Although a role has been suggested for gut bacteria[2] — and such a role has been implicated in a spondyloarthritis-like syndrome in transgenic rats[3] — no clear indicators of such a mechanism exist in man.

In contrast, evidence of genetic factors is abundant. Among white individuals with AS, 95% carry the major histocompatibility complex (MHC) gene, HLA-B27, although this occurs in only 8% of most white populations and only approximately 2% of HLA-B27 carriers develop AS.[4] Thus, testing for HLA-B27 is not routinely useful in making the diagnosis of AS. However, MHC genes account for considerably less than 50% of the genetic susceptibility and recent genome-wide association studies have identified significant associations with the endoplasmic reticulum aminopeptidase ERAP-1, (also called ARTS-1) and interleukin (IL)-23 receptor genes. ERAP-1, which has the second strongest association with AS, is involved in the processing of peptides by MHC class I molecules. AS is associated with the same single nucleotide polymorphisms of the IL-23 receptor as those linked to psoriasis and IBD. Other loci elsewhere in the genome are likely to contribute to susceptibility to AS; some, including the killer cell immunoglobulin-like receptor (KIR) genes, may actually protect against development of AS or modulate the disease expression.[5]

Hypotheses as to mechanisms by which HLA-B27 leads to AxSpA have been reviewed by McHugh and Bowness.[6] The association of ERAP-1 with the development of AS may support the so-called 'arthritogenic peptide hypothesis' whereby the disease

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is triggered by the presentation of a peptide by HLA-B27 molecules on the surface of antigen-presenting cells to cytotoxic CD8-positive T cells. Evidence that HLA-B27 misfolds intracellularly, leading to the production of IL-23, has recently been complemented by the finding of a population of T cells resident in entheses, which promote inflammation characteristic of spondyloarthritis in response to IL-23.[7]

Clinical features

AxSpA usually begins in the late teens or 20s, typically presenting with inflammatory back pain (Table 1).[8] Back pain and stiffness are usually worse after inactivity and may awaken the sufferer from sleep. Symptoms improve with movement so that exercise is usually helpful. Sacroiliitis often causes buttock pain that may radiate down the back or front of either or both thighs but not below the knee. Typically, symptoms affect one side for a period of weeks or months and then subside, only to be followed by similar symptoms on the other side. This is known as alternating buttock pain.

In up to one-third of patients the peripheral skeleton is affected. Extra-articular sites, including entheses or the eye, may also be involved; both may precede spinal symptoms. Chest wall pain is also common, resulting either from costochondritis or referred pain from the thoracic spine. Fatigue is often a disabling symptom.

Male predominance is the rule when radiographic changes are present (in a ratio of 3:1) but in non-radiographic axial spondyloarthritis (nrAxSpA) the sex ratio is equal. Morbidity in nrAxSpA is similar to that in established AS.

Poor quality of life and socioeconomic consequences are critically important. People with AxSpA are less likely to be married and more likely to be divorced, and women with the condition are less likely to have children than their healthy counterparts.[9] Work disability is associated with heavy societal costs.[10]

Spinal deformity is not unusual amongst those severely affected and flexed posture may be aggravated by hip involvement. Deformity often leads to personal isolation as well as practical difficulties.

Lesions of AS

Enthesitis

The key pathological lesion of AxSpA is enthesitis. Entheses are complex and variable structures at the junction between the ligament, joint capsule or tendon and bone. In the spine, entheses are affected at the attachment of joint capsules around facet joints and sacroiliac joints, at the discovertebral junctions and at the attachments of the interspinous ligaments. Initially, lesions may be detectable by magnetic resonance imaging (MRI) – though this is not always of sufficient sensitivity – as areas with high water signal. Later, radiographs may show areas of decalcification ('erosions') that subsequently give place to new bone formation. Ultrasound scanning is increasingly used to identify peripheral entheseal lesions.[11]

Peripheral enthesitis is a characteristic feature of AxSpA. Most commonly, the heel is involved. Achilles tendon enthesitis occurs at the point of attachment, in marked contrast to the thickening and pain higher up the tendon seen in athletes. Enthesitis is often associated with formation of an Achilles tendon bursa, seen best from behind with the patient standing. Involvement of the plantar fascia is also characteristic, with troublesome pain and formation of a fluffy bony spur on X-ray. These changes may be impossible to distinguish from degenerative plantar fasciitis. Evaluation of the entheseal lesions can be performed using the Maastricht Ankylosing Spondylitis Enthesis score (MASES).

Sacroiliitis

Sacroiliitis is often the cause of the presenting symptoms of buttock and/or thigh pain. It is diagnosed characteristically by radiographic appearances, graded as 0–4, but such changes take several months or years to become diagnostic. MRI scanning may allow detection of pre-radiographic change and hence facilitate early diagnosis. Typical appearances are of juxta-articular bone marrow oedema best seen on STIR sequence, with later fatty change also seen on T1. Diagnostic appearances are defined and well illustrated in the Assessment of SpondyloArthritis International Society (ASAS) handbook.[12] While undoubtedly valuable, MRI scanning remains problematic. The sensitivity of MRI is limited by the relatively dynamic bone marrow changes and distinction from degenerative change may be difficult.

Spinal lesions

Radiographic changes occur late, but are highly specific, whereas changes on MRI may be detected earlier but are less specific. Inflammatory corner lesions are characteristic, appearing as bone oedema or fatty change on MRI and as sclerotic 'shiny corners' on X-ray. In older adults such changes of osteitis are relatively non-specific, though osteitis at the pedicle is strongly linked with AxSpA. Osteitis may occur around the facet joints and vertebral spines. Such changes may lead on to new bone formation that is eventually visible on radiographs as syndesmophytes or bony obscuration of the facet and sacroiliac joints.

Extraspinal arthritis

Up to 30% of patients with AxSpA also develop peripheral arthritis. This is usually asymmetrical oligoarthritis affecting the hip, knee and metatarsophalangeal joints, in contrast to the symmetrical changes in rheumatoid disease. Synovitis is histologically non-specific but MRI may demonstrate extensive entheseal lesions within the joint area. Dactylitis usually affecting a single toe ('sausage toe') is highly suggestive of spondyloarthritis.

Inflammatory spinal pain[8]

ASAS definition – spinal pain ≥3 months and
Onset <40 years of age
Insidious onset
Improvement with exercise
No improvement with rest
Pain at night (with improvement on getting up)
The criteria are fulfilled if four or five parameters are met

Table 1