Ankylosing spondylitis: diagnosis and management


Abstract
This article provides an overview of ankylosing spondylitis, including signs and symptoms, diagnosis and management. The article focuses on the difficulties and delays associated with diagnosing this chronic inflammatory disease and developments in diagnostic criteria. Changes in the management of patients with the disease are also discussed, particularly in light of anti-tumour necrosis factor therapy.

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Introduction
Ankylosing spondylitis is a chronic inflammatory disease primarily affecting the spine and sacroiliac joints. It is the most common of a group of diseases known as spondyloarthritides, which are rheumatic diseases with common clinical symptoms. The disease is estimated to affect up to 1% of the general population (Baraliakos et al 2011). However, prevalence varies depending on race, with 0.04-0.06% of non-Caucasians affected by the disease compared with 0.1-1.4% of Caucasians (Boonen and van der Heijde 2004). Variation in prevalence is thought to occur because of the presence of the human leucocyte antigen (HLA)-B27 gene within different populations. HLA-B27 is a protein on the surface of white blood cells. The effect of the gene is unclear (Bowness 2002), but over 90% of people with ankylosing spondylitis have the...
HLA-B27 gene, although only one in 15 people who carry it will develop the disease (Miceli-Richard and Dougados 2004). This suggests that environmental factors such as stress might also influence the development of the disease.

Ankylosing spondylitis is more common in men than in women, although the reason for this is unknown. However, estimates vary: Gladman (2003) reported a 9:1 male to female ratio of the disease, Rudwaleit et al (2004) stated that it affects twice as many men as women, and McKenna (2010) suggested a 5:1 male to female ratio of ankylosing spondylitis.

The onset of ankylosing spondylitis is typically between 30 and 50 years, although it can occur earlier (Gossec and Dougados 2004). Like all inflammatory diseases, there are periods of flare and dormancy that make it difficult to distinguish inflammatory back pain from mechanical back pain (Table 1). As a result, there may be a delay in diagnosis of up to ten years (Khan 2003).

Ankylosing spondylitis causes pain and stiffness in the back, eventually resulting in joint damage and fusion predominantly of the sacroiliac joints, and ankylosing of the vertebrae leading to a classic bamboo spine (Figure 1), although this does not always occur. It can affect the rest of the axial skeleton (shoulders and hips), leading to reduced range of motion and pain. Some individuals develop joint destruction and may require total joint replacement. This can occur at a much earlier age than usual in individuals with ankylosing spondylitis. The disease can also cause peripheral symptoms affecting the knees, hands and feet, which can appear similar to rheumatoid arthritis, with patients experiencing pain and swelling. This can lead to misdiagnoses, thereby delaying appropriate treatment (Khan 2003).

There are several extra-articular (non-skeletal) features that may be associated with ankylosing spondylitis, for example acute anterior uveitis affects between 25% and 40% of people with ankylosing spondylitis (Gossec and Dougados 2004). Acute anterior uveitis or iritis, characterised by inflammation of the iris, may be the first indication that a person has ankylosing spondylitis. This condition needs to be treated as an emergency to prevent long-term problems such as glaucoma or reduced vision (Khan 2003). Cardiovascular manifestations such as valve disorders and aortic incompetence may be more common in those who are HLA-B27 positive and can worsen with age (Bakland et al 2011).

Ankylosing spondylitis can have a significant effect on patients’ lives, affecting work, family and social activities, and increasing the risk of depression (National Ankylosing Spondylitis Society (NASS) 2010a). Therefore, early disease management is essential to prevent damage and disability. In a survey of people with ankylosing spondylitis, 72% of respondents were in employment, however only 38% of these individuals received advice or help on coping with symptoms of the condition while at work (NASS 2010b). Pain, fatigue and physical limitations were identified as the main factors affecting a person’s ability to work.

Symptoms

There are a variety of symptoms of ankylosing spondylitis, and these include:

<table>
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<th>TABLE 1</th>
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<tr>
<td><strong>Comparison of inflammatory and mechanical back pain</strong></td>
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<tr>
<td><strong>Inflammatory back pain</strong></td>
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<tr>
<td>Onset in those under 40 years.</td>
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<tr>
<td>Insidious onset.</td>
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<tr>
<td>Symptoms improve with exercise.</td>
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<tr>
<td>No improvement in symptoms with rest.</td>
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<tr>
<td>Pain at night, with improvement on getting up.</td>
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(Adapted from Sieper et al 2009a, Harris et al 2012)
Early morning stiffness – can take from a few minutes to many hours to ease, and it can take up to two or more hours for a person to get going in the morning. Sitting down for any length of time can cause the spine to stiffen up again (Khan 2003).

Pain – tends to develop gradually over weeks or months rather than days, and occurs mainly in the spine. Pain is worse at rest and is eased by exercise (Sieper et al 2009a).

Enthesitis – is pain and swelling where ligaments and tendons attach to bone. A common site is the heel and pain on walking can be significant, particularly in the morning when the heel has been rested overnight (Gossec and Dougados 2004).

Fatigue – constant exhaustion not relieved by sleep (Mengshoel 2010).

Feverishness or night sweats – are commonly reported symptoms in people with ankylosing spondylitis. However, these symptoms are also associated with other inflammatory and autoimmune disorders and there is a lack of evidence about the cause of feverishness or night sweats (Mold et al 2012).

Shortness of breath – as the disease progresses it can cause fusion of the thoracic vertebrae and also the attached ribs, limiting expansion of the chest. If the spine becomes fully ankylosed it can lead to a stoop, which will also limit chest expansion (Khan 2003).

Flares – individuals can go through periods where ankylosing spondylitis is dormant and then flares up. Cooksey et al (2009) suggested that 70% of people with the disease experience flares in any one week.

Complete time out activity

In individuals where ankylosing spondylitis starts at a young age, there may be increased comorbidities such as cardiovascular disease, amyloidosis and infection, and complications of a fused spine such as spinal fractures, resulting in increased mortality (Bakland et al 2011). According to Peters et al (2010), the risk of myocardial infarction is almost four times higher in people with the disease compared with the general population – this is similar to other inflammatory disorders. It is, therefore, important that people with the disease are monitored carefully and that developing comorbidities such as hypertension or hypercholesterolaemia are managed appropriately.

Diagnosis

A better understanding of ankylosing spondylitis and developments in diagnostic techniques have led to changes in the diagnostic criteria for the disease. Initially, ankylosing spondylitis was thought to be a variation of rheumatoid arthritis, however it was not until the advent of diagnostic tests such as that for the HLA-B27 gene that ankylosing spondylitis was recognised as being different from rheumatoid arthritis. The modified New York criteria can be used to diagnose ankylosing spondylitis (van der Linden et al 1984) (Box 1).

One of the difficulties associated with using the modified New York criteria is that it can take up to five years before there is radiological evidence of sacroiliitis, by which time there might be significant joint destruction. Use of more advanced imaging technology such as magnetic resonance imaging reduces the time to diagnosis, with images showing inflammatory changes years before bony damage occurs. In 2009, the Assessment of SpondyloArthritis International Society (ASAS) published a consensus statement on the classification of axial spondyloarthritis (Rudwaleit et al 2009) (Figure 2).

Assessment

There is an internationally recognised set of outcome measures for use with patients who have ankylosing spondylitis known as the Bath indices. These were designed to provide comprehensive information relating to an individual’s disease and the effect on his or her life and health (Irons and Jeffries 2004). The indices were devised in the 1990s and include (Irons and Jeffries 2004):

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**BOX 1**

**Modified New York criteria for diagnosis of ankylosing spondylitis**

Clinical criteria:
- Low back pain for more than three months, which is improved by exercise and not relieved by rest.
- Limitation of lumbar spine motion in both the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values for age and sex.

Radiological criterion:
- Sacroiliitis grade 2 or above. Grade 2 is bilateral sacroiliitis, grade 3-4 can be unilateral or bilateral depending on the degree of fusion.

Diagnosis:
- Definite ankylosing spondylitis if radiological criterion is present, including at least one clinical criterion.
- Probable ankylosing spondylitis if three clinical criteria are present, or if the radiological criterion is present, but there are no clinical signs of disease.

(van der Linden et al 1984)
Bath ankylosing spondylitis disease activity index (BASDAI).
Bath ankylosing spondylitis functional index (BASFI).
Bath ankylosing spondylitis global score (BAS-G).
Bath ankylosing spondylitis metrology index (BASMI).

The Bath indices are patient-reported outcome measures and use visual analogue scales (VASs). These scales are designed to gauge an individual’s level of agreement with a statement. Scores range from 0-10, with 0 being good and 10 being bad. The use of VASs has limitations in that patients’ experiences, perceptions and life issues can affect how they perceive their disease and scores can be influenced by other events that may act as additional stressors. It is, therefore, possible that the patient’s physical, objective score, such as inflammatory markers and metrology, indicate improvement, while subjective measures, such as pain, may worsen (Kievit et al 2010). The Bath indices, in particular the BASDAI, are used as part of the screening process to assess the patient’s suitability for anti-tumour necrosis factor (TNF) therapy (Irons and Jeffries 2004).

Complete time out activity

Alternatives to the Bath indices have been suggested, such as the ankylosing spondylitis disease activity score (ASDAS) (Gossec and Dougados 2004). This scoring system attempts to make assessment a more objective process, with the use of inflammatory markers such as C-reactive protein or erythrocyte sedimentation rate. However, it is important to note that as many as 50% of individuals with ankylosing spondylitis will not have raised inflammatory markers, thereby reducing the reliability of the ASDAS (Gossec and Dougados 2004).

 Treatment
For many patients, ankylosing spondylitis remains a mild disease that has minimal effects on their activities of daily living and can be self-managed.

Non-pharmacological interventions

Exercise Daily exercise might be helpful in the treatment of ankylosing spondylitis, and should include stretching and strengthening activities. Daghrud et al (2008) found sufficient evidence to support the conclusion that any form of exercise is better than no exercise in the management of ankylosing spondylitis, and that supervised group therapy is preferable to group physiotherapy alone.

Patients can access NHS run courses that include education on various topics, including exercise, treatments and self-management of ankylosing spondylitis. These courses are available on an inpatient or outpatient basis and some run on a one-day-a-week basis, while

FIGURE 2
Assessment in SpondyloArthritis International Society classification criteria for axial spondyloarthritis (in patients with chronic back pain and age at onset under 45 years)

<table>
<thead>
<tr>
<th>Sacroilitis on imaging plus one or more axial spondyloarthritis feature or Positive test for HLA-B27 gene plus two or more other axial spondyloarthritis features</th>
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<tbody>
<tr>
<td>Sacroilitis on imaging:</td>
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<tr>
<td>Active (acute) inflammation on magnetic resonance imaging highly suggestive of sacroilitis associated with axial spondyloarthritis.</td>
</tr>
<tr>
<td>Or:</td>
</tr>
<tr>
<td>Definite radiographic sacroilitis according to the modified New York criteria.</td>
</tr>
<tr>
<td>Axial spondyloarthritis features:</td>
</tr>
<tr>
<td>Inflammatory back pain.</td>
</tr>
<tr>
<td>Arthritis.</td>
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<tr>
<td>Enthesitis (heel).</td>
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<tr>
<td>Uveitis.</td>
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<tr>
<td>Dactylitis.</td>
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<tr>
<td>Psoriasis.</td>
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<tr>
<td>Crohn’s disease or diagnosis of colitis.</td>
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<tr>
<td>Good response to non-steroidal anti-inflammatory drugs.</td>
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<tr>
<td>Family history of axial spondyloarthritis.</td>
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<tr>
<td>Positive test for HLA-B27 gene.</td>
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<tr>
<td>Elevated C-reactive protein levels.</td>
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</tbody>
</table>

(Adapted from Rudwaleit et al 2009, Sieper et al 2009b)
others are an intensive two-week programme. **Education** An understanding of ankylosing spondylitis and the various aspects of management is one of the most important aspects of treatment. Patients who are engaged with and participate in the management of their disease are more likely to have better outcomes than those who do not actively participate in disease management (NASS 2012). Individuals’ understanding of the disease and learning will vary, therefore education should be tailored to the individual. However, there is some basic information that all patients will need to be given about the disease, including signs and symptoms, short and long-term effects, treatment options, and general health issues such as smoking reduction and cessation, weight management and limiting alcohol intake. Individuals should also be provided with information that they can give to employers, schools and family members (NASS 2010a).

**Symptom control**

If possible, management of ankylosing spondylitis should involve the multidisciplinary team. For many patients, pain, physical limitations and fatigue are the main symptoms that need to be addressed (Heiberg et al 2011). Pain and physical limitations are managed most effectively through a combination of medication and exercise (NASS 2010a). Physical limitations might also be addressed with physiotherapy, occupational therapy and medication.

Fatigue, although significant, is frequently ignored by healthcare professionals (Davies et al 2013, Hammoudeh et al 2013). Physical, mental and activity-related fatigue, and loss of motivation may be common in people with ankylosing spondylitis (Missaoui and Revel 2006). Fatigue can also be associated with the disease, drug treatment or other conditions such as depression. It is not unique to ankylosing spondylitis and is common in other inflammatory disorders such as rheumatoid arthritis (Husted et al 2009, National Rheumatoid Arthritis Society 2010).

There appears to be a link between fatigue and factors such as pain, sleep and activity. If sleep patterns can be improved, pain and fatigue will also be improved (Mengshoel 2010). Mengshoel (2010) distinguished between tiredness associated with daily life such as work and sport, and fatigue associated with illness. She described fatigue as an unnatural whole body tiredness that leads to feelings of exhaustion, helplessness and pain.

Pain at night is significant because it leads to disturbed sleep. Lack of sleep affects function and the individual’s ability to cope with fatigue (Farren et al 2013). Hammoudeh et al (2013) stated that pain at night occurs in 62–63% of people with ankylosing spondylitis and Mengshoel (2010) suggested that fatigue levels increase about 24 hours after pain peaks. Advice for patients should be centred on managing factors that worsen fatigue as shown in Box 2.

There is some debate as to whether medications lessen fatigue, particularly in relation to the use of non-steroidal anti-inflammatory drugs (NSAIDs) (Dernis-Labous et al 2003). There is no definitive answer to this and pharmacological management of patients’ fatigue appears to depend on individual response. There have been more encouraging reports of fatigue reduction with anti-TNF therapies, with

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**BOX 2**

**Advice for patients on managing factors that worsen fatigue**

**Good sleep hygiene:**
- Avoid stimulants before bed.
- Ensure hot baths are taken at least one hour or more before bed to allow body temperature to drop.
- Ensure the bedroom is not too hot and bedclothes are not too heavy. A good supportive mattress may also be helpful to ensure comfort.

**Diet and fluids:**
- Consume a healthy and balanced diet and remain hydrated with non-alcoholic fluids.

**Exercise:**
- Ensure exercise is regular, varied and manageable, including exercises designed to improve muscle strength, spinal flexibility and stability.

**Pacing:**
- Understand and apply pacing to break activities into small more manageable parts.
- Plan ahead. If an individual knows he or she has a busy day, the advice would be to take it easy before and afterwards.
- Identify activity patterns through the use of diaries and activity records. This can help to pace and plan activity.

**Pain management:**
- Use non-pharmacological interventions, such as exercise.
- Use pharmacological interventions, such as non-steroidal anti-inflammatory drugs and anti-tumour necrosis factor therapy.

(National Rheumatoid Arthritis Society 2010)
Ongoing use of NSAIDs can result in a number of inflammatory conditions, however they seem to have little or no effect on patients with axial ankylosing spondylitis (Zochling et al 2006). Methotrexate or sulfasalazine may be used in the treatment of patients with peripheral problems such as pain and swelling of the joints of the hands and feet (Zochling et al 2006).

**Biologic disease-modifying anti-rheumatic drugs**  The development of biologic therapies such as anti-TNF drugs has resulted in advances in the treatment of ankylosing spondylitis and the limitation of disease progression potentially leading to reduced disease activity. Evidence suggests that anti-TNFs are the most effective of the biologics in treating ankylosing spondylitis (Zochling et al 2006).

Before an individual can be considered for anti-TNF therapy, active disease as defined by NICE (2008) must be established. This includes a diagnosis of ankylosing spondylitis using the modified New York criteria, previous NSAID use, and appropriate BASDAI and pain scores of 4 or above on the VAS. The BASDAI and pain scores have to be repeated three months apart in line with NICE requirements.

The patient should undergo a thorough assessment to identify actual and potential risk factors before treatment. The Royal College of Nursing (RCN) (2009) provides useful information on assessing, managing and monitoring biologic therapies for inflammatory arthritis. Relevant investigations such as chest X-ray also need to be completed.

**Complete time out activity**

Several biologic therapies are used in rheumatology, including anti-TNF agents, B cell depleters, interleukin-6 inhibitors and T cell modulators. However, only anti-TNF therapy appears to have an effect in the management of ankylosing spondylitis (Singh et al 2011). The main anti-TNF therapies are adalimumab, etanercept, golimumab and infliximab. Certolizumab pegol is also awaiting licensing for this indication. These therapies are grouped according to their mode of action, which is to block the action of a protein or eliminate a cell. In this case, the purpose of these therapies is to block the action of TFN proteins. Soluble receptors (cepts) compete with TNF-receptors to reduce the amount of TNF attaching to cell receptors (Abbas and Lichtman 2006).

**Complete time out activity**

**Pharmacological interventions**  For the majority of patients, symptoms of ankylosing spondylitis will be managed using a variety of treatment options. At all times, the prescriber needs to be aware of the risk and benefit of particular drugs, as well as any other comorbidities the individual may have. This is especially important in people who have long-term health conditions that may require lifelong use of medications. This article focuses on the use of pharmacological treatments aimed at controlling disease activity; however, many patients will require other treatments such as analgesics, antidepressants, hypnotics and antispasmodics.

**Non-steroidal anti-inflammatory drugs**  NSAIDs can be effective in reducing the pain and inflammation associated with ankylosing spondylitis and rheumatoid arthritis (Escalas et al 2010). Poddubnyy et al (2012) and Kroon et al (2012) published evidence suggesting that NSAIDs have a disease-modifying action in ankylosing spondylitis and may limit the development of ankylosis. NSAIDs should be taken on a regular basis if the individual is experiencing prolonged, active and symptomatic disease (Braun et al 2011).

For most patients, the use of NSAIDs such as naproxen or ibuprofen is preferable because they are associated with a low risk of cardiovascular problems (National Institute for Health and Care Excellence (NICE) 2009). It is important to be aware that there are safety risks associated with NSAIDs and they should only be prescribed when the patient’s full medical history is known. These drugs should be avoided where there is a history of cardiovascular, renal or gastric problems. It is recommended that an appropriate proton pump inhibitor is prescribed at the same time as the NSAID especially when, as with ankylosing spondylitis, patients may be receiving treatment for many years (NICE 2009).

With regular use of NSAIDs, effectiveness can diminish and many patients will have tried three or more NSAIDs over the years to maintain a reduction in pain and stiffness (Dougdados et al 2002). NSAIDs in combination with analgesics tend to be more effective than either treatment alone (NICE 2009, Ong et al 2010).

**Disease-modifying anti-rheumatic drugs**  Disease-modifying anti-rheumatic drugs are used regularly in rheumatology to treat a positive responses to etanercept (Hammoudeh et al 2013), golimumab (Deodhar et al 2010) and adalimumab (Revicki et al 2008).
Monitoring

Once on a treatment regimen, patients need to be monitored to ensure the safety and effectiveness of any drugs. They should be advised to have regular blood tests to identify any adverse events that may occur as a result of immunosuppression, such as increased infections (Ding et al 2010). There also needs to be evidence that the treatment has reduced disease activity as identified by NICE (2008). This means that the BASDAI and pain scores have to drop by 2cm or 50% from the original VAS scores before treatment, and this has to be reassessed every three months. If there is any indication of initial non-response or later failure, the scores should be repeated six weeks later, and if there has been no improvement the treatment should be stopped.

Although NICE (2008) does not recommend switching to an alternate anti-TNF drug, there is some evidence to show that individuals might respond to an alternative anti-TNF because the drugs are slightly structurally different from each other (Lie et al 2011, Glintborg et al 2013).

Conclusion

Ankylosing spondylitis can cause severe pain, fatigue and disability, thereby affecting all aspects of an individual’s life. Identifying the disease early is crucial to limit the physical and psychological effects on patients. Involvement of the multidisciplinary team and local support groups can help the individual to maintain a normal life with minimal disruption. It has been shown that regular exercise can reduce pain and maintain mobility. This, combined with appropriate pain management, can reduce the effect of fatigue and the incidence of depression. NSAIDs and analogics are the mainstay of treatment for many people and may limit disease progression. However, for those with more advanced or debilitating disease, newer biologics have been developed and are associated with reduced pain and disability.

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