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Frequency of HLA-B51 in Behçet's Patients and Relationship with Clinical Findings

Behçet Hastalarında HLA-B51 Sıklığı ve Klinik Bulgularla İlişkisi

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ABSTRACT Objective: The most important genetic factors known in the pathogenesis of Behçet's disease (BD) is HLA-B51. It has been shown that HLA-B51 positivity is high in countries on the 'Silk Road' where BD is frequent. HLA-B51 is thought to be a prognostic marker that is related to severe clinical forms of BD. In this study, we aimed to investigate the prevalence of HLA-B51 positivity in patients diagnosed with BD and the relationship between the demographic and clinical findings of the patients. **Material and Methods:** Between March 2013 and 2018, the files of the patients who were diagnosed with BD according to the criteria of the International Study Group for Behçet Disease in dermatology polyclinic of Selçuk University Medical Faculty were reviewed retrospectively. Forty-seven patients (22 women and 25 men) with HLA-B51 were included in the study. **Results:** In our study, no correlation was found between HLA-B51 positivity and gender, age at onset, family history, clinical findings (such as oral and genital ulcer, papulopustular eruption, erythema nodosum, pathergy test positivity, thrombophlebitis, ocular involvement, arthritis) and systemic manifestations. **Conclusion:** In previous studies, conflicting results have been reported on the relationship between HLA-B51 and BD manifestations in different ethnic groups. In our study, no statistically significant correlation was found between HLA-B51 positivity and demographic and clinical findings of Behçet patients. We believe that there is a need for larger comparative prospective studies investigating the relationship between HLA-B51 and BD in different ethnic groups.

Keywords: Behçet's disease; HLA-B51

ÖZET Amaç: Behçet hastalığının (BH) patogenezindeki bilinen genetik faktörlerin en önemlisi HLA-B51'dir. Behçet hastalığının sık görüldüğü "İpek yolu" üzerindeki ülkelerde HLA-B51 pozitifliğinin yüksek olduğu gösterilmiştir. HLAB-51'in, BH'nin şiddetli klinik formları ile ilişkili prognostik bir marker olabileceği düşünülmüştür. Bu çalışmada, BH tanısı ile takip edilen hastalarda, HLA-B51 pozitifliğinin sıklığı ve hastaların demografik ve klinik bulguları ile ilişkisini araştırmayı amaçladık. **Gereç ve Yöntemler:** Mart 2013-2018 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi dermatoloji polikliniğinde takip edilen, Uluslararası Behçet Hastalığı Çalışma Grubu kriterlerinine göre BH tanısı olan hastaların dosyaları retrospektif olarak incelendi. HLA-B51 bakılan 47 hasta (22 kadın ve 25 erkek) çalışmaya dahil edildi. **Bulgular:** Çalışmamızda HLA-B51 pozitifliği ile cinsiyet, başlangıç yaşı, aile öyküsü, klinik bulgular (oral ve genital ülser, papülopüstüler erüpsiyon, eritema nodozum, paterji testi pozitifliği, tromboflebit, oküler tutulum, artrit gibi) ve sistemik bulgular arasında bir ilişki bulunmadı. **Sonuç:** Daha önceki çalışmalarda, farklı etnik gruplarda, HLA-B51'in BH'nin klinik bulguları arasındaki ilişkiyle ilgili çelişkili sonuçlar bildirilmiştir. Bizim çalışmamızda HLA-B51 pozitifliği ile Behçet hastalarının demografik ve klinik özellikleri arasında istatistiksel olarak anlamlı bir ilişki bulunamamıştır. Bu nedenle HLA-B51 ile BH'nin ilişkisini araştıran farklı etnik grupları kapsayan daha geniş karşılaştırmalı prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Behçet hastalığı; HLA-B51

Behçet's disease (BD) is a chronic multisystemic inflammatory disease, which was first described by the Turkish dermatologist Hulusi Behçet with a triple symptom of oral aphthous ulcer, genital ulcer and uveitis.[1] Although the etiopathogenesis of BD is unknown, it is thought to be a multifactorial disease triggered by viral, bacterial and environmental factors in individuals with genetic predisposition.[2]

BD shows a wide geographical distribution covering the countries located on 'Silk Road' in the Middle East such as Syria, Iran, Iraq, Turkey and Far Eastern countries such as Japan, Korea and China, The highest prevalence of the BD is Turkey.[3] The fact that HLA-B51 positivity is found to be high in this geographic distribution in which BD is common leads to think that HLA-B51 is the strongest genetic susceptibility factor for BD.[4] There are also studies showing that HLA-B5/51 carriage is associated with clinical symptoms, disease severity, and gender in BD.[5,6]

In this study, we aimed to investigate the prevalence of HLA-B51 positivity in patients diagnosed with BD and the relationship between the demographic and clinical findings of the patients.

MATERIAL AND METHODS

The files of the patients who were diagnosed with BD according to the criteria of the International Study Group for Behçet Disease and followed-up between March 2013 and 2018 in Dermatology Outpatient Clinic of Selçuk University Medical Faculty were retrospectively reviewed. Prior to the study, the local ethics committee approval no 2018/186 was obtained. The study was carried out according to the principles expressed in the Declaration of Helsinki. Chi square test and SPSS version 21 computer program were used for statistical analyses and $p<0.05$ was considered as statistically significant. Student t test was used to compare the mean age.

RESULTS

Forty-seven out of 79 patients followed up in our polyclinic with BD and whose files included HLA-B51 results and their results data were included in the study. Age of the patients varied between 20 and 58, 22 were women and 25 were men. Demographic data, age at disease onset and frequency of clinical findings were compared between HLA-B51 positive and negative Behçet patients. In 47 patients with HLA-B51 results, HLA-B51 was found to be positive in 27 patients and negative in 20 patients and there was no statistically significant difference in the mean age and gender distribution of the patients in both groups (Table 1). There was no statistically significant difference between HLA-B51 positive (29.22±7.73) and negative patients with regard to age (31.05±9.87) (p=0.692). In our study, papulopustular eruption (81.5%/70%), pathergy positivity (44.4%/30%), ocular involvement (48.1%/35%), thrombophlebitis (7.7%/0%), deep vein thrombosis (DVT) (7.4%/5%), arthritis (29.6%/20%), genitourinary system (GUS) (3.7%/%0), and family history for BD (33.3%/25%) were found to be higher in HLA-B51 positive patients than HLA-B51 negative patients but no statistically significant difference was found between two groups. All patients had oral aphthae (100%), while none had neurological involvement, gastrointestinal system (GIS) involvement. Genital ulcer (57.7%/ 85.0%) and erythema nodosum (37%/45%) were lower in patients with HLA-B51 positivity, but no statistically significant difference was found between HLA-B51 negative ones (Table 2).

TABLE 1: Mean age and gender distribution of the patients.

				Age				
				Mean.±SD	Min	Max	N	p-value
HLA-B51	Positive	Gender	Female	37.0±8.74	21	53	11	
			Male	35.5±10.05	22	58	16	0.692
	Negative		Female	39.64±9.27	24	55	11	
			Male	33.11±11.31	20	47	9	0.173

TABLE 2: Clinical manifestations of Behçet's disease according to HLA-B51 positivity.

		HLA-B51				
		Positive		Negative		
		n	%	n	%	p-value
Gender	Female	11	40.7	11	55	0.501
	Male	16	59.3	9	45	
Oral ulceration	Absent	0	0	0	0	-
	Present	27	100	20	100	
Genital ulceration	Absent	11	42.3	3	15	0.094
	Present	15	57.7	17	85	
Erythema nodosum	Absent	17	63	11	55	0.803
	Present	10	37	9	45	
Thrombophlebitis	Absent	24	92.3	20	100	0.498
	Present	2	7.7	0	0	
Papulopustular eruption	Absent	5	18.5	6	30	0.498
	Present	22	81.5	14	70	
Ocular involvement	Absent	14	51.9	13	65	0.546
	Present	13	48.1	7	35	
Arthritis	Absent	19	70.4	16	80	0.682
	Present	8	29.6	4	20	
CNS involvement	Absent	27	100	20	100	-
	Present	0	0	0	0	
DVT	Absent	25	92.6	19	95	1
	Present	2	7.4	1	5	
Positive pathergy test	Absent	15	55.6	14	70	0.482
	Present	12	44.4	6	30	
GUS involvement	Absent	26	96.3	20	100	1
	Present	1	3.7	0	0	
Family history	Absent	18	66.7	15	75	0.768
	Present	9	33.3	5	25	

DVT: Deep vein thrombosis, CNS: Central nervous system, GUS: Genitourinary system.

CONCLUSION

The etiology of BD is a systemic inflammatory disease is still unknown today.[7] The disease can show multisystemic findings including mucocutaneous, which is the most common, and also eye, joint, GIS, neurological, cardiovascular, pulmonary and genitourinary ones.[8] It was first presented by Ohno et al. in 1973 that BD was associated with the HLA-B5 molecule, and it was later found that HLA-B51 was strongly associated with BD in detailed gene-level studies in 1982.[9,10] HLA-B51 is located in the HLA class I located in the major histocompatibility complex (MHC) locus on chromosome 6p21.[8,11] HLA-B51 is thought to play a role in neutrophil activation. Abnormal neutrophil hyperfunction is therefore important in the etiopathogenesis and clinical course of BD. Therefore, HLA-B51 has been reported as a marker that determines the prognosis as well as the susceptibility to BD.[2,12] The prevalence of HLA-B51 in BD among populations, is also observed as different. While the frequency of HLA-B51 is around 50-80% all along the Silk Road, it is as low as 15% in Northern Europe and America.[13] Generally, HLA-B51 positivity in Behçet's patients ranges from 30% to 80%.[14,15] Kaya et al. reported the rate of HLA-B51 positivity as 54.1% in Turkish Behçet patients.[16] Similarly with this

study, we observed HLA-B51 in 27 (57.4%) of our 47 patients. In some ethnic groups, such as Japan, HLA-B51 may be positive in 15% of healthy individuals and negative in 30% of those with BD. Thus, HLA-B51 may not always be useful in the diagnosis of BD.[17] In several studies, it was reported that men with HLA-B51 were more at risk for BD and it was associated with early onset age.[18] However, in our study, no correlation was found between HLA-B51 positivity and age at gender and onset.

In the literature, there are studies showing the relationship between various clinical findings of BD and disease severity and HLA-B51. The conflicting results of HLA B51 in relation to the symptoms of BD have been reported in different ethnic groups.[5] Even in studies comparing the clinical manifestations of HLA-51 and BD in people of the same ethnic background, different results have been reported. For example, in a study conducted on 61 BD patients from Korea, uveitis and erythema nodosum were more common in patients with HLA-B51 positivity, and it was suggested that HLA-B51 may be a genetic marker of severe BD associated with uveitis. In a study reported again from Korea, in Behçet's patients with HLA-B51 positivity, while the age at onset of the disease was earlier and pseudofolliculitis was higher in these patients, GIS and neurologic involvement were less than those with HLA-B51 negativity.[19,20] In a study conducted with Tunisian patients, HLA-B51 is a predisposing factor for BD and in those with HLA-B51 positive; while retinal vasculitis and pathergy positivity were more frequent, neurological involvement, disease severity and arterial aneurysm were found to be less.[6]

In our study, oral aphthous ulceration (100%) was the most common symptom of the patients similarly to previous studies.[18,21-23] In their study, Müftüoğlu et al. found no positive or negative association betwe en HLA-B5 and age at onset, gender, ocular involvement, arthritis, thrombophlebitis and erythema nodosum.[24] In another study conducted in Turkey including 406 patients HLA-B51 was positive in 170 patients out of 372 (45.7%). In addition, the association of HLA-B51 positivity with gender, frequency and severity of ocular inflammatory attacks has not been reported.[21] Similarly, in our study, no correlation was found between HLA-B51 positivity and gender and clinical findings. In patients with BD, mortality is often associated with neurological, pulmonary artery involvement and intestinal perforation.[25] None of our patients had GIS involvement, neurological involvement and major vascular involvement. It was found that HLA-B51 positivity was higher in men and genital ulcers, ocular and mucocutaneous involvement were more frequent. On the contrary, GIS involvement has been reported to be less in these patients.[5] Despite all these data, there is not enough data to allow the use of HLA-B51 positivity as a diagnostic and prognostic marker in BD.[11]

In conclusion, some data obtained in this retrospective study are similar to other studies. However, the relationship between the frequency of HLA-B51 positivity in our patients and the demographic and clinical findings of the patients could not be determined. We think that this is due to the different number of cases included in the study and the geographical region variety and also due to the socioeconomic and cultural differences. The results are contradictory although there are several studies from different countries showing the association of HLA-B51 positivity with clinical findings and the frequency of HLA-B51 positivity. Our study is the first study to cover the clinical data of a group of Behçet patients in the Konya region, the largest city in the region of Central Anatolia. We believe that this study will contribute to future multicenter studies which determine whether there are regional differences across the country.

Source of Finance

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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.

Authorship Contributions

Idea/Concept: *Fatma Tuncez Akyürek;* ***Design:*** *Fatma Tuncez Akyürek;* ***Control/Supervision:*** *Fatma Tuncez Akyürek;* ***Data Collection and/or Processing:*** *Nadir Koçak;* ***Analysis and/or Interpretation:*** *Nadir Koçak;* ***Literature Review:*** *Fatma Tuncez Akyürek;* ***Writing the Article:*** *Fatma Tuncez Akyürek;* ***Critical Review:*** *Fatma Tuncez Akyürek, Nadir Koçak;* ***References and Fundings:*** *Nadir Koçak;* ***Materials:*** *Nadir Koçak.*

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