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STUDY OF HLA-B27 IN PATIENTS WITH SERONEGATIVE SPONDYLOARTHROPATHY

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ABSTRACT

Introduction: The human leukocyte antigens (HLA) are gene loci in the major histocompatibility complex class I of genes on chromosome 6, present on all nucleated cells. This activity reviews the varied presentations of HLA-B27 associated syndromes. Diverse disease presentations often require interprofessional approaches to care for patients with HLA-B27 syndromes. **Objectives of the study:** The objective of the present study is to estimate HLA-B27 levels in patients with seronegative spondyloarthropathies. **Materials and methods:** In the present study, we included the patients with seronegative spondyloarthropathies in the age group of 20-70 years. We included a total of 80 patients with SNSA. The diagnosis of SNSA include the absence of RA factor, subcutaneous nodules, sacroilitis, inflammatory peripheral arthritis, ocular inflammation, alteration of skin, buccal ulceration, enthesopathy, thrombophlebitis, pyoderma gangraenosum, familial aggregation and association with HLA-B27. Serologic-based HLA typing using Antigen-specific sera was used to determine a patient's HLA type. **Results:** In the present study, we included a total of 80 patients of SNSA based on the inclusion criteria mentioned above, the patients were in the age group of 20-70 years. The majority of the patients in our study were in the age group of 30-40 years. There were 20 patients in the age group of 21-30 years, 26 in 31-40 years, 12 in 41-50 years, 12 in 51-60 years and 10 in the age group of 61-70 years respectively, out of 80 patients 52 were males and 28 were females. (table 1). It is evident from table 2 that, 22 patients presented with spondylitis, 42 had peripheral arthritis, 16 had ocular inflammation, 14 had alteration of skin, 8 had buccal ulceration and 6 had enthesopathy. It is evident that out of the 80 patients studied HLA-B27 was detected in 11 patients and it is not detected in 69 patients. The prevalence of HLA-B27 in patients with SNSA is found to be 13.75%. **Discussion and conclusion:** In conclusion, our findings confirm the strong association of the HLA B27 allele with various types of seronagative SpAs. No association between each of major clinical manifestations with age and sex distribution. We suggest that HLA Typing would help in the diagnosis of seronagative SpAs specially AS where clinical presentation is unclear and in identifying the family members at risk.

Key-words: seronegative spondyloarthropathies, major histocompatibility complex, human leukocyte antigen, spondylitis and rheumatoid arthritis factor.

INTRODUCTION

The human leukocyte antigens (HLA) are gene loci in the major histocompatibility complex class I of genes on chromosome 6, present on all nucleated cells. This activity reviews the varied presentations of HLA-B27 associated syndromes. Diverse disease presentations often require interprofessional approaches to care for patients with HLA-B27 syndromes. Evaluation and management strategies for these diseases are reviewed. The correlation

between the presence of HLA-B27 and ankylosing spondylitis has been a known entity since the early 1970s. Although common in the general population, this allele strongly contributes to the susceptibility of development of the linked family of inflammatory rheumatologic conditions collectively known as spondyloarthritis. Additional associated diseases, particularly acute anterior uveitis, are also highly correlated with possession of HLA-B27. Although associated with spondyloarthritis, the pathologic role of this allele in immune dysregulation remains under investigation. With lower frequency, the presence of the HLA-B27 allele has correlated with inflammatory bowel disease, psoriatic arthritis, and reactive arthritis. The presence of the HLA-B27 allele is not essential for the development of spondyloarthropathy, but it is highly associated with the development of the disease. Research has identified more than forty other genetic loci in genome-wide mapping studies. HLA-B27 contributes to approximately thirty percent of the heritability of ankylosing spondylitis.^{1,2} The incidence of acute anterior uveitis in HLA-B27 positive patients has shown on meta-analysis to vary from 40 to 82.5%. It can precede the onset of ankylosing spondylitis by approximately three years.³ In contrast to the prevalence of roughly ninety percent of patients with ankylosing spondylitis, HLA-B27 is present in less than half of patients with psoriatic arthritis and inflammatory bowel disease (IBD). Seronegative spondyloarthropathies (SNSA) include a group of diseases with arthritis that are negative for rheumatoid factor. The borders of the disease are sometimes obscure, and SNSA has its own classification criteria. The investigation on the prevalence of HLA-B27 will be important for the understanding of SNSA pathogenesis. The association of HLA-B27 with ankylosing spondylitis was first described in 1973,² and is among the strongest described for a HLA locus. The recent demonstration that HLA-B27 can interact with a number of different immunoreceptors on different cell types has opened up promising new avenues of research into clarifying its role in the pathogenesis of spondyloarthropathy. The natural role of HLA molecules is peptide binding and presentation to T cells, leading to the suggestion that the spondyloarthropathies result from the ability of HLA-B27 to bind a unique set of peptides. This 'arthritogenic' peptide hypothesis proposes that disease results from an HLA-B27-restricted cytotoxic T-cell response to a peptide or peptides found only in joint and other affected tissues. Such a peptide could be bound and presented by all disease-associated HLA-B27 subtypes, but not by other class I molecules. Pathogenic T cells might be primed in the joint or at other sites such as the genital or gut mucosa. A modification of this original hypothesis could entail a breakdown of self-tolerance by initial HLA-B27-restricted presentation of a peptide or peptides derived from one of the triggering pathogens. If the disease association of HLA-B27 is indeed a consequence of its physiological role in peptide presentation, HLA-B27-restricted cytotoxic T lymphocytes (CTL), specific for self-epitopes or bacterial epitopes, should be demonstrable in the involved joints of patients with spondyloarthropathies.⁴⁻¹⁰

The objective of the present study is to estimate HLA-B27 levels in patients with seronegative spondyloarthropathies.

MATERIALS AND METHODS

In the present study, we included the patients with seronegative spondyloarthropathies in the age group of 20-70 years. We included a total of 80 patients with SNSA. The diagnosis of SNSA include the absence of RA factor, subcutaneous nodules, sacroilitis, inflammatory peripheral arthritis, ocular inflammation, alteration of skin, buccal ulceration, enthesopathy, thrombophlebitis, pyoderma gangraenosum, familial aggregation and association with HLA-B27. Serologic-based HLA typing using Antigen-specific sera was used to determine a patient's HLA type. The complement mediated micro cytotoxicity test was performed using commercial kit including antigen-coated microplates, and the test was done according to manufacturer's instruction. This was a prospective descriptive-analytic research study and our method for sampling was census. Each of HLA-B27 positive patients were evaluated for age and sex distribution and at least one of the major clinical features of NSAs. Data Analysis: Collected data were analysed with SPSS version 10.0 and Pearson's chi square test was used.

RESULTS: In the present study, we included a total of 80 patients of SNSA based on the inclusion criteria mentioned above, the patients were in the age group of 20-70 years. The majority of the patients in our study were in the age group of 30-40 years. There were 20 patients in the age group of 21-30 years, 26 in 31-40 years, 12 in 41-50 years, 12 in 51-60 years and 10 in the age group of 61-70 years respectively, out of 80 patients 52 were males and 28 were females. (table 1).

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It is evident that out of the 80 patients studied HLA-B27 was detected in 11 patients and it is not detected in 69 patients. The prevalence of HLA-B27 in patients with SNSA is found to be 13.75%.

DISCUSSION

In the present study, we included a total of 80 patients of SNSA based on the inclusion criteria mentioned above, the patients were in the age group of 20-70 years. The majority of the patients in our study were in the age group of 30-40 years. There were 20 patients in the age group of 21-30 years, 26 in 31-40 years, 12 in 41-50 years, 12 in 51-60 years and 10 in the age group of 61-70 years respectively, out of 80 patients 52 were males and 28 were females. (table 1). It is evident from table 2 that, 22 patients presented with spondylitis, 42 had peripheral arthritis, 16 had ocular inflammation, 14 had alteration of skin, 8 had buccal ulceration and 6 had enthesopathy. It is evident that out of the 80 patients studied HLA-B27 was detected in 11 patients and it is not detected in 69 patients. The prevalence of HLA-B27 in patients with SNSA is found to be 13.75%.

Seronegative spondyloarthropathies are a group of disorders characterized by inflammation of the spine, sacroiliac joints, and peripheral arthritis along with various characteristic extra-articular features. Their pathogenesis and immunogenetics have not yet been fully elucidated. Ankylosing Spondylitis (AS) is probably the best studied of these diseases. It has now been 35 years since the association of human leukocyte antigen (HLA) B27 and AS has been demonstrated. Since then, a plethora of association studies and linkage studies unequivocally demonstrate that genetic determinants within or near the major histocompatible complex (MHC) are critical to the etiology of AS. In population surveys, 1 to 6% of adults inheriting HLA-B27 have been found to have AS.⁸ In contrast in families with AS, the prevalence is 10 to 30% among adult first – degree relatives inheriting HLA-B27¹¹.

The concordance rate in identical twins is approximately 65%. It is currently believed that susceptibility to AS is determined almost entirely by genetic factors, with HLA-B27 comprising about one-third of the genetic component. HLA-B27 and associate antigens incidence were studied by Rivera et al¹² in 620 cases of seronegative spondyloarthropathies (SNS) and 262 controls of a Venezuelan mestizo population from Zulla state between 1985 and 1995. The incidence of HLA-B27 was 20.96% of all cases of SNS. It was increased in patients with ankylosing spondylitis (AS) 33.33% and Reiter's syndrome (RS) 30%, but not in uveitis (Uv) 20% and psoriatic arthropathy (PsA) 0%.

Luukkainen RK et al¹³ investigated sacroiliitis in patients with seronegative Oligoarthritis. Thirty consecutive patients with seronegative oligoarthritis and no other signs of spondylarthropathy were included. Sacroiliac (SI) joints were investigated by both radiography and magnetic resonance imaging. HLA B27 antigen was studied and family history was reexamined in 2006. Five patients had sacroiliitis. Additionally, 15 patients had HLA B27 antigen or family history of either psoriasis or ankylosing spondylitis. Their conclusion was that during the first decade of seronegative oligoarthritis, HLA B27 antigen, family history, and especially imaging of SI joints reveal in two thirds of the patients the spondylarthritic nature of their disease.

Shankarkumar et al¹⁴ in their study described that patients in the 20-40 age group were more vulnerable. Their findings confirm the strong association of the HLA B27 allele with various types of spondyloarthritis and suggest that allele detection would help in the diagnosis of AS where clinical presentation is unclear and in identifying the family members at risk. In our study, both inflammatory peripheral arthritis and Sacroiliitis/Spondylitis were most frequent in 20-40 years old group.

CONCLUSION

In conclusion, our findings confirm the strong association of the HLA B27 allele with various types of seronegative SpAs. No association between each of major clinical manifestations with age and sex distribution. We suggest that HLA Typing would help in the diagnosis of seronegative SpAs specially AS where clinical presentation is unclear and in identifying the family members at risk.

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TABLES

Table 1: Shows age wise and gender wise distribution of study subjects

21-30 years	20	25
31-40 years	26	32.5
41-50 years	12	15
51-60 years	12	15
61-70 years	10	12.5
Males: Females	52:28	65%/35%

Table 2: Shows the distribution of study subjects based on clinical presentation

Spondylitis	22	27.5
Peripheral arthritis	42	52.5
Ocular inflammation	16	20
Alteration of skin	14	17.5
Buccal ulceration	8	10
Enthesopathy	6	7.5

Table 3: Shows the Prevalence of association of HLA-B27 positivity in patients with SNSA

HLA-B27 detected	11	13.75
HLA-B27 not detected	69	86.25