

Ankylosing spondylitis

Not just another pain in the back

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ABSTRACT

OBJECTIVE To review recent developments in diagnosis and treatment of ankylosing spondylitis (AS).

QUALITY OF EVIDENCE Level I evidence from three randomized placebo-controlled trials shows that AS is highly responsive to anti-tumour necrosis factor- α (anti-TNF α) therapies when the standard approach of nonsteroidal anti-inflammatory drugs (NSAIDs) and physical modalities fails.

MAIN MESSAGE Ankylosing spondylitis is associated with disability comparable to that of rheumatoid arthritis. Diagnosis should first focus on eliciting a history of nocturnal back pain, diurnal variation in symptoms with prolonged morning stiffness, and a good response to NSAID therapy. Physical examination is often unrevealing. Pelvic x-ray results are often normal in early disease. Magnetic resonance imaging is the most sensitive imaging technique for detecting early inflammatory lesions and should be considered when history supports the diagnosis but results of plain radiography are normal. When patients have failed at least two courses of NSAID therapy, anti-TNF α therapies are of proven benefit.

CONCLUSION New magnetic resonance imaging techniques and highly effective therapies make AS more readily detectable and manageable.

RÉSUMÉ

OBJECTIF Recenser les plus récentes données sur le diagnostic et le traitement de la spondylite ankylosante (SA).

QUALITÉ DES PREUVES Des preuves de niveau I tirées de trois essais randomisés avec placebo montrent que la SA répond très bien à un traitement anti-facteur nécrosant des tumeurs (anti-TNF- α) lorsque les anti-inflammatoires non stéroïdiens (AINS) et les thérapies physiques s'avèrent inefficaces.

PRINCIPAL MESSAGE La SA cause une incapacité comparable à celle de l'arthrite rhumatoïde. Le diagnostic repose d'abord sur une histoire de lombalgie nocturne avec des symptômes variables le jour, sur une raideur matinale plus tenace et sur une bonne réponse aux AINS. L'examen physique contribue rarement au diagnostic. La radiographie pelvienne est souvent normale au début. L'imagerie par résonance magnétique est l'examen le plus sensible pour déceler les lésions inflammatoires précoces et on doit penser à cette technique quand l'histoire suggère une SA mais que la radiographie simple est normale. Après l'échec de deux traitements aux AINS, l'administration d'anti-TNF- α peut être bénéfique.

CONCLUSION Grâce aux nouvelles techniques d'imagerie par résonance magnétique et à des traitements très efficaces, la SA est maintenant plus facile à détecter et à traiter.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

Can Fam Physician 2004;50:257-262.

A 33-year-old man presents with a 12-year history of low back pain that was diagnosed as ankylosing spondylitis by his primary care physician 4 years ago and initially treated with indomethacin and physical modalities. He is told “there is not much that we can do for this disease other than anti-inflammatories and physiotherapy, but not to worry, as this is not a serious arthritis.”

Currently he has ongoing low back pain, morning stiffness lasting 2 hours, joint pain in the right knee and right hip despite indomethacin (150 mg daily), and difficulty turning his head to shoulder check while driving. Examination reveals a flexed spinal posture (distance of 5 cm between the occiput and wall with the patient standing back and heels against the wall), lateral rotation of the neck restricted to 40°, limited chest expansion at 3 cm, and limited lumbar spinal forward flexion as recorded by a fingertip-to-floor deficit of 24 cm. Peripheral joint examination shows synovitis with moderate effusion in the right knee and restricted internal rotation of the right hip.

The patient described above recently came to my subspecialty practice with this far-from-uncommon clinical presentation. This case raises important challenges, and there are ongoing misconceptions regarding management of ankylosing spondylitis (AS). Several recent surveys have shown that a delay of 8 to 9 years between onset of symptoms and diagnosis is the norm,¹ and many primary care physicians still believe that, although treatment options are limited, this is a mild form of arthritis with limited disability and effect on quality of life that eventually “burns out” after a

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variable period of active disease. The purpose of this review is to:

- discuss new developments in our understanding of this disease;
- describe a diagnostic framework based on simple clinical observations and new developments in diagnostic imaging; and
- inform primary care physicians about remarkable new developments in therapy for this disease.

Sources of evidence

A systematic review of the literature using a MEDLINE search and the key words ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, infliximab, etanercept, and tumor necrosis factor- α sought articles on therapeutic developments. Studies graded as providing level I evidence according to the Agency for Health Care Policy and Research (evidence based on at least one randomized controlled trial) were chosen.

Studies describing the burden of disease have been selected based on their application of newly developed diagnostic criteria encompassing a broader spectrum of disease. Studies cited in support of this diagnostic approach describe new developments in magnetic resonance imaging (MRI) of the spine and sacroiliac joints.

Main message

Epidemiology and burden of disease. Early studies of disease prevalence were largely based on hospitalized populations and reported a disease prevalence of only 0.2%.² Classification criteria used to ascertain cases relied on finding sacroiliitis through plain radiography.³ More recent classification criteria recognize the fact that AS is the prototypic disorder of a group of related arthritides collectively termed spondyloarthritis (Table 1).⁴ Primary hallmarks of this group of arthritides are presence of the HLA B27 gene marker, sacroiliitis, and inflammation at entheses (sites where ligaments or tendons attach to bone, such as the Achilles insertion into the calcaneum). The European Spondyloarthropathy Study

Table 1. Types of spondyloarthritis

Ankylosing spondylitis
Psoriatic arthritis
Undifferentiated spondyloarthritis
Juvenile spondyloarthritis
Colitic spondyloarthritis
Reactive spondyloarthritis

Group (ESSG) classification criteria acknowledge the potentially diverse presentations of disease as well as the fact that radiographic manifestations of sacroiliitis might not be evident for several years in patients who present with other symptoms typical of sacroiliitis.⁵ A recent epidemiologic study showed that applying ESSG criteria for evaluation of disease prevalence resulted in an overall prevalence of 1.9% for spondyloarthritis and 0.9% for AS.⁶ These rates resemble estimates of the prevalence of rheumatoid arthritis (RA). A recent survey showed that approximately 5% of patients presenting to their primary care physicians with low back pain have this disease.⁷

Diagnosis. Average delay between onset of symptoms and diagnosis is about 8 to 9 years¹ and reflects infrequent consideration of this disease in the differential diagnosis of patients presenting with low back pain, inability to ascertain key facets of the history indicative of axial inflammation, lack of physical findings early in the disease course, lack of diagnostic markers with sufficient sensitivity and specificity, and overreliance on plain radiographic analysis for detection of sacroiliitis.

History: Nocturnal pain and diurnal variation of symptoms with prominent symptoms in the morning (especially stiffness lasting longer than 30 minutes) are among the two most important historical features.⁸ Response to a trial of nonsteroidal anti-inflammatory drug (NSAID) therapy can also be diagnostically useful. A beneficial clinical response was seen in 77% of patients within 48 hours compared with 15% of patients with other causes of back pain in one study while the absence of such response has been shown to have a negative predictive value of 97% for AS.⁹ Patients reporting no response to the maximum recommended dose of

an NSAID (eg, 500 mg of naproxen twice daily) are, therefore, unlikely to have AS.

Peripheral arthritis affects few patients (<20%) and typically affects the large joints of the lower limbs in an asymmetrical pattern. Acute anterior uveitis, psoriasis, or inflammatory bowel disease can precede onset of AS, and family history sometimes turns up disorders.

Physical examination: There is often little to find on examination in the first years of disease. A variety of so-called pelvic stress tests purported to indicate sacroiliitis are described in physical examination texts. Prospective systematic evaluation showed that such tests are of little value in diagnosing sacroiliitis and are more likely to identify mechanical back pain.¹⁰ Sacroiliitis alone does not impair spinal mobility, and normal spinal mobility by no means excludes a diagnosis of AS.

Laboratory examination: Acute-phase reactants, the erythrocyte sedimentation rate and C-reactive protein, are often used as “screening tools” for inflammatory joint diseases. Results are, however, abnormal in only 40% of AS patients and therefore lack sensitivity as well as specificity. Rheumatoid factor is negative and need not be tested.

The HLA B27 test is often ordered as part of a “connective tissue disease screen” for patients presenting with joint pain. This should be strongly discouraged, as it often leads to a high rate of false positives because HLA B27 occurs in about 10% of white populations.

Diagnostic imaging: Reports of symptoms should prompt a plain pelvic x-ray examination to look for sacroiliitis, despite the fact that several years might pass before unequivocal radiographic features of sacroiliitis are apparent.⁵ Findings can also be difficult to interpret, particularly in young patients where the epiphyses do not close until the late teens.

Results of isotope bone imaging of the sacroiliac joints often become positive earlier than results of x-ray examinations, but the test lacks specificity and sometimes shows positive findings when degenerative changes affect the upper two thirds of the joint. Computed tomography is highly specific in demonstrating joint erosions and sclerosis of the sacroiliac joints but lacks sensitivity in early disease.

A recent advance has been use of fat-suppression sequences in MRI technology, which allows detection of edema associated with inflammation within subchondral bone marrow, often obscured by marrow fat in conventional MRI. Studies of this imaging technology indicate that at least three lesions are evident in patients with early sacroiliitis; capsulitis, synovitis, and subchondral bone marrow inflammation appears within sacral and iliac portions of the sacroiliac joint¹¹ (Figure 1). Prospective studies over 2 years have indicated that subchondral bone marrow inflammation has almost 100% sensitivity for subsequent development of plain radiographic sacroiliitis, although specificity still requires further evaluation in longer follow-up studies.

Figure 1. Fat-suppressed magnetic resonance image showing coronal view through sacroiliac joints. Thick arrows point to subchondral marrow inflammation shown by increased MRI signal. Thin arrow points to joint cavity.



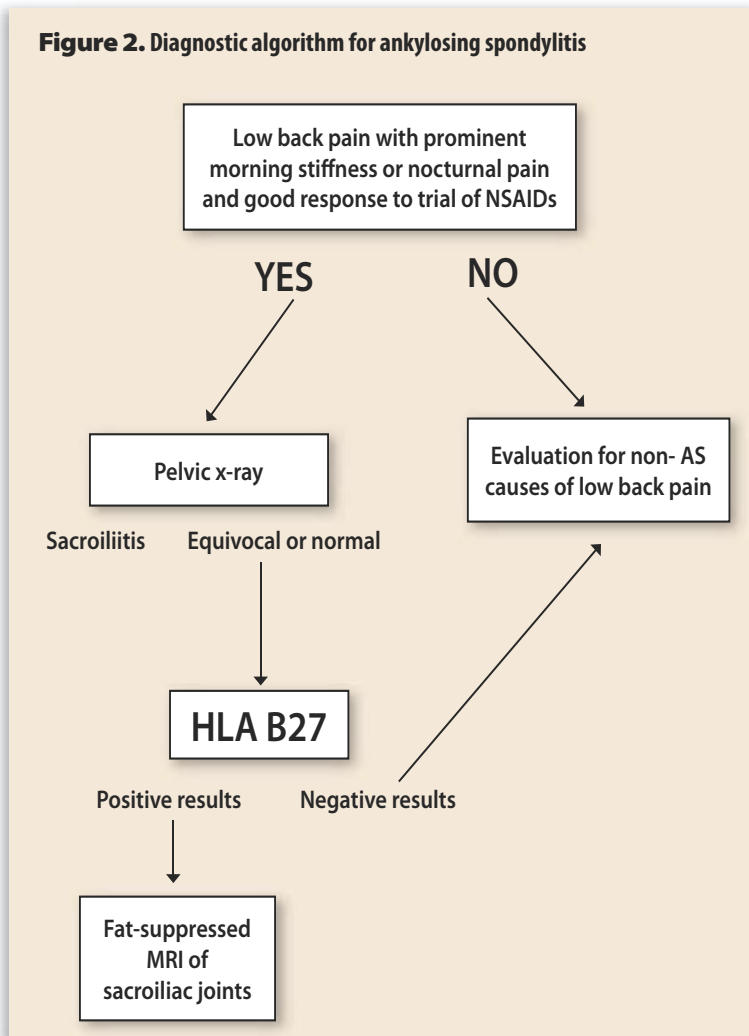
When is an MRI indicated? It is particularly useful for evaluating patients with a positive history for AS who are HLA B27–positive but have normal results from plain x-ray of the sacroiliac joint and have a questionable response to NSAIDs (Figure 2). It could also help in established AS when deciding whether back pain unresponsive to NSAIDs truly reflects inflammation resistant to therapy or a non-inflammatory source of back pain.

Course and prognosis. Cross-sectional data comparing age- and sex-matched patients with AS and with RA in German rheumatic disease centres shows that patients with AS have functional

impairment comparable to that among patients with RA.¹² This likely reflects the earlier onset of disease in patients with AS. These data also show that disease does not “burn out,” as is widely perceived, but continues to cause symptoms into the later decades of life. Approximately 20% of AS patients become unable to work.¹³ No prospective data allow identification of clinical or laboratory features that might predict a poor prognosis.

Management. As for many other chronic diseases, education influences function and prevents work disability. Many rheumatic disease units in Canada have organized educational programs to assist patients in understanding the disease and its management. The Canadian Arthritis Society also has comprehensive web resources (www.arthritis.ca) and access to other educational materials, such as videos, that facilitate home physiotherapy and introduce patients to the complex biologic therapies used for AS (eg, *Attack from Within* video, Access TV Network, www.accesstv.ca/distribution.shtml). Because AS management ideally requires a team approach, referral to a rheumatologist is recommended.

For the past 30 years, the mainstay of therapy has been use of a variety of NSAIDs and physical modalities to maintain spinal mobility and good posture. Most NSAIDs are effective with the exception of acetylsalicylic acid and its derivatives. This includes the cyclooxygenase-2 inhibitor–selective anti-inflammatory agents. Examination of individual patient responses in one recent trial comparing celecoxib, ketoprofen, and placebo showed, however, that only 40% to 50% of patients experienced at least a 50% reduction in pain scores using visual analogue scales (level I).¹⁴ Adverse events associated with these agents are a concern, particularly in the context of a requirement for long-term administration over several decades. Such treatment appears largely to relieve symptoms only and has not yet been shown to prevent structural damage. Intra-articular steroids are effective for noninfective peripheral joint inflammation, regardless of the precise etiology.

Figure 2. Diagnostic algorithm for ankylosing spondylitis

A variety of second-line agents commonly used to treat RA have also been employed to manage AS. However, placebo-controlled studies evaluating these therapies have been confined to sulfasalazine. Nine placebo-controlled trials have assessed sulfasalazine in treatment of AS.¹⁵ Most of these trials used different outcome parameters, and few assessed functional outcomes. Further, conclusions have been largely based on analyses of patients who completed the trials (ie, completors) rather than of those who received at least one dose of study drug (ie, intention-to-treat analyses). Two large, well conducted, multicentre clinical trials have shown that sulfasalazine is not efficacious for most AS patients other than the few who have concomitant peripheral arthritis (level I).^{16,17}

Two recent placebo-controlled studies evaluated a monoclonal antibody, infliximab, directed against TNF α , a pivotal pro-inflammatory factor detected in inflamed joints (level I).^{18,19} A rapid amelioration of symptoms, usually evident within a couple of weeks, was demonstrable in 80% of patients, together with substantial reductions in erythrocyte sedimentation rate and C-reactive protein as well as MRI parameters of inflammation. Similar results were observed with a second anti-TNF α -directed agent, namely etanercept (level I).²⁰

What remains to be determined is which patients are the most appropriate candidates for therapy and whether this treatment is also capable of preventing structural damage. Although serious adverse events are uncommon and primarily related to development of serious infections, such as tuberculosis and histoplasmosis, treatment is very costly and cost benefit has yet to be determined through long-term observational studies. The Spondyloarthritis Research Consortium of Canada has recently recommended that these therapies be considered for AS patients whose symptoms persist despite maximum recommended doses of at least two NSAIDs.²¹

Case resolution

Evidence supports use of intra-articular steroids or a second-line agent more commonly used to treat RA, sulfasalazine, for peripheral synovitis in this patient with AS. Anti-TNF α -directed therapies should also be considered for this patient, who has active spinal inflammation and progressive ankylosis despite NSAID therapy. Accordingly, he was given intra-articular injections of steroids into the affected hip and knee and was started on gradually increasing doses of sulfasalazine to a maximum of 3g daily. He has also consented to being placed on a list of candidate patients for clinical trials of anti-TNF α -directed therapies in AS.

Conclusion

Ankylosing spondylarthritis is more prevalent in primary care than most family physicians expect. Heightened awareness coupled with the advent of new MRI techniques and highly effective therapies represents a substantial advance in management of AS.

Competing interests

None declared

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EDITOR'S KEY POINTS

- Ankylosing spondylitis is more prevalent than is usually realized in primary care, is comparable to rheumatoid arthritis, and causes substantial disability.
- There is usually a 7- to 9-year delay in diagnosis because physical examination and plain x-ray results are often unrevealing.
- A history of nocturnal back pain, morning stiffness, and a good initial response to nonsteroidal anti-inflammatory drugs are usually reliable diagnostic clues.
- Magnetic resonance imaging has become very useful for diagnosis when history supports ankylosing spondylitis but x-ray results are normal.
- When nonsteroidal anti-inflammatory drugs have failed, new, expensive treatments with anti-tumour necrosis factor- α therapies have been shown to be effective.

POINTS DE REPÈRE DU RÉDACTEUR

- La spondylite ankylosante est plus fréquente que ce qu'on croit habituellement en médecine de première ligne. Elle est comparable à l'arthrite rhumatoïde et cause une importante incapacité.
- Le diagnostic accuse souvent un retard de 7 à 9 ans parce que l'examen physique et la radiographie simple sont fréquemment négatifs.
- Une histoire de lombalgie nocturne et de raideur matinale et une réponse aux anti-inflammatoires non stéroïdiens initialement satisfaisante constituent habituellement des éléments diagnostiques fiables.
- L'imagerie par résonance magnétique est très utile lorsque l'histoire suggère un diagnostic de spondylite ankylosante mais que la radiologie est négative.
- Là où les anti-inflammatoires non stéroïdiens se sont avérés inefficaces, un traitement anti-facteur nécrosant des tumeurs (anti-TNF- α) s'est montré efficace.

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