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Inflammatory back pain and axial spondyloarthritis: lessons for clinical practice and epidemiological research

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The delay between symptom onset and diagnosis in axial spondyloarthritis (axSpA) remains unacceptably long; recently estimated to still be more than 6 years.¹ Accumulating data demonstrates that early treatment with TNF-inhibitors reduces both disease activity and radiographic progression in ankylosing spondylitis, the prototypic form of axSpA.²³ To encourage timely and correct diagnosis and enable early treatment, strategies to better identify patients with axSpA have been studied in several populations.⁴ Many of these strategies relied on the presence of inflammatory back pain (IBP) as a criterion for referral to a rheumatologist, and IBP is one of the parameters used for classification of axSpA.⁵ However the specificity of IBP for a SpA diagnosis is limited, which makes it challenging to distinguish SpA from other causes of back pain, given that back pain is highly prevalent.

The term “inflammatory” back pain, suggests that a patient’s back pain is caused by inflammation, however the definition for IBP is neither sensitive nor specific for SpA, meaning that not all SpA patients suffer from IBP *and* that a substantial number of patients with other back pain diagnoses report the presence of IBP. IBP is generally considered present in people whose chronic back pain began insidiously at a young age, is associated with morning stiffness, and improves with movement but not with rest.⁶ However, the precise definition for this decades-old concept “remains elusive” despite attempts to refine it.⁷ As an example, although IBP criteria specify insidious onset of the pain and improvement with exercise, some SpA patients may report the opposite pattern- that heavy exertion worsens pain acutely, particularly during flares. Similarly, SpA patients who experience stiffness much of the day may not recognize “morning stiffness” as outlined in IBP criteria.⁷ The published specificity of IBP for a SpA diagnosis ranges from 72 to 92%, and subsequent attempts to revise IBP criteria resulted only in similar specificities.⁸⁹

Nonetheless, IBP is a relevant clinical parameter as a screening and diagnostic tool for axSpA because back pain is so common. Indeed, the larger landscape of back pain is staggering: in the US, 19.4% of adults have chronic back pain. However only about 5% of people with chronic back pain have SpA.¹⁰ Thus, the pretest probability for a chronic back pain patient to have SpA is 5%. As an example, if IBP is assumed to have a sensitivity of 75% and a specificity of 76% for SpA (resulting in a positive likelihood ratio of 3.1), the presence of IBP in a chronic back pain patient only increases the posttest probability of SpA to 14%.¹¹ Thus, although the symptom of IBP is an important parameter in the evaluation of people with chronic back pain, the value of IBP lies within the context of other clinical, laboratory and imaging parameters.

Referral strategies have been developed with the aim to increase the likelihood that patients who are referred from primary care to the specialist do have the diagnosis of axSpA. These referral strategies are necessary to avoid overwhelming the constrained resources that exist within the US (or any) health care system. When IBP was used as one of several screening parameters, about 33–46% of referred patients were ultimately diagnosed as axSpA by the rheumatologist in different studies.⁴ Thus, IBP seems to be suitable as a referral parameter for identifying axial SpA patients in primary care. If these criteria were incorporated as part of a more restrictive referral strategy, it would mean that more axSpA patients would fail to be referred, and the opportunity to prevent morbidity among those patients would thereby be lost.

In this issue of *Arthritis & Rheumatology*, Wang and colleagues report the clinical course of 124 patients with new onset IBP in the Rochester Epidemiology Project (REP), finding that 30% of IBP patients ultimately received a diagnosis of SpA.¹² This study adds to the limited literature on IBP in the US, and by its observational nature, provides insight into how care of back pain patients is truly provided in the real world, outside of specialized referral centers and structured research protocols.

This study importantly highlights lost opportunities in the real world care of patients with back pain, and specifically those with axSpA. Firstly, Wang reports that only 2.3% of back pain subjects were determined to have IBP. In contrast, estimates from the (US) National Health and Nutrition Examination Survey (NHANES), in which subjects were systematically queried about IBP features, suggests that nearly a quarter of adults with chronic back pain have IBP.¹³ Thus the present study findings suggest that front line providers either did not document IBP features in the electronic health record (EHR) in a way that researchers could access, or more likely that providers did not systematically ask chronic back pain patients about IBP features.^{4,14} The challenge of defining and eliciting the presence of IBP may explain the low prevalence of IBP in this study. Rheumatologists, who are familiar with the nuanced features and descriptions of IBP may capture its presence as part of a detailed history, however the same nuance may not be appreciated by generalists in a referral intervention study, or in generalists' notes, as assessed in the Wang study.⁴ A standardized assessment of patients with chronic back pain is likely to pick up more IBP cases, as compared to the varied assessments during routine clinical care by general practitioner (25–31% in NHANES versus 2.3% of chronic back pain patients had IBP in this study).^{12,13}

A second lost opportunity is reflected in the low proportion of patients who received an evaluation by a rheumatologist; just 23%. Similarly, only 21% of IBP patients underwent HLA-B27 testing, and a limited number of patients had pelvic radiographs or MRI. Both HLA-B27 testing and pelvic radiographs would be standard management of IBP patients under the care of a rheumatologist. One line of thinking may be that some patients did not require a rheumatologist's evaluation because their symptoms were mild or transient. However it is likely that since the majority of IBP patients were not evaluated further, at least some patients with SpA were incorrectly diagnosed and undertreated, with resulting functional losses and other morbidity. Therefore, these findings highlight the need for primary care providers to better understand the importance of IBP as a screening tool for SpA and the value of early diagnosis and treatment in SpA.

Overall, despite the limited detection of IBP and low referral rate, the Wang study finding, that 30% of IBP patients received a SpA diagnosis is fairly consistent with results of studies on referral strategies. Together, the Wang study and existing literature clearly demonstrate that IBP is a syndrome that is common to diseases beyond SpA.

Beyond clinical practice, there is also the need to identify subjects with axSpA in large datasets to allow epidemiologic research. Many studies on the epidemiology of extra-articular manifestations, comorbidities or the comparative effectiveness of treatments in SpA would be prohibitively lengthy or expensive to perform prospectively. Thus an accurate algorithm to predict axSpA is also needed for research.

Accurately identifying SpA in observational studies also has challenges. The Wang study demonstrates some of the challenges of using large EHR or claims datasets to address important research questions. Firstly, although the Wang study began with more than 5000 eligible subjects with back pain, the pool was reduced to 124 subjects with IBP; a number that is insufficient to provide precise estimates for many clinically important outcomes. Secondly, the process by which the larger pool was reduced (i.e.- IBP patients selected) was chart review, which is labor intensive and prone to human error and fatigue. Despite these challenges, large datasets like the REP have an important place in SpA research. These datasets are likely the only way in which we can learn about rare but severe disease manifestations or comorbidities in the near future. The large samples from such datasets are also necessary to detect small but common treatment effects, which are important on a population level (e.g.- reductions in cardiovascular events or mortality).

In order to fully harness the potential of EHR databases such as REP, more sophisticated programming tools are necessary to accurately predict and detect disease, and to more finely phenotype SpA subjects. Some predictive methods, including algorithms that incorporate diagnostic codes, and natural language processing, have been used in other diseases but rarely applied in SpA. SpA, with the myriad of potential manifestations, represents an ideal family of diseases for the application of some of these advanced methods *because* the disease heterogeneity makes statistical methods such as stratification or adjustment implausible. As computing power continues to become more accessible, these methods may become more common.

Furthermore, the Wang study highlights the limitations of existing EHR infrastructure, particularly in the US. In the current system, potential subject populations are segmented into EHRs on the basis of geography or insurer, rendering study samples fairly small, and thereby limiting the precision of outcome estimates. Indeed, other observational studies based on EHR or administrative data from the US have suffered similar limitations, and many useful epidemiologic studies are performed in countries with single-EHR healthcare systems or other nationwide databases.

From the Wang study and preexisting literature on IBP as a referral strategy or as a parameter for identification of axSpA, several lessons have been learned. Firstly, awareness of axSpA must be increased among general practitioners and others who provide care to back pain patients in order to effectively channel those who have a moderate or high probability of SpA into care by a rheumatologist. While IBP may form the basis for referral strategies, IBP alone is neither necessary nor sufficient to diagnose axSpA; rather an IBP assessment must be part of a comprehensive evaluation that includes HLA-B27 testing and sacroiliac joint imaging. Strategies for identifying axSpA patients must have high sensitivity, so that the vast majority of persons with axSpA are evaluated by a rheumatologist. Simultaneously these strategies must exert caution not to overburden rheumatologists with the care of patients with non-inflammatory pain, who would be better suited in the care of other providers. Finally, epidemiologic research in SpA is likely to require large EHR databases and the use advanced programming methods to accurately find and phenotype SpA cases. Taken together, the results of the current study and of earlier trials of IBP as a referral or classification parameter clearly indicate that the majority of patients with the symptoms of IBP do not have or do not develop axSpA. Nonetheless, IBP is a relevant clinical tool as part of the assessment for axSpA.

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