

Review article

HLA-B27 and spondyloarthropathy: value for early diagnosis?

Jan Tore Gran, Gunnar Husby

The seronegative spondyloarthropathy complex

The seronegative spondyloarthropathy complex embraces a group of inflammatory rheumatic disorders linked together by certain clinical, laboratory, and radiological manifestations.

Clinically, the disorders are characterised by asymmetrical peripheral oligoarthritis and involvement of the sacroiliac joints (table 1). Manifestations in the eyes, mucocutaneous membranes, and genitourinary system not infrequently accompany the often predominant arthritis. The patients lack detectable rheumatoid factors in serum, hence the term "seronegative". Other serum autoantibodies, often found in inflammatory rheumatic diseases, are notably absent in the spondyloarthropathies. Unlike in rheumatoid arthritis, radiological examinations of peripheral joints rarely show destructive changes. However, radiological sacroiliitis is essential for the diagnosis of many of these diseases.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is regarded as the prototype of the seronegative spondyloarthropathies (table 1). In its classic but quite rare form, complete ankylosis of the whole spine develops within a few years. More often, however, the clinical picture is dominated by pain and stiffness of the back with radiological examination showing sacroiliitis and varying degrees of spinal inflammation.¹

Table 1 The seronegative spondyloarthropathy complex: disorders, common disease manifestations, and frequencies of HLA-B27

Disorders	%
Ankylosing spondylitis	90-95
Reiter's disease	70-85
Reactive arthritis	36-100
Psoriatic arthritis	54
Arthritis in inflammatory bowel diseases	50
<i>Manifestations</i>	
Seronegativity for rheumatoid factors	
Absence of antinuclear antibodies	
Absence of rheumatic nodules	
Peripheral arthritis	
Genitourinary (urethritis, vaginitis, balanitis)	
Mucocutaneous (stomatitis, dermatitis)	
Intestinal (enteric infections or chronic inflammation)	
Radiological sacroiliitis	
Genetic (familial aggregation, HLA-B27)	

REACTIVE ARTHRITIS

Reactive arthritis (ReA) is a term introduced by Aho *et al*² in 1973. It denotes an asymmetrical non-infectious arthritis in a few joints, appearing days or weeks after infection elsewhere in the body, most often in the genitourinary or gastrointestinal system. Previously, the term postinfectious arthritis was preferred.

PSORIATIC ARTHRITIS

The arthritis associated with psoriasis is most often localised to a few joints in an asymmetrical pattern, frequently affecting the distal interphalangeal joints of the hands.³ It occasionally manifests radiological sacroiliitis, but complete ankylosis of the spine ("bamboo spine") is definitely less frequent than in AS. Psoriatic arthritis (PsA) may also present a clinical picture almost indistinguishable from that of rheumatoid arthritis. Although serum rheumatoid factors are notably absent, this form of psoriatic arthritis affecting peripheral joints bears little resemblance to the other spondyloarthropathies.

INFLAMMATORY BOWEL DISEASES

A seronegative arthritis may also accompany the inflammatory bowel disorders ulcerative colitis and Crohn's disease.⁴ As in other spondyloarthropathies, radiological sacroiliitis may be seen.

A striking feature of the seronegative spondyloarthropathies is the association with the histocompatibility antigen HLA-B27.

The association between HLA-B27 and spondyloarthropathy

The study of products of genes located on a region of chromosome 6, known as the major histocompatibility complex, has provided valuable insight into many diseases of as yet unknown aetiology. In 1973, two independent groups of workers found a striking association between one of these genes, HLA-B27 and AS.^{5,6} Subsequently, associations between HLA-B27 and ReA and PsA were established.^{7,8} Why subjects carrying HLA-B27 are prone to develop spondyloarthropathy is not fully understood.⁹

Department of Rheumatology, Aust Agder Central Hospital, 4800 Arendal, Norway
J T Gran

Oslo Sanitetsforening Rheumatism Hospital, Oslo, Norway
G Husby

Correspondence to: Dr Gran.

Table 2 Diagnostic criteria and tentative disease definitions for various seronegative spondyloarthropathies

New York criteria for ankylosing spondylitis

- (1) Limitation of motion of the lumbar spine in all three planes (anterior flexion, lateral flexion, and extension).
- (2) History or the presence of pain at the dorsolumbar junction or in the lumbar spine.
- (3) Limitation of chest expansion to 2.5 cm or less, measured at the level of the fourth intercostal space.

The diagnosis of ankylosing spondylitis requires the presence of grade 3–4 bilateral sacroiliitis with at least one clinical criterion, or grade 3–4 unilateral or grade 2 bilateral with criterion 1 or with both clinical criteria 2 and 3.

Reactive arthritis

A seronegative arthritis occurring shortly after infection in the genitourinary or gastrointestinal canal.

Reiter's syndrome

One or more episodes of urethritis or conjunctivitis in connection with seronegative arthritis.

Psoriatic spondylitis

Pain/stiffness of the spine with radiological examination showing sacroiliitis/spondylitis in a patient with psoriasis.

Spondylitis in inflammatory bowel disease

Pain/stiffness of the spine with radiological examination showing sacroiliitis/spondylitis in a patient with either Crohn's disease or ulcerative colitis.

HLA-B27 IN SPONDYLOARTHROPATHIES

Approximately 95% of white patients with AS are HLA-B27 positive¹⁰ (table 1). The prevalence of HLA-B27 among patients with ReA appears somewhat less, about 70–85%⁷ (table 1). In PsA, there is a clear association between HLA-B27 and the group of patients exhibiting radiological sacroiliitis,⁸ whereas the frequency of this tissue antigen among cases with symmetrical polyarthritis resembling rheumatoid arthritis equals that in the general population.⁸ In the inflammatory bowel disorders, HLA-B27 does not confer an increased risk of contracting peripheral arthritis,⁴ but a moderate association between HLA-B27 and spondylitic disease is present.⁴

HLA-B27 IN VARIOUS POPULATIONS

The distribution of HLA-B27 among various ethnic groups appears strikingly uneven.¹¹ Among certain North American Indians, Lapps, and inhabitants of northern Scandinavia the frequency of HLA-B27 ranges from 26 to 50%.¹¹ Most European populations show B27 prevalences between 7 and 10%.¹¹ In blacks, HLA-B27 is virtually absent.¹¹

Diagnostic value of HLA-B27 in spondyloarthropathy

DEFINITE DIAGNOSES

The diagnostic criteria and tentative definitions of various seronegative spondyloarthropathies are given in table 2. Clearly, none of the diseases under consideration requires a positive HLA-B27 test for a definite diagnosis. All diagnoses are based on the appearance of certain clinical signs and symptoms, and for AS the demonstration of radiological sacroiliitis is mandatory for diagnosis.¹²

SENSITIVITY AND SPECIFICITY

The diagnostic value of the HLA-B27 test for AS in a randomly selected person can be

obtained by expressing the test sensitivity. Sensitivity is defined as the proportion of patients with positive test results, and is between 90 and 95% in AS. The specificity of the test gives the proportion of healthy subjects with negative test results (HLA-B27 negative). With a prevalence of AS of 0.1%, a population frequency of HLA-B27 of 10%, and a sensitivity of 95%, the specificity of the HLA-B27 test in AS is 90.1%. If the prevalence of AS amounts to 1%, the specificity is 90.8%.

PREDICTIVE VALUE OF A POSITIVE HLA-B27 TEST

The predictive value indicates the proportion of HLA-B27 positive AS patients among persons with HLA-B27. Populations who have a prevalence of HLA-B27 of 10%, disease prevalences of 0.1% and 1%, would give predictive values of 0.95% and 9.5%, respectively. These figures correspond well to the findings in epidemiological surveys, in which it has been calculated that between 1 and 6% of persons with HLA-B27 suffer from AS.¹⁰

PREDICTIVE VALUE OF A NEGATIVE HLA-B27 TEST

This figure gives the proportion of persons without HLA-B27 who are healthy. It can be calculated that the probability of not having AS for a HLA-B27 negative person is about 99.9%.

INTERPRETATIONS OF THE STATISTICAL CALCULATIONS

From the above mentioned statistical considerations, it can be concluded that although the HLA-B27 test exhibits both high sensitivity and specificity, the test cannot be used to diagnose AS in randomly selected persons. The predictive value of a positive test which is between 0.95 and 9.5% indicates that the overwhelming majority of HLA-B27 positive persons do not suffer from AS. Thus, HLA-B27 appears not to be useful as a screening test for AS among randomly selected persons.

However, the predictive value of a negative test result for the absence of AS reaches exceptionally high values. Consequently, the chance of having AS for a person without HLA-B27 is extremely low. The HLA-B27 test may therefore possess some value in clinical practice when dealing with randomly selected persons. A negative test result should be interpreted as an exclusion criterion for the diagnosis of AS. However, this is unrealistic as there is no reason to test for HLA-B27 in randomly selected persons. The HLA-B27 test should always be performed after clinical suspicion of seronegative spondyloarthropathy has been evoked. Thus, the discussion of the potential use of this test is reserved for cases presenting with symptoms and signs suggestive of seronegative spondyloarthropathy.

PRETEST LIKELIHOOD

In epidemiological surveys it has been found that the prevalence of AS among HLA-B27

positive persons with back pain or stiffness is as high as 22.5%.¹⁰ This figure clearly contrasts the estimate of a 1 to 6% prevalence of AS among a random sample of B27 positive people. Thus, selecting people with back pain and stiffness for B27 testing increases the likelihood of finding AS.

However, more than 75% of cases with back pain and stiffness suffer from diseases other than AS. Thus, the pretest likelihood must be increased further to meet the cost-benefit demands. It has been calculated¹³ that for a positive HLA-B27 test to provide an acceptable 95% chance that the diagnosis is correct, the physician must be more than 50% certain of the diagnosis before the test is performed. Unfortunately, the many attempts at constructing useful clinical diagnostic criteria for AS independent of radiological examination have all been unsuccessful.^{14,15} At present it seems difficult to diagnose AS clinically with a 50% chance of correct diagnosis. Consequently, HLA-B27 does not appear helpful in differentiating spondyloarthropathies meeting traditional definitions from other causes of back complaints.

THE CONCEPT OF UNDIFFERENTIATED SPONDYLOARTHROPATHY AND SPONDYLITIC DISEASE

It has been suggested recently that the traditional clinical view on diagnosing seronegative spondyloarthropathies should be broadened.¹⁶ Some workers have suggested that AS may manifest with clinical symptoms of inflammatory back pain but without the radiological features of classical AS.¹⁶ In family studies this clinical picture appears significantly associated with HLA-B27. It has been found that between 13 and 18% of B27 positive first degree relatives of B27 positive cases express clinical symptoms of inflammatory spinal disease without concomitant radiological signs of the disease. The clinical picture has been entitled "spondylitic disease".¹⁶

A new set of classification criteria for spondyloarthropathies has also been suggested¹⁷ (table 3). According to these criteria, a diagnosis of undifferentiated spondyloarthritis is preferred in patients who complain of inflammatory spinal pain or synovitis and in addition have psoriasis, inflammatory bowel disease, positive familial history, or enthesopathy.¹⁷

If the concept of AS is broadened to include such clinical pictures, the value of HLA-B27 testing, especially in first degree relatives of AS

probands, should be re-evaluated. Until the aetiology of AS has been described, these suggestions cannot be proven nor refuted.

However, the eventual clinical usefulness of expanding the diagnostic net of spondyloarthropathies may be disputed. Evidently, no effective prophylaxis is available for either the classical spondyloarthropathies or for the "new" group of spondylitics. Thus, adding a new group of patients to the already existing cases of AS does not help to solve the primary task of medicine, to prevent disease development.

Moreover, we do not know the effect of therapy on these new syndromes. To diagnose "spondylitic disease" for the benefit of early therapy, whether physical therapy or administration of drugs, does not seem justified. Furthermore, whether or not undifferentiated spondyloarthritis in due time will lead to restricted mobility of the spine and chest as seen in AS is not yet known, so the purpose of physical therapy directed at increasing spinal mobility appears limited.

Finally, another important problem is adequate patient information. At present, the possible risk of developing disease complications, such as cardiac conduction disturbances, dislocations of the upper cervical spine, and renal amyloidosis has not been studied properly. Thus, defining a new group of spondylitics creates the problem of offering adequate patient information regarding disease outcome. However, the concept of a wider spectrum of HLA-B27 associated spondyloarthritis is intriguing and the cases under consideration should be subjected to research based follow up and further clinical and laboratory analyses.

It should also be stressed that the new criteria¹⁷ were primarily meant to serve as classification criteria and not as a diagnostic aid in everyday clinical practice. Unfortunately, classification criteria are often confused with diagnostic criteria and the confusion is not infrequently enhanced by the general accessibility of the HLA-B27 test. Therefore, it seems necessary to review the individual clinical syndromes of the seronegative spondyloarthritis complex and their associations with HLA-B27.

VALUE OF THE B27 TEST IN PATIENTS WITH ASYMMETRICAL PERIPHERAL OLIGOARTHRITIS

The presence of asymmetrical peripheral arthritis in a few joints may raise the suspicion of either psoriatic arthritis (PsA) or reactive arthritis (ReA).

In young and middle aged patients with an acute onset of oligoarthritis in the absence of psoriasis, ReA is a likely diagnosis. A definite diagnosis is based on the findings of serological or microbiological evidence of genitourinary or gastrointestinal infection antedating the arthritis. As the prevalence of HLA-B27 among cases with ReA is lower than in AS, the predictive value of both a positive and a negative test is less when compared to AS. Although the presence of HLA-B27 may increase the

Table 3 European Spondylarthropathy Study Group (ESSG) preliminary classification criteria for spondyloarthropathies

Inflammatory spinal pain or synovitis
Asymmetrical
Predominantly in the lower limb
And one of the following
Positive family history
Psoriasis
Inflammatory bowel disease
Alternate buttock pain
Enthesopathy

suspicion of ReA, it remains unhelpful as an aid to diagnosis.

In PsA, the association between spondylitis and HLA-B27 is less pronounced than that of AS and ReA.⁸ At most, the frequency of HLA-B27 in psoriatic spondylitis is about 50%.⁸ Consequently, the predictive diagnostic value of the HLA-B27 test in psoriatic spondylitis does not meet the demands of clinical medicine.

THE VALUE OF HLA-B27 IN JUVENILE CHRONIC ARTHRITIS

In contrast to adult AS, juvenile AS less frequently causes symptoms of axial skeleton disease at onset.¹⁸ Perhaps as few as 24% of children complain of pain and stiffness of the lumbar spine.¹⁸ Instead, manifestations from the peripheral joints often dominate the initial clinical picture. The association between juvenile AS and HLA-B27 is, however, as strong as that in adult disease.¹⁸ In patients with established juvenile chronic arthritis a positive HLA-B27 test can be of help in focusing the diagnosis towards development of AS later on. However, the test shows the same limitations as in adult AS, and cannot be regarded as of diagnostic value.

THE VALUE OF HLA-B27 IN ACUTE UVEITIS

It has been found that the prevalence of HLA-B27 is increased to about 50% in acute anterior uveitis (AAU),¹⁹ and that between 15 and 25% of the patients have clinical and radiographic evidence of AS.¹⁹ Thus, even in the absence of concomitant AS, AAU seems to be associated with HLA-B27, and the test appears to be of limited value in diagnosing coexisting AS.

Patients with AAU should not undergo routine rheumatological examinations. Only those cases with AAU who report significant stiffness or pain of the back or peripheral joints should be referred to a rheumatologist for further examination.

SCREENING FOR HLA-B27 IN FAMILIES OF AS PROBANDS

As HLA-B27 is inherited in a codominant fashion, the prevalence of HLA-B27 among first degree family members will be in the order of 25 to 100%, depending on homozygosity and HLA status of the mate. The prevalence of AS among first degree relatives of AS probands has been estimated as 1.3 to 11%.^{20,21} Consequently, only a small proportion of HLA-B27 positive probands will develop AS as defined by traditional diagnostic criteria. Moreover, as no prophylaxis is available to prevent the development of AS, there is no cause for routine testing of HLA-B27 among family members. The determination of HLA-B27 in first degree relatives of AS probands will only increase the risk of introducing "iatrogenic HLA-B27-itis".

As discussed earlier, clinical spondylitic disease is suggested to occur quite frequently among HLA-B27 positive family members of AS probands.¹⁶ It is the authors' opinion that the problems associated with this diagnosis are

so significant that HLA-B27 typing based on the assumption of clinical spondylitic disease is not justified.

HLA-B27 AS A CONFIRMATORY TEST IN AS

The diagnosis of AS rests on the demonstration of radiological sacroiliitis in patients having pain or stiffness of the back. The demonstration of a negative HLA-B27 test in such cases will not alter the diagnosis. The absence of HLA-B27 in a patient with AS should, however, alert the physician to the possibility of concurrent psoriasis or inflammatory bowel disease. There are undoubtedly, however, true cases of HLA-B27 negative cases of AS showing no signs of concurrent dermatological or intestinal disease.

HLA-B27 AND PROGNOSIS IN AS

Apart from a higher prevalence of AAU in B27 positive subjects compared to B27 negative cases, the clinical picture appears similar in B27 positive and B27 negative AS.²² As more than 90% of AS patients carry B27, and only 25% contract AAU, tissue typing is of no help in selecting those cases that are prone to develop eye complications.

Conclusions

HLA-B27 is essential to the aetiopathogenesis of spondyloarthropathies. This statement has been so widely accepted that the term "HLA-B27 associated disease" is sometimes used to replace "the seronegative spondyloarthropathy complex" introduced by Moll *et al.*²³ However, for the practising physician it is important to bear in mind that only a minority of HLA-B27 positive subjects contract a "B27 associated disease" and that the overwhelming majority of patients with musculoskeletal complaints do not suffer from inflammatory rheumatic disease. These two simple facts should serve as guidelines to the use of the HLA-B27 test in everyday clinical practice.

It is our conviction that the benefit of the HLA-B27 test is very limited. The test cannot be used for confirming a diagnosis of spondyloarthropathy or predicting the prognosis in patients with an established diagnosis of inflammatory rheumatic disease. The test can be used in three ways.

First, if the likelihood of spondyloarthropathy based on symptoms and signs is greater than 50%, a B27 positive test result significantly increases the chance of a correct diagnosis. Such a high pretest likelihood, however, requires reliable clinical diagnostic criteria which are not readily available in rheumatology. It is, however, our hope that such criteria will be developed in the near future.

Secondly, in patients with back pain and stiffness, a negative B27 test result very strongly indicates that the complaints are caused by diseases other than AS. In the absence of concurrent psoriasis or inflammatory bowel disease, a negative B27 test result virtually excludes a diagnosis of AS, provided the test is properly done.

Thirdly, a positive B27 test in children with established inflammatory joint disease may help the physician focus on a possible development of seronegative spondyloarthropathy.

Today's increasing demands for an effective and rationalised health system do not allow uncritical use of expensive laboratory tests. The results of such tests may at worst lead to incorrect diagnoses and initiation of therapeutic strategies of virtually no benefit to the patients.

- 1 Gran JT, Husby G. Ankylosing spondylitis: a comparative study of patients in an epidemiological survey and those admitted to a department of rheumatology. *J Rheumatol* 1984;11:788-93.
- 2 Aho K, Ahvonen P, Lassus A, Sievers K, Tiilikainen A. HLA antigen 27 and reactive arthritis. *Lancet* 1973; ii: 157.
- 3 Wright V. Arthropathia psoriatica. A clinical entity? *Scand J Rheumatol* 1980;suppl 32:25-30.
- 4 Gran JT, Husby G. Joint manifestations in gastrointestinal diseases. *Dig Dis* 1992;10:274-94.
- 5 Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DCO, Sturrock RD. Ankylosing spondylitis and HL-A27. *Lancet* 1973;i:904-7.
- 6 Schlosstein L, Terasaki PI, Bluestone R, Pearson CM. High association of an HL-A antigen, w27, with ankylosing spondylitis. *N Engl J Med* 1973;288:704-6.
- 7 Calin A. Reiter's syndrome: epidemiology and immunogenetics. *Scand J Rheumatol* 1980;suppl 32:178-83.
- 8 Scarpa R, Oriente P, Pucino A. The clinical spectrum of psoriatic spondylitis. *Br J Rheumatol* 1988;27:133-7.
- 9 Khan MA. Spondyloarthropathies. *Curr Opin Rheumatol* 1993;5:405-7.
- 10 Gran JT, Husby G, Hordvik M. Prevalence of ankylosing spondylitis in males and females in a young middle-aged population in Tromsø, northern Norway. *Ann Rheum Dis* 1985;44:359-67.
- 11 Gran JT, Husby G. The epidemiology of ankylosing spondylitis. *Semin Arthritis Rheum* 1993;22:319-34.
- 12 Moll JMH, Wright V. New York clinical criteria for ankylosing spondylitis. *Ann Rheum Dis* 1973;32:354-63.
- 13 Hawkins BR, Dawkins RL, Christiansen FT, Zilko PJ. Use of the B27 test in the diagnosis of ankylosing spondylitis: a statistical evaluation. *Arthritis Rheum* 1981;24:743-6.
- 14 Gran JT. An epidemiological survey of the signs and symptoms of ankylosing spondylitis. *Clin Rheumatol* 1985;4: 161-9.
- 15 Baron M, Zeidel I. HLA-B27 testing in ankylosing spondylitis: an analysis of pretest assumptions. *J Rheumatol* 1989;16:631-6.
- 16 Khan MA, van der Linden SM, Kushner I, Valkenburg HA, Cats A. Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. *Arthritis Rheum* 1985;28:40-3.
- 17 Khan MA, van der Linden SM. Ankylosing spondylitis and other spondyloarthropathies. *Rheum Dis Clin North Am* 1990;16:551-79.
- 18 Cassidy JT, Petty RE. Spondyloarthropathy. In: Cassidy JT, Petty RE, eds. *Textbook of pediatric rheumatology*. 2nd ed. New York: Churchill Livingstone, 1990:221-59.
- 19 Brewerton DA, Webley M, Murphy AH, Ward AM. The alpha-1-antitrypsin phenotype MZ in acute anterior uveitis. *Lancet* 1978;i:1103.
- 20 Rogoff B, Freyberg RH. The familial incidence of rheumatoid spondylitis. *Ann Rheum Dis* 1949;8:139-42.
- 21 van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. *Arthritis Rheum* 1984;27:241-9.
- 22 Linssen A, Feltkamp TEW. B27 positive diseases versus B27 negative diseases. *Ann Rheum Dis* 1988;47:431-9.
- 23 Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies and Behcet's syndrome. *Medicine (Baltimore)* 1974;53:343-64.