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Editorial

Pain in Axial Spondyloarthritis: More to It Than Just Inflammation

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The conceptual paradigm of axial spondyloarthritis (axSpA) has evolved and now comprises an expanded spectrum that includes more females and patients with little or no radiographic changes in sacroiliitis or syndesmophyte formation in the spine.[1] This broadened paradigm is often, but not always, characterized by an inflammatory magnetic resonance imaging (MRI) signature. Multiple studies have demonstrated a similar burden of symptoms, physical dysfunction, and disability across the full spectrum of disease presentation, regardless of the presence of radiographic damage, including pain.[2,3,4] Does the pain experienced by these patients only represent a summation of arthritis, enthesitis, and osteitis, both axial and peripheral (i.e., purely induced by inflammation and structural damage), or could there be broader pathologic processes that contribute to and amplify the pain experience?

Studies have shown that in a substantial proportion of patients with axSpA, as well as other chronic inflammatory diseases,[5] some of the pain and other symptoms such as fatigue represent fibromyalgia (FM) or analogous terminology: chronic widespread pain (CWP), central sensitization, "fibromyalgianess," or the newest term, "nociplastic pain."[6] The conditions these terms denote are not fully synonymous, but all allude to the phenomenon of increased nociception mediated through the central nervous system. The proportion of pain that is mediated by the underlying inflammatory condition, the "-itis", vs the centrally mediated pain condition, the "-algia," often varies depending upon such factors as the patient's sex, the effectiveness of immunomodulatory treatment of the inflammatory disease, disease duration, genetic risk for central sensitization, and other contextual factors.[7] Since the degree of central pain can confound our ability to measure the degree of inflammatory pain, how can we more accurately assess their relative contributions so as not to undertreat or mistreat the "-itis" component and overtreat or mistreat the "-algia" component? In this issue of *The Journal of Rheumatology*, Mogard and colleagues[8] investigate these questions using questionnaires and physical assessment techniques in a cross-sectional analysis of patients with axSpA representing both radiographic axSpA (r-axSpA) or ankylosing spondylitis (AS), and nonradiographic axSpA (nr-axSpA).

Comorbid FM characterized by widespread pain, stiffness, fatigue, nonrestorative sleep, and cognitive impairment is frequently seen in patients with both r-axSpA and nr-axSpA.[9,10] A recent systematic analysis revealed a 14% prevalence of FM among patients with the radiographic disease and 11% in those with various clinical features of axSpA but without imaging evidence of sacroiliitis, whereas prevalence was higher among those with MRI-positive nr-axSpA (20%).[11] Overall, around 1 in 6 patients with axSpA met the criteria for FM in the study. Similarly, another study revealed that FM was seen more frequently in r-axSpA compared with nr-AxSpA, suggesting widespread pain also occurs in patients with the established disease.[12]

Assessing pain levels and discerning whether the pain is caused exclusively by inflammation or secondary to central sensitization remains a challenge in axSpA,[13] since there is a lack of specific biomarkers of disease activity in axSpA and FM.[14] Moreover, about 30–40% of patients with axSpA may present with painful enthesitis—inflammation at ligament and tendon attachments in multiple areas—which can pose a diagnostic dilemma, particularly in patients without definitive imaging findings of axSpA.[15]

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See Pain sensitivity in axSpA, *page xxx*

Mogard and colleagues[8] conducted a population-based study from Sweden that assessed pain intensity and sensitivity between patients with AS and nr-axSpA and studied how pain sensitivity measures were related to health outcome measures in these patients. The study is unique as it is the first study that has used cuff pressure algometry to comprehensively assess pain sensitivity in patients with axSpA. Cuff pressure algometry is used to quantify deep-tissue pain sensitivity using pressure-induced pain and thus allows for pain assessment on a large volume of tissue.[16] This technique is better than using a visual analog scale (VAS), the standard method for assessing pain, as VAS is subjective and lacks the precision for accurately measuring the degree of pain.

The study revealed that the majority of the patients with axSpA had chronic pain, with 44% reporting CWP and 33% reporting chronic regional pain. This reiterates that pain is a predominant symptom in these patients and a potential treatment target.

Interestingly, the authors did not find a significant difference in the pain sensitivity measures (pain thresholds, pain tolerance, or temporal summation) between AS and nr-axSpA groups (42 % vs 47%) despite a significantly higher number of women and enthesitis scores in the nonradiographic group. Women have been shown to have lower pain thresholds and greater temporal summation to brief repetitive stimuli compared to men.[17] The findings in the study suggest that CWP in axSpA is more complex than just being attributable to pain perception and/or local inflammation at tendon insertion sites. A functional MRI of the brain to assess cerebral activation during the application of painful pressure may be helpful in answering this.[18]

The study[8] confirmed the findings of previous studies that the patients with nr-axSpA are more likely to be female with shorter disease duration and less objective inflammation (as measured by C-reactive protein [CRP] levels).[2,3]

The disease activity based on the AS Disease Activity Score (ASDAS)-CRP (SD) of 2.0 (1.0) and 1.9 (0.9) and Bath AS Disease Activity Index (SD) of 3.2 (2.3) and 3.4 (2.2) was low in both groups, suggesting that inflammation alone may not be driving the CWP. However, lower pain tolerance was associated with higher ASDAS-CRP and worse physical function, more pain regions, unacceptable pain, higher enthesitis score, worse fatigue, impaired health-related quality of life, and increased anxiety. Similar results have been seen in other rheumatic diseases, suggesting that this may be a common feature of musculoskeletal diseases.[19] The higher pain sensitivity observed in this cohort could be due to abnormal processing of the affective component of pain.

One of the concerns with the study[8] is that patients with undifferentiated SpA were included. About 20 of 51 patients classified as nr-AxSpA had sacroiliac joint (SI) edema alone on an MRI, raising the concern that some patients may have been misclassified as nr-axSpA. Edema on an MRI of SI joints has also been observed in 20–25% of patients with nonspecific chronic back pain.[20] Similarly, patients with undifferentiated SpA that fulfilled the clinical arm of the Assessment of SpondyloArthritis international Society (ASAS) classification criteria could have also been wrongly identified as nr-axSpA, as some of these criteria can easily be fulfilled by patients with nonspecific back pain.[21] This is a deficiency inherent with current ASAS classification criteria. Nevertheless, a large international study, CLASSIC (Classification of Axial SpondyloarthritiS Inception Cohort), is ongoing to validate the performance of the current ASAS classification criteria in a prospective cohort of patients, increasing the specificity of the criteria to 90%; therefore, this classification issue may be resolved in the future.

It is a well-known observation that chronic pain related to the spectrum of FM/CWP dampens subjective treatment response in patients with inflammatory rheumatic diseases.[22,23,24] The cross-sectional design of this study precluded detection of the effect of chronic pain on the efficacy of immunomodulatory treatment in the patients with axSpA. Moltó, *et al*[25] conducted a longitudinal observational study of patients with axSpA initiating tumor necrosis factor inhibitor (TNFi) therapy, wherein 38% of 509 patients answered positively to at least 5 of 6 questions on the FM Rapid Screening Tool (FiRST), considered consistent with having a diagnosis of concomitant FM. At 12 weeks of evaluation after starting a TNFi, the patients with concomitant FM were less likely to achieve thresholds of low disease activity or inactive disease. Interestingly, at 12 weeks only half as many patients remained FiRST questionnaire–positive for FM, raising the possibility that effective immunomodulatory treatment was associated with some amelioration of centralized pain experience. This type of observation needs to be replicated in more rigorous studies that include an objective assessment of CWP such as that incorporated in the Mogard, *et al* study.[8] To derive both cross-sectional and longitudinal data about the presence of concomitant FM/CWP and effect of therapies, the Corrona psoriatic arthritis/AxSpA registry has now incorporated the Widespread Pain Index/Symptom Severity Scale for all patients to complete,[26] and a previous study reported that the scale is useful in evaluating patients with AS.[9]

In conclusion, the authors have objectively measured pain in patients with axSpA and shown that pain etiology is multifactorial and continues to be a challenging problem. They have demonstrated that the pain disease burden is similar in patients with axSpA with radiographic manifestations and in those without, thus supporting the concept that axSpA is a unitary disease with a spectrum of presentation. This study[8] also underlines the importance of assessing FM/CWP in clinical trials and observational registries as an important contextual factor of disease activity and treatment response. Until serum biomarkers or brain activation fingerprints become available for this purpose, the assessment can be accomplished with validated subjective questionnaires as well as with objective methods, such as those employed in this study.

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