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Editorial

# Axial spondyloarthritis: coming of age



## Introduction

The last two decades have seen major advances in the understanding of axial spondyloarthritis (axSpA), a chronic inflammatory syndrome that primarily affects axial entheses and joints especially the fibrocartilagenous bone. Despite being one of the oldest diseases known to man, with human skeletons showing evidence of radiographic axSpA (r-axSpA) or ankylosing spondylitis (AS) dating back to ancient Egypt [1], axSpA remains, to date, a challenge to researchers, particularly in its non-radiographic (nr-axSpA) form. This is largely related to the variability of outcome seen with some individuals having a 'benign' disease course with no significant symptoms or disease progression allowing for self-management, while others develop irreversible structural damage of the sacroiliac joints or even the spine [2], with the consequent loss of functional capacity and decreased quality of life, often early in the disease course. The latter, thought to represent an early, pre-radiographic sub-group is well characterized as a young, predominantly male population, HLA-B27 +ve and often presenting with MRI-related bone oedema. However, there is significant heterogeneity in nr-axSpA. This issue of *Rheumatology* aims to appraise the literature in the understanding of the different disease subsets within the axSpA spectrum, it discusses the ongoing challenges in diagnosis, the impact of sex and co-morbidities, and summarizes recent findings in pathogenesis and treatment strategies.

## The challenge with diagnosis in axSpA

The study of axSpA has been traditionally hampered by the lack of pathognomonic symptoms and signs, and in particular, specific serological or immunological biomarkers. As a result, the diagnosis of axSpA relies on clinical pattern recognition, aided by laboratory and imaging features such as CRP or bone marrow oedema suggestive of sacroiliitis, which by themselves lack enough sensitivity and specificity, and are seen only in roughly over half the patients. The rheumatologist or assessing physician's opinion represents the 'gold standard' after careful consideration of the index of suspicion of the disease and the range of possible differential diagnosis, which is one of the reasons why the diagnosis of axSpA is rarely made outside secondary care.

This lack of an 'objective' gold standard has led clinicians to apply available classification criteria such as the modified New York Criteria (mNYC) [3] or the more recently developed ASAS criteria [4] in the clinic, with significant impact on diagnosis and treatment at the individual level. Applying the mNYC too early in the disease course, for example, may lead to under-diagnosis, as radiographic changes of sacroiliitis needed to fulfil these criteria, may only be evident many years after inflammation of the sacroiliac joints occurs; or may not even occur at all in a proportion of patients. By contrast, misinterpretation of the ASAS criteria can lead to over-diagnosis and eventually over-treatment, when used as a 'tick' box exercise, partly due to the lack of specificity of MRI. Such scenarios are of significant impact at the individual level, so it is crucial for clinicians to remember that disease classification can only be considered once the diagnosis is made, and the whole range of possible differential diagnosis has been considered, as we are elegantly reminded by Denis Poddubnyy in his contribution to this supplement [5].

A significant advance in axSpA thanks to the wider availability of MRI and increased disease understanding facilitated by the ASAS classification criteria is the ability to diagnose disease at an earlier stage, with nr-axSpA cohorts including patients with substantially shorter symptom duration [6] than previous studies of established r-axSpA/AS. Not all 'early' disease, however, is non-radiographic. Indeed, 20% [7] or even 60% [8] of individuals may have radiographic findings despite limited symptom duration of 2 or 3 years, suggesting that factors other than time contribute to disease severity (understood here as rapid radiographic progression). In addition, other trials of nr-xSpA have reported on populations with a disease duration of up to 10 years, similar to those of r-axSpA/AS, where only 30% of patients were found to be radiographic on *post hoc* analysis [9]. This suggests that the term 'non-radiographic' is an 'umbrella' that encompasses at least two different groups: that of an early disease stage who may still evolve with time and dependent on risk factors (i.e. male sex, HLA-B27 +ve, smoking status, etc.) onto r-axSpA/AS, which hence constitute a true 'pre-radiographic' or 'early AS' population. The second group is a more heterogeneous population lacking these poor prognostic factors (i.e. female sex, HLA-B27 negative) who may progress at a very slow rate or may indeed never progress into r-axSpA/AS, representing a 'true' non-radiographic category (Table 1). Interestingly, part of this non-radiographic population may remain largely asymptomatic for many years, presenting typically around the fifth decade of life with an acute, reactive inflammatory flare reminiscent of a PMR type syndrome, known as 'late onset AS' [10]. The main difficulty to fully

**Table 1** Different populations in non-radiographic axSpA

| (True) Non-radiographic | Pre-radiographic (or early AS) |
|---|---|
| F>M | M>F |
| HLA-B27 Neg | HLA-B27 Pos |
| MRI-ve | MRI+ve |
| CRP-ve (unless peripheral arthritis) | CRP+ve |
| More likely to be classified according to the "clinical arm" of the ASAS criteria | More likely to be classified according to the "imaging arm" of the ASAS criteria |
| Slow progression, some may never progress | Variable progression rate according to confounders, i.e.: smoking, male sex |
| May present later on in life (>40) with sudden onset of inflammatory (reactive/PMR) type symptoms | Presents second or third decade of life |

F: female; M: male.

characterize these cohorts is the inability to conduct observational studies into the natural history of disease, due to ethical considerations of leaving people untreated. Xabier Michelena *et al.* reflect on these considerations and propose that in order to facilitate research in this area, axSpA needs to be thought of as a spectrum of disease within a continuum [11].

Delay to diagnosis in axSpA remains significantly longer than that seen in other inflammatory arthritides such as rheumatoid or psoriatic arthritis [12] translating into an, as yet, unquantified number of undiagnosed individuals living with chronic back pain and other symptoms. The hidden human and societal costs attached to this 'lost tribe' are likely to be substantial through early loss of work, impaired quality of life and impact on mental health in addition to inappropriate referrals to community and secondary care services. Raj Sengupta and colleagues [13] discuss some of the reasons behind the diagnostic delay in axSpA highlighting the need to rescue this 'lost tribe'. Improved education of health care professionals and the general public, together with the implementation of existing referral strategies and treatment recommendations should allow for prompt diagnosis and management of all those in need.

## Epidemiology and clinical considerations

Axial spondyloarthritis starts in young adulthood. Recent estimates suggest similar numbers of males and females affected in the nr-axSpA sub-group with a higher male prevalence seen in the r-axSpA/AS form [14], suggesting that male sex may be a marker of disease severity rather than susceptibility. There is a growing understanding of the impact of sex in disease manifestations and outcome in axSpA. Females have a longer diagnostic delay [15] and report higher pain sensitivity and intensity than their male counterparts, often leading to a misdiagnosis of fibromyalgia [16]. In addition, females have lower prevalence of radiographic changes, lower baseline levels of CRP and show lower efficacy and drug survival to TNFi [17]. Irene van der Horst-Bruinsma and colleagues appraise the literature in this respect and discuss possible reasons underpinning these findings, which may in part be related to different anatomical, hormonal and immunological characteristics [18].

Individuals with axSpA are at higher risk of other medical conditions, which include extra-articular or non-musculoskeletal disease manifestations such as uveitis, psoriasis or IBD or inter-related co-morbidities such as obesity, hypertension and cardiovascular disease. The reasons for this are multifactorial and probably related to shared risk factors, and consequences of inflammation, treatments or disease impact on the individual. Steve Zhao *et al.* [19] performed a systematic literature review and meta-analysis of the latest data to explore the prevalence of commonly reported co-morbidities in axSpA compared with controls and to examine the impact of co-morbidity burden on axSpA outcomes for the individual through increasing disease severity, and negative impact on work productivity, quality of life and mortality.

## Pathogenesis

The pathogenesis of axSpA remains incompletely understood although evidence points towards adaptive and innate immune mechanisms being involved. Aside from the strong association to HLA-B27, there is clear evidence for significant hereditability with studies suggesting high concordance rates in monozygotic twins of >50% [20], which is greater than other rheumatic conditions. Further evidence for a genetic basis comes from recent genome wide studies (GWAS) that have identified multiple disease-associated loci outside the major histocompatibility complex with shared heritability between different conditions of the spondyloarthritis spectrum such as IBD or psoriasis [21]. These similarities have facilitated the development of polygenic risk scores that capture a high proportion of genetic variation between disorders and may be of value as clinical biomarkers

with the potential to improve disease classification, as discussed by Matt Brown and colleagues [22] in their contribution to this supplement.

Anatomical localization of axSpA to the enthesis and other sites of biomechanical stress outside the axial skeleton suggests that local tissue factors may contribute to the initiation of the inflammatory response in axSpA through activation of innate immunity. Further evidence comes from the link between intestinal inflammation that can be found in 60% of patients with axSpA at the subclinical level [23] and is thought to stem from gut barrier dysfunction. The interaction between this barrier dysregulation, the intestinal immune system, and possibly the microbiome with axial joint inflammation is not fully understood but may be facilitated by IL-23 and HLA-B27 adaptive mechanisms [24, 25]. These and other considerations in the role of gut inflammation and innate immunity in the initiation and propagation of the inflammatory response in axSpA are discussed by Dennis McGonagle and colleagues in their review [26].

## Treatment advances

Treatment of axSpA is ultimately aimed at improving health-related quality of life (HRQoL). There are many targets needed to achieve this and, clearly, one treatment modality cannot fit all. In order to address the pathogenic factors contributing to disease, any treatment strategy should ideally address both biomechanical and immune triggers. Indeed, physical exercise has long been considered a main staple on the treatment of axSpA with significant numbers of patients achieving good symptom response to exercise and NSAIDs [27].

High disease activity related to inflammation leads to significant symptoms of pain and fatigue, which in turn translate into reduced quality of life and inability to work in many affected individuals. To counteract this, research into drug therapies targeting different inflammatory cytokines has grown considerably in recent years, with clinical trials showing rapid and sustained responses, with a favourable safety profile for TNFi and IL-17i in axSpA. Significant levels of response have been reported across the axSpA spectrum in both r-axSpA (AS) and nr-axSpA populations, particularly in patients with objective signs of high disease activity or inflammation as shown by an increased CRP and bone marrow oedema lesions on MRI. This effect appears enhanced in the early stages of disease as shown by studies targeting axSpA populations of short disease duration [7]. Further, achieving sustained remission or a state of low disease activity appears feasible in the majority of patients with axSpA treated with biologic therapies. A relevant question relating to young individuals starting bDMARD treatment at an early age is whether therapy can be discontinued. Two studies have recently evaluated drug tapering in axSpA [28, 29], with the most recent using the TNFi certolizumab, showing that treatment dose may be reduced in patients who achieve sustained remission on full dose, regardless of age, gender or axSpA sub-population (nr or r-axSpA); however, withdrawal is not recommended due to the high risk of flare regardless of sub-group [29].

High disease activity is linked to accelerated spinal radiographic progression [30], known to correlate with functional impairment, leading to the current treatment paradigm based on the potential role of early abrogation of inflammation on suppressing new bone formation, still unproved. Ultimately, the question of whether progression from nr- to r-axSpA or even disease presentation could be prevented remains to be answered. Some of these considerations relevant in the decision making process are discussed by George Fragoulis and Stefan Siebert [31] in their excellent review on 'what' treatments to use, 'when' to intervene and treatment strategies to be considered across the SpA spectrum.

For now, rheumatologists need to remain discerning as not all aspects of axSpA are amenable to anti-inflammatory drug treatment. Indeed, other possible causes for pain such as structural joint damage, concomitant degenerative joint disease or mental health issues are known confounders for symptoms. An interesting analysis performed by Sepriano *et al.* [32] in two axSpA cohorts, DESIR and SPACE, showed that up to 50% of people diagnosed with axSpA may in reality have an SpA-like disease, reporting multiple clinical symptoms but with no objective evidence of inflammation.

## Conclusions

Awareness of the challenges when making the diagnosis of axSpA and associated co-morbidities is of utmost importance in order to choose the most appropriate management strategy for each person at every time. The complexities surrounding axSpA are felt not only by clinicians and researchers but by patients, who report mixed feelings of 'relief' and 'confusion' as they face the challenges of understanding and living with an 'invisible' disease of 'impossible' name. New insights into disease pathogenesis including genetic variation and potential biomechanical or tissue-specific key drivers will help understand the variability of spectrum and outcome. As we move into a new era of artificial intelligence and precision medicine, axSpA is finally coming of age.

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