

Frequency of HLA-B27 gene among patients with ankylosing spondylitis and its consequences on clinical manifestation

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Abstract

Background: Ankylosing spondylitis is an inflammatory disease and leading cause of back pain worldwide. It is thought that the gene human leukocyte antigen-B27 (HLA-B27) provides a strong tendency in people to develop ankylosing spondylitis. This study was designed to evaluate the frequency of HLA-B27 among patients with ankylosing spondylitis and clinical manifestation among the HLA-B27 positive and negative patients.

Methods: A cross-sectional study was done in the Department of Medicine and Department Rheumatology of BSMMU, Shahbag, Dhaka, Bangladesh from 1st January 2016 to 30th June 2016.

Results: Total 70 patients were included in this study, among those 54 were male and 16 were female and total 54 patients (77.14%) were HLA-B27 positive and 16 patients (22.86%) were HLA-B27 negative. Most HLA-B27 positive patients had extra-articular manifestation, family history of low back pain and high level of BASDAI score, compared to those who were negative. Among the 54 positive patients, 9 (16.67%) had combination of tendinitis, enthesitis and uveitis and 2 (3.70%) had all four of extra-articular manifestation. Among the 16 negative patients, 2 (12.5%) had all four extra-articular manifestation. Among 16 negative patients 9 (56.25%) had raised erythrocyte sedimentation rate (ESR) and 5 (31.25%) had raised C-reactive protein (CRP). On the other hand, among 54 positive patients 48 (88.89%) had raised ESR and 44 (81.48%) had raised CRP.

Conclusion: The association of HLA-B27 might be the reason of disease severity among the positive patients.

Key words: Ankylosing spondylitis, HLA-B27, clinical manifestation.

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Introduction

Spondyloarthropathies (SpA) are a family of long-term (chronic) diseases of joints. These diseases occur in children and adults.¹ Two types of spondyloarthritis are

commonly known: seropositive and seronegative. The term “seropositive spondyloarthropathy” is used to describe the presence of rheumatoid factor (RF) in patients with rheumatoid arthritis or other autoimmune diseases affecting the spine. On contrary, the term “seronegative spondyloarthropathy” is most commonly used to denote a set of inflammatory conditions that tend to involve the vertebral column or spine but are not associated with the presence of RF. Seronegative spondyloarthropathies include ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA) and the arthritis that may accompany inflammatory bowel disease (IBD).²

AS is the most common with prevalence in the Asian population of 16.7 per ten thousand. The number of AS cases is estimated at 1.30-1.56 million in Europe and 4.63-4.98 million in Asia.^{3,4} AS is a chronic, systemic,

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inflammatory disease that affects primarily the sacroiliac joints and the axial skeleton. Certain peripheral joints and tendons can also be affected and other clinical manifestation include peripheral arthritis, enthesitis and extra-articular organ involvement. The disease typically affects young adults and there are strong genetic features.^{5,6} A direct relationship between AS and the human leukocyte antigen-B27 (HLA-B27) gene has been determined. The precise role of HLA-B27 in precipitating AS remains unknown; however, it is believed that HLA-B27 may resemble or act as a receptor for an inciting antigen, such as bacteria.⁶ There is no statistics of frequency of HLA-B27 gene in AS patients in our country. HLA-B27 gene is modified by environmental factor and the environmental factor varies from country to country. Moreover, there may be some difference in clinical manifestations of HLA-B27 positive and negative AS patients. That is why this study has been undertaken with a view to determine the HLA-B27 gene status in patients with AS in hospital setting and to compare the different clinical manifestation between HLA-B27 positive and negative AS patients.

Methods

The study was a cross-sectional observational one having both descriptive and analytic components. This study was conducted in the Rheumatology out-patient department (OPD) and Medicine OPD of Bangabandhu Sheikh Mujib Medical University (BSMMU) from 1st January 2016 to 30th June 2016. Study population were all the patients attending OPD of Rheumatology and Medicine Department during above period. Purposive sampling was done and all the patients fulfilled the 1984 Modified New York Criteria for AS.⁶ Patient fulfilling the inclusion criteria, were enrolled in this study. The detail history regarding the duration of low back pain, family history of AS, chest tightness, difficulty in movement of lumbar spine, morning stiffness were taken. A thorough clinical examination involving examination of joints, chest expansibility, Schober's test, BASDAI scoring were done. A few specific laboratory investigations like HLA-B27, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), x-ray pelvis antero-posterior view were done. All the records were documented in a pre-designed data collection sheet.

Then the disease severity was compared between HLA-B27 positive and negative patients. After completion of collection of data in a pre-designed, structured questionnaire by interviewing and examining every case, tables were prepared by the observed values like percentage of HLA-B27 positive patient, distribution among male and female, difference between clinical manifestation among HLA-B27 positive and negative patients.

Results

A total of 70 patients were included in this study. Among those, 54 (77.14%) patients were HLA-B27 positive and 16 (22.86%) patients were negative. Frequency of the HLA-B27 gene among the AS patients was 77.14%. There were total 16 female patients and 54 male patients. So, the ratio of men to women was 13.5:4. Among 16 female patients 10 were HLA-B27 positive and 6 were negative. Out of 54 males 44 were HLA-B27 positive and 10 were negative. In this study clinical parameters were compared among the HLA-B27 positive and negative patients (Table I). Among the patients with AS, 49 (90.74%) HLA-B27 positive and 10 (62.5%) negative patients had a family history of inflammatory back pain and the difference was statistically significant.

Table II shows the BASDAI scores for HLA-B27 positive and negative male-female patients. There were 37 (84.09%) positive male patients and 9 (90%) positive female patients who had BASDAI score ≥ 4 and a static value of 1 which is not significant. There were 7 (15.91%) positive male patients and only 1 (10%) positive female patients who had BASDAI score < 4 and a static value of 1 which is also not significant. There were 7 (70%) negative male patients and 2 (33.33%) negative female patients who had BASDAI score less than 4 and a statistic value of 0.302 which is not significant. There were 3 (30%) negative male patients and 4 (66.67%) negative female patients who had BASDAI score ≥ 4 and a statistic value of 0.302 which is also not significant. In this study the disease activity of female patients were more than the male patients as they had high number of BASDAI scores.

Table I Clinical and lab manifestations in HLA-B27 positive and HLA-B27 negative patients (n=70)

Criteria		HLA B27 positive (n=54)	HLA B27 negative (n=16)	P value
Family History (F/H)	49 (90.74%)	10 (62.5%)	0.0135	
Joint Involvement	Knee	40 (74.07%)	7 (43.75%)	0.034
	Elbow	26 (48.15%)	8 (50%)	1
	Hand joint	9 (16.67%)	3 (18.75%)	1
	Shoulder	9 (16.67%)	4 (25%)	0.476
	Buttock pain	5 (9.26%)	1 (6.25%)	1
	Ankle	21 (38.89%)	3 (18.75%)	0.229
Sacroilitis	Grade 2	39 (71.22%)	9 (56.25%)	0.238
	Grade 3	15 (27.78%)	7 (43.75%)	0.238
Extra-articular manifestations	Enthesitis	28 (51.85%)	8 (50%)	1
	Tendinitis	26 (48.15%)	6 (37.5%)	0.571
	Uveitis	20 (37.04%)	6 (37.5%)	1
	Conjunctivitis	7 (12.96%)	1 (6.25%)	0.672
	Tendinitis, enthesitis & uveitis combination	9 (16.67%)	2 (12.5%)	1
	Tendonitis, enthesitis, uveitis & conjunctivitiscombination	2 (3.70%)	1 (6.25%)	0.547
Lab criteria	Raised ESR	48 (88.89%)	9 (56.25%)	0.007
	Raised CRP	44 (81.48%)	5 (31.25%)	0.0003

Table II Showing the BASDAI scoring of HLA-B27 positive and negative patients

HLA-B27 Status	Criteria	Male (n = 54)	Female (n = 16)	P value
Positive (54)	BASDAI \geq 4	37 (84.09%)	9 (90%)	1
	BASDAI $<$ 4	7 (15.91%)	1 (10%)	1
Negative (16)	BASDAI $<$ 4	7 (70%)	2 (33.33%)	0.302
	BASDAI \geq 4	3 (30%)	4 (66.67%)	0.302

There were two identical twins who had AS. They were of 23 years and had been suffering from AS for 3 years. They both were HLA-B27 positive. Both had BASDAI score more than 4 and had family history of undiagnosed inflammatory back pain with other joint involvement. They had the same joint involvement and extra-articular manifestations. Also, they had high CRP and ESR and both had sacroilitis grade 3.

Discussion

AS is a persistent chronic rheumatic disease of unknown cause. The word spondylitis means inflammation of the spine. The word ankylosing means bones that tend to join together (fuse) across a joint. In AS, the ligaments of the lower spines become inflamed at the points where they attach to the spinal bones (vertebrae). In time, this can stimulate the bone-making cells and cause some

bone to grow and form within the ligaments. In time, these bony growths may become larger and form bony bridges between vertebrae that are next to each other. This may, over time, cause some of the vertebrae in the spine to fuse together with this new abnormal bone material.⁷

It is difficult to diagnose AS and the causes of AS is unknown, but one of the most influential factors is the HLA-B27 gene. Detection of the gene would improve the diagnosis of the disease.⁸

In this study, it has been noticed that AS affects males more than females and it affects a person at a younger age. As there are more patients with HLA-B27 positive, now it has been cleared that, with the involvement of the environmental factors, genetic predisposition might be a major reason for causing AS. In Spain, 94.3% of the AS patients are HLA-B27 positive.⁹ But, in Bangladesh there is no such data. The prevalence of HLA-B27 in Spain is more than that is observed in this study because they worked with huge population and worked with patients with different areas.

From our study, it has been seen that the clinical course of the disease is some how related to HLA-B27 positivity. Scientists suspect that other genes, along with a triggering environmental factor, such as a bacterial infection, are needed to trigger AS in susceptible people. HLA-B27 probably accounts for about 40% of the overall risk, but then there are other genes working in concert with B27.¹⁰

When individual BASDAI items scores were analyzed separately, there were some patients who could not specify the accurate scoring for the BASDAI questions. So, the scoring was done by assuming their conditions of the disease. In one study of AS which was conducted in Korea, it has been observed that the patient's BASDAI scores were statistically significant.¹¹ From our study it is cleared that HLA-B27 positive patients have BASDAI scores e⁷4 than the negative patients but in both cases the data were not statistically significant. It is because, there might be some male patients who were already diagnosed, because of why they had less disease activity.

In this study, it is understandable that men are more likely to have higher cumulative AS-associated outpatient visits compared to women. There are several possible explanations to the findings here. First, men may have worse disease severity that drives higher

healthcare utilization. Second, the longer delay in diagnosis in women previously reported may be a cause of later age of utilization onset found in this study and lead to an underestimation of healthcare utilization. A person is suffering from AS was not perceived only on the basis of HLA-B27 test. In this study, clinical diagnosis was made on the basis of the clinical history, physical examination, and radiographic reports. Any patient who had signs of AS but did not suffer from inflammatory low back pain and stiffness for at least 3 months were excluded from the study as the first rule in 1984 Modified New York Criteria is that the patient must have low back pain and stiffness for at least 3 months. Some HLA-B27 positive patients had no signs and symptoms at an early age. They were affected by the disease after reaching an older age. There might be some people who had HLA-B27 gene but does not have any signs or symptoms of AS or any other seronegative SpA.³ A strong possibility in regard to most HLA and disease associations is that the disease susceptibility gene may not be the particular HLA-A or -B locus genes found to be associated with the disease but are genes at closely linked loci in linkage disequilibrium with the A and B locus genes. If the HLA linked AS gene were not B27 itself, two findings might be expected. The first is that aggregation of B27 negative individuals with spondylitis should occur in families to the same degree as is observed in the case of HLA-B27 positive patients. So far, no pair of HLA-B27 negative first-degree relatives with spondylitis appears to have been documented. The only instance has been observed is two brothers who both had AS with HLA-B27 positive and they had a history of inflammatory low back pain of their mother. It is of interest that the parents in this family were related, suggesting the possibility of a recessive trait predisposing to the spondylitis. Secondly, one might expect to see examples of disassociation of B27 from AS within a family, i.e., evidence of recombination between the B locus and the supposed locus for the AS gene.¹² There was a family in which a girl had AS with HLA-B27 negative and her father also had a history of apparent disassociation of spondylitis from HLA-B27. In these instances, genetic recombination would be the explanation if it were certain that other, non-HLA linked genes predisposing to spondylitis were not segregating in the families. There is some evidence that AS is genetically heterogeneous

and that in HLA-B27 negative persons it differs from the disease in HLA-B27 positive persons by having a later mean age of onset and in some cases features of reactive arthritis. But, patients with the features of other disease were not taken in the study.

Conclusion

Nearly four-fifths of AS patients were found to have HLA-B27 gene positive. It has been observed that HLA-B27 positive patients are at higher risk of developing extra axial joint involvement like knee, elbow, shoulder, small joints of hands, also extra articular manifestations like enthesitis, uveitis, tendinitis, more chance of having sacroiliitis grade 3, raised ESR and CRP than negative patients. So, the disease activity is more severe in HLA-B27 positive patients in comparison to negative patients.

Limitation of the study

This study has some limitations which should be kept in mind while deciding on the implications of the findings of the study.

- a) It was a hospital based study, community or mass people were not included.
- b) The sample size was relatively small. In a large sample size frequency might have been different.
- c) The short duration of study might had limited the ability of the study to compare the clinical outcome between HLA-B 27 positive and negative AS patients.

Recommendations

In this study patients were recruited from single center only, so multi-centered or community based large scale studies are needed to increase the power of the study. Further prospective study will be required to see the association between different types of HLA gene in AS patients with disease activities to confirm findings of this study.

Conflicts of interest: Nothing to declare.

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