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Original Article

Low frequency of HLA-B27 in ankylosing spondylitis and its relationship with clinical findings in patients from Turkey

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Abstract

Objective: Human leukocyte antigen B27 (HLA-B27) is strongly associated with ankylosing spondylitis (AS). However, the association between clinical findings and HLA-B27 vary in terms of geographic area. This study aimed to determine the frequency of HLA-B27 positivity and its relationship with clinical findings.

Material and Methods: All subjects fulfilling the modified New York diagnosis criteria for AS enrolled in study. The demographic data and histories of the patients were collected retrospectively from patient files. Polymerase chain reaction-based HLA-B27 analysis of all cases was performed.

Results: The male to female ratio was 2.5, and mean age of disease onset was 28.3 years. HLA-B27 positivity was detected in 115 patients (70%). Although there was no significant connection between the clinical findings and HLA-B27 positivity, there was a positive relationship between the presence of syndesmophytes and HLA-B27 positivity (p=0.044). The number of patients treated with anti-tumor necrosis factor was higher in the HLA-B27-positive group; however, the difference was not significant (39.1% and 28.9%, respectively). More patients were treated with anti-tumor necrosis factor in the HLA-B27-positive group than in the HLA-B27-negative group; however, the difference was not significant (39.1% and 28.9%, respectively).

Conclusion: Compared with northern Europe, HLA-B27-positive rate of patients with AS has been shown to be lower in Turkey. Except for the presence of syndesmophytes, there was not a statistically significant relationship between HLA-B27 positivity and clinical and radiologic findings.

Keywords: Ankylosing spondylitis, HLA-B27, inflammatory back pain

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Introduction

Ankylosing spondylitis (AS) and chronic, systemic, and inflammatory rheumatic diseases characterized by flares and remission are associated with human leukocyte antigen B27 (HLA-B27) (1, 2). The prevalence of AS varies from population to population, but in recent studies, the ratio was found to be between 0.2-1.4% in the Caucasians and more often among males (3, 4). A family history of AS is accepted to be one of the primary risk factors.

There is a proven genetic tie between spondyloarthropathies (SPA) and the HLA-B27 gene. This connection is obvious in AS; however, HLA-B27 positivity is gradually lower in other SPA diseases group. The ratio of this association changes in terms of race and ethnicity. While HLA-B27 positivity is 6-8% in the population as a whole, it is about 90-95% in AS patients living in northern European countries (3). The highest HLA-B27 positivity is observed in American Indians; however, HLA-B27 positivity is found 50% maximum in Canadian Haida people, and it is relatively lower in African Americans (5). In our country, HLA-B27 positivity was found to be 70% in AS patients (6).

The relationship between AS and HLA-B27 has been known since 1973, but its contribution to the AS pathogenesis is not well understood (7). Some studies have demonstrated that genetic factors are also associated with the severity of diseases (8). This study aims to determine the frequency of HLA-B27 positivity and its relationship with clinical findings.

Material and Methods

Study population

One hundred sixty-three AS patients who fulfilled the modified New York criteria were enrolled into the study (9). The demographic, laboratory, and clinical data were recorded on a special form. HLA-B27 detection was performed with a polymerase chain reaction-based method. Approval for the study was obtained

from the local ethics committee. The study was conducted in accordance with the principles set forth in the World Medical Association Declaration of Helsinki. All patients and control subjects gave written informed consent.

Statistical analysis

Statistical analyses of the present study were performed using the Statistical Package for Social Sciences 17.0 for Windows software package (SPSS Inc.; Chicago, IL, USA). Results of descriptive analyses were presented as mean ± standard deviation if normal distribution was present and, if not, as median (interquartile range). For pairwise comparisons, the independent t-test was used for normally distributed numerical variables, and the chi-square test or Fisher's exact test was used, when appropriate, for categorical variables. Two-sided p less than 0.05 were considered statistically significant.

Results

The mean age of the 163 patients was 37.37±11.53 years (18-65), the mean age of disease onset was 28.31±9.05 years (10-55), and the mean age of diagnosis was 32.42±10.38 years (15-63). The mean lag time between the onset of symptoms and the diagnosis of AS was 4.16±4.23 years. One hundred sixteen patients (71%) were males (Table 1). With respect to the frequency of symptoms, 92% had inflammatory back pain, 61.3% had hip pain, and 31.2% had heel pain. Achilles tendinitis associated wi th pain was found in 33 patients (20%), peripheral arthritis was found in 24.5% of patients, and uveitis was detected in 13 patients (7.9%). The proportion of patients with prostheses was 3.68% (Table 2).

Of the 163 patients, HLA-B27 positivity was detected in 115 patients (70%), and the mean age of disease onset was 27.6±9.0 years in these patients. However, the mean onset age was 29.8±8.9 years among the HLA-B27-negative patients. The mean lag time between the onset of symptoms and the diagnosis of AS was 4.3±4.4 years in HLA-B27-positive patients and 3.6±3.7 years in HLA-B27-negative patients. There was no significant difference between HLA-B27-positive and HLA-B27-negative patients in terms of ages of disease onset and the time between the onset of symptoms and the diagnosis.

Of the HLA-B27-positive patients, 107 had inflammatory back pain (93%), 33 had heel pain (28%), 30 had peripheral arthritis (26%), and 71 had hip pain (61%). Uveitis was detected in nine patients (7.8%), 23 cases had Achilles tendinitis-associated pain (20%), and four patients had prostheses (3.4%) (Table 2).

In the radiologic evaluation of the patients, we detected enthesitis in 37 patients (22%), and 30 patients had syndesmophytes (18%) (Table 2). Of all the HLA-B27-positive patients, 29 cases had enthesitis (25.2%) and 26 cases had (22.6%) syndesmophytes (Table 2). As far as the relationship between clinical findings and HLA-B27 positivity is concerned, only the presence of syndesmophytes was significantly associated with HLA-B27 positivity (22.6%, 8.33%, respectively; p=0.044). Four of the six cases with prostheses had (66%) HLA-B27 positivity, but this relationship was not statistically significant. Two cases had AA amyloidosis in biopsy analyses, and both patients' HLA-B27 results were positive (Table 2).

In total, 58 patients were on treatment with anti-tumor necrosis factor (TNF), and 45 patients on biologic treatment were HLA-B27-positive (ratio of biologic treatment in HLA-B27-positive cases: 39.1%; ratio of biologic treatment in HLA-B27-negative cases: 28.9%). The number of patients treated with anti-TNF drugs was higher in patients with HLA-B27-positive group compared to HLA-B27-negative group; however, the difference was not significant (Table 2).

Discussion

Most of the prevalence studies in AS revealed that it is 2-5 times more frequent in males (10). In our study, the male to female ratio was 2.5. In a study conducted, by Feldtkeller et al. (10), the onset age of AS patients was found to be 25.1±8.5 years; however, it was 23.5±8.9 years in a Turkish population-based study (6). In our study, the mean age of disease onset in AS patients was found to be 28.3±9.0 years, similar with the findings of the previous studies. Feldtkeller et al. (10) also revealed that the mean lag time between the onset of symptoms and the diagnosis of AS with HLA-B27 positivity was significantly low; therefore, the authors recommended HLA-B27 as a detection test in

Table 1. Demographic features of patients

Parameters	Patients (n=163)
Age (years)	37.37±11.53
Age of disease onset (years)	28.31±9.05
Age of diagnosis (years)	32.42±10.38
Time between disease onset and diagnosis (years)	4.16±4.23
Sex (male/female)	116/47
Extra-articular manifestation, n %	15 (%9)
HLA-B27 positivity, n %	115 (%70.5)

Values are expressed as mean ± standard deviation.
HLA-B27: human leukocyte antigen B27

Table 2. Clinical and radiologic findings of all patients and comparison of HLA-B27-positive and HLA-B27-negative patients

	All patients n=163	HLA-B27-positive n=115	HLA-B27-negative n=48	p
Inflammatory back pain, n %	150 (92.0)	107 (93)	43 (89.5)	0.528
Heel pain, n %	51 (31.2)	33 (28.6)	18 (37.5)	0.200
Peripheral arthritis, n %	40 (24.5)	30 (26)	10 (20.8)	0.550
Hip pain, n %	100 (61.3)	71 (61.7)	29 (60.4)	1
Uveitis, n %	13 (7.98)	9 (7.82)	4 (8.33)	1
Prostheses, n %	6 (3.7)	4 (3.84)	2 (4.16)	1
Achilles tendinitis, n %	33 (20.2)	23 (20)	10 (20.8)	1
Syndesmophytes, n %	30 (18.4)	26 (22.6)	4 (8.33)	0.044*
Enthesitis, n %	37 (%22.7)	29 (25.2)	8 (16.6)	0.306
Kidney involvement, n %	2 (1.2)	2 (1.73)	0	-
Patients under anti-TNF treatment, n %	58 (35.6)	45 (39.1)	13 (28.9)	0.156

*Significance p<0.05.
HLA-B27: human leukocyte antigen B27; TNF: anti-tumor necrosis factor

patients with evident clinical and physical examination findings (10). However, in our study, there was no significant relationship between the mean lag time from the onset of symptoms to the time of diagnosis and HLA-B27 positivity.

Our findings, in parallel with those studies, presumably indicate the absence of any potential relationship of disease severity and age with MHC (major histocompatibility complex) group genes including HLA-B27 (8). Some recent clinical studies proved the relationship between HLA-B27 positivity and the early onset of symptoms; however, some studies reported a negative relationship (11, 12). In the present study, there was no significant relationship between the age of disease onset and HLA-B27 positivity.

HLA-B27 positivity among patients diagnosed with AS varies according to race and ethnicity. However, our findings are similar to those of a recent study with Turkish subjects by Gunal et al. (6) Alamanos et al. (13) reported an HLA-B27 frequency analysis among Greek patients, and, as in Turkish studies, their findings were also lower. This may be attributed to the geographic similarity between Turkish and Greek populations. Additionally, Breban et al. (14) reported also low HLA-B27 positivity among the Turkish cases. This was attributed to the certain predominant genetic and environmental factors associated with the etiopathogenesis of AS.

In general, peripheral arthritis is localized to the lower extremities and presents as peripheral mono-oligoarthritis (1, 15). According to the study by Feldtkeller et al. (10), hip involvement and peripheral arthritis were higher in HLA-B27-positive patients; however, these findings were not statistically significant. Sonkar et al. (16) evaluated the potential relationship between HLA-B27 positivity and hip, shoulder, and knee joint involvement among patients diagnosed with SPA. They found that joint involvement was more severe in HLA-B27-positive patients. On the other hand, peripheral arthritis is more common among female cases and juvenile AS patients (17, 18). Gunal et al. (6) demonstrated 52.7% peripheral joint involvement among the Turkish cases. In our study, 24.5% of the patients had peripheral involvement, and HLA-B27 positivity was obviously higher in this group, but the difference was not statistically significant. One possible explanation for the absence of such significant data is the limited number of female and juvenile cases in our patient sample.

Gunal et al. (6) also evaluated the potential relationship between clinical findings of AS including inflammatory back pain, heel pain, hip pain, peripheral arthritis, and Achilles tendinitis-associated pain and HLA-B27 positivity. There was no relationship between the clinical findings and HLA-B27. In one of the earliest studies reported by Spencer et al. (19), the presence of syndesmophytes was more frequent in patients with HLA-B27 positivity and those diagnosed with uveitis. In our study, there was a significant association between HLA-B27 positivity and the presence of syndesmophytes. However, other clinical and radiologic parameters were not related with HLA-B27 positivity.

Uveitis is one of the most prevalent extra-articular manifestations of AS, and the reported frequencies vary between 25% and 40%. Clinically, patients with peripheral joint involvement are assumed to have more uveitis involvement (20). According to Feldtkeller et al. (10), there is a positive relationship between HLA-B27 positivity and uveitis involvement in AS patients. Another study, by Khan et al. (11), revealed predominantly increased anterior uveitis incidence among cases with HLA-B27 positivity. In our study, only 7.9% of the total cases had uveitis. Moreover, 69% of these cases (9 out of 13) had HLA-B27 positivity, but the findings were not statistically significant. This study was retrospective, so the patients might not have mentioned that they had had uveitis involvement.

Freeston et al. (21) investigated the association between HLA-B27 frequency and anti-TNF treatment. Despite the absence of statistical significance, the number of HLA-B27-positive patients treated with anti-TNF drugs was larger than the number of HLA-B27-negative patients (39.1% and 28.9%, respectively).

The retrospective design of the study and the small number of subjects enrolled are the two major limitations of our study. The different results between the previous studies and our study may be explained by the genetic and geographic factors.

Consequently, our finding of HLA-B27 positivity was 70.5%, similar with the findings of previous studies reported in Turkey. Further studies with larger groups are required to reveal the possible contribution of genetic and geographic factors on disease characteristics in HLA-B27-positive patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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