Editorial

The Challenge of Early Diagnosis in Ankylosing Spondylitis



Ankylosing spondylitis (AS) is a chronic, disabling rheumatic disease characterized by inflammatory back pain, restricted spinal mobility, and frequently peripheral arthritis, enthesitis, and acute anterior uveitis. Patients fulfill classification criteria for AS if characteristic radiological changes of the sacroiliac (SI) joint are present, together with defined clinical symptoms and physical findings[1].

AS belongs to a larger, more encompassing group of related diseases termed spondyloarthropathies (SpA). The European Spondylarthropathy Study Group has developed classification criteria for SpA[2] in which sacroiliitis, although frequently found in patients with SpA, is not obligatory. With an estimated prevalence of 0.2–1.2% in European Caucasian populations[3], AS is a significant health burden. Symptoms of AS commonly begin in late adolescence and early adulthood, thus at a normally productive time of life. If undiagnosed or inadequately untreated, continuous pain, stiffness, and fatigue are the consequences. Further, a potentially progressive loss of spinal mobility and function result in a reduction in the quality of life.

In the context of all the inflammatory rheumatic diseases, there is an unacceptably long delay between the onset of symptoms and the time of diagnosis for AS — an average interval of 8–11 years has been reported[4]. Until recently, treatment options for AS were limited. Conventional disease-modifying antirheumatic drugs, which are effective in other chronic inflammatory diseases such as rheumatoid arthritis, have only a very limited effect on spinal inflammation. Thus, while an early diagnosis has been recognized as important in these patients, this seemed less urgent for many physicians because of the lack of therapeutic options.

This treatment approach has now changed. Nonsteroidal antiinflammatory drugs, long the mainstay of treatment for control of symptoms, may have a protective effect on structural damage when taken on a regular basis[5]. Anti-tumor necrosis factor (TNF) agents offer an exciting new possibility for effective treatment and possibly arrest of disease progression. It has been shown that the anti-TNF agents have a prompt and robust effect on almost all aspects of active disease — most notably pain and fatigue, but also function, spinal mobility, peripheral arthritis, enthesitis, bone density, and acute inflammation as reflected by acute phase reactants and magnetic resonance imaging (MRI)[6-9]. It has also been shown that AS patients with shorter disease duration are more likely to respond to anti-TNF agents than patients with longstanding disease[10].

There are a number of reasons for the long delay in the diagnosis of AS. First, the established classification criteria for AS, which date back over 20 years, rely on the combination of clinical symptoms plus unequivocal radiographic sacroiliitis of at least grade 2 bilaterally or grade 3 unilaterally. The radiographs are often normal when symptoms arise and it usually takes several years for definite radiographic sacroiliitis to evolve[11]. Second, there is no pathognomonic clinical feature or laboratory test to make the diagnosis of AS. Thus it is a huge challenge to attempt to identify the estimated 5% of chronic low back pain that represents AS[12]. In this regard, AS presents a distinct diagnostic problem since it occurs in the context of a highly prevalent condition — low back pain — in which it represents a small subset. This is not true for polyarthritis, in which rheumatoid arthritis represents a large subset.

The modified New York criteria[1] have been used widely for the diagnosis of AS, and generally have defined the entry criteria for both genetic studies and therapeutic trials. The use of classification criteria for diagnostic purposes occurs frequently in daily clinical practice, particularly, as in the case of AS, where set diagnostic criteria are absent. Yet classification criteria should serve as a tool for the research and scientific community, providing uniform criteria by which to classify patients with the same disease[13]. Making a diagnosis is ultimately based on probabilities, in

See Color and duplex Doppler sonography to detect sacroiliitis and spinal inflammation in AS, *page 110*

the setting of a known prevalence of a condition in any given population. But the background figure cited above of 5% of back pain patients having an underlying SpA has not been rigorously examined. Also, neither the incidence nor the range of radiographic abnormalities in the SI joint has clearly been documented. Both these are topics of ongoing research in our unit.

Choosing clinical characteristics for screening patients for underlying AS is attractive because their determination is not expensive. The clinical symptom of inflammatory back pain (IBP) has been recognized as a cardinal symptom for AS for years, and assessment requires neither laboratory tests nor radiographic studies. It has been estimated that when symptoms of IBP are present in a patient with chronic low back pain, the post-test probability for this patient having the diagnosis of axial SpA is 14%[14]. Recent refinement of these clinical features has identified a candidate core set of criteria for IBP: (1) morning stiffness of > 30 minutes, (2) improvement in back pain with exercise but not with rest, (3) awakening because of back pain during the second half of the night only, and (4) alternating buttock pain[15]. These features were defined by a study that sought to identify the most sensitive and specific combination of characteristics for IBP using a cohort of patients with established diagnoses of AS and mechanical back pain. If at least 2 of these 4 characteristics were fulfilled, this yielded a sensitivity of 70% and a specificity of 81%, with a positive likelihood ratio of 3.7 for AS. If at least 3 of the 4 characteristics were fulfilled, the positive likelihood ratio increased to 12.4. How these discriminating features perform in a large population with nonspecific back pain remains to be examined.

Currently, imaging is essential for the diagnosis of AS for the purpose of identifying the presence of sacroiliitis. Although plain radiography is always the initial method for evaluating the SI joints, its accuracy is limited by the lack of sensitivity in early stages of the inflammation and by high intra- and interobserver variability in interpretation[16,17]. The grade of sacroiliitis is critical for the diagnosis of AS, and plain radiographs of the SI joints are divided into 4 grades, from normal to fully ankylosed. Differentiation of grade 1 (suspicious change) and grade 2 (minimal abnormality — small localized areas with erosions or sclerosis without alteration in joint width) is where most of the diagnostic variability arises. In these cases, different imaging techniques might be helpful.

Quantitative SI joint scintigraphy, computed tomography (CT), and MRI are the currently available imaging modalities to evaluate sacroiliitis[18]. Despite the use of these different modalities, difficulties in diagnosing sacroiliitis remain. By using CT, sclerosis and ankylosis can easily be diagnosed, and for the detection of bony changes, CT can be superior to MRI. However, MRI also identifies abnormalities thought to reflect inflammatory disease activity in the joint and subchondral bone. The sensitivity of quantitative SI joint scintigraphy is reportedly high, but the increased bone turnover in SI joints lowers the specificity of this technique[18].

MRI has been proposed by many investigators as the best method of detecting sacroiliitis, especially early in the course of the disease. It can demonstrate early predestructive alterations of sacroiliitis[19-22]. However, the availability of MRI is often limited and the technique is time-consuming and costly, imposing practical difficulties for its clinical application in all patients with inflammatory back pain and suspected sacroiliitis. MRI is also limited in patients with metal implants or pacemakers, or with claustrophobia.

Where exactly MRI fits in our diagnostic armamentarium is not yet fully resolved. It has recently been shown that conventional radiography can detect structural changes in the SI joint with greater sensitivity than MRI[23]. However, inflammation on MRI can be found in a substantial proportion of patients with IBP but with normal radiographs. Applying only MRI (even if this were practical in the real world) might underestimate structural changes of sacroiliitis. Recent studies have suggested that assessment of structural changes, first by conventional radiography followed by assessment of inflammation on MRI in patients with negative radiographic studies, yields the highest probability of detecting involvement of the SI joints in patients with recent onset IBP.

In this issue of *The Journal*, Unlu and colleagues present some interesting data on the role of color and duplex Doppler ultrasound in detecting SI and spinal inflammation[24]. Although their number of patients studied is small (39 patients with AS), they were able to demonstrate a significant difference in the ultrasound appearance between AS patients and healthy controls — the variable measured was the resistive index, which is a measure of vascularity. They were also able to demonstrate a significant change in the resistive index in response to anti-TNF therapy in a smaller subgroup of patients with AS. Unfortunately, there is no comparison to MRI findings in the AS patients or controls in the study. However, it has been shown previously that contrast-enhanced color Doppler ultrasound compares favorably with MRI in its ability to demonstrate SI joint inflammation[25]. In the current study, one radiologist performed all the procedures, and although blinded to the clinical condition of the various subjects, direct pressure on the SI joint is an inherent part of the procedure — eliciting tenderness in this situation has the potential to unblind the examiner. Different size and shape transducers were used depending on the size of the subject, in an attempt to correct for the fact that it is more difficult to perform this procedure on obese patients than on thin patients.

Ultrasonography has proved a highly sensitive, noninvasive, and practical tool in assessment of bone and joint pathology, and is gaining increasing attention in many different areas of rheumatology practice[26]. Within the area of

SpA, Doppler ultrasonography is currently being used to detect enthesitis and to assess response of enthesitis to therapy[27,28].

The presence or absence of sacroiliitis as detected by whatever reliable, reproducible, and affordable method will continue to be a cornerstone for earlier diagnosis of AS. Potentially, Doppler ultrasonography, due to its relative availability and low cost, may be a useful tool in diagnosing patients with AS and assessing response to therapy. Further work is definitely warranted in this area.

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