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The Frequency of HLA-B27 Antigen Positivity in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis and the Relationship between HLA-B27 Antigen and Other Autoantibodies

Romatoid Artritli ve Ankilozan Spondilitli Hastalarda HLA-B27 Antijen Pozitifliği Sıklığı ve HLA-B27 Antijeni ile Diğer Otoantikorlar Arasındaki İlişki

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The Frequency of HLA-B27 Antigen Positivity in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis and the Relationship between HLA-B27 Antigen and Other Autoantibodies

ABSTRACT

Objective: The aim of this study was to research the frequency of Human Leukocyte Antigen (HLA)-B27 antigen positivity and relationship between HLA-B27 positivity and other autoantibodies and between HLA-B27 positivity and treatment in patients diagnosed with rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Material and Method: The study is a retrospective study. Patients diagnosed with RA and AS as a result of the examinations performed at Physical Medicine and Rehabilitation outpatient clinic between January 2017 and September 2022 were retrospectively screened, and patients whose HLA-B27 antigen was tested were included in study.

Results: A total of 569 patients, 199 with RA and 370 with AS were included in study. While HLA-B27 was positive in 11% of patients with RA, it was 37.5% in patients with AS and there was a significant difference between the groups. When we analyzed the correlation of autoantibodies with HLA-B27, we found that HLA-B27 was not correlated with RF, Anti-cyclic citrullinated peptides (Anti-CCP) or Anti-nuclear antibody (ANA). When we analyzed the relationship between HLA-B27 and the treatment method, there was no significant relationship between HLA-B27 and treatment method.

Conclusion: While HLA-B27 was found to be 5% positive in the general population in the literature, we found 11% in 199 patients with RA. This study is important because it shows that HLA-B27 positivity is not very common in patients diagnosed with AS recently contrary to popular belief. More studies are needed to evaluate HLA-B27 frequency in RA and AS

Keywords: Ankylosing Spondylitis, correlation of autoantibodies, HLA-B27 antigen, Rheumatoid Arthritis.

ÖZET

Amaç: Bu çalışmanın amacı, romatoid artrit tanılı hastalarda İnsan Lökosit Antijeni (HLA-B27) antijen pozitifliği sıklığını ve romatoid artrit (RA) ve ankilozan spondilit (AS) tanılı hastalarda HLA-B27 pozitifliği ile diğer otoantikorlar ve tedavi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Ocak 2017-Eylül 2022 tarihleri arasında Fiziksel Tıp ve Rehabilitasyon polikliniğinde yapılan tetkikler sonucunda RA ve AS tanısı alan hastalar retrospektif olarak tarandı ve HLA-B27 antijeni bakılanlar çalışmaya alındı. Hastaların yaşı, cinsiyeti, HLA-B27 antijen incelemesi sırasında Sedimantasyon (SED) ve C-reaktif protein (CRP) değerleri, Romatoid Faktör (RF), Anti-CCP, Anti-nükleer antikor (ANA), HLA-B27 sonuçları, AS tanısı alan hastalarda sakroiliak Manyetik Rezonans (MR) sonuçları ve verilen ilaç tedavileri kaydedildi.

Bulgular: : Çalışmaya RA'lı 199 ve AS'li 370 olmak üzere toplam 569 hasta dahil edildi. HLA-B27 RA'lı hastaların %11'inde pozitif bulunurken AS'li hastalarda %37.5 idi ve gruplar arasında anlamlı fark vardı. Otoantikorların HLA-B27 ile korelasyonunu analiz ettiğimizde, HLA-B27' nin RF, Anti-CCP veya ANA ile korele olmadığını bulduk. HLA-B27 ile tedavi yöntemi arasındaki ilişkiyi incelediğimizde, HLA-B27 ile tedavi yöntemi arasında anlamlı bir ilişki yoktu.

Sonuç: Literatürde genel popülasyonda HLA-B27 pozitifliği %5 iken biz 199 RA hastasında %11 pozitif bulduk. Bu çalışma, sanılanın aksine yeni AS tanısı alan hastalarda HLA-B27 pozitifliğinin çok yaygın olmadığını göstermesi açısından önemlidir. RA ve AS'de HLA-B27 sıklığını ve prognoza etkisini değerlendirmek için hasta sayısının daha çok olduğu çalışmalar gereklidir.

Anahtar Sözcükler: Ankilozan Spondilit, HLA-B27 antijeni, otoantikorların korelasyonu, Romatoid Artrit.

Introduction

Rheumatoid Arthritis (RA) is a systemic autoimmune disease characterized by chronic widespread inflammation and increased morbidity and high risk of mortality. RA is a rheumatological disease from collagen vascular disease group and is recognized as an Human Leukocyte Antigen (HLA)-DR4-associated autoimmune disease. Although it can be seen at any age and in both sexes, epidemiological studies show that RA is 3 times more common in women than in men (1). The prevalence of RA varies between 0.5-1 % in Europe and North America (2). Tuncer et al. reported that the prevalence of RA in Turkey was calculated as 0.5% in men and 0.89% in women (3). Ankylosing Spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial spine, causing structural damage and functional disability (4). Patients are most often diagnosed in young adulthood. In about 80% of patients, signs begin before the age of 30 (5). The prevalence of AS is about 0.9% in the world. (6) The frequency of AS in the general population in Turkey has been reported as 0.46% (3).

HLA-B27 is part of the Major Histocompatibility Complex (MHC) gene family and is the general name for a set of antigenic substances that are encoded in the B locus of chromosome 6 and used by T cells to distinguish between self and foreign cells. The prevalence of HLA-B27 antigen positivity was 4% in North Africa, 8% in Caucasian races, 2-9% in China, and 0.1-0.5% in Japan (7). This rate for Turkey was stated to be between 2.8% and 6.8% in a meta-analysis published in 2017 (8). RA was associated with HLA-DR4 and HLA-DR1 antigens, while AS was associated with HLA-B27 antigen in previous studies (9, 10). Although it was stated in previous studies that 90% of patients diagnosed with AS have HLA-B27 antigen positivity, there is also a study in our country in which this rate was found to be 70% (11). HLA-B27 antigen was found to be positive in 534 (70.1%) of 762 AS patients and 62 (63.3%) of 98 patients with a diagnosis of non-radiographic axial spondyloarthritis in another study conducted in Turkey in 2021 (12). It was stated that the relationship between RA and HLA-B27 was not significant in a meta-analysis examining the relationship between RA and HLA-B27 antigen, but HLA-B27 antigen positivity could be a potential risk factor for pharmacogenomics and personalized therapy (13).

There is no literature revealing the effect of HLA-B27 antigen positivity on treatment and its relationship with other autoantibodies in patients with RA. The aim of this study is to retrospectively show the frequency of HLA-B27 antigen positivity and the relationship between HLA-B27 antigen positivity and other autoantibodies in patients with RA and AS.

Material and methods

Study Design

This retrospective study was conducted between January 2017 and September 2022. The medical records of the patients were accessed from that date since the hospital was opened in January 2017. Ethical approval was obtained on 07.09.2022 with the number (E2-22-2356) before study.

Patients

Those who were examined in the physical therapy and rehabilitation outpatient clinic of City Hospital and were diagnosed with AS according to modified New York Criteria or Assessment in Spondyloarthritis International Society (ASAS) criteria; Patients diagnosed with RA according to the RA 2010 ACR/EULAR classification criteria and consecutively seen in the outpatient clinic were screened (14-16). Since RA and AS can be seen together and may mimic each other's symptoms, HLA-B27 antigen was examined in some patients with RA. HLA-B27 was studied in patients diagnosed with seronegative RA, especially those with inflammatory waist and hip pain. Patients between 18-65 years of age and whose HLA-B27 antigen was studied, were included in the study. Patients with uncertain RA and AS diagnoses, diagnosed with late-onset RA, with lack of clinical data, and no follow-up records were excluded from the study.

Demographic information of patients such as age and gender; and laboratory parameters such as sedimentation (SED), C-reactive protein (CRP), HLA-B27 antigen, Rheumatoid Factor (RF), Anti-cyclic citrullinated peptides (Anti-CCP), Anti-nuclear antibody (ANA) at first diagnosis entry and sacroiliac magnetic resonance imaging (MRI) of patients with AS

were recorded. HLA-B27 allele mutation screening was performed by flow cytometry from peripheral venous whole blood taken with ethylenediaminetetraacetic acid (EDTA)-containing tubes from patients.

Statistical analysis

All analyses were carried out with SPSS 26.0 (IBM, USA). The normality of the numerical data distribution was examined using the Shapiro- Wilk normality test. Continuous variables with normal distribution were presented as median± standard deviation. The categorical data were compared using the Chi-squares test. Binary logistic regression analysis was used to investigate relationship between autoantibodies. *p<0.05* was accepted for statistical significance.

Results

Nine hundred thirty patients diagnosed with RA and 635 patients diagnosed with AS were screened, and patients whose HLA-B27 was tested were included in the study. A total of 569 patients, 199 with RA and 370 with AS were included in the study. One hundred forty-five (72.9%) of the patients with RA were female; 133 (35.9%) of the patients with AS were female. There was a statistically significant difference between the groups in terms of gender and RA was more common in women (*p=0.001*). The mean age of patients with RA was 49.10±14.78 years, while the mean age of patients with AS was 39.29±1.1 years, and there was no significant difference between the groups in terms of mean age (*p=0.198*). While HLA-B27 was positive in 11% of patients with RA, it was in 37.5% of patients with AS and there was a significant difference between the groups (*p=0.001*). While 49 (17.6%) of the female patients were HLA-B27 positive; 106 (36.4%) of the male patients were HLA-B27 positive, and there was a statistically significant difference between the groups in terms of gender, and HLA-B27 positivity was more common in male patients (*p=0.001*). While 12 (8.27%) of 145 female patients diagnosed with RA were HLA-B27 positive; While 36 (27.06%) of 133 female patients diagnosed with AS were HLA-B27 positive, and 10 (18.51%) of 54 male patients diagnosed with RA were HLA-B27 positive; HLA-B27 was positive in 102 (43.03%) of 237 male patients diagnosed with AS. HLA-B27 positivity was more common in male patients in both the RA group and AS group (*p=0.001*). RF was positive in 44.7% of patients with RA, it was 10.3% in patients with AS with a significant difference between the groups (*p=0.001*). Anti-cyclic citrullinated peptides (Anti-CCP) was positive in 35.7% and 0.3% of patients with RA and AS, respectively; and there was a significant difference between the groups (*p=0.001*). Anti-nuclear antibody (ANA) was positive in 33.2% of patients with RA, it was 6.5% in patients with a significant difference between the groups (*p=0.001*). Sedimentation (SED) and C-reactive protein (CRP) levels were significantly lower in AS patients respectively (*p<0.001*), (*p=0.032*) (Table I).

Table I. Demographic features and clinical findings of the patients

		RA (N=199)	**AS** (N=370)	***p***
Age (Mean±standart deviation)		49.10±14.78	39.29±1.1	*0.198*[a]
Gender (N/%)	Female	145 (72.9)	133 (35.9)	***<0.001***[b]
	Male	54 (27.1)	237 (64.1)	
HLA-B27 (N/%)	Positive	22 (11)	138 (37.5)	***<0.001***[b]
	Negative	177 (89)	232 (62.7)	
RF (N/%)	Positive	89 (44.7)	38 (10.3)	***<0.001***[b]
	Negative	110 (55.3)	332 (89.7)	
ANTI-CCP (N/%)	Positive	71 (35.7)	1 (0.3)	***<0.001***[b]
	Negative	110 (55.3)	149 (40.5)	
ANA (N/%)	Positive	66 (33.2)	24 (6.5)	***<0.001***[b]
	Negative	133 (66.8)	100 (27)	
SED (Mean±standart deviation)		23.98±19.56	13.93±12.98	***<0.001***[a]
CRP (Mean±standart deviation)		2.5±6.58	1.60±2.35	***0.032***[a]
Sacroiliac MR (N/%)	Normal		39 (10.6)	
	Suspicious		9 (2.4)	
	Positive		322 (87)	
Medications (N/%)	NSAII	145 (72.86)	163 (44.11)	***<0.001***[b]
	NSAII+SLZ	2 (1)	70 (18.9)	***<0.001***[b]
	Methotrexate	130 (65.32)	0 (0)	***<0.001***[b]
	Other DMARDs	60 (30.15)	0 (0)	***<0.001***[b]
	Biological agent	35 (17.58)	137 (37)	***<0.001***[b]

RA: Rheumatoid Arthritis, AS: Ankylosing Spondylitis, N: number, RF: Rheumatoid Factor ANA: Anti-nuclear antibody,
SED: Sedimentation, CRP: C reactive protein, MR: Magnetic Resonance, NSAII: non-steroidal anti-inflammatory drugs,
SLZ: Salazopyrin, DMARDS: Disease-modifying antirheumatic drugs

[a] *Independent samples t-test,* [b] *Chi-square test*

Table II. Logistic regression analysis of autoantibodies with HLA-B27

	B	S.E.	Wald	df	Sig.	OR
RF	-0,390	0,634	0,379	1	0,538	0,677
Anti-CCP	-0,163	0,687	0,056	1	0,813	0,850
ANA	0,237	0,562	0,178	1	0,673	1,267

Binary logistic regression analysis OR: Odds ratio, RF: Rheumatoid Factor, Anti-CCP: cyclic citrullinated peptides,
ANA: Anti-nuclear antibody

Binary logistic regression analysis found no association between RF, Anti-CCP, and ANA with HLA-B27 positivity (Table II). When we analyzed the relationship between HLA-B27 and the treatment method, there was no significant relationship between the HLA-B27 and the treatment method (*p=0.056*) (Table III).

Table III. Analysis of the association between HLA B27 and the treatment method in patients diagnosed with RA

			Treatment		Total
			Biological agents ± DMARD	DMARD	
HLA-B27	Negative	Count	22_a	150_a	172
		Expected Count	24,7	157,3	182,0
		% within the treatment group	81,5%	93,0%	91,5%
		Residual	-2,7	2,7	
		Adjusted Residual	-2,0	2,0	
	Positive	Count	8_a	14_a	22
		Expected Count	2,3	14,7	17,0
		% within the treatment group	18,5%	7,0%	8,5%
		% of Total	2,5%	6,0%	8,5%
		Residual	2,7	-2,7	
		Adjusted Residual	2,0	-2,0	
Total		Count	27	172	199
		Expected Count	27,0	172,0	199,0
		% within the treatment group	100,0%	100,0%	100,0%
		% of Total	13,6%	86,4%	100,0%

Each subscript letter denotes a subset of treatment categories whose column proportions do not differ significantly from each other at the 0.05 levels.

Pearson Chi-square *p=.056,* DMARD: disease

Discussion

The incidence of the RA was 2-3 times higher in women in many studies conducted on patients with RA (17-19). Similar to the literature, the female/male ratio was found to be 2.68 in our study. The incidence of the AS was 2-4 times higher in men in many studies conducted on patients with AS (5, 6, 20). Similar to the literature, the male/female ratio was found to be 1.78 in our study. HLA-B27 positivity was found to be more common in male patients with AS in some studies (21, 22). Contrary to these studies, Omar et al. and Arévalo et al. did not detect a significant relationship between HLA-B27 and gender in their studies (23, 24). A statistically significant difference was found between HLA-B27 positive and HLA-B27 negative groups in terms of gender and HLA-B27 was more common in male patients in our study. The reason why AS is more common in men may be that HLA-B27 positivity is more common in male patients as seen in our study. The prevalence of HLA-B27 antigen positivity varies (25, 26). While the incidence of HLA-B27 in the unaffected people in Europe is 8%, it ranges from 3-5% in China (27). The prevalence of HLA-B27 in the general population was reported that 5-8% in studies conducted in Türkiye (28). The prevalence of HLA-B27 in AS patients was reported that 70-90% in various studies conducted in Türkiye (12, 29). While HLA-B27 is found in 5% of the population, AS is found in only 1-5% of individuals with HLA-B27 (30). The presence of AS in 5% of HLA-B27 antigen-positive individuals indicates that not only HLA-B27 but also other genes contribute to the pathogenesis of AS (31).

We found 11% positivity in 199 RA patients while HLA-B27 positivity is 5% in the general population in the literature. We could not find any article to compare our study. Some previous studies on HLA-B27 positivity in patients with RA are very old and small-scale case-control studies. Therefore, it was stated that the relationship between RA and HLA-B27 was not significant in a meta-analysis examining the relationship between RA and HLA-B27 antigen, but HLA-B27 antigen positivity could be a potential risk factor for pharmacogenomics and personalized therapy (13). In our study, unlike the literature, the frequency of HLA-B27 was found to be

37.5% in 370 AS patients. We think that this different result may be due to the difference in the number of patients, clinical variations, different ethnic origins and genetic factors.

There was no statistically significant difference in terms of medications used between the 22 HLA-B27 positive patients and the 177 negative patients in 199 patients diagnosed with RA. Similarly, there was no statistically significant difference in terms of medications used between 138 HLA-B27 positive patients and 232 negative patients in 370 patients diagnosed with AS. There was no difference in drug regimens between HLA-B27 negative and positive patients in our study and HLA-B27 positivity was used as a diagnostic tool not appear to affect the choice and change of treatment regimen. Similarly, it was determined that HLA-B27 positivity or negativity did not affect the decision (biological and non-biological) of the treatment regimen in the studies examining the role of HLA-B27 in disease activity and effectiveness of treatment in AS patients by Omar et al. (24). We could not compare the situation in which HLA-B27 positivity or negativity does not affect the treatment regimen in RA since there is no previous study examining the role of HLA-B27 in disease activity and treatment effectiveness in patients diagnosed with RA.

The lack of a healthy control group and the low number of patients with RA compared to AS were limitations of our study. Other limitations of my study were that the number of patients routinely seen in the outpatient clinic was not known and that patients whose HLA-27 levels were not tested were not included in the study which could cause bias.

Conclusion

Our findings suggest that the prevalence of HLA-B27 positive was higher in RA compared to the normal population, and lower in AS than in previous studies. More studies are needed to evaluate HLA-B27 frequency in RA and AS and the impact of HLA-B27 positive on prognosis and treatment of RA and AS.

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