Ankylosing spondylitis: update on an ancient disease

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This month, Dr Taylor reviews developments in ankylosing spondylitis, including the newer therapies that offer hope for severely affected patients.

Ankylosing spondylitis is a chronic, systemic, inflammatory rheumatic disease that mainly affects the spine. It is an ancient disease – the Egyptian Pharaoh Rameses II is believed to have been a sufferer. The first definite description appeared in 1691, and over the years it has been known by several names, including Bechterew's disease, Marie Strümpell spondylitis and rheumatoid spondylitis.

Ankylosing spondylitis is one of the seronegative spondyloarthropathies (see the box on page 51). It is not an uncommon disease, and it has a significant impact on physical functioning and well-being. Our understanding of ankylosing spondylitis has improved in recent years, with significant progress being made in the areas of genetics and clinical assessment. In addition, exciting developments in therapy for more severely affected patients are emerging.

Epidemiology

It is well established that ankylosing spondylitis is associated with the HLA-B27 gene: 90 to 97% of affected patients are HLA-B27 positive, and the gene is more strongly associated with spondylitis than the other seronegative spondyloarthropathies. There is considerable worldwide geographic variation in the prevalence of HLA-B27 in the general population, and this has an impact on the occurrence of the disease. In Australia, about 8% of the population is HLA-B27 positive and the prevalence of ankylosing spondylitis is approximately 1%.

Ankylosing spondylitis was once regarded as a rare disease in women, but it is now recognised that the ratio of affected men to women is actually about 2.5 to 1. Men are more severely affected than women.

Clinical features

The characteristic feature of ankylosing spondylitis is an inflammatory arthritis of the axial skeleton. It usually commences in late adolescence and early adult life; onset beyond the age of 45 years is very rare. Patients generally present with:

- spondylitis (inflammatory spinal pain) – see the Table
- sacroiliitis, which manifests as pain and stiffness in the buttock, sometimes radiating into the thigh.

Spondylitis progresses towards ankylosis, with ossification of spinal ligaments as well as those of the chest wall and costovertebral joints (Figure). With time, this leads to abnormal posture and functional impairment. Spinal osteoporosis is a characteristic feature, and arthritis of the hip and shoulder occur in some patients.

An inflammatory arthritis of peripheral joints occurs in up to 20% of patients. This is usually oligoarticular and asymmetrical, with the lower limbs being predominantly affected. Dactylitis is a common form of peripheral arthritis where an entire digit is swollen, resembling a sausage. Enthesitis, which is a painful inflammation at the sites of bony insertion of ligaments and tendons (e.g. plantar fasciitis), is a characteristic feature.

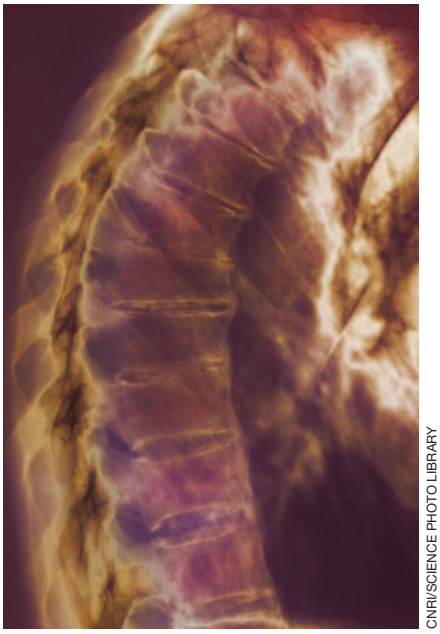

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Figure. X-ray showing spinal ankylosis and the complication of a wedge compression fracture due to osteoporosis.

Extra-articular manifestations can occur. The most common is acute anterior uveitis, which is experienced by up to 40% of patients at some point. Cardiac involvement with aortitis and conduction defects occur less often.

Assessment

A careful history and examination provide the cornerstones of clinical diagnosis and assessment in patients with ankylosing spondylitis. Certain diagnosis relies on demonstration of sacroiliitis on plain radiographs but this may take up to five years to become apparent; CT and MRI provide opportunities to detect it earlier. In more longstanding cases, plain radiographs provide firm diagnostic evidence of the extent and consequence of disease in the spine and peripheral joints.

Erythocyte sedimentation rate (ESR) and levels of acute phase reactants such as C-reactive protein are elevated in the majority of patients at some stage in their disease, but these do not correlate clearly with clinical activity and therefore their

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role in assessment and management is limited. Their clinical usefulness is greater in patients who have peripheral synovitis. Assessment of clinical activity of ankylosing spondylitis relies on application of disease-specific validated indices such as BASDAI[1] and BASFI,[2] self-administered questionnaires that provide a measure of disease activity and patient function, respectively. Measures such as these have greatest use in the clinical monitoring of patients with ankylosing spondylitis.

Prognostic features

The presence of three of the following factors within two years of disease onset has been shown to be predictive of more severe disease:

- ESR greater than 30 mm/hour
- disease that is unresponsive to NSAIDs
- limitation of spinal movement
- dactylitis
- oligoarthritis
- early onset (prior to 16 years of age).

Hip involvement is also known to be indicative of a poorer prognosis.

Management

Physical therapy

Physical therapy is an essential part of management for all patients with ankylosing spondylitis. The main aims are:

- to improve and maintain mobility, slowing progression to ankylosis
- to lessen pain and stiffness
- to maintain posture.

Daily floor-based stretching exercise programs, hydrotherapy and sporting activities are all employed. Patient education about the nature of the disease and the physical management principles is essential – especially at the onset of disease. Group exercise and hydrotherapy classes run by physiotherapists are often employed with good results. Patient motivation and encouragement are key factors in the success of physical therapy.

NSAIDs

NSAIDs provide first line drug treatment for ankylosing spondylitis. They usually have a rapid and significant effect on symptoms, reducing pain and stiffness and also improving function. In combination with physical therapy, NSAIDs help to maintain normal mobility and slow the progression to ankylosis.

DMARDs

DMARDs (disease modifying antirheumatic drugs) are second line treatments prescribed with the intention of reducing signs or symptoms, improving physical function, and preventing or significantly reducing the rate of progression of structural damage. Often, out of a sense of desperation and a desire to help more severely affected patients, traditional DMARDs that are efficacious in rheumatoid arthritis have been used to treat ankylosing spondylitis.

Sulfasalazine

Sulfasalazine (Pyralin EN, Salazopyrin) is the most widely used second line agent. In large placebo-controlled trials for ankylosing spondylitis it has been shown to be of no benefit in spondylitis, but it has a positive effect on peripheral synovitis.

Methotrexate

A recent small study has suggested short term efficacy of methotrexate (Ledertrexate, Methoblastin) in ankylosing spondylitis.[3] Further studies involving larger numbers of patients and of longer duration are required.

Glucocorticoids

Glucocorticoids are often used in treating ankylosing spondylitis. Intra-articular or entheseal injections have short term benefits. Although technically difficult, injections given under sacroiliac joint imaging are of value. Oral glucocorticoids can have a short term effect on spondylitis and are sometimes used in low dose, longer term therapy for patients with peripheral arthritis. Caution must be used with longer term therapy or higher doses because of steroid related side effects and the underlying association with osteoporosis.

Table. Characteristics of inflammatory spinal pain

Insidious onset before the age of 40 years
Duration longer than three months
Association with morning stiffness
Improvement in symptoms with physical activity or exercise
Symptomatic response to NSAIDs

What are seronegative spondyloarthropathies?

The seronegative spondyloarthropathies comprise a family of interrelated arthropathies that affect the spine, peripheral joints and periarticular structures and can be associated with characteristic extra-articular features (see box below). Members of this family are:

- ankylosing spondylitis
- psoriatic arthritis
- enteropathic arthritis (i.e. associated with Crohn's disease and ulcerative colitis)
- reactive arthritis
- undifferentiated spondyloarthropathy.

Clinical features common to the seronegative spondyloarthropathies

Features of arthritis

Spondylitis characterised by sacroiliitis

Absence of rheumatoid factor

Association with the HLA-B27 gene

Characteristic peripheral arthritis (asymmetrical, predominant lower limb involvement, distal, dactylitis)

Enthesitis

Associated features

Psoriasiform skin and nail lesions

Anterior uveitis

Chronic gastrointestinal inflammation

Chronic genitourinary inflammation

Pamidronate

Pamidronate (Aredia, Pamisol), a bisphosphonate administered as an intravenous infusion, has been shown to result in a suppression of inflammation and improvement in disease activity and function in patients who have refractory ankylosing spondylitis. It needs to be administered monthly for three to six months.

Antitumour necrosis factor α agents

Tumour necrosis factor α (TNFα) is an important cytokine mediating inflammation and disease regulation in ankylosing spondylitis. Development of biological blocking therapies is providing exciting new therapeutic options for patients with severe ankylosing spondylitis. There is now considerable experience with these agents in rheumatoid arthritis, and it is hoped that long term studies will show that anti-TNFα agents will be the first interventions to demonstrate a sustained modification of ankylosing spondylitis and prevention of structural damage.

There are two anti-TNFα agents indicated for ankylosing spondylitis and available on the PBS:

- infliximab (Remicade)
- etanercept (Enbrel), which is PBS-listed for this disease from 1 December.

Both of these drugs can be prescribed by consultant rheumatologists (authority required) for patients with active ankylosing spondylitis unresponsive to NSAIDs and exercise. The immediate concerns with therapy are infections, including tuberculosis due to TNFα suppression. Prior to commencing anti-TNFα therapy, all patients need to be screened for latent and active tuberculosis.

Infliximab

Infliximab has been shown in clinical trials to result in significant improvements in disease activity and function in patients with ankylosing spondylitis – about 50% of those with severe and refractory disease showed a 50% improvement in measures for disease activity and 21% of patients entered partial remission.[4,5] These trials have been extended to 48 weeks with sustained benefit.

Infliximab is administered by intravenous infusion at 0, 2 and 6 weeks and thereafter six-weekly. Patients who meet the initial criteria for PBS subsidised therapy are reassessed at six weeks and thereafter six monthly. Infliximab is continued if the required improvement in disease activity can be demonstrated.

Etanercept

Etanercept has also been shown in a large placebo-controlled clinical trial of 277 patients with active ankylosing spondylitis to produce significant benefits in all measures of disease activity.[6] Treatment with 25 mg subcutaneously twice weekly

resulted in 22% of patients achieving 50% improvement after six months of treatment.

Summary

Our understanding of ankylosing spondylitis has improved in recent years. Many patients can be managed adequately with physical therapy, with or without NSAIDs. For those with active disease despite NSAIDs and physical therapy, the TNFα biological blocking therapies offer new options. We are entering a new era in the management of this ancient disease. MT

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DECLARATION OF INTEREST: Dr Taylor is a member of an advisory board for Schering Plough and has worked in an advisory capacity for Wyeth, receiving financial support for travel and research activities from both companies.