Juvenile Versus Adult-Onset Ankylosing Spondylitis: Are We Comparing Apples and Oranges?

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J Rheumatol 2012;39;887-889
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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Ankylosing spondylitis (AS) is a chronic disabling inflammatory disease affecting the spine, peripheral joints, and extraarticular structures. Depending on the population studied, its prevalence varies between 0.5% and 1% in white populations. Most frequently presenting in early adulthood, AS can lead to substantial functional limitation in people of working age. As such it presents a significant burden of morbidity and health care expenditure.

An increasing research interest in the disease over recent years has lead to a number of significant insights in AS. The significant symptomatic relief achievable with nonsteroidal antiinflammatory drugs in a proportion of patients has been known for many years. The use of biologic agents for symptomatic relief and control of inflammation has been a major step forward. These agents achieve significant symptomatic and functional improvement, minimizing the loss of productivity heretofore inherent in AS. We have seen the development of a new specific disease activity score, the Ankylosing Spondylitis Disease Activity Score (ASDAS), enabling standardized measuring and monitoring of patients with AS in the outpatient setting. The Bath Ankylosing Spondylitis Disease Activity Index has been the most widely used disease measure in AS but has been criticized: the BASDAI includes only patient-reported variables, does not weight different clinical manifestations, measures only part of the disease process, and lacks specificity for inflammatory processes. Similar to the Disease Activity Score (DAS) in rheumatoid arthritis, the ASDAS integrates patient-reported variables and acute-phase reactants to produce a validated disease measure that is highly discriminatory and sensitive to change. New classification criteria for both axial and peripheral spondyloarthritis have also been developed. It is hoped that the concept of axial spondyloarthritis and the new classification criteria will facilitate the diagnosis and treatment of patients before they develop significant structural changes visible on radiographs and previously required for a definitive diagnosis.

Despite these significant advances a number of challenges remain. The initial enthusiasm around the biologic agents has been tempered by the discovery that they do not appear to halt the structural bony changes characteristic of AS. This surprising finding has spurred further research aimed at elucidating the disease pathways responsible for the disconnect between inflammation and bone overgrowth in AS. Our increased awareness of the typical presentation of AS has not necessarily led to a significant improvement in the well documented diagnostic delay in the disease, with substantial scope remaining for improvement.

Traditionally, AS has been divided into 2 subgroups based on the patient’s age at time of onset of first symptoms. Those with age of onset ≤ 16 years are termed juvenile-onset AS and those with age of onset ≥ 17 years, adult-onset AS. There is ongoing debate with regard to defining disease duration, and hence time of disease onset in AS. The very nature of AS leads to this difficulty. The initiating event in AS remains unknown as does the mean time from this initiating event to first symptoms. The interval between first symptoms and diagnosis by a healthcare provider takes on average 4 to 9 years. This raises the problem of recall bias when defining disease onset as time of first symptoms. An alternative approach used in other chronic diseases such as diabetes, hypertension, and gout is defining disease onset as the time of diagnosis by a healthcare professional. While in one sense more standardized, this approach has its own difficulties inherent in the diagnostic delay. Another debate arises over what constitutes the first symptom in AS: Should it be confined to inflammatory back pain? Should peripheral arthritis count? What of extraarticular manifestations such as uveitis, enthesitis, or even psoriasis? The Assessment in Ankylosing Spondylitis International Working Group has published a consensus statement exploring these issues.

The differences between juvenile and adult-onset AS represents an ongoing controversy. It is still uncertain...
whether these 2 entities are distinct disease processes or different manifestations of the same disease modulated by age of onset. A number of groups have looked at this aspect of the disease using a variety of methodologies and publishing a number of contrasting findings. One of the authors (FOS) was involved in a single-center cross-sectional study using an AS clinical database to assess this issue. This study found that peripheral involvement was more common in juvenile-onset AS, whereas axial features were more common in adult-onset disease; moreover, adult onset was associated with worse functional and quality of life measures and higher fatigue scores. Gensler, et al performed a multicenter cross-sectional study, finding similar functional outcomes in the 2 groups with more severe radiographic hip disease and less severe radiographic spinal disease in juvenile-onset AS. Stone, et al used a postal questionnaire to patients who had received a diagnosis of AS to compare the 2 groups, finding a worse functional outcome in juvenile-onset AS. A number of other studies have also been published, again with a variety of findings and methodologies. There are many possible reasons for the differences observed in these studies, including differing study design and methodology, as well as the possibility of genuinely distinct patient cohorts, or an effect of changing treatment patterns.

The above 3 studies have been conducted in predominantly white populations. As we know from both the AS literature and other rheumatic diseases, ethnicity can have a substantial effect on disease presentation and clinical course. It is important therefore to evaluate the differences between juvenile and adult-onset AS in different ethnic groups. In this issue of The Journal, Chen, et al present the findings of a study assessing this in an ethnic Chinese population. The estimated prevalence of AS in China is 0.24%, which, based on an estimated Chinese population of 1.3 billion, makes Han Chinese the most common ethnicity in terms of total numbers of patients with AS.

In their study, Chen, et al have divided AS into 3 groups based on age of symptom onset, juvenile (JoAS), adult (AoAS), and late-onset AS (LoAS; age ≥ 40 years). Consistent with previous studies, Chen, et al have shown an increased frequency of peripheral arthritis (37.3% vs 21.5%) and decreased frequency of back pain (73.1% vs 85.2%) at disease onset in juvenile compared to AoAS. In this cohort, patients with juvenile onset had a worse functional outcome than patients with adult onset as assessed by Bath AS Functional Index (3.7 ± 2.5 vs 2.9 ± 2.5, respectively). This was matched by a worse patient global score in patients with JoAS as assessed by the Bath AS Patient Global Score (6.4 ± 2.6 vs 5.2 ± 2.8). The study also showed a younger age at symptom onset in male patients who were HLA-B27-positive.

In their study, Chen, et al have added to our knowledge of this field by evaluating an unresolved issue in a different ethnic cohort. This was a large study, with 546 patients included, 67 with JoAS, 460 with AoAS, and 19 with LoAS. Unfortunately, the low number of patients with LoAS makes it difficult to draw much useful information from this particular group. The differences in clinical presentation between JoAS and AoAS described are consistent with previous studies in this area. The younger age at symptom onset in HLA-B27-positive males is interesting, but is in contrast to previous studies and requires replication in this ethnic cohort to confirm the finding. The finding of worse functional outcomes in patients with JoAS adds to the ongoing controversy in this area, with a number of different papers now reporting better, the same, or worse functional outcomes in the juvenile-onset group.

A multitude of reasons account for these discrepancies, and further large-scale studies in well characterized cohorts are required to clarify the issue. The differences between juvenile and adult onset may be crucial in advancing our understanding of AS pathogenesis and improving our management of these patients. It is possible that genetic studies may shed light on the subtle differences between juvenile and adult onset AS. Recently, a large volume of research has been published on the genetics of AS. It is obviously hoped that these genetic clues will give insight into the prognosis and even the therapy of AS. However, it must be remembered that even though HLA-B27 has been known about for more than 30 years, the exact role it plays in AS pathogenesis remains unclear. Moreover its presence or absence has no influence on any known therapy.

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