Challenges in the management and research of juvenile-onset ankylosing spondylitis

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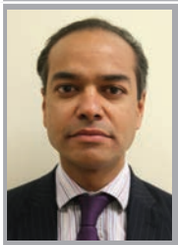
KEYWORDS: adolescent ■ adult ■ adult-onset ankylosing spondylitis ■ ankylosing spondylitis ■ juvenile-onset ankylosing spondylitis ■ late-onset ankylosing spondylitis ■ management ■ prognosis ■ stratified medicine

Deepak R Jadon

Author for correspondence: Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, BA1 1RL, UK
jadondr@yahoo.com



Raj Sengupta

Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, BA1 1RL, UK

Athimalaipet V Ramanan

Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, BA1 1RL, UK
and
Bristol Royal Hospital for Children, Bristol, UK

Ankylosing spondylitis (AS) is a chronic musculoskeletal disorder characterized by inflammatory axial disease and extra-articular features that can include uveitis, enthesitis, osteoporosis, inflammatory bowel diseases and cardiovascular–respiratory disease.

The symptoms of AS usually start in the third decade of life. However, Wilkinson and Bywaters were among the first to document that 18% of patients experience symptom onset before the third decade of life, with cases as young as 11 years having been observed [1]. AS has three main modes of onset: juvenile-onset AS (JoAS), when patients experience symptoms aged ≤16 years; adult-onset AS (AoAS), when patients experience symptoms aged ≥17 years; late-onset AS, when patients experience symptoms aged >40 years. All three subsets share plain radiographic sacroiliitis, and conform to the 1984 Modified New York Criteria.

There are little data on the prevalence and incidence of JoAS. The symptoms of JoAS can be episodic; with disease flare cycling with prolonged remission. The literature reports that axial disease often develops 5–10 years after initial peripheral manifestations [2,3]. An important caveat is that inflammatory back pain criteria have not been comprehensively validated in children [4]. There are no laboratory tests specific to JoAS.

The management and research of JoAS patients poses several challenges; each will be discussed in this editorial.

Differentiating JoAS from other juvenile arthritides

Knowledge of the presentation and course of JoAS is important in order to differentiate it from juvenile idiopathic arthritis and spondyloarthropathy (SpA). SpA in children is characterized by arthritis and enthesitis, usually involving the lower limbs, inflammatory back pain, an association with *HLA-B27* [5], a male preponderance and extra-articular manifestations such as uveitis. The International League of Associations for Rheumatology classification of juvenile idiopathic arthritis proposes the term enthesitis-related arthritis (ERA) to refer to children with arthritis and enthesitis, or arthritis plus several other features characteristic of SpA [6]. Like many chronic diseases, manifestations develop over time. Although 17–44% of ERA children experience spontaneous symptom resolution without further sequelae [7], a study in Mexico demonstrated that a significant proportion of ERA patients develop back symptoms and radiographic sacroiliitis, fulfilling the diagnostic criteria for JoAS from the third to fifth year of the disease (47–75%) and thereafter (92%) [8]. It has been shown that up to 30% of children with ERA/juvenile idiopathic arthritis develop clinical and dynamic MRI evidence of sacroiliitis within 1 year of disease onset [9].

It is thought that JoAS (often termed a 'complete' SpA) may account for a fifth of juvenile SpA cases [10]. 'Incomplete/early' childhood SpA is more frequent and may take 5–10 years to develop axial manifestations [10]; perhaps therefore being the more stereotypical ERA. A MRI study by Stoll *et al.* found that juvenile SpA patients are at risk for sacroiliitis, often silently, without clinical symptoms or signs [11].

Is JoAS a different disease to AoAS?

It is yet to be determined whether JoAS is a distinct subtype of AS, or simply AS modulated by early age of onset and longer disease duration. Some propose that JoAS is a juvenile disease manifesting in early adulthood. Others argue it is simply part of the normal spectrum for AS onset.

Future Medicine part of fsg

A recent systematic review identified 12 articles directly comparing JoAS and AoAS cohorts [12]. The literature suggests that JoAS patients are more prone to peripheral joint involvement (both clinically and radiographically), especially of the hip, shoulder, knee and ankle. JoAS patients often initially present with peripheral, rather than axial symptoms. AoAS patients appear to be more prone to axial symptoms and radiographic disease of the lumbar spine, accompanied by worse axial metrology. These two subsets of AS appear to be similar in terms of male preponderance, *HLA-B27* positivity and occurrence of uveitis, enthesitis and cutaneous psoriasis. Further research is needed to clarify if JoAS and AoAS are different or similar in other respects.

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It should be noted that the age criteria cutoffs for JoAS and AoAS are derived from when patients usually transition from pediatric to adult rheumatology services. To date, no studies have reported data on how clinical, radiographic and social outcomes in AS vary when age is treated as a continuous variable, rather than dichotomizing age for JoAS and AoAS.

Why is it difficult to compare JoAS with AoAS clinical cohorts?

The definition of disease duration is complicated by the choice of defining disease onset from the date of symptom onset or from the date of diagnosis. A study by van der Linden *et al.* of AS, reported an average of 4–9 years between symptom onset to formal diagnosis [13]. Therefore, recall bias is more problematic in retrospective studies of AS using symptom onset to calculate disease duration. While JoAS and AoAS patients can be matched for disease duration, one must also consider the confounding effect of 'absolute age at assessment' on parameters influenced by concurrent degenerative changes, including functional, metrology and radiographic indices. One may attempt to accommodate for this by performing a series of regression analyses; however, few published studies of JoAS have implemented this method.

In countries such as the UK, with a national prescribing framework, JoAS patients with predominately peripheral disease may not qualify for biological therapy. This could potentially contribute to worse clinical outcome. For clinicians wishing to intervene earlier to potentially improve outcomes, there may be value in revisiting the appropriateness of the 1984 modified New York Criteria for early diagnosis of JoAS, given the time taken for radiographic sacroiliitis to develop. Exceptional circumstance funding or reclassification as seronegative inflammatory polyarthritis may also need discussing with the patient.

Importance of treating JoAS appropriately & intensively

To date, no large robust study has directly compared outcomes in JoAS versus AoAS according to biological or conventional disease modifying antirheumatic drug use.

Given that this age group of patients has the potential to contribute substantially to society, impairment of function could have serious economic consequences to the individuals and society as a whole. Onset of AS in childhood might impact on school performance, and social and psychological development. The burden of AS during working life has been shown to pose substantial functional limitation, as well as greater morbidity and healthcare costs [14]. While income and socioeconomic status appear to be comparable or better in AoAS patients, results on educational attainment have been inconsistent. This may be in part explained by the difficulties of comparing cohorts in different countries with differing education structures, and thresholds for qualifications and socioeconomic demands on unwell patients at different junctures in their life.

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There are little good quality data on work disability in JoAS. The most robust of the three studies investigating this, Gensler *et al.* reported no difference between the two AS subsets [15]. The ability to identify AS subsets with poorer functional prognosis is of economic value, since studies suggest that functional outcome is a key predictor of total costs associated with AS [16]. While physiotherapy, NSAIDs and biologicals can improve symptoms and function, research is currently being carried out to quantify the ability to improve work disability in terms of presenteeism and absenteeism [17].

There are emerging data that JoAS patients are more likely to require hip arthroplasty than AoAS

patients [15,18–20]. Earlier and better management of JoAS may allow the prevention of orthopedic surgeries. This may reduce the economic and social impact of morbidity leading up to surgery, the actual surgery, rehabilitation postoperatively, and result in less absence from productivity.

Conclusion

While studies in AS have identified certain prognostic markers, studies exploring age of onset as a predictor of disease severity have had conflicting results, perhaps due to heterogenous cohorts including AoAS, JoAS and late-onset AS cases. This is important, since being able to stratify patients according to likely prognosis allows for tailored therapeutic decisions and being better able to balance the benefits of therapy with the potential side effects and economic costs. It allows both clinician and patient to make a better informed choice on healthcare provision and uptake, respectively. As in rheumatoid arthritis, AS has a 'window of opportunity' in which intensive management might reduce long-term clinical sequelae. Prognostic markers would guide such early therapeutic decisions.

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