Thoughts concerning the early diagnosis of ankylosing spondylitis and related diseases

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ABSTRACT

The diagnosis of ankylosing spondylitis is mainly based on a radiograph of the sacroiliac joints. Thus, this is the standard imaging test. However, in the early phase of disease, conventional radiographs are often too insensitive to show sacroiliitis. In this clinical situation, HLA B27 testing and new imaging modalities such as magnetic resonance imaging may be helpful. Early forms of AS can be initially classified as undifferentiated spondyloarthritis. All subsets of spondyloarthritides may evolve later into AS. Since AS in association with psoriasis and chronic inflammatory bowel diseases is often HLA B27-negative, this test is of limited value under these circumstances. The usefulness of testing for HLA B27 and its subtypes differs among ethnic and racial groups. The value of this test for diagnosis depends on the individual pre-test probability in each setting.

Introduction

The diagnosis of ankylosing spondylitis (AS) and related spondyloarthropathies (SpA) is based on clinical features (1-8). Although, chronic inflammatory back pain and stiffness are usually the first or presenting manifestations of AS, they alone are of limited clinical value in disease diagnosis because a single clinical feature is not sufficient to make the diagnosis. The probability of the disease presence is enhanced when one or more additional features that are typical of AS/SpA are also present. There is no specific diagnostic laboratory test, and a normal erythrocyte sedimentation rate and/or serum C-reactive protein do not exclude disease presence.

Radiographic evidence of sacroiliitis is the best non-clinical indicator of the presence of AS, and is the most consistent finding (9). However, the status of the sacroiliac joints on routine pelvis radiographs may not always be easily interpretable in the early phase of the disease because of slow evolution in some patients, and also during adolescence (2-7). Some patients may not have have sacroiliitis detected by plain radiography for many years (10-15).

No validated diagnostic criteria

There are no validated *diagnostic* criteria for AS. The modified New York *classification* criteria set is commonly used in clinical practice, and it has 83% sensitivity and 98% specificity (4, 9). In other words, its *likelihood ratio positive* (calculated by taking the sensitivity, and dividing it by 1 minus specificity) is 41.5, and its *likelihood ratio negative* (1 minus sensitivity, divided by specificity) is 0.17. For the currently recognized wider spectrum of SpA, the most widely used classification criteria set is that recommended by the European Spondyloarthropathy Study Group (the ESSG criteria set) (16). It has been validated in various population groups, and its sensitivity and specificity generally exceed 85% (17-19), and when utilized for patients with AS, it has a sensitivity of 94%, and a specificity of 87%.

Delay in diagnosis

The diagnosis of AS is usually delayed by 5 to 6 years, especially among those with an early or incomplete clinical picture (2,7,10,11,13-15). Multiple referrals of such patients for the same symptoms often do not yield a correct diagnosis, and during this prolonged diagnostic delay, many unnecessary and invasive investigations are performed (2). The undifferentiated forms of SpA are very much underdiagnosed, and these include isolated clinical syndromes such as seronegative oligoarthritis or polyarthritis, mostly of the lower extremities, without any recognizable preceding bacterial infectious trigger (2,17,19-21). Such patients have no extra-articular clinical features, or associated inflammatory bowel disease or psoriasis. Some may have just dacty-

litis ("sausage digits") or enthesitis (Achilles tendonitis and plantar fasciitis) (6, 20-23). Others may present with an episode of acute anterior uveitis (acute iritis) or have a syndrome of aortic incompetence plus heart block (1-7, 24-29). This cardiacsyndrome as well as one or more episodes of acute anterior uveitis may occur in patients with no signs of arthritis or enthesitis, or these extra-articular features may accompany or follow the onset of arthritis. On a long term follow up, close to 70% of patients with undifferentiated SpA may ultimately evolve into AS (15).

Newer imaging modalities

An antero-posterior radiograph of the pelvis (AP view) is usually sufficient to detect sacroiliitis in affected patients (2,30,31). However, when there is a reasonably high clinical suspicion of early AS but standard radiography of the sacroiliac joints is normal or only shows equivocal changes, one may require computerized tomography (CT) or magnetic resonance imaging (MRI), particularly MRI with gadolinium enhancement (dynamic MRI). These imaging techniques, although quite expensive, produce excellent evidence of sacroiliitis, and can detect this finding earlier than conventional radiography (32-35). CT is more specific but less sensitive than MRI. MRI is radiation-free and is especially valuable in identifying sacroiliitis in children and adolescents. However, additional studies are required before dynamic MRI can be accepted as a better substitute for conventional radiography for early detection of sacroiliitis or for monitoring disease activity or progression.

There is therefore a place for a less expensive and non-invasive laboratory test as an aid to diagnosis of AS and related SpA in order to help minimize the degree of uncertainty of the diagnosis in certain clinical situations, such as equivocal results on conventional radiography. HLA-B27 typing could be such a laboratory test in this clinical situation, or when an unusual or atypical clinical presentation of AS is suspected, and in the diagnosis of undifferentiated forms of SpA (36-38).

Table I. HLA-B27 association with spondyloarthropathies in populations of western European extraction.

Disease	Approximate HLA-B27 prevalence (%)
Ankylosing spondylitis	~ 90%
Reactive arthritis	40 – 80%
Juvenile spondyloarthropathy	~ 70%
Enteropathic spondyloarthritis	35 – 75%
Psoriatic spondyloarthritis	40 – 50%
Undifferentiated spondyloarthropathy	~ 70%
Acute anterior uveitis (acute iritis)	~ 50%
Aortic incompetence with heart block	~ 80%
General healthy population*	~ 8%

*Although the prevalence of HLA-B27 in the general population of western European extraction (the so-called "whites") is generally stated as approximately 8%, there is a marked variation within that group and more so among the various Caucasoid population groups as a whole (see Table II).

HLA-B27 test as an aid to diagnosis

HLA-B27, an allele of the major histocompatibility complex, shows a strong association with AS and related SpA, including the undifferentiated forms (2, 5, 39). HLA-B27 is present in approximately 8% of the general white population (of western European extraction) and in more than 90% of patients with 'primary'AS (2,5). However, this association varies markedly among the different forms of SpA (Table I), and also among the many different ethnic/racial groups in the world, although it is generally quite strong, even in patients with the undifferentiated form. For example, in one Scandinavian study more than 80% of male AS patients with aortic incompetence and severe cardiac conduction disturbance, but without any musculoskeletal symptoms were positive for HLA-B27 (26). Approximately 50% of patients with acute anterior uveitis have this gene, and more than half of this subset (i.e., HLA-B27-positive patients) with acute anterior uveitis have some form of SpA (24, 25).

HLA-B27 is present in approximately 8% of the normal white population (of western European extraction) and in more than 90% of patients with 'primary' AS, indicating that HLA-B27 typing as a test for AS is highly specific (100 - 8 = 92%) and also highly sensitive (more than 90%) (Table I). In other words, the test is 8% "false-positive" (i.e., the HLA-B27 presence is unrelated to the clinical problem) and less than 10% "false-negative" (i.e., less than 10% of patients with 'primary'AS lack HLA-B27) in whites. Therefore, as with other clinical tests that are neither 100% sensitive nor 100% specific (40), the clinical usefulness (predictive value) of the HLA-B27 test depends on the clinical situation in which it is ordered (36-38).

The clinical usefulness of the HLA-B27 test differs appreciably among the various ethnic and racial groups. For example, as shown in Table II, there is a marked variation in the general prevalence of HLA-B27 in the various popu-

Table II. HLA-B27 prevalence among the Caucasoid population groups.

Population groups	HLA-B27 frequency (%)
Ugro-Finnish	12-18%
Northern Scandinavians	10-16%
Slavic populations	7-14%
Western Europeans	6-9%
Southern Europeans	2-6%
Sardinians	5%
Basques	9-14%
Gypsies (Spain)	16-18%
Arabs*, Jews, Armenians, & Iranians	3-5%
Pakistanis	6-8%
Indians (Asian)	2-6%

*Prevalence of B27 may be much lower (closer to 1%) in the United Arab Emirates and adjacent parts of Saudi Arabia, and among Lebanese Maronite Christian Arabs.

lations in the world (5, 41, 42). Therefore, the "false-positivity" of the test can vary markedly among different world populations. Moreover, as discussed below, the strength of the disease association with HLA-B27 also varies markedly among different races.

HLA-B27 typing as an aid for the diagnosis of AS is most useful when used in a clinical 'toss-up' situation; this principle is based on Bayesian analysis (37, 38). Thus, when the sacroiliac x-rays are equivocal or normal, and yet the patient shows clinical findings that suggest that the pre-test probability of AS is anywhere between 30-70%, HLA-B27 typing can be clinically useful.

The prevalence (i.e. the pre-test probability) of AS/SpA among all patients presenting to a primary care physician with chronic low back pain is very low, because back pain is a very prevalent condition and has diverse etiologies (2, 43). Let us assume that the pre-test probability of AS/SpA may be about 5%, but if the chronic back pain has inflammatory features, then the probability of AS increases to 14%. When the result of sacroiliac roentgenography is equivocal/negative, the additional presence of one or more of the other clinical features of AS/SpA increases the probability of inflammatory disease to the above mentioned clinical toss-up range. These clinical features may include the presence of a history of acute anterior uveitis, a family history of AS or related diseases, impaired spinal mobility, or diminished chest expansion. Another clinical clue can be the presence of enthesitis with resultant tenderness over the sacroiliac joints and the spine, and sometimes at other sites, such as the heels, iliac crest, and anterior chest (2, 38). If HLA-B27 testing is done in such a patient (with approximately 50% pre-test probability of AS) who is white and the result is positive, the probability of early AS/SpA increases to 80-90%. A negative result will markedly drop that probability down to 2%.

As a rule, in those patients in whom the history and physical examination suggest AS, but radiographic findings do not permit this diagnosis to be made, the HLA-B27 test may allow the presumptive diagnosis of AS to be accepted or rejected with less uncertainty. In patients with back pain or arthritis in whom AS is suggested neither by history nor by physical examination, HLA-B27 testing is inappropriate because a positive result would still not permit the diagnosis of AS to be made.

The clinical usefulness (predictive value) of a positive test result will be highest in those population groups in which HLA-B27 has low general prevalence but still shows a strong association with AS. This is the case among the Japanese, who show a strong association (> 85%) of HLA-B27 with AS, but this gene is present in less than 1% of their general population (Table III). On the other hand, a positive test result will be relatively less useful among Eskimos (in spite of a strong association of HLA-B27 (> 90 %) with AS because of a high prevalence of HLA-B27 (25% - 40%) in the general population. If the HLA-B27 test is ordered in an Eskimo patient in whom the pre-test probability of AS or a related SpA is very low and the test result is positive, the probability that the patient has the disease still remains relatively low.

Among African Americans, on the other hand, HLA-B27 is present in 2 to 4% of the general population, but in only about 50% of AS patients (36). Therefore, if the HLA-B27 test were ordered because of a reasonable clinical suspicion ('toss-up' situation) of AS, the likelihood of the disease presence would be markedly strengthened by a positive test result. However, a negative test result would be of little value in

Table III. Prevalence of HLA-B27 in other population groups. (The numbers are rounded off for simplicity, and indicate percentage prevalence in the general population).

Population groups	HLA-B27 frequency (%)
Native American populations divided by linguistic groups	
Eskimo-Aleut	25-40%
Na-Dene (Haida Tlingit Dogrib Navajo)	20-50%
Amerind	
North American	7-26%
Mexicans Mestizo	3-6%
Central American	4-20%
South American	0%
North and Central Asiatic linguistic population groups	
Chukchic	19-40%
Uralic	8-24%
Altaic	
Siberians	6-19%
Japanese	< 1%
Ainu (Native Japanese)	4%
Koreans	3-8%
Mongolians	3-9%
Uygurs, Kazakhs, Turkic, Uzbek	3-8%
Sino-Tibetan	
Chinese	2-9%
Tibetans	12%
Other Asiatic population groups	
Southeast Asians	5-12%
Micronesians (Nauru, Guam)	2-5%
Melanesians (Papua New Guinea, Fiji, etc.)	4-26%
Polynesians	0-3%
Australian Aborigines	0%
African population groups	
North Africans	1-5%
West Africans (Mali, Gambia & Senegal)	2 -10%
Pygmies	7-10%
Bantu (Nigeria, Southern Africa)	0%
San (Bushmen)	0%

excluding the disease because 50% of African American patients with AS lack this gene (36).

The HLA-B27 test should not be thought of as a 'routine', 'diagnostic', 'confirmatory' or 'screening' test for AS in patients presenting with back pain or arthritis (36-38). Most patients with AS presenting to a rheumatologist can be readily diagnosed clinically on the basis of the history, physical examination and radiographic findings, and they do not need to be tested for HLA-B27. Moreover, this test does not help to distinguish between AS, reactive arthritis and other SpA, because all of these diseases are associated with HLA-B27, although the strength of such an association varies among these diseases. The differentiation between the various forms of SpA is based primarily on clinical grounds.

Although HLA-B27 typing can define a population at a higher risk for AS and related SpA, it is of very limited practical value for that purpose because no effective means of prevention are currently available. Moreover, most HLA-B27 positive persons in the general population never develop AS or related diseases. However, HLA-B27 typing may help an ophthalmologist better define a patient presenting with acute anterior uveitis, and refer HLA-B27 positive patients for rheumatology consultation, especially those with associated musculoskeletal symptoms. The justification for such a referral is based on the fact that up to 75% of such patients have or will develop AS or related SpA (24, 25).

Patients with AS or related SpA who are HLA-B27 more often have acute anterior uveitis, hip joint involvement, and aortic incompetence plus heart block, than those who do not have this gene. Moreover, HLA-B27 positive patients tend to develop disease at a younger age and more often show familial aggregation of AS and related SpA (2, 5, 44, 45). HLA-B27 is also associated with development of more severe and prolonged joint symptoms in reactive arthritis, and an increased risk for sacroiliitis and spondylitis. However, knowledge of HLA-B27 status at disease onset in an individual patient is of uncertain value in predicting the patient's long-term prognosis. On rare occasions, HLA-B27 typing can be clinically helpful when there is difficulty in the roentgenographic differential diagnosis of ankylosing hyperostosis (Forestier's disease) and AS (46).

HLA-B27 itself is not an allele but a family of at least 25 different alleles – HLA-B*2701 to B*2725 (39,47). Their assignment to the HLA-B27 family is based on nucleotide sequence homology that results in nearly all members of the family typing as HLA-B27 using traditional serologic methods. These alleles, also called subtypes, differ from each other by one or more amino-acid substitutions, mostly resulting from changes in exons 2 and 3, which encode the alpha 1 and the alpha 2 domains, respectively, that form the peptide binding cleft (39). The most widely distributed subtype around the world is HLA-B*2705, and it is clearly associated with AS and related SpA except in the West African populations of Senegal and Gambia (39,47). HLA-B* 2704, another strongly disease associated subtype, is predominant among Chinese and Japanese populations (39, 47).

Not all of the HLA-B27 subtypes are equally disease associated. Data from Southeast Asia indicate that HLAB* 2706 may not be associated with AS and related SpA (48, 49). HLA-B* 2709, a subtype primarily observed among Italians residing on the island of Sardinia, seems to lack any association with AS among Sardinians (50), although a few patients with undifferentiated SpA (but lacking inflammatory back pain or sacroiliitis) have been reported from the Italian mainland (51). The clinical need to request HLA-B27 subtyping does not arise for physicians who are not confronted with patients from Southeast Asia or Sardinia.

Concluding remarks

In conclusion, the status of the SI joints on routine pelvic radiographsis is the "best test" in the diagnosis of AS and related SpA, and is relatively easily interpreted in most patients. However, the radiograph may not always be easy to interpret in the early phase of AS and related SpA, especially in adolescent patients. Use of better imaging modalities or HLA-B27 test can be helpful in such situations by decreasing diagnostic uncertainty. As a rule, in those patients in whom AS is suspected clinically but radiographic findings do not permit this diagnosis to be made, the HLA-B27 test may allow the *presumptive* diagnosis of AS to be accepted or rejected with less uncertainty. In patients with back pain or arthritis in whom AS is not suggested by history or by physical examination, HLA-B27 testing is inappropriate because a positive result would still not permit the diagnosis of AS to be made.

Clinical usefulness of the HLA-B27 test may differ appreciably among various ethnic and racial groups, and is highest in those population groups that have a low general prevalence of HLA-B27 and yet show a strong disease association. The test is most useful when the physician faces a clinical 'toss-up' situation, i.e., 30-70% pre-test probability of disease, and the sacroiliac radiographs are either normal or demonstrate possible (equivocal) sacroiliitis. Routine HLA-B27 testing is not clinically advisable; SpA can occur in its absence, and no preventive or curative therapy is available that would justify this test in unaffected or asymptomatic relatives of HLA-B27 positive patients. Close to 90% of HLA-B27 positive individuals in the general population will never develop any form of SpA, although the risk is increased three-fold (30% instead of 10%) among those HLA-B27-positive persons who have a first-degree relative affected with AS.

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