Abstract:

Objectives: Ankylosing spondylitis should be a diagnostic consideration in young patients with back pain, particularly young men. Simple clinical and diagnostic methods can distinguish between back pain due to ankylosing spondylitis and back pain caused by other factors. Early diagnosis allows the clinician to prescribe anti-inflammatory therapy, to identify extra-articular involvement, and to provide counseling on the importance of maintaining proper posture. Perhaps more important, early diagnosis can avoid the costly and unnecessary diagnostic or therapeutic procedures that may be performed if back pain is misdiagnosed as mechanical. Ankylosing spondylitis (AS) is an inflammatory rheumatic disease which is thought to be rarely seen in Kashmiri ethnic population. Its genetic predisposition has been stressed in Caucasians where the HLA-B27 antigen is firmly linked to the disease.

Methods: In the present study, HLA-B27 antigen was determined in 266 patients suffering from low back pain from last six years referred to our Department from osteoarticular disease clinics.

Results: Only 5 of these subjects were found to possess HLA-B27 antigen.

Conclusions: This hospital based study correlates the low frequency of HLA-B27 with the observed scarcity of AS in patients attending tertiary care centre in Sheri Kashmir Institute of Medical Sciences, Srinagar, for osteoarticular diseases.

Keywords: Ankylosing spondylitis, HLA-B27, Back pain, Osteoarticular diseases, Ethnic, Caucasians.
INTRODUCTION

HLA-B27 is a MHC class I molecule consisting of an alpha chain encoded in the MHC region on chromosome 6 and a non-MHC encoded beta chain, β₂ microglobulin. 26 different alleles have been identified which code for 24 different proteins designated HLA-B*2701–B*2725, B*2722 was deleted on the discovery that it had the same sequence as B*2706 (Khan et al., 2002). These allotypes differ from one another by a few amino acid substitutions and the multiple alleles may have evolved from the most widespread subtype, B*2705. They vary in frequency among ethnic and racial groups and at least two of them, B*2706 in South East Asia and B*2709 in Sardinia, do not seem to be linked with ankylosing spondylitis.

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease of the spine involving the sacroiliac joint and is sometimes associated with an asymmetrical peripheral arthritis and other extraarticular manifestations. The exact etiology of the disease is still unknown. However, the genetic predisposition to AS has been stressed for many years, because between 88% and 96% of patients carry the tissue type antigen HLA-B27 compared with between 4% and 8% of the normal population (Benjamin et al., 1990; Dausset et al., 1989; Sieper et al., 1996; Colombani et al., 1993). The prevalence of the disease in people with HLA-B27 is about 1% and the relative risk for subjects with HLA-B27 of developing AS is 30 to 400 fold that of the normal population. A higher prevalence of HLA-B27 is seen in Haida Indians, but it is less common in Negroes than in Caucasians, with an overall male predominance (Sieper et al., 1996). The risk factors that predispose a person to ankylosing spondylitis include:

Testing positive for the HLA-B27 marker
A family history of AS
Frequent gastrointestinal infections

Unlike other forms of arthritis and rheumatic diseases, general onset of AS commonly occurs in younger people, between the ages of 17-35. However, it can affect children and, those who are much older. The AS prevalence in Caucasians is 0.1%. HLA-B27 positive Caucasians have a 20-fold risk of developing any spondylarthropathy, particularly ankylosing spondylitis and undifferentiated spondarthritis (Braun et al., 1998). Although the exact cause of AS is unknown, we do know that genetics play a key role in AS. Most individuals who have AS also have a gene that produces a "genetic marker" - in this case, a protein - called HLA-B27. This marker is found in over 95% of people in the caucasian population with AS as the association between ankylosing spondylitis and HLA-B27 varies greatly between ethnic and racial groups. In a European population study, ankylosing spondylitis was found in 1.3% of HLA-B27 positive individuals in the population at large and in 21% of HLA-B27 positive relatives of B27 positive patients with spondylitis, giving a 16-fold risk of ankylosing spondylitis in HLA-B27 positive relatives compared with B27 positive individuals in the general population (Van der Linden et al., 1984). Family and twin studies of ankylosing spondylitis have shown a polygenic pattern of genetic susceptibility with heritability in excess of 90%. The contribution of HLA-B27 to genetic susceptibility has been estimated to be 20–50% of the total (Brown et al., 1998). Other HLA alleles, most notably HLA-B60 and HLA-DR1, may predispose to ankylosing spondylitis either independently of B27 or in conjunction with it (Brown et al., 1997). Homozygosity for HLA-B27 does not appear to enhance the risk of developing ankylosing spondylitis. Non-MHC susceptibility loci have been identified on other chromosomes (Laval et al., 2001) whilst other HLA genes may have a protective effect against ankylosing spondylitis (Laval et al., 2000). The gender bias in ankylosing spondylitis is not due to X-chromosome encoded genetic effects (Hoyle et al., 2000).

The present study was carried out to determine the frequency of HLA-B27 in kashmiri population and to correlate this low frequency with the scarcity of AS as seen in osteoarticular diseases in a tertiary care centre in Srinagar.

MATERIALS AND METHODS

Subjects: Two hundred and Sixty six blood samples were obtained from patients suffering from low backache (193 men, 73 women) at immunology Department in the SKIMS Hospital Srinagar. Similar numbers of blood samples were taken from general outdoor patients who apparently appear healthy as controls. All subjects included in this hospital based study belong to Kashmiri ethnic group, which constitutes more than 55% of the total Jammu & Kashmir population. The samples from both subjects and controls were taken randomly to avoid bias. The population is thought
to be genetically homogenous.

Methodology: Lymphocytes were separated from whole blood by gradient centrifugation using Ficoll solution at a density of 1.077 at 18-22°C, according to techniques already described by Kaplan et al., (1988). Determination of HLA-B27 antigen was performed according to the microlymphocytotoxicity technique of Terasaki and McClelland (1964). The basis of this procedure is cytolysis mediated by specific antibody in the presence of complement. The procedure is a modified NIH method. This is a two stage test that employs a sensitization step of cells (antigen) with serum (antibody). The second stage is the specificity step achieved by addition of rabbit complement. HISTO TRAY B27 with predropped anti-sera and controls for HLA-B27 typing from BAG (Bilogische Analysensystem GmbH) source was used.

RESULTS

Only five of these patients were found to possess HLA-B27 antigen. The control group was negative for the antigen. The frequency of genes was calculated according to the methods of Ceppellini et al., (1995) and Larsen et al., (1979). The gene frequency of HLA-B27 in our population is 0.93%, showing low frequency of this antigen. This is the first epidemiological report on HLA B27 from our part of state.

DISCUSSION

The present study shows that HLA-B27 is very low 0.93% in Kashmiri population. The reason for this scarcity is unknown. Some Questions arise, among others, as to whether or not environmental factors might hinder or facilitate the real expression of the HLA-B27 allele and AS in the population studied. This hypothesis merits further investigation because gene frequencies are found to be variable, being higher in Haida Indians (Tsuji et al., 1992), Caucasians and other black populations, while they are lower in South Africans, UAE (Al-Atta et al., 1995), Lebanon (1%) (Awada et al., 1997) compared to our population. Analysis has revealed an increased B27 antigen frequency among the north Indian groups (>5%) compared to the south Indian groups (<5%) (Kumar, 2003). Similarly in another study, the frequency of the tissue antigen HLA-B27 is studied on the multi-ethnic island of Mauritius, the majority of the population of which is of Indian descent. The results showed a prevalence rate of 4.3%, inter-racial variation was not observed between the major ethnic groups (P>0.05). These findings are comparable with the results of studies on HLA-B27 prevalence rate in India, and lend support to the argument that the HLA-B27 test should not be used on a routine basis to diagnose HLA-B27-related rheumatic disorders (Sun et al., 2003). As the population prevalence of HLA-B27 in different countries is varied, from (1-8%) and only around 1% of B27 positive individuals develop ankylosing spondylitis, screening the general population for the antigen would not be helpful for identifying cases of spondylitis. The predictive value of testing for HLA-B27 depends upon the particular clinical situation (Leirisalo et al., 1982). The usefulness of a positive result will be greatest in populations, such as the Japanese, that have a low general prevalence of HLA-B27 and yet its association with ankylosing spondylitis is strong. For the other spondarthritides, which are less strongly linked with HLA-B27, diagnosis is based primarily on the associated clinical features. Thus, in practice, typing for HLA-B27 can be helpful in a patient complaining of low back pain of an inflammatory character in the absence of radiological signs of sacroilitis or in patients with an asymmetrical oligoarthritus but without other features of spondarthritis (Amor et al., 1990).

However genetic factors are not the only factors to be taken into account, because both reactive arthritis and severe AS have been reported in patients who did not appear to have HLA B27 (Stein et al., 1990). Several theories have been proposed to explain the various ways in which HLA-B27 might predispose to spondarthritus Supporting evidence has been provided for some but not all. For example, HLA-B27 is capable of presenting potentially arthritogenic peptides to cytotoxic T lymphocytes and it also has unusual cell biology (Lahesmaa-Rantala 1987). By contrast, the bacteria implicated in reactive arthritis have not been found to produce superantigens and there is little evidence to support antibody cross-reactivity or receptor-mediated mechanisms (Bowness, 2002). Although molecular mimicry has been described between an aminoacid sequence in HLA-B*2705 and Klebsiella and Shigella products, this exact aminoacid sequence is not found in HLA-B*2702 or B*2704 which are also disease-associated subtypes (Bowness, 2000). The discovery of the link between HLA-B27 and a large family of inflammatory
rheumatic diseases was one of the seminal advances in rheumatology in the last century (Hammer et al., 1990). Associations have subsequently been identified with other musculoskeletal and non-rheumatic diseases. New ways to employ HLA-B27 as a diagnostic and prognostic aid will continue to emerge.

REFERENCES


