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Prevalence of HLA-B27 in Turkish Patients with Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis

Ankilozan Spondilitli ve Non-radyografik Aksiyal Spondiloartritli Türk Hastalarda HLA-B27 Prevalansı

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ABSTRACT Objective: Human leukocyte antigen (HLA)-B27 is a genetic risk factor associated with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Although there are studies regarding the HLA-B27 prevalence in patients with AS in Turkey, there is insufficient information on the HLA-B27 prevalence in patients with n-axSpA. We aimed to evaluate the prevalence of HLA-B27 positivity among patients with AS and nr-axSpA, and its association with disease activity. **Material and Methods:** A cross sectional study was conducted on 860 participants (762 with AS and 98 with nr-axSpA), fulfilling the modified New York criteria and/or Assessment of Spondyloarthritis International Society (ASAS) classification criteria. Disease activity was assessed through the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP). **Results:** HLA-B27 was positive in 69.3% of all patients, in 70.1% of patients with AS, and in 63.3% of patients with nr-axSpA. There was a significant difference in HLA-B27 positivity among the AS patients with a higher ASDAS and higher BASDAI score (respectively; p<0.001, p=0.002), while there was no relation between the HLA-B27 positivity and disease activity in patients with nr-axSpA (p=0.6, p=0.5, respectively). **Conclusion:** The prevalence of HLA-B27 is relatively low among patients with AS and nr-axSpA in Turkey, which might be attributed to the geographic location of Turkey leads a multi-ethnic society. Moreover, HLA-B27 is associated with higher disease activity in AS patients, but there is no such relationship in nr-axSpA patients.

Keywords:HLA-B27 antigen; spondylitis, ankylosing; prevalence

ÖZET Amaç: İnsan lökosit antijeni (HLA)-B27, ankilozan spondilit (AS) ve non-radyografik aksiyal spondiloartrit (nr-axSpA) ile ilişkili genetik bir risk faktörüdür. Türkiye'de AS'li hastalarda HLA-B27 prevalansı ile ilgili çalışmalar olmasına rağmen n-axSpA hastalarında HLA-B27 prevalansı hakkında yeterli bilgi bulunmamaktadır. Bu çalışmada, AS ve nr-axSpA hastalarında HLA-B27 pozitifliğinin görülme sıklığı ve hastalık aktivitesi ile ilişkisinin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya, modifiye New York ve/veya ASAS (Uluslararası Spondilo Artrit Değerlendirme Derneği) kriterlerini karşılayan 762 AS ve 98 nr-axSpA olmak üzere toplam 860 hasta dâhil edilmiştir. Hastalık aktivitesi Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI) ve C-reaktif protein içeren Ankilozan Spondilit Hastalık Aktivite Skoru (ASDAS-CRP) ile değerlendirildi. **Bulgular:** HLA-B27 tüm hastaların %69,3'ünde, AS'li hastaların %70,1'inde ve nr-axSpA'lı hastaların %63,3'ünde pozitifti. AS hastalarında daha yüksek ASDAS ve BASDAI skoru ile HLA-B27 pozitifliği arasında anlamlı bir ilişki bulunurken, (sırasıyla; p<0,001, p=0,002), nr-axSpA hastalarında HLA-B27 pozitifliği ile hastalık aktivitesi arasında anlamlı bir ilişki saptanmadı (sırasıyla; p=0,6, p=0,5). **Sonuç:** HLA-B27 prevalansı, Türkiye'deki AS ve nr-axSpA hastalarında nispeten düşük olup, bu durum Türkiye'nin coğrafi konumuna ve farklı etnik yapıları içermesine atfedilebilir. Ayrıca HLA-B27 pozitifliği AS hastalarında daha yüksek hastalık aktivitesi ile ilişkili olup, nr-axSpA hastalarında böyle bir ilişki yoktur.

Anahtar Kelimeler: HLA-B27 antijeni; spondilit, ankilozan; prevalans

Human leukocyte antigen (HLA) class I molecule *HLA-B27* was considered the first distinctive genetic risk factor specifically associated with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA).[1,2] The recent studies on twins and families showed that the *HLA-B27*

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is the most important genetic risk factor for AS and nr-axSpA.[3] About 100 sub-alleles of *HLA-B27* have been described up to the present.[1]

Prevalence studies and animal models suggest that *HLA-B27* is involved in the pathogenesis of both AS and nr-axSpA.[1,2] Despite several genetic studies concerning the mechanism and activation process of *HLA-B27*, the real triggering act of this gene is still unknown.[4-7] There are several hypotheses for the role of *HLA-B27* in the pathogenesis of AS and nr-axSpA. The most accepted one is the abnormal processing of antigenic peptides and endoplasmic reticulum stress resulting from the tendency of *HLA-B27* to misfold and form homo-dimers.[2]

The frequency of the *HLA-B27* also varies in terms of ethnicity and geography.[8] A decrease in *HLA-B27* prevalence is observed in the Northern Hemisphere from north to south and from west to east.[2] It is assumed that these differences are due to the negative selection of malaria, and in regions where malaria is endemic, the prevalence of *HLA-B27* is low and vice versa.[9] The prevalence of *HLA-B27* in the normal population is significantly lower in the Middle Eastern and Arab countries than in Western countries.[10]

Although there are studies regarding the *HLA-B27* prevalence in patients with AS in Turkey, there is insufficient information on the *HLA-B27* prevalence in patients with nr-axSpA.[11-14] Therefore, in this study, we aimed to evaluate; (1) the prevalence of *HLA-B27* positivity among patients with AS and nr-axSpA, and (2) its association with disease activity, which was evaluated through the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP).

MATERIAL AND METHODS

DESIGN

A cross-sectional study was planned on AS and nr-axSpA patients, who applied to rheumatology and physical therapy and rehabilitation outpatient clinic. Ankara University Clinical Research Ethics Committee approved the study approval and written informed consent of participants were obtained prior to the performance of any study procedures, which was in accordance with the Helsinki Declaration.

PARTICIPANTS

A total of 860 patients, 98 with nr-axSpA and 762 with AS, were included in the study. Patients, who fulfilled the modified New York criteria and/or the Assessment of Spondyloarthritis International Society (ASAS) classification criteria, were enrolled starting from April 2014 to June 2018. Patients, who had already a diagnosis and had been followed up in the outpatient clinic, were included in this study during their routine control. Patients, who had a new diagnosis during the study period, were excluded in the study since it might be a factor that would disturb the comparison of ongoing treatment efficacy.

DEMOGRAPHIC VARIABLES

Age and gender were used for analysis.

CLINICAL FEATURES

Disease duration, time on antitumor necrosis factor (TNF) and nonsteroidal antiinflammatory drugs (NSAIDs) treatment, time from disease onset to anti-TNF treatment, time from diagnosis to anti-TNF treatment were recorded.

LABORATORY MEASUREMENTS

All assays were performed in the same biochemical laboratory. Blood samples of all patients were obtained at the time of enrollment of the study. A total of 10 cc blood was collected from the participants, who had no *HLA-B27* results during their follow-up, after 12 hours of fasting. Blood samples were centrifuged at 4,000 repetitions per minute for 10 minutes. Also, as an acute phase reactant, CRP was studied at the time of enrollment.

DISEASE ACTIVITY

Disease activity was assessed through BASDAI and ASDAS-CRP. Thresholds were determined as follows: for BASDAI inactive disease (<4) and active disease (≥4); for ASDAS-CRP inactive disease (<1.3), moderate disease activity (1.3-2.1), high disease activity (2.1-3.5) and very high disease activity (>3.5).

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 software (IBM SPSS Statistics for Windows, Version 21.0., Armonk, New York, USA). The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine normal or non-normal distributions. Descriptive analyses were presented using means, standard deviations and frequencies. The Student's t-test was used to compare age, disease duration, time on anti-TNF and NSAIDs treatment, time from disease onset to anti-TNF treatment, time from diagnosis to anti-TNF treatment. The Chi-square test was used to compare the gender and *HLA-B27* positivity among groups. A 5% Type-I error level was used to infer statistical significance.

RESULTS

DEMOGRAPHIC AND CLINICAL FEATURES OF THE PATIENTS

Demographic and clinical features of the patients are given in Table 1. Disease duration, time on anti-TNF treatment, time on NSAIDs, time from disease onset to anti-TNF treatment and time from diagnosis to anti-TNF treatment were lower in nr-axSpA group compared to AS ($p<0.001$ for all comparisons). *HLA-B27* was positive in 596 patients (69.3%), while there was no difference between the groups in terms of *HLA-B27* positivity (AS: 70.1%, nr-axSpA: %63.3, $p=0.2$).

ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE WITH C-REACTIVE PROTEIN AND HLA-B27 POSITIVITY

Mean ASDAS-CRP and BASDAI scores were higher in the AS group when compared to nr-axSpA group ($p<0.001$ for both) (Table 1). Table 2 shows the *HLA-B27* positivity of the patients according to the baseline ASDAS-CRP values. There was a significant difference in *HLA-B27* positivity among the AS patients with a higher ASDAS-CRP ($p<0.001$). However, no significant difference was observed in *HLA-B27* positivity among the nr-axSpA group ($p=0.6$).

BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX AND HLA-B27 POSITIVITY

Table 3 gives information about the HLA-B27 positivity of the patients according to the baseline BASDAI scores. There was a significant difference in *HLA-B27* positivity among the AS patients with a higher BASDAI score ($p=0.002$). However, no significant difference was observed in *HLA-B27* positivity among the nr-axSpA group ($p=0.5$).

TABLE 1: Demographic and clinical features of the patients.

n=860	AS (n=762)	Nr-axSpA (n=98)	p
Male sex, n (%)	458 (60.1)	46 (46.9)	**0.012**
Age, years	46.4±12.2	49.0±13.2	0.07
Disease duration, months	122.5±93.6	63.4±39.7	**< 0.001**
ASDAS-CRP	2.9±0.8	2.5±0.7	**<0.001**
BASDAI	4.7±1.2	3.6±0.9	**<0.001**
Anti-TNF treatment, n (%)	259 (34)	33 (39)	0.9
Time on anti-TNF, months	28.1±24.9	14.1±8.1	**< 0.001**
Time on NSAIDs, months	43.9±46.8	17.5±11.5	**< 0.001**
Time from disease onset to anti-TNF treatment, months	109.9±87.1	57.04±41.3	**< 0.001**
Time from diagnosis to anti-TNF treatment, months	56.5±68.0	21.1±10.4	**< 0.001**
HLA-B27 positivity, n (%)	534 (70.1)	62 (63.3)	0.2

Data are presented as mean ± standard deviation unless otherwise specified.

AS: Ankylosing spondylitis; ASDAS: Ankylosing spondylitis disease activity score; BASDAI: Bath ankylosing spondylitis disease activity index; CRP: C-reactive protein; HLA: Human leukocyte antigen; nr-axSpa: Non-radiographic axial spondyloarthritis; NSAIDs: nonsteroidal antiinflammatory drugs; TNF: Tumor necrosis factor.

TABLE 2: HLA-B27 positivity among the patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis according to the baseline ankylosing spondylitis disease activity score with C-reactive protein.

N=860	HLA-B27	ASDAS-CRP <1.3	ASDAS-CRP 1.3-2.1	ASDAS-CRP 2.1-3.5	ASDAS-CRP >3.5	p
AS	+	41	68	214	211	**<0.001**
(n=762)	(n=534)	(7.7)	(12.7)	(40.1)	(39.5)	
	-	16	62	104	46	
	(n=228)	(7.0)	(27.2)	(45.6)	(20.2)	
Nr-axSpA	+	5	14	28	15	0.6
(n = 98)	(n=62)	(8.0)	(22.6)	(45.2)	(24.2)	
	-	2	6	21	7	
	(n=36)	(5.6)	(16.7)	(58.3)	(19.4)	

Data are presented as number (percent).

AS: Ankylosing spondylitis; ASDAS: Ankylosing spondylitis disease activity score; CRP: C-reactive protein; HLA: Human leukocyte antigen; nr-axSpa: Non-radiographic axial spondyloarthritis.

DISCUSSION

The discovery of a potential association between *HLA-B27* and AS produces a series of clinical studies describing the geographical prevalence and its potential relationship with the disease activity.[2,4,6,10] In this study, we presented the prevalence of *HLA-B27* positivity among patients with AS and nr-axSpA, and its association with disease activity. Although *HLA-B27* positivity among the Turkish patients diagnosed with AS has been investigated before, this is the first study evaluating the *HLA-B27* positivity among the patients with AS and nr-axSpA in Turkey.[11-14] The fact that nr-axSpA patients were included in our analysis is the strength of our study. However, it is known that the different subtypes (*HLA B2705, B2701, B2703, B2707, B2708, B2710, B2713, B2714, B2715, B2719* and *B2725*) and its distribution differ in terms of geography.[15] Therefore, the absence of *HLA-B27* subtyping might be seen as a limitation of our study.

We found the *HLA-B27* positivity 69.3% in all patients, 70.1% in patients with AS, and 63.3% in patients with nr-axSpA. Günal et al. compared the clinical features of AS and the frequencies of *HLA-B27* and its alleles in patients from Turkey with other series.[11] Similarly to our results, *HLA-B27* was found to be positive in 70% of patients. The authors concluded that the lower frequency of *HLA-B27* in their study than the other studies with Caucasians may be attributed to different genetic and/or environmental factors in Turkey. This was also valid in our study.

TABLE 3: *HLA-B27* positivity among the patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis according to the baseline Bath ankylosing spondylitis disease activity index scores.

n=860	HLA-B27	Moderate (<4)	Severe (≥4)	p
AS	+	182	352	**0.002**
(n=762)	(n=534)	(34.1)	(65.9)	
	-	105	123	
	(n=228)	(46.1)	(53.9)	
Nr-axSpA	+	32	30	0.5
(n=98)	(n=62)	(51.6)	(48.4)	
	-	21	15	
	(n=36)	(58.3)	(41.7)	

Data are presented as number (percent).

AS: Ankylosing spondylitis;

BASDAI: Bath Ankylosing spondylitis disease activity index;

HLA: Human leukocyte antigen; nr-axSpa: Non-radiographic axial spondyloarthritis.

The geographic location is accepted as one of the determining factors for the prevalence of *HLA-B27* positivity. There were different results when the countries close to Turkey were examined. Kassimos et al. investigated the *HLA-B27* antigen in young Greek males with AS, and they found that the 90% of the patients had *HLA-B27* antigen.[16] Fallahi et al. assessed the prevelance of HLA-B27 positivity in AS patients in Iran. Similarly with our findings, they

found that 74.8% of AS patients was *HLA-B27* positive.[17] Having also a different ethnicity and environmental factors in Iran, like Turkey, might have given this result. In a recent study, Ziade et al. calculated the prevalence *HLA-B27* in axSpA in Lebanon.[18] With the agreement of our findings, they found that the low prevalence of *HLA-B27* (41.1%) in axSpA.

We found a significant difference in *HLA-B27* positivity among the AS patients with a higher ASDAS and higher BASDAI score ($p<0.001$, $p=0.002$, respectively), while there was no relation between the *HLA-B27* positivity and disease activity in patients with nr-axSpA. Popescu et al. examined the relationship between functional and activity scores in AS.[19] Similarly to our results, the authors found that *HLA-B27* positive patients had a median BASDAI 5 times higher than *HLA-B27* negative patients ($p=0.033$).[19] Fallahi et al. searched the potential relationship between disease severity and the *HLA-B27* positivity.[17] They found the severity markers toward higher values in the *HLA-B27* positive group with no significant difference.

As mentioned above, one of the interesting findings of our study was that the *HLA-B27* positivity had no relation with disease activity in the nr-axSpA group. Although treatment modalities, such as anti-TNF, were used in both AS and nr-axSpA groups at similar rates, this result in the nr-axSpA group might be explained with the shorter disease duration and earlier use of anti-TNF treatment. The fact that the basal ASDAS-CRP and BASDAI scores were significantly higher in the AS group compared to the nr-axSpA group is another indicator that could explain this finding. Similarly to our findings, in a recent study, Lubrano et al. found that one of the most important indicators of achieving low disease activity following the onset of anti-TNF therapy in patients with axial spondyloarthritis (AS + nr-axSpA) was short disease duration.[20] The reason we could not explain this situation with the use of NSAIDs is that we did not differentiate patients based on continuous and/or intermittent NSAID use. On the other hand, the cross-sectional nature of our study is the biggest limitation in terms of the generalizability of these results.

Although it is not one of the main objectives of our study, an important point is noteworthy when we consider the above-mentioned paragraph. In the last decade, both the common use of the sacroiliac magnetic resonance imaging system and the introduction of new axial spondyloarthritis classification criteria developed by ASAS, which enables diagnosis of nr-axSpA patients, have led not only to early diagnosis but also to effective treatments to start earlier.

CONCLUSION

Consequently, the frequency of *HLA-B27* positivity in patients with AS and nr-axSpa is low, similar to the other studies conducted in our geography. Moreover, *HLA-B27* is associated with higher disease activity in AS patients, but there is no such relationship in nr-axSpA patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

REFERENCES

1. Thomas GP, Brown MA. Genetics and genomics of ankylosing spondylitis. Immunol Rev. 2010;233(1):162-80.[Crossref] [PubMed]
2. Roberts RL, Wallace MC, Jones GT, van Rij AM, Merriman TR, Harrison A, et al. Prevalence of HLA-B27 in the New Zealand population: effect of age and ethnicity. Arthritis Res Ther. 2013;22;15(5):R158. [Crossref] [PubMed] [PMC]
3. Akassou A, Bakri Y. Does HLA-B27 status influence ankylosing spondylitis phenotype? Clin Med Insights Arthritis Musculoskelet Disord. 2018;8;11.[Crossref] [PubMed] [PMC]
4. Khan MA, Kushner I, Braun WE. Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis. Arthritis Rheum. 1977;20(4):909-12.[Crossref] [PubMed]
5. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int. 2003;23(2):61-6.[Crossref] [PubMed]
6. Wu Z, Lin Z, Wei Q, Gu J. Clinical features of ankylosing spondylitis may correlate with HLA-B27 polymorphism. Rheumatol Int. 2009;29(4):389-92.[Crossref] [PubMed]
7. Al-Rawi ZS, Al-Shakarchi HA, Hasan F, Thewaini AJ. Ankylosing spondylitis and its association with the histocompatibility antigen HL-A B27: an epidemiological and clinical study. Rheumatol Rehabil. 1978;17(2):72-5. [Crossref] [PubMed]
8. Khan MA. HLA-B27 and its subtypes in world populations. Curr Opin Rheumatol. 1995;7(4):263-9. [Crossref] [PubMed]
9. Mathieu A, Cauli A, Fiorillo MT, Sorrentino R. HLA-B27 and ankylosing spondylitis geographic distribution as the result of a genetic selection induced by malaria endemic? A review supporting the hypothesis. Autoimmun Rev. 2008;7(5):398-403. [Crossref] [PubMed]
10. Ziade NR. HLA B27 antigen in Middle Eastern and Arab countries: systematic review of the strength of association with axial spondyloarthritis and methodological gaps. BMC Musculoskelet Disord. 2017;29;18(1):280. [Crossref] [PubMed] [PMC]
11. Gunal EK, Sarvan FO, Kamali S, Gul A, Inanc M, Carin M, et al. Low frequency of HLA-B27 in ankylosing spondylitis patients from Turkey. Joint Bone Spine. 2008;75(3):299-302. [Crossref] [PubMed]
12. Acar M, Cora T, Tunc R, Acar H. HLA-B27 subtypes in Turkish patients with ankylosing spondylitis and healthy controls. Rheumatol Int. 2012;32(10):3103-5.[Crossref] [PubMed]
13. Fırat SN, Yazıcı A, Yılmazer B, Coşan F, Savlı H, Cefle A, et al. Low frequency of HLA-B27 in ankylosing spondylitis and its relationship with clinical findings in patients from Turkey. Eur J Rheumatol. 2017;4(4):268-71. [Crossref] [PubMed] [PMC]
14. Vahidfar S, Sunar İ, Ataman Ş, Yılmaz G, Azarabadi JM, Bölükbaşı A, et al.. Ultrasonographic evaluation of Achilles tendon: Is there any difference between ankylosing spondylitis, non-radiographic axial spondyloarthropathy and controls? Int J Rheum Dis. 2020;23(4):511-9. [Crossref] [PubMed]
15. Khan MA. Update: the twenty subtypes of HLA-B27. Curr Opin Rheumatol. 2000;12(4):235-8. [Crossref] [PubMed]
16. Kassimos DG, Vassilakos J, Magiorkinis G, Garyfallos A. Prevalence and clinical manifestations of ankylosing spondylitis in young Greek males. Clin Rheumatol. 2014;33(9):1303-6. [Crossref] [PubMed]
17. Fallahi S, Mahmoudi M, Nicknam MH, Gharibdoost F, Farhadi E, Saei A, et al. Effect of HLA-B*27 and its subtypes on clinical manifestations and severity of ankylosing spondylitis in Iranian patients. Iran J Allergy Asthma Immunol. 2013;28;12(4):321-30. [PubMed]
18. Ziade N, Abi Karam G, Merheb G, Mallak I, Irani L, Alam E, et al. HLA-B27 prevalence in axial spondyloarthritis patients and in blood donors in a Lebanese population: Results from a nationwide study. Int J Rheum Dis. 2019;22(4):708-14. [Crossref] [PubMed]
19. Popescu C, Trandafir M, Bădică A, Morar F, Predeţeanu D. Ankylosing spondylitis functional and activity indices in clinical practice. J Med Life. 2014;15;7(1):78-83. [PubMed] [PMC]
20. Lubrano E, Perrotta FM, Manara M, D'Angelo S, Ramonda R, Punzi L, et al. Improvement of function and ıts determinants in a group of axial spondyloarthritis patients treated with TNF inhibitors: a real-life study. Rheumatol Ther. 2020;7(2):301-10. [Crossref] [PubMed] [PMC]