Diagnosis and management of ankylosing spondylitis

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Ankylosing spondylitis is a chronic inflammatory rheumatic disorder that primarily affects the axial skeleton. Sacroiliitis is its hallmark, accompanied by inflammation of the entheses (points of union between tendon, ligament, or capsule and bone) and formation of syndesmophytes, leading to spinal ankylosis in later stages. Prevalence estimates vary between 0.1% and 2% in different populations.¹ The male:female ratio is around 5:1, and the peak age of onset is at 15–35 years.

Because of its insidious nature, the diagnosis is sometimes delayed until late stages of the disease. Until recently, treatment has been limited to non-steroidal anti-inflammatory drugs and physiotherapy, but the development of cytokine inhibitors that inhibit the activity of tumour necrosis factor α has been an important advance in treatment.

Sources and selection criteria

We searched Medline for clinical trials and reviews using the keywords “ankylosing spondylitis,” “treatment,” “physiotherapy,” “NSAIDs,” “DMARDs,” “anti-TNF,” and “biologics.”

How is it diagnosed?

The most commonly used criteria for the classification of ankylosing spondylitis were developed in 1966 and modified in 1984.^{2–3} They are:

1. Low back pain of at least three months duration with inflammatory characteristics (improved by exercise, not relieved by rest)
2. Limitation of lumbar spine motion in sagittal and frontal planes
3. Decreased chest expansion (relative to normal values for age and sex)
4. Bilateral sacroiliitis grade 2 or higher
5. Unilateral sacroiliitis grade 3 or higher.

Definite ankylosing spondylitis is said to be present when the fourth or fifth criterion presents with any clinical criteria. However, radiological sacroiliitis may not develop for many years, and the development of new criteria (including magnetic resonance imaging) has been proposed to allow confirmation of the diagnosis in patients with early disease (see below).⁴

History

The key point in a patient's history is inflammatory back pain.⁵ This typically presents as low back pain and stiffness of insidious onset that is worse first thing in the morning or after rest, lasts at least 30 minutes, and

Summary points

Ankylosing spondylitis is a chronic inflammatory rheumatic disease that primarily affects the sacroiliac joints, spine, and entheses

It has a strong genetic predisposition associated with human leukocyte antigen B27

Early diagnosis can be difficult but is important; magnetic resonance imaging of the sacroiliac joints can be helpful in early disease

Traditional treatment begins with physiotherapy, regular use of non-steroidal anti-inflammatory drugs, local corticosteroid injections, and sometimes sulphasalazine

The advent of drugs that inhibit the activity of tumour necrosis factor α has revolutionised management

Patients presenting with features of inflammatory back pain should be referred to a rheumatologist at an early stage

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BMJ 2006;333:581–5

improves with activity. Sacroiliitis may present as ill defined unilateral or bilateral buttock pain, with radiation sometimes felt into the upper posterior thigh. Pain may also be felt in the cervical or thoracic region or in the chest. Occasionally, patients present with symptoms arising from peripheral joint synovitis or enthesitis (such as achilles enthesitis or plantar fasciitis). Sleep disturbance and daytime fatigue are common.

A recent study to try to identify a new candidate set of criteria for inflammatory back pain found a sensitivity of 70% and specificity of 81% when at least two of the following four criteria were present—morning stiffness of more than 30 minutes duration; improvement in back pain with exercise but not with rest; waking because of back pain during the second half of the night only; and alternating buttock pain.⁶

Ankylosing spondylitis may overlap with other spondyloarthropathies—including psoriatic arthritis, reactive arthritis, and enteropathic arthropathy—which can be difficult to distinguish from ankylosing

Extra references w1-w31 are on bmj.com.

Fig 1 Plain radiograph showing bilateral sacroiliitis in a patient with ankylosing spondylitis

spondylitis, particularly in early stages. Clinicians should therefore have a high index of suspicion in patients presenting with inflammatory back pain and a history of iritis, psoriasis, inflammatory bowel disease, or recent infection.

Examination

Clinical findings may be subtle in the early stages or in milder cases. Clinical examination should include measurement of forward lumbar flexion (Schober's test, >5 cm flexion is normal), lateral lumbar flexion, and chest expansion, as well as palpating and stressing the sacroiliac joints. The peripheral joints should also be examined for evidence of synovitis or enthesitis. Patients should be assessed for the presence of extra-articular manifestations of disease, including anterior uveitis (which occurs in up to 40% of patients), aortic incompetence, cardiac conduction disturbances, and pulmonary fibrosis.^{5 w1 w2}

Genetics

About 90-95% of white western European patients with ankylosing spondylitis have the tissue human leukocyte antigen B27 (HLA-B27), compared with around 8% in the general population,¹ though prevalences vary in different populations.^{w3} The association is complex, as there are several subtypes of HLA-B27, not all of which are pathogenic, and other non-HLA-B27 genes also play a role. The disease is likely to be triggered by an unknown environmental factor in patients who are genetically predisposed.^{w4} It should be remembered that most individuals who possess HLA-B27 will never develop ankylosing spondylitis.

Laboratory findings

Most, but not all, patients with ankylosing spondylitis will have elevated levels of C reactive protein and erythrocyte sedimentation rates. Levels of inflammatory markers are less useful for monitoring disease activity in ankylosing spondylitis than they are in other

inflammatory conditions such as rheumatoid arthritis, and may relate more to disease activity in peripheral joints than axial disease. A normocytic normochromic anaemia may be present, particularly in patients with active disease.

Imaging

Sacroiliitis is the hallmark of the disease. Changes classically occur in the lower third of the sacroiliac joints. Initially the joint may seem blurred and indistinct, followed by bony erosions, sclerosis, and the apparent widening of the joint (fig 1). Complete bony fusion may occur in longstanding disease.⁵ Spinal radiographic changes include marginal vertebral body erosions, squaring of the vertebral bodies, and the formation of bony bridges or syndesmophytes between adjacent vertebrae. Ossification of spinal ligaments may occur, and spinal osteopenia is common. In severe longstanding disease, almost complete fusion of the vertebral column may occur ("bamboo spine").

Plain radiographs may be normal in early disease, and further imaging, particularly magnetic resonance imaging, plays an important role in the early diagnosis of ankylosing spondylitis (fig 2). Magnetic resonance imaging of the sacroiliac joints has been shown to be more sensitive than either plain radiography or computed tomography in detecting sacroiliitis.⁷ It may therefore be considered in patients presenting with typical characteristics of inflammatory back pain but normal plain radiographs, particularly if they are seropositive for HLA-B27.^{w5 w6} Magnetic resonance imaging may also be used to monitor treatment in patients with active ankylosing spondylitis.^{8 9 w7} Musculoskeletal ultrasound scanning is particularly helpful in the diagnosis of enthesitis.¹⁰

Osteoporosis and fracture

Osteoporosis and fracture are common in ankylosing spondylitis.^{w8-w10} Dual energy x ray absorptiometry may underestimate the fracture risk in ankylosing spondylitis because of new bone formation, particularly in the spine. Measurement of biochemical markers of bone turnover has been used in research into ankylosing spondylitis and may be of clinical value in future.¹¹ Fractures most commonly occur at the thoracolumbar and cervicothoracic junctions and may occur with

Fig 2 Coronal STIR (short tau inversion recovery) magnetic resonance image showing unilateral (right) sacroiliitis

minimal trauma. Clinicians should have a low threshold of suspicion of fracture, particularly in patients with previously stable ankylosing spondylitis who present with acute persistent spinal pain.

How is it treated?

New evidence based recommendations for the management of ankylosing spondylitis have been produced by the International Assessment in Ankylosing Spondylitis working group in collaboration with the European League Against Rheumatism.^{12 13}

Physiotherapy

This is a key element of the overall management of all patients. A recent Cochrane review found evidence that physiotherapy had beneficial effects for patients with ankylosing spondylitis, but it was not clear which specific treatment protocol should be followed.¹⁴ Many patients find hydrotherapy particularly beneficial.^{w11}

Non-steroidal anti-inflammatory drugs

Randomised controlled trials have shown that, compared with placebo, NSAIDs improve spinal pain, peripheral joint pain, and function in ankylosing spondylitis.¹³ Cyclo-oxygenase-2 selective inhibitors and traditional NSAIDs seem broadly similar in efficacy. One study has suggested that regular use of NSAIDs, starting with celecoxib, inhibits radiographic progression in ankylosing spondylitis compared with NSAID use on demand, giving some support to the regular use of NSAIDs in active ankylosing spondylitis.¹⁵ The decision on which NSAID to use should be on an individual patient basis taking into account risk factors, particularly for gastrointestinal and cardiovascular disease. Analgesics, including paracetamol and opioids, may be considered when NSAIDs are contraindicated or not tolerated.

Disease modifying antirheumatic drugs

Sulfasalazine has inconclusive evidence for efficacy in ankylosing spondylitis. A recent Cochrane review of 12 randomised controlled trials has found some evidence of benefit in peripheral joint symptoms and in reducing morning stiffness and erythrocyte sedimentation rate but no evidence of benefit in physical function, pain, spinal mobility, enthesitis, or patient or physician global assessment.¹⁶

A Cochrane review of methotrexate for treating ankylosing spondylitis concluded that there was no evidence to support its use.^{w12} It included only two papers, however, and a subsequent small study of low dose methotrexate did suggest some clinical benefit in ankylosing spondylitis.^{w13} There is little evidence to support the use of other traditional disease modifying antirheumatic drugs in ankylosing spondylitis.^{w14}

Corticosteroids

Intra-articular or periarticular corticosteroid injections for sacroiliitis have been shown to be effective in small trials.^{w15 w16} Local corticosteroid injections for peripheral arthritis and enthesitis in ankylosing spondylitis are widely used in clinical practice to good effect, but no clinical trials exist to support this use. Intravenous methylprednisolone is occasionally used in severe unresponsive cases, but this use may decline with the availability of tumour necrosis factor inhibitors.

Bisphosphonates

Oral bisphosphonates are commonly used for fracture prevention in ankylosing spondylitis.^{w17} Bisphosphonates also have an anti-inflammatory action and may have an effect on disease activity. Intravenous pulses of the bisphosphonate pamidronate have been investigated in several studies and have produced significant clinical improvements in some but not all studies.^{11 17 w18 w19}

Cardiovascular risk

In common with other inflammatory rheumatic conditions, ankylosing spondylitis is associated with increased rates of cardiovascular morbidity and mortality.^{w20} This may be only partially explained by traditional risk factors, and it seems likely that the chronic inflammatory nature of the condition is partially responsible. Clinicians should be alert to this and take action to identify and treat traditional modifiable cardiovascular risk factors. It has been proposed that better control of the underlying inflammatory condition may improve this risk. It is also possible that chronic use of NSAIDs may increase this risk. As well as their effect on lipids, statins also have an anti-inflammatory effect, and a recent small open study has reported that rosuvastatin treatment produced clinical improvement in ankylosing spondylitis.^{w21}

Surgery

A large proportion of patients with ankylosing spondylitis develop hip arthritis. Hip replacement should be considered in patients with refractory pain or disability and with radiographic evidence of structural damage, independent of age.^{12 w22 w23} Spinal surgery may be of value in selected patients and is performed for a variety of reasons in ankylosing spondylitis patients, including fusion procedures for segmental instability and wedge lumbar osteotomy for fixed kyphotic deformity.¹² Patients with severe ankylosing spondylitis present anaesthetic difficulties, and the risks and benefits of surgery need to be carefully considered.

Tumour necrosis factor inhibitors

Drugs that inhibit tumour necrosis factor (TNF) have revolutionised the treatment of ankylosing spondylitis. Three different drugs are currently available—etanercept, a recombinant TNF receptor; Fc fusion protein that is administered subcutaneously; infliximab, a chimeric monoclonal antibody to TNF given by intravenous infusion; and adalimumab, a humanised monoclonal antibody to TNF given subcutaneously. These drugs have been widely used in the treatment of severe rheumatoid arthritis.^{w24}

Evidence from randomised controlled studies supports the use of etanercept^{18–20} and infliximab^{21 22} to treat ankylosing spondylitis for spinal pain, function, and peripheral joint disease. More recently adalimumab has also been shown to be effective.^{23 w25} The drugs have rapid and substantial clinical effects. Recent studies have also shown marked persistent reduction of spinal inflammation as detected by magnetic resonance imaging.^{9 24} Treatment with TNF inhibitors should be considered for patients with persistently high disease activity despite conventional treatments.¹²

The case for using these drugs in ankylosing spondylitis is perhaps even more compelling than in rheumatoid arthritis: they are at least as effective in

treating ankylosing spondylitis as they are in rheumatoid arthritis,^{w26} whereas the evidence to support the use of other disease modifying antirheumatic drugs in ankylosing spondylitis is much weaker. The British Society for Rheumatology has produced guidelines for the use of TNF inhibitors in ankylosing spondylitis.²⁵ Patients should have persistent active disease as defined by the Bath ankylosing spondylitis disease activity index (BASDAI)²⁶ and persistent spinal pain despite trials of two or more NSAIDs.

TNF inhibitors seem to achieve higher rates of remission in patients with shorter duration of disease: in one study, remission occurred in 35% of patients with less than 10 years since first symptoms, in 24% of those with disease duration of 10-20 years, but in none of those who had had the condition for more than 20 years.²⁷ The possibility that treatment early in the disease course improves remission rates needs confirmation, but it underlines the importance of diagnosing ankylosing spondylitis early, before established radiological changes are evident.

Stopping treatment with TNF inhibitors results in rapid relapse for most patients with longstanding disease.^{w27} However, in patients with early rheumatoid arthritis (<1 year duration) remission induction with infliximab plus methotrexate significantly reduced joint inflammation and erosion (shown by magnetic resonance imaging) at one year, and the functional and quality of life benefits were sustained at two years despite stopping infliximab treatment.²⁸ Further study is required to determine whether treating patients with early ankylosing spondylitis with a TNF inhibitor could produce remission that is sustained on withdrawal of treatment. If so, then it would be logical to treat patients with a short course of TNF inhibitor at an early stage (perhaps at diagnosis) rather than later in the disease course, when the treatment needs to be continued long term, perhaps for life (though long term data are lacking).

TNF inhibitors are powerful drugs and carry the risk of significant adverse effects. Increased rates of infection have been reported, including tuberculosis, and pretreatment screening is carried out routinely as part of assessment.^{w28 w29} Active infection is a contraindication to treatment, and patients taking the drugs are warned to stop treatment and consult their doctor immediately if they develop any symptoms suggestive of infection.²⁹ If any patient receiving a TNF inhibitor presents feeling unwell the possibility of infection should always be considered. If there is doubt the drug should be withheld and advice sought from a rheumatology department. It is also possible that long term use of the drugs may predispose patients to the development of some malignancies.^{w29} Other reported side effects include demyelinating disease, lupus-like syndromes, and worsening of pre-existing congestive cardiac failure, as well as injection site or infusion reactions.

TNF inhibitors are also expensive, and formal cost benefit analyses are complex. However, the large improvements in pain and function may outweigh the initial high financial costs, particularly if patients can remain in employment and out of hospital.^{w30} Early treatment with the drugs may also reduce later requirement for surgery. The availability of funding for the drugs varies between the different countries of the

Additional educational resources

For doctors

- Keat et al. BSR guidelines for prescribing TNF- α blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. *Rheumatology (Oxford)* 2005;44:939-47. (<http://rheumatology.oxfordjournals.org/cgi/content/full/44/7/939>)
- Zochling et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;54:442-52. (<http://ard.bmjournals.com/cgi/content/full/65/4/442>)

For patients

- National Ankylosing Spondylitis Society. (www.nass.co.uk)
- Arthritis Research Campaign. (www.arc.org.uk)
- Ankylosing Spondylitis Association of Ireland. (www.ankylosing-spondylitis.ie)
- Spondylitis Association of America. (www.spondylitis.org)

United Kingdom. At the time of writing, the National Institute for Health and Clinical Excellence (NICE) is reviewing the clinical and cost effectiveness of these drugs for ankylosing spondylitis for England and Wales. It is expected to issue guidance in 2007. The Scottish Medicines Consortium has approved the use of etanercept and infliximab in NHS Scotland for ankylosing spondylitis according to the British Society for Rheumatology guidelines. In Northern Ireland patients meeting these guidelines are also eligible for treatment, but funding is restricted and a waiting list has developed.^{w31}

We thank David Taylor, consultant radiologist, Musgrave Park Hospital, Belfast, for providing the images.

Contributors: CMMcV performed the literature search and wrote the initial draft of the paper. APC planned the review, wrote the outline, and the final version. Both approved the final version.

Competing interests: CMMcV has received funding to attend meetings from MSD, Pfizer, Sanofi-Aventis, Novartis, Schering-Plough, Wyeth and Roche. She has given talks for Sanofi-Aventis. APC has received funding to attend meetings from MSD, Pfizer, Abbott, Schering-Plough, Wyeth and Roche. He has given talks for MSD, Pfizer, Sanofi-Aventis, and Abbott, and has received an equipment grant from Wyeth.

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doi 10.1136/bmj.38954.689583.DE

Health and money

A man in his early 30s was admitted for severe head injury after a fall from height. He was brought to Tribhuvan University Teaching Hospital, a tertiary centre for neurosurgical care. During admission he was hemiplegic and had even lost the power of speech. After surgical intervention, his power over his limbs slowly improved and he began speaking a few words. He and his wife were delighted with his improvement, and he was always eager to greet the surgical team during the morning ward round. After four weeks, the neurosurgical team planned to discharge him, and the patient seemed very happy. The day before his discharge, some of his relatives and neighbours came to visit him and to help take him back to his home village.

The next day the patient, who had been jubilant over his recovery, looked very sad; he did not say a word and soon started crying. When we asked what had happened to him, his wife replied: "Yesterday a few relatives and friends came to meet him, and they said that, during his stay at the hospital, all his property was sold for his treatment; and, although he is alright now, he would have to face difficulties to look after his family of seven. This made him worried since yesterday, and he hasn't even spoken a word to me." Depression was diagnosed, and he spent three more weeks in hospital before he was discharged.

Economic burden has been the main setback of health systems in Nepal and many other areas in the developing world. As most people live below the poverty line and have to pay for their medical

treatment, many cannot afford to seek even primary care. Those who need a hospital stay run out of money within days. Many have to sell the small piece of land (their sole property) which supports their family. Although their disease gets treated, their subsequent rehabilitation is totally uncared for in Nepal so psychiatric problems often arise.

Every morning during the ward rounds, patients always ask if a free bed (less than 1% of the hospital beds) is available or if rather cheaper beds are available. Many patients do not get any care (food and drugs) after they are admitted because they cannot pay for these basic requirements. So ward rounds become economic rounds where patients and their families tell of their poverty and inability to pay for their treatment.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com>. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.