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Editorial

Spondyloarthritis Among Patients With Uveitis: Can We Improve Referral Pathways?

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Delays in diagnosis remain a major gap in the care of patients with axial spondyloarthritis (axSpA). Despite efforts to improve awareness among family physicians and nonrheumatologist specialists, the average duration from onset of symptoms to diagnosis of axSpA is approximately 8 years,[1] which is one of the longest in rheumatology. Such delays in diagnosis are associated with late initiation of therapy and worse disease outcomes. Acute anterior uveitis (AAU), the most common extraarticular manifestation in SpA, affects 50% of patients and has been associated with longer delays in diagnosis.[2] For many patients, AAU is the first encounter with a medical specialist, offering a unique opportunity for an early referral to rheumatology. Thus, studying the association between these 2 conditions could inform the development of more effective referral pathways from ophthalmology to rheumatology, ultimately improving early diagnosis of axSpA.

In this edition of *The Journal of Rheumatology*, van Bentum et al describe the effect of an initiative aimed to increase awareness and referrals to rheumatology of patients with AAU and chronic back pain (CBP) seen in academic and community ophthalmology centers in Amsterdam.[3] The referral criteria comprised an accepted definition of CBP (back pain of ≥ 3 months' duration that started prior to the age of 45 years) among patients with new or recurrent AAU. All patients were assessed by a rheumatologist for clinical signs and symptoms of axSpA. Additionally, radiographic assessment of the sacroiliac joints was performed and HLA-B27 status determined in all patients. Magnetic resonance imaging (MRI) of the spine was performed only if deemed clinically necessary for diagnostic purposes.

Among patients with AAU and CBP, the study found a prevalence of 23% (19 out of 81 patients) for previously undiagnosed axSpA, which was almost equally distributed between radiographic and nonradiographic SpA.[3] A total of 32 patients (40%) were diagnosed with suspicion of axSpA. AxSpA was associated with male sex, having inflammatory back pain, and HLA-B27 positivity. Overall, this study expands our current knowledge regarding the link between AAU and axSpA, and raises several points that merit further discussion.

The association between AAU and axSpA has been studied previously and is thought to be related to shared genetic and environmental risk factors.[2] The study by van Bentum et al[3] identified 23% of patients with AAU and CBP as having previously undiagnosed axSpA. This estimate falls within the lower prevalence range compared to previous studies on the same topic. A study from Ireland reported a prevalence of previously undiagnosed SpA in 41.6% of patients with AAU and CBP or joint pain. This population was enriched for SpA risk factors including HLA-B27 and psoriasis (PsO).[4] A large study from Spain assessed the prevalence of undiagnosed SpA in 798 patients with AAU who either were HLA-B27 positive or had recurrent AAU.[5] The study reported a prevalence of 41% for axSpA and 12% for peripheral SpA, with HLA-B27 conferring a higher risk for SpA diagnosis.[5] A smaller study from the UK assessed spinal MRI abnormalities in patients with AAU and found that 23% of patients had previously undiagnosed axSpA,[6] similar to the estimates reported in the present study by van Bentum et al.[3] As noted by the authors,[3] differences in inclusion criteria, referral patterns, case definition, and diagnostic processes including type of imaging modalities used could explain these differences. Studies that enriched the source population (patients with AAU) with known risk factors for axSpA, such as HLA-B27 positivity or recurrent AAU, typically report higher prevalence estimates. Additionally, defining SpA cases by classification criteria rather than by clinical diagnosis may result in misclassification of patients who should otherwise have been classified as having nonspecific back pain. Finally, studies such as this[3] that carefully assessed consecutive patients following standard protocols are expected to detect a greater number of milder SpA cases that would have otherwise escaped diagnosis in a real-world setting. The fact that all patients with axSpA in the present

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study[3] required therapy strengthens the clinical relevance of these new diagnoses. However, it remains unclear whether these patients with previously undiagnosed SpA will have the same risk of developing short- and long-term complications compared to patients with typical SpA. This issue could not be resolved in this article due to its cross-sectional nature; however, the planned prospective design of this cohort could perhaps address some of these questions in the future.

The issue of sex/gender differences in the diagnosis of axSpA has received more attention in recent years. Notable gender gaps were identified in time to diagnosis of axSpA, with more delays observed in female patients.[7] Some of these differences were attributed to the fact that female patients tend to develop characteristic radiographic spinal changes later in the course of disease, thus making the diagnosis of axSpA more challenging in women.[8] Differences in disease presentation with more peripheral joint involvement and widespread pain in females that do not fit the "typical" male-predominant characteristics of axSpA could also explain some of the challenges in the diagnosis of this condition in females.[8] A previous study suggested that male patients were more likely to be diagnosed with axSpA prior to the first episode of AAU, whereas female patients were more likely to be diagnosed after the first AAU attack.[9] It has been hypothesized that given the challenges in diagnosing axSpA in female patients, physicians may be more inclined to make the diagnosis of axSpA in patients with objective features of this disease, such as those with AAU. The authors specifically tested the effect of gender on axSpA prevalence and its link with AAU history.[3] Their results do not support previous findings of female predominance of AAU occurrence in patients with early axSpA. In fact, axSpA diagnosis was more frequent in males (33% vs 13% female); prior episodes of AAU were also more common in male patients, although not statistically different. However, it should be noted that the lack of MRI data may have disproportionally affected the diagnosis of axSpA between men and women, as woman are more likely to present with typical imaging abnormalities in MRI than in radiographs. More studies are needed to inform the development of strategies to reduce delays in axSpA diagnosis, especially in women.

Development and testing the performance of referral strategies for patients with AAU are clearly needed to optimize care. The Assessment of SpondyloArthritis international Society (ASAS) recommends that all patients with AAU who developed CBP prior to the age of 45 years should be referred to rheumatology for assessment of suspected axSpA.[10] The present study[3] used these referral guidelines to promote referrals of patients with AAU to rheumatology. Since they were developed for nonrheumatologists, these recommendations favor simplicity (eg, not ordering laboratory tests/imaging) over specificity. Another referral strategy was tested in the DUET study that applied more specific criteria for rheumatology referral among patients with AAU.[4] In addition to the initial requirement for having CBP, which is similar to that of the ASAS referral recommendations, the DUET study required having a positive HLA-B27 test or PsO to meet referral criteria. This referral strategy was tested and validated in an external cohort showing high sensitivity and specificity (95% and 98%, respectively). While the performance metrics of the referral strategy tested in the study by van Bentum et al were not reported,[3] applying more restricted criteria could have resulted in higher specificity without compromising sensitivity. A total of 18 out of 19 patients with definite axSpA were positive for HLA-B27 (95%); thus, if the referral strategy included only those who tested positive for HLA-B27 (in addition to CBP criteria), the prevalence of definite axSpA would have almost doubled to 40% (18 out of 45 patients). Therefore, while the need to order an HLA-B27 test may slightly complicate the referral pathway, it could optimize efficiency of rheumatology assessments, reducing the number of unnecessary referrals. Future efforts to optimize this referral pathway should involve interdisciplinary discussions involving both ophthalmologists and rheumatologists considering issues such as feasibility, efficiency, and cost.

In summary, the study by van Bentum et al[3] enhances our knowledge of the link between AAU and axSpA, and offers some novel preliminary data on feasibility and effectiveness of referral pathways between ophthalmology and rheumatology. Future results from this study and other interdisciplinary care models are needed to refine current guidelines and improve collaboration between the 2 specialities, ultimately leading to improved patient care.

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