Evidence-based recommendations for the diagnosis of ankylosing spondylitis: results from the Australian 3E initiative in rheumatology

Tracey Kain, Jane Zochling, Andrew Taylor, Nicholas Manolios, Malcolm D Smith, Mark D Reed, Matthew A Brown and Lionel Schachna

ABSTRACT

- As part of the 3E program, we conducted a systematic literature review and gathered consensus from 23 practising Australian rheumatologists to develop guidelines for early identification of ankylosing spondylitis and specialist referral.
- In three rounds of break-out sessions followed by discussion and voting, the specialist panel addressed three questions related to diagnosis of ankylosing spondylitis:
  - In individuals with back pain, what are the early clinical features that suggest ankylosing spondylitis?
  - How useful is imaging in identifying early ankylosing spondylitis?
  - Based on which clinical features should a general practitioner refer a patient to a rheumatologist for further evaluation?
- The panel agreed on six recommendations related to the three questions:
  - 1a. Early clinical features to suggest ankylosing spondylitis include inflammatory back pain and age at symptom onset < 45 years.
  - 1b. The absence of symptomatic response to an appropriate course of non-steroidal anti-inflammatory drugs makes the diagnosis of ankylosing spondylitis less likely.
  - 1c. Raised inflammatory markers are supportive, but their absence does not rule out the diagnosis of ankylosing spondylitis.
  - 2a. Despite low sensitivity to detect changes of early ankylosing spondylitis, plain radiographs of the pelvis and spine are appropriate initial imaging techniques.
  - 2b. Magnetic resonance imaging is a useful imaging modality for detecting early changes of ankylosing spondylitis.
  - 3. Individuals with inflammatory back pain should be referred to a rheumatologist for further evaluation.
- Effective dissemination and implementation of these recommendations are important to standardise the approach to early diagnosis of ankylosing spondylitis.

MJA 2008; 188: 235–237

Ankylosing spondylitis is a chronic disabling rheumatic condition occurring in 0.2%–1.0% of the population and characterised by pain, disability and loss of spinal mobility.[1] Diagnosis is typically delayed by 5–7 years,[2] often because of delayed referral from the general practitioner.[3] In the modern era of effective treatment with tumour necrosis factor inhibitors, the consequences of delayed diagnosis are significant. These include inappropriate costly investigations and therapies, loss of spinal mobility and progressive decline in productivity and employability.[4] As a result, education of GPs for early recognition of ankylosing spondylitis is increasingly vital.

Classification criteria of ankylosing spondylitis are fulfilled if definite radiographic changes of the sacroiliac joints occur in the setting of defined clinical symptoms and reduced measures of spinal mobility.[5] However, the appearance of radiographic changes is commonly delayed by a decade or more after onset of symptoms.[6] "Axial spondyloarthritis" is a recently introduced term to denote patients with symptoms of ankylosing spondylitis without radiographic sacroiliitis.[7] Almost 60% of these patients will progress to radiographic sacroiliitis (and therefore ankylosing spondylitis) over 10 years.[6]

Ankylosing spondylitis and axial spondyloarthritis comprise up to 5% of patients with chronic back pain in primary care.[8] The major challenge in general practice is to identify these patients among the large patient population presenting with chronic back pain. This article summarises a set of Australian consensus recommendations addressing early diagnosis of ankylosing spondylitis, with the goal of facilitating timely referral to a rheumatologist.

The recommendations

The objective of this study was to provide a consensus of recommendations to facilitate early recognition of ankylosing spondylitis in general practice. The importance of such recommendations is ever-increasing with the introduction into clinical practice of effective biological treatments for ankylosing spondylitis.[9]

Box 1 summarises the methods used. Because of the limitations of the medical literature in providing firm guidelines for evaluating patients with possible ankylosing spondylitis, a study design that incorporated the opinion of practising local rheumatologists was desirable.

The recommendations themselves are presented in Box 2. For almost all recommendations, there was strong consensus among participating rheumatologists, and therefore we propose a standardised national approach for early identification of ankylosing spondylitis.

Discussion

By astute recognition of inflammatory back pain, GPs play a critical role in the early identification of ankylosing spondylitis. Inflammatory back pain represents the sine qua non of ankylosing spondylitis and has traditionally been identified by insidious onset of symptoms before the age of 40 years, symptoms persisting longer than 3 months, morning stiffness, and improvement with exercise.[10] Recently, a new definition of inflammatory back pain among patients younger than 50 years with chronic back pain was proposed. This definition requires two or more of morning stiffness, improvement with exercise but not by rest, alternating buttock pain, and awakening with pain only in the second half of

1 Methods

The 3E (evidence, expertise and exchange) program is a multinational effort to develop recommendations for daily management of rheumatic disorders. It combines systematic literature research (evidence) with the opinion of local rheumatologists (expertise) to ensure that recommendations are relevant to clinical practice. Local recommendations are then combined with other countries (exchange) into a set of international recommendations.

Rheumatologists from 10 countries participated in three rounds of discussion and Delphi voting to determine a set of nine questions, three for each domain of diagnosis, monitoring and treatment of ankylosing spondylitis. Questions were selected by experts with in-depth knowledge of the literature to address areas of uncertainty in clinical practice. To avoid conflict of interest with the pharmaceutical sponsor (Abbott Immunology), questions related to biological disease-modifying antirheumatic drugs were not considered.

Proposed questions for the domain of diagnosis were:

- In individuals with back pain, what are the early clinical features that suggest ankylosing spondylitis?
- How useful is imaging in identifying early ankylosing spondylitis?
- Based on which clinical features should a general practitioner refer a patient to a rheumatologist for further evaluation?

A systematic literature review was conducted by international rheumatology Fellows using MEDLINE and PubMed for studies published up to August 2006. The search strategy included all relevant terms for ankylosing spondylitis combined with different sets of keywords specific for each question.

A summary of the results was presented to the 23 participants of the 3E Australian meeting, who were clinical rheumatologists experienced in the day-to-day management of ankylosing spondylitis. Following three rounds of break-out sessions, a set of recommendations was finalised after discussion and voting. The category of evidence and strength of recommendation was determined for each recommendation.

Category of evidence	Strength of recommendation
Ia: Meta-analysis of randomised controlled trials	A: Category I evidence
Ib: Randomised controlled trial	
IIa: Controlled study without randomisation	B: Category II evidence or extrapolated from category I evidence
IIb: Quasi-experimental study	
III: Non-experimental descriptive studies such a comparative, correlation and case–control studies	C: Category III evidence or extrapolated from category I or II evidence
IV: Expert committee reports or opinion or clinical experience of respected authorities, or both	D: Category IV evidence or extrapolated from category II or III evidence ◆

2 Recommendations

1a. Early clinical features to suggest ankylosing spondylitis include inflammatory back pain and age at symptom onset < 45 years. (III, C, 100%)

1b. The absence of symptomatic response to an appropriate course of non-steroidal anti-inflammatory drugs makes the diagnosis of ankylosing spondylitis less likely. (III, C, 91%)

1c. Raised inflammatory markers are supportive, but their absence does not rule out the diagnosis of ankylosing spondylitis. (III, C, 90%)

2a. Despite low sensitivity to detect changes of early ankylosing spondylitis, plain radiographs of the pelvis and spine are appropriate initial imaging techniques. (IV, D, 91%)

2b. Magnetic resonance imaging is a useful imaging modality for detecting early changes of ankylosing spondylitis. (IV, D, 100%)

3. Individuals with inflammatory back pain should be referred to a rheumatologist for further evaluation. (III, C, 77%)

The parentheses contain the category of evidence, strength of recommendation, and level of agreement among the panel. ◆

the night.[11] These criteria appear more sensitive and specific than traditional definitions of inflammatory back pain, but remain to be validated in large populations with non-specific back pain. More importantly than explicit definitions, GPs have the ability to accurately identify patients with inflammatory back pain on the basis of typical clinical presentations.[12]

Non-selective and cyclooxygenase-2-selective non-steroidal anti-inflammatory drugs (NSAIDs) rapidly relieve symptoms of axial disease.[13] About 75% of patients with ankylosing spondylitis show good or very good response to NSAIDs within 48 hours of commencement of treatment, compared with only 15% of patients with mechanical back pain,[14] and this can be a useful discriminating feature. Failure to respond to a trial of at least two different NSAIDs at full dose over a 3-month period was thought to make the diagnosis of ankylosing spondylitis less likely. However, this finding does not rule out the diagnosis of ankylosing spondylitis, and may in effect identify a subgroup with a poorer prognosis,[15] who may benefit from early referral and treatment. Similarly, raised inflammatory markers are supportive of early ankylosing spondylitis, but erythrocyte sedimentation rate or C-reactive protein are elevated in only 50%–70% of patients with active ankylosing spondylitis.[16]

Magnetic resonance imaging (MRI) provides an opportunity for early identification of sacroiliitis not demonstrable on plain radiography. Fat suppression sequences eliminate high signal from fat in the marrow and allow high signal from excess water at sites of inflammation to be seen. The presence of bone oedema in such images of the sacroiliac joints indicates subcortical osteitis and predicts the development of radiographic sacroiliitis with sensitivity of 85% and specificity of 47%.[17] At present, there is no evidence to show that MRI abnormalities of the sacroiliac joints or spine predict the development of bony fusion of the spine, the outcome measure most associated with morbidity in ankylosing spondylitis. As a result of limited availability, high cost and non-standardisation of interpretation of images, the panel did not recommend MRI as a screening tool in general practice.

Early referral recommendations for patients with suspected ankylosing spondylitis have been recently proposed,[18] but their effect on altering outcomes for ankylosing spondylitis has not been evaluated. The authors of those recommendations advocate referral of patients with chronic back pain with symptom onset before the age of 45 years with either inflammatory features or human leukocyte antigen (HLA)-B27 positivity.[18] By contrast, we recommend early referral of all patients with inflammatory back pain, irrespective of age and HLA-B27 status. The positive predictive value in an unselected population of chronic back pain is low. HLA-B27 has its most useful role in patients with clinical or imaging features to suggest ankylosing spondylitis, and the panel

was concerned that inaccurate interpretation of the result may delay referral to a rheumatologist. A single highly sensitive clinical parameter, inflammatory back pain, was thought to be preferable as a screening tool for referral to a rheumatologist.

Effective dissemination and implementation of these recommendations are important to standardise the approach to early diagnosis of ankylosing spondylitis. Longitudinal studies will be of interest to document the effects of these recommendations in limiting variability in clinical practice and reducing health care costs.

Acknowledgements

We acknowledge the following rheumatologists who participated in the Australian 3E meeting: Helen Cooley (Tas), Julien de Jager (Qld), Roland Ebringer (Vic), John Edmonds (NSW), Sam Engel (Vic), Marie Feletar (Vic), Chris Fong (Vic), Patrick Hanrahan (WA), Charles Inderjeeth (WA), Roman Jaworski (NSW), Geoffrey Littlejohn (Vic), Christopher Mack (Vic), Gabor Major (NSW), Prudence Manners (WA), Michael Shanahan (SA), Kathleen Tymms (ACT), and Raymond White (NSW). The 3E initiative is supported by an unrestricted grant provided by Abbott Immunology.

Competing interests

None identified.

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References

1 Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002; 136: 896-907.
2 Feldtkeller E, Khan MA, van der Heijde D, et al. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003; 23: 61-66.
3 Boyer GS, Templin DW, Bowler A, et al. A comparison of patients with spondyloarthropathy seen in specialty clinics with those identified in a communitywide epidemiologic study. Has the classic case misled us? *Arch Intern Med* 1997; 157: 2111-2117.
4 Rudwaleit M, Listing J, Brandt J, et al. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor α blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004; 63: 665-670.
5 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-368.
6 Mau W, Zeidler H, Mau R, et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J Rheumatol* 1988; 15: 1109-1114.
7 Rudwaleit M, van der Heijde D, Khan MA, et al. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004; 63: 535-543.
8 Underwood MR, Dawes P. Inflammatory back pain in primary care. *Br J Rheumatol* 1995; 34: 1074-1077.
9 Zochling J, Braun J. Developments and current pharmacotherapeutic recommendations for ankylosing spondylitis. *Expert Opin Pharmacother* 2006; 7: 869-883.
10 Calin A. Early diagnosis of ankylosing spondylitis. *Lancet* 1977; 2: 1293.
11 Rudwaleit M, Metter A, Listing J, et al. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006; 54: 569-578.
12 Brandt HC, Spiller I, Song IH, et al. Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. *Ann Rheum Dis* 2007; 66: 1479-1484.
13 Zochling J, van der Heijde D, Burgos-Vargas R, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 442-452.
14 Amor B, Dougados M, Listrat V, et al. Are classification criteria for spondylarthropathy useful as diagnostic criteria? *Rev Rhum Engl Ed* 1995; 62: 10-15.
15 Amor B, Santos RS, Nahal R, et al. Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol* 1994; 21: 1883-1887.
16 Spoorenberg A, van der Heijde D, de Klerk E, et al. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. *J Rheumatol* 1999; 26: 980-984.
17 Oostveen J, Prevo R, den Boer J, van de Laar M. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *J Rheumatol* 1999; 26: 1953-1958.
18 Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. *Ann Rheum Dis* 2005; 64: 659-663.

(Received 15 Jul 2007, accepted 23 Oct 2007) ❑