Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disorder of uncertain aetiology that primarily affects the axial skeleton (sacroiliac joints and spine). Sacroiliac joint involvement (sacroilitis) is its hallmark. The course of AS is highly variable and can be characterised by spontaneous remissions and exacerbation, particularly in early disease. The disease activity, however, generally persists for many decades, rarely entering a long remission. The disease in some patients may be relatively mild or stay limited to the sacroiliac joints and the lumbar spine. Many patients may not seek medical help, which combined with the insidious nature of AS, may preclude an early diagnosis. There is currently no cure for AS, nor is there any medical intervention which can prevent or retard its progression.

**DISEASE ONSET TO DIAGNOSIS: A BRIDGE TOO FAR**

Only a doctor who is fully cognisant of the clinical nature of AS might consider the possibility of a spondyloarthropathy (SpA), much less AS, when presented with a young individual in their teens or early to mid-20s with chronic back pain. Yet, this is a typical initial presentation of AS. Unfortunately, the presence of inflammatory back pain during the clinically unrecognised “pre-spondylitic” phase, which on average might last 5–10 years or longer, is accompanied by progressive structural damage that may take place inconspicuously.

Diagnosis is often established when AS reaches the stage where structural damage has led to easily recognisable abnormal physical findings or readily apparent radiographic abnormalities of the sacroiliac joints and spine, or both.

Figure 1, which represents data collected by a 78 item professional study of patients with AS conducted by the German AS society in 1996, illustrates well the protracted time delay between onset of AS and its diagnosis. A total of 1614 patients with AS responded to the questionnaire. The average age at onset of the disease was 25.7 years, and the average delay in diagnosis was 8.9 years. A significantly greater delay in diagnosis was seen among women than among men (9.8 years; p<0.01). This discrepancy in disease detection between the sexes reflects the common problem of underdiagnosis of AS among women, probably owing to the misconception that women rarely have AS.

This misconception may also result from slower progression of the typical spinal radiographic manifestations in women with AS. A longitudinal study found that the vast majority (81%) of patients with AS had lost most of their spinal mobility within the first 10 years of onset of AS, and that the disease progresses enough to cause severe restriction of spinal mobility in about 40% of the patients. Loss of function correlated significantly with radiographic changes of AS in the spine, the development of “bamboo spine,” and the occurrence of appendicular (hip and shoulder) and peripheral arthritis. Thus, patients with a definite diagnosis of AS face a lifetime of progressive structural deterioration and associated pain and functional disability, which contribute to substantial socioeconomic loss and reduced quality of life.

Many investigators have tried to set and refine guidelines for the diagnosis of AS. The modified New York diagnostic criteria commonly used today are readily applicable to patients showing clear radiological evidence of AS, but they are of limited use in the absence of defined radiological signs. For example, the definite diagnosis of AS cannot be made unless the patient shows unequivocal radiological evidence of grade II sacroilitis bilaterally, or grade III sacroilitis unilaterally. This criterion does not acknowledge juvenile patients or those in their late teens or early twenties with disease activity that has not yet progressed to the point where their sacroilitis is unequivocally detectable by x-ray examination. This is also true for those patients who may have an undifferentiated form of SpA that may progress over some years to meet eventually the modified New York criteria established for AS. Thus, the diagnosis and treatment of AS and related SpA in the early stages may often be related more to patients’ clinical presentation and to clinicians’ personal experience and intuition than precise diagnostic criteria. This clinical dilemma represents the wide chasm that exists between the onset of AS and its definite diagnosis and, subsequently, its appropriate treatment. Many researchers have attempted to bridge this...
chasm by establishing criteria for the early diagnosis of AS; however, none of these criteria have been universally accepted. Thus, at present, doctors cannot look to established criteria for assistance in detecting early or atypical AS.

Early diagnosis of AS is highly desirable because it enables the institution of treatment before permanent limitation of spinal mobility and spinal deformity have set in, and it provides the clinician with the opportunity to monitor trends in spinal pathology that might result in abnormal posture. However, considerable progress is needed to improve the staging of AS—the aspects of clinical management that are fundamental to designing effective treatment strategies. Also, current diagnostic and classification systems for AS do not reflect the broad range of clinical and radiological presentations of the disease. This limits the ability of clinicians to diagnose patients with AS at an early stage and provide proper management.

These needs were recently acknowledged in a questionnaire based survey conducted by the experts participating in the Ankylosing Spondylitis Workshop held in Berlin, Germany, in January 2002, and resulted in a proposal for staging of patients with AS that is presented in this supplement. These offerings are an excellent starting point for establishing basic understandings among investigators and clinicians for the evaluation of treatment outcomes.

At present, a wide assortment of methods for assessment of AS has been suggested, but no particular method has been accepted universally, and no guidelines for the use of assessment measures have been established. Disease outcomes depend on the speed of spinal ankylosis. There are many indicators for a severe disease outcome in patients with AS, such as onset at 16 years of age or younger, severe pain, grade IV radiographic spinal structural damage, limited spinal mobility, significant functional impairment, a need for regular pharmacological intervention, the lack of efficacy of non-steroidal anti-inflammatory drugs (NSAIDs), a requirement for corticosteroid or sulfasalazine treatment, ocular involvement, hip or knee involvement, and a requirement for surgery. Recently, the Assessments in Ankylosing Spondylitis Working Group defined a core set of domains for the evaluation of AS in the setting of disease controlling antirheumatic treatment and symptom modifying antirheumatic drug treatment in conjunction with physical therapy, and also for clinical record keeping. Which instruments most appropriately assess these domains—for example, the Bath Ankylosing Spondylitis Functional Index (BASFI) or theDougados Functional Index (DFI) for function, and the visual analogue scale or the Bath AS Disease Activity Index (BASDAI) for pain, have yet to be determined. Moreover, application of the selected instrument in the assessment of treatment outcome, and the definition of treatment efficacy, are other unresolved issues.

TREATMENT: IS IT TIME FOR A CHANGE IN PARADIGMS?

Perhaps the most disheartening inadequacy in the care of patients with AS is the lack of therapeutic options which significantly impact and slow or halt disease progression. Unarguably, the use of NSAIDs rapidly relieves inflammatory back pain in patients with AS, earning these agents the status as the “gold standard” for drug treatment in AS. In fact, a dramatic response to NSAID treatment generally confirms the diagnosis of AS in a patient with a high index of clinical suspicion of the disease. However, patients experience clinical benefit only when they are regularly taking NSAID preferably in full anti-inflammatory dose.

The clinical benefit of these agents does not continue once these drugs are stopped. Furthermore, in many cases, NSAID use is limited by gastrointestinal side effects, with minimal clinical benefit from NSAIDs as the disease progresses. The inflammatory cytokine interleukin 1, which is overexpressed in patients with AS, is also overexpressed in rheumatoid arthritis (RA) and Crohn’s disease, a condition strongly associated with AS in either its subclinical or clinical form. In RA, TNFα mediates inflammation, development of pannus, and joint destruction. Its effects on endothelial cells result in up regulation of adhesion molecules, which facilitates leucocyte trafficking (E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1) and stimulates angiogenesis mediated by vascular endothelial growth factor. TNFα also stimulates inflammatory cells (up regulates proinflammatory cytokines including interleukin 1, interleukin 6, and granulocyte macrophage colony stimulating factor) and synovial fibroblasts (stimulates synthesis of metalloproteinases that mediate bone and cartilage destruction, and induces proliferation of fibroblasts). In patients with RA there is a correlation between serum TNFα levels and disease severity and joint pain.
In Crohn's disease, TNFα up-regulates cell surface adhesion molecules, platelet activating factor, and interleukin 8 in endothelial cells, and stimulates local production of chemotactic substances, thus facilitating the recruitment of circulating inflammatory cells to sites of mucosal inflammation. As in RA, TNFα in Crohn's disease induces the production of other proinflammatory cytokines. In both RA and Crohn's disease, neutralisation of the biological effects of TNFα has proved to be effective in managing these two diseases. Clinical trials with the two anti-TNFα agents currently in clinical use, infliximab (a monoclonal anti-TNFα antibody) and etanercept (a soluble TNFα receptor fusion protein), have established their efficacy in reducing the signs and symptoms of RA. Infliximab has also been approved for the treatment of moderately to severely active RA who have had an inadequate response to methotrexate. Infliximab is also approved for the treatment of RA, and in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Several lines of evidence suggest a role of TNFα in the pathogenesis of AS. Firstly, the overexpression of TNFα has been documented in sacroiliac joints of patients with AS. Secondly, increased levels of TNFα have been detected in synovial fluid and synovial tissue from patients with psoriatic arthritis, another SpA. Thirdly, in vitro studies have demonstrated high concentrations of TNFα in gut mucosa biopsy samples taken from patients with Crohn's disease, an inflammatory bowel disease strongly associated with AS. Finally, studies have shown abnormalities in the helper T cell subtype 1 (Th1) cytokine profile in patients with AS and related SpAs, and in gut mucosal lymphocytes from patients with SpA. The latter finding links the gut immune system abnormalities to the pathogenesis of SpAs.

The hypothesis that TNFα has an important role in the pathogenesis of AS and related SpAs has been validated by the observed ability of anti-TNFα therapy (infliximab) to reverse Th1 cytokine abnormalities. Reduction in the thickness of the synovial layer has been seen in patients with SpA who are receiving anti-TNFα therapy, together with down regulation of endothelial adhesion molecules and reduction of inflammatory infiltrates in the synovial sublining area. Randomised, double blind, placebo controlled clinical trials have demonstrated the significant efficacy of infliximab and etanercept in reducing disease activity in patients with AS. Controlled studies have also shown their efficacy in psoriatic arthritis and other forms of SpAs. However, it is yet to be determined whether the immunomodulatory effects of anti-TNFα therapy that have thus far been observed will alter radiographic disease progression. There are also some new treatments under study, including paminorlate and thalidomide.

The emergence of data on the pathogenesis of these diseases and the molecular mechanism of the inflammatory process, as well as the development of new treatments that redress underlying pathogenic abnormalities, appear to be occurring in tandem. The workshop on the new treatment strategies was a timely event that provides a solid foundation for the betterment of the patients.


Ankylosing spondylitis: introductory comments on its diagnosis and treatment

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