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Evolving Diagnostic Criteria for Axial Spondyloarthritis

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Abstract

Anterior uveitis is far more common than intermediate, posterior or panuveitis. About 50% of patients with acute anterior uveitis are HLA B27+. Those who are HLA B27 + are highly likely to have associated joint or tendon disease, especially if the ASAS classification criteria for axial spondyloarthritis are applied.

Keywords

HLA B27; acute anterior uveitis; ankylosing spondylitis; axial spondyloarthritis; spondyloarthropathy

The scenario is all too familiar to most ophthalmologists and to every uveitis specialist. You are evaluating a 26 year old man with an episode of unilateral, acute, anterior uveitis. He denies a previous similar episode. You ask him about his health in general and he states that this is excellent. But when you probe a little further, you discover that he has been having back pain for 3 years, that this sometimes wakes him at night, and that it improves with exercise or with a nonsteroidal anti-inflammatory drug such as ibuprofen.

In addition to the treatment for this episode, a number of questions flash through your mind. Should you order HLA B27 typing? Do you need to exclude other possible causes of uveitis such as sarcoidosis or syphilis? Should you order an x-ray of his sacroiliac (SI) joints? If these radiographs are normal, is an MRI of the SI joints indicated? What studies must be abnormal in order to diagnose ankylosing spondylitis? What is the difference between ankylosing spondylitis and spondyloarthritis? What is the difference between ankylosing spondylitis and axial spondyloarthritis?

Since 80% or more of all patients with uveitis have anterior uveitis (1) and since HLA B27-associated anterior uveitis accounts for about half of all patients with anterior uveitis in many portions of the world (2), these are questions that should be answerable by all uveitis specialists. The best approach to diagnose spondyloarthritis is not universally accepted. What follows is opinion based on 3 decades or more of experience practicing rheumatology while specializing in the evaluation of patients with uveitis.

Is it important to know if a patient's anterior uveitis is HLA B27-associated? The usual reason to order a diagnostic test is to obtain therapeutic or prognostic information (3). HLA B27 typing satisfies these criteria in evaluating uveitis. HLA B27-associated anterior uveitis

has distinguishing characteristics that influence therapeutic decisions. B27-associated uveitis tends to be recurrent. Accordingly the patient may wish to consider a prophylactic strategy as with sulfasalazine (4, 5), an approach which the author tends to restrict to patients who have especially frequent and recalcitrant attacks. But even for patients with relatively mild attacks, prompt initiation of therapy with topical corticosteroids and mydriatics is often helpful. Patients with HLA B27-associated anterior uveitis frequently describe a prodrome during which a slit lamp examination might detect few or no leukocytes in the anterior chamber. However, topical corticosteroids are appropriately initiated during the prodrome. Frequent use of the drop is appropriate at this time even if the documented inflammation is initially mild. Patients with HLA B27-associated anterior uveitis have a relatively good prognosis with a high likelihood that the episode will resolve completely (6). Patients with iritis associated with B27 are especially likely to have low back, joint or tendon disease that is causally related to the eye disease (7–9). Thus, a positive HLA B27 result has prognostic and therapeutic implications.

Ophthalmologists frequently have the opportunity to diagnose spondyloarthritis. The majority of patients with HLA B27-associated anterior uveitis are unaware that their back pain is causally related to uveitis (9, 10). While several authors have made this observation, this conclusion was tested prospectively in a study known as DUET, the Dublin Uveitis Emergency Treatment trial (9). In this report, an algorithm was used to recognize axial spondyloarthritis among patients attending an emergency department in Dublin, Ireland. Patients were excluded if they had a known diagnosis of spondyloarthropathy. Excluding this group left 101 patients with uveitis of unknown etiology. By asking questions about inflammatory back pain and testing for HLA B27 with subsequent referral to a rheumatologist, the investigators concluded that 42% of their cohort with acute anterior uveitis was suffering from axial spondyloarthritis that had not been previously diagnosed.

So we have established that HLA B27 testing is appropriate, if this is positive, is it still critical to exclude syphilis and sarcoidosis? The presence of HLA B27 does not establish absolute causality. Many individuals are HLA B27 + and never develop back pain or eye disease. Conversely, the detection of HLA B27 does not exclude another diagnosis. However, if the phenotype of the uveitis fits well with the HLA B27 phenotype, i.e. sudden onset, unilateral, anterior, it is highly likely that the B27 type is causally related and further testing is unnecessary. In contrast, if the uveitis has atypical features such as bilaterality, insidious onset, or marked vitreous involvement, excluding other causes of uveitis becomes incumbent.

To address the questions relating to imaging of the SI joints, a review of classification criteria for ankylosing spondylitis, spondyloarthritis, and axial spondyloarthritis is required. Criteria to classify ankylosing spondylitis were first proposed in Rome in 1961 and then revised in New York in 1966 (11) (Table 1). Uveitis is explicitly included in the Rome criteria but it was dropped from the New York criteria. Both sets of criteria rely heavily on radiographic evidence for sacroiliitis. However, the normalcy of SI joints is difficult to determine on a plain x-ray regardless of the angle used to obtain the image. There are not only errors between observers; often the same observer is inconsistent in interpreting the same film (12). To diagnose ankylosing spondylitis by the New York or Rome criteria, one

would definitely obtain an x-ray of the sacroiliac joints and one would exclude the diagnosis of AS if these x-rays are either interpreted as being normal or as showing only grade one sacroiliitis (suspicious for disease but not definite).

Spondyloarthropathy is considered a broader diagnostic category than ankylosing spondylitis. Spondyloarthropathy includes patients with reactive arthritis, inflammatory bowel disease, or psoriasis. Two sets of criteria, the European Spondylitis Study Group (ESSG) or the Amor criteria (13) (Table 2) each perform well. The limited history provided for our prototype patient would not allow a diagnosis of spondyloarthropathy based on either Amor or ESSG criteria. The definition of inflammatory back pain is not universally accepted, but if one accepts that our patient has inflammatory back pain, a diagnosis of spondyloarthritis is made if the x-rays show sacroiliitis according to ESSG criteria. To satisfy the Amor criteria, our patient must have abnormal SI xrays and be B27 +.

An astute reader will note that I am using the criteria to establish “diagnosis” when technically the criteria are for classification rather than diagnosis (14). While there are important differences between classification and diagnosis, many practitioners use classification criteria as a surrogate for diagnostic criteria and I have thus used a liberal interpretation of the word “diagnose”.

If a patient has rheumatoid arthritis, she might develop characteristic bone changes known as erosions in hand joints such as those at the metacarpal phalangeal joint or at the proximal interphalangeal joint. But many patients with rheumatoid arthritis never develop these erosions. And logic would argue that every patient with rheumatoid arthritis takes a measurable amount of time to develop erosions. Therefore, every patient with rheumatoid arthritis at some point in time would theoretically have a hand x-ray that did not show changes in the bone. Surely the same pertains to ankylosing spondylitis. The logical extrapolation is that it is possible to have ankylosing spondylitis even if x-rays of the SI joints are normal! It is impossible to satisfy New York or Rome criteria for ankylosing spondylitis if the SI joints are normal radiographically. It is very difficult to satisfy the Amor criteria for spondyloarthropathy with normal x-rays. The ESSG criteria are more liberal but uveitis is not included in the criteria.

The issue of normal radiographs has been most directly addressed by ASAS, the Assessment of Spondyloarthritis International Society. ASAS has proposed and tested classification criteria for what it has labelled axial spondyloarthritis (Table 3) (15) or peripheral spondyloarthritis (Table 4) (16). These are the only criteria to incorporate MRI imaging, which has greater sensitivity than plain x-rays. MRI alone, however, is not adequate to diagnose axial spondyloarthritis since some specificity is lost in relying on MRI. ASAS criteria are divided into an imaging arm and a clinical arm. Using the clinical arm, our prototypical patient would be diagnosed as having axial spondyloarthritis if he is HLA B27+ since the triad of inflammatory back pain, HLA B27 and uveitis are sufficient to make a diagnosis. No imaging is necessary. And if imaging is ordered, a normal x-ray of the SI joint would not exclude the diagnosis. A patient with spondyloarthropathy and normal x-rays of the SI joints has non-radiographic axial spondyloarthritis, or nr-Ax-SpA. Based on the ASAS criteria, a patient who is HLA B27 + with uveitis and inflammatory back pain does

not require any imaging studies of his SI joints in order to arrive at a diagnosis. ASAS has also published classification criteria for peripheral spondyloarthritis, a recognition that it is ironically possible to fall within this family of disease and yet have no spinal involvement.

The concept of nr-Ax-SpA makes perfect sense but raises the fear that many patients with mechanical back pain or fibromyalgia, roughly 30% of the US or European population, will be mistakenly diagnosed as nr-Ax-SpA. The therapeutic response of nr-Ax-SpA has been studied in at least two clinical trials involving tumor necrosis factor (TNF) inhibitors, one involving adalimumab (17) and one involving certolizumab (18). In both studies, the TNF inhibitors were superior to the placebo. However, the US Food and Drug Agency refused to grant approval for the indication of nr-Ax-SpA on the grounds that an inordinate number of patients with non-inflammatory disease would be mistakenly treated (19). One study found that nr-Ax-SpA accounted for more than 20% of patients with chronic back pain.

Even without using ASAS criteria, a highly respected group from Paris reported that nearly 80% of patients with HLA B27-associated acute anterior uveitis also had associated spondyloarthropathy (7). The ASAS criteria, by not requiring radiographic change, liberalize the classification criteria. The new term, axial spondyloarthritis, has been proposed to replace ankylosing spondylitis. Everyone with ankylosing spondylitis presumably has axial spondyloarthritis but the converse is not true: one can have axial spondyloarthritis without having ankylosing spondylitis.

Spondyloarthropathies are generally characterized by involvement of tendinous insertions known as entheses. Musculoskeletal ultrasound is an excellent way to identify an enthesitis. A study from Spain found that 55% of patients with HLA B27-associated AAU and no known spondyloarthropathy nonetheless have ultrasound evidence for enthesopathy.

The ASAS criteria raise additional questions. What percent of patients with nr-Ax-SpA will evolve into radiographically confirmed disease? Even after ten years of observation, the majority of patients with nr-Ax-SpA might not develop radiographic change (20, 21). This suggests that non-radiographic axial spondyloarthritis could either be a precursor to ankylosing spondylitis or a variant that lacks the genetic or environmental stimuli to induce the bone changes identifiable on x-ray. Is uveitis as common with nr-Ax-SpA as it is with ankylosing spondylitis? At least two studies indicates that uveitis is as common in non-radiographic disease as it is in ankylosing spondylitis (17, 22).

Ophthalmologists should familiarize themselves with ASAS criteria for axial or peripheral spondyloarthritis. The majority of patients with acute anterior uveitis and inflammatory low back pain are suffering from axial spondyloarthritis and radiographic evidence for abnormal SI joints is not required to make this diagnosis.

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References

1. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. *Ophthalmology*. 2004; 111(3):491–500. discussion PubMed PMID: 15019324. [PubMed: 15019324]
2. Brewerton DA, Caffrey M, Nicholls A, Walters D, James DC. Acute anterior uveitis and HL-A 27. *Lancet*. 1973; 302(7836):994–996. PubMed PMID: 4127279. [PubMed: 4127279]
3. Rosenbaum JT, Wernick R. Selection and interpretation of laboratory tests for patients with uveitis. *International Ophthalmology Clinics*. 1990; 30:238–243. [PubMed: 2228469]
4. Dougados M, Berenbaum F, Maetzel A, Amor B. Prevention of acute anterior uveitis associated with spondyloarthropathy induced by salazosulfapyridine. *Revue du Rhumatisme*. 1993; 60:81–83. [PubMed: 7902159]
5. Munoz-Fernandez S, Hidalgo V, Fernandez-Melon J, Schlincker A, Bonilla G, Ruiz-Sancho D, Fonseca A, Gijon-Banos J, Martin-Mola E. Sulfasalazine reduces the number of flares of acute anterior uveitis over a one-year period. *J Rheumatol*. 2003; 30(6):1277–1279. Epub 2003/06/05. PubMed PMID: 12784403. [PubMed: 12784403]
6. Feltkamp TEW. HLA B27, acute anterior uveitis, and ankylosing spondylitis. *Advances in Inflammation Research*. 1985; 9:211–216.
7. Monnet D, Breban M, Hudry C, Dougados M, Brezin AP. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: a study of 175 cases. *Ophthalmology*. 2004; 111(4):802–809. [PubMed: 15051216]
8. Munoz-Fernandez S, de Miguel E, Cobo-Ibanez T, Madero R, Ferreira A, Hidalgo MV, Schlincker A, Martin-Mola E. Enthesis inflammation in recurrent acute anterior uveitis without spondylarthritis. *Arthritis Rheum*. 2009; 60(7):1985–1990. PubMed PMID: 19565479. [PubMed: 19565479]
9. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). *Ann Rheum Dis*. 2014 PubMed PMID: 24928841.
10. Rosenbaum JT. Characterization of uveitis associated with spondyloarthritis. *J Rheumatol*. 1989; 16(6):792–796. Epub 1989/06/01. PubMed PMID: 2778762. [PubMed: 2778762]
11. The HSG, Steven MM, van der Linden SM, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, New York and modified New York criteria in patients with a positive clinical history screening test for ankylosing spondylitis. 1985; 24:242–249.
12. Hollingsworth PN, Cheah PS, Dawkins RL, Owen ET, Calin A, Wood PH. Observer variation in grading sacroiliac radiographs in HLA-B27 positive individuals. *J Rheumatol*. 1983; 10(2):247–254. PubMed PMID: 6223140. [PubMed: 6223140]
13. Collantes-Estevez E, Ciscal del Mazo A, Munoz-Gomariz E. Assessment of 2 systems of spondyloarthropathy diagnostic and classification criteria (Amor and ESSG) by a Spanish multicenter study. European Spondyloarthropathy Study Group. *J Rheumatol*. 1995; 22(2):246–251. PubMed PMID: 7738946. [PubMed: 7738946]
14. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, Brunner HI, Ogawa R, Felson D, Ogdie A, Aletaha D, Feldman BM. Distinctions Between Diagnostic and Classification Criteria? *Arthritis Care Res (Hoboken)*. 2015; 67(7):891–897. PubMed PMID: 25776731; PMCID: 4482786. [PubMed: 25776731]
15. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, Braun J, Chou CT, Collantes-Estevez E, Dougados M, Huang F, Gu J, Khan MA, Kirazli Y, Maksymowych WP, Mielants H, Sorensen IJ, Ozgocmen S, Roussou E, Valle-Onate R, Weber U, Wei J, Sieper J. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009; 68(6):777–783. PubMed PMID: 19297344. [PubMed: 19297344]
16. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, Dougados M, Huang F, Gu J, Kirazli Y, Van den Bosch F, Olivieri I, Roussou E, Scarpato S, Sorensen IJ, Valle-Onate R, Weber U, Wei J, Sieper J. The Assessment of SpondyloArthritis International Society

- classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011; 70(1):25–31. PubMed PMID: 21109520. [PubMed: 21109520]
17. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, Arora V, Pangan AL. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis.* 2013; 72(6):815–822. PubMed PMID: 22772328; PMCID: 3664374. [PubMed: 22772328]
18. Song IH, Rudwaleit M. Certolizumab pegol in axial spondyloarthritis. *Expert Rev Clin Immunol.* 2013; 9(12):1161–1172. PubMed PMID: 24215406. [PubMed: 24215406]
19. Deodhar A, Reveille JD, van den Bosch F, Braun J, Burgos-Vargas R, Caplan L, Clegg DO, Colbert RA, Gensler LS, van der Heijde D, van der Horst-Bruinsma IE, Inman RD, Maksymowych WP, Mease PJ, Raychaudhuri S, Reimold A, Rudwaleit M, Sieper J, Weisman MH, Landewe RB. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol.* 2014; 66(10):2649–2656. PubMed PMID: 25154344. [PubMed: 25154344]
20. Boonen A, Sieper J, van der Heijde D, Dougados M, Bukowski JF, Valluri S, Vlahos B, Kotak S. The burden of non-radiographic axial spondyloarthritis. *Semin Arthritis Rheum.* 2015; 44(5):556–562. PubMed PMID: 25532945. [PubMed: 25532945]
21. Sampaio-Barros PD, Bortoluzzo AB, Conde RA, Costallat LT, Samara AM, Bertolo MB. Undifferentiated spondyloarthritis: a longterm followup. *J Rheumatol.* 2010; 37(6):1195–1199. PubMed PMID: 20436080. [PubMed: 20436080]
22. Jeong H, Yoon JY, Park EJ, Hwang J, Kim H, Ahn JK, Lee J, Koh EM, Cha HS. Clinical characteristics of nonradiographic axial spondyloarthritis in Korea: a comparison with ankylosing spondylitis. *International journal of rheumatic diseases.* 2015; 18(6):661–668. PubMed PMID: 25195726. [PubMed: 25195726]

Table 1

Classification criteria for ankylosing spondylitis

Rome Criteria	Modified New York Criteria
Low back pain 3 months, improved by exercise, not relieved by rest	Low back pain 3 months, improved by exercise, not relieved by rest
Limitation of lumbar mobility	Limitation of lumbar mobility
Limitation of chest expansion	Limitation of chest expansion
Pain and stiffness in the thoracic region	Sacroiliitis 2 bilaterally or grade 3 or 4 unilaterally
History of uveitis	Probable if 3 clinical criteria or single radiographic criterion
Bilateral sacroiliitis, at least grade 2	
Diagnosis based on any clinical criterion plus the radiographic criterion	
Definite if radiographic criterion and one clinical criterion	

Table 2

Classification Criteria for spondyloarthropathy

Amor Criteria for Spondyloarthropathy	ESSG Criteria for Spondyloarthropathy
<i>Score must be 6</i> Lumbar or back pain at night or morning stiffness (1) Asymmetric oligoarthritis (2) Buttock pain (1) if alternating (2) Dactylitis (2) Heel pain or enthesopathy (2) Iritis (1) Non-gonococcal urethritis or cervicitis (1) Psoriasis, balanitis, or inflammatory bowel disease (2) Sacroiliitis by NY criteria (3) HLA B27 + or Family history of AS, reactive arthritis, Uveitis, psoriasis, or IBD (2) Clear cut benefit from NSAIDs (2)	<i>Inflammatory back pain or synovitis plus one of the following:</i> Family history (1 st or 2 nd degree relative) of AS, iritis, reactive arthritis, IBD, or psoriasis History of IBD diagnosed by a physician History of psoriasis diagnosed by a physician Alternating buttock pain Achilles tendon pain or plantar fasciitis Diarrhea one month before onset of arthritis Non-gonococcal urethritis or cervicitis one month before onset of arthritis Radiographic sacroiliitis by NY criteria

Table 3

Classification criteria for axial or peripheral spondyloarthritis

ASAS Criteria for Axial Spondyloarthritis
<i>Sacroiliitis on imaging plus one of the following;</i>
<i>Or HLA B27 plus two of the following:</i>
Dactylitis
Psoriasis
Inflammatory back pain
Good response to NSAIDs
Arthritis
Elevated C reactive protein
Inflammatory bowel disease
HLA B27 +
Uveitis
Family history of spondyloarthropathy
ASAS criteria for peripheral spondyloarthritis
Arthritis/Enthesitis/ or Dactylitis Plus
1 of the following:
Uveitis
Psoriasis
Crohn's/colitis
Antecedent infection
HLA B27
Sacroiliitis on imaging
Or 2 of the following:
Arthritis
Enthesitis
Dactylitis
Inflammatory back pain
Family history of Spondylarthropathy