Arch Rheumatol 2015;30(4):319-325
doi: 10.5606/ArchRheumatol.2015.5600

ORIGINAL ARTICLE

Effects of Smoking and HLA-B51 on Clinical Manifestations in Behçet's Disease: Retrospective Analysis of 209 Patients in a Turkish Population

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ABSTRACT

Objectives: This study aims to investigate the separate and cumulative effects of smoking and human leukocyte antigen (HLA)-B51 on the severity and clinical manifestations of Behçet's disease (BD).

Patients and methods: A total of 209 patients (119 males, 90 females; mean age 42.97±10.44 years; range 23 to 75 years) with BD were included in this retrospective study. The severity and clinical manifestations of BD, smoking habits, and presence of HLA-B51 of patients were obtained from medical records. The severity of BD was evaluated with Behçet's Syndrome Activity Scale (BSAS). Relationship between smoking habits and presence of HLA-B51 with disease severity and clinical manifestations was investigated.

Results: Presence of HLA-B51 was effective on BSAS, erythema nodosum (EN), articular, ocular and neurological involvements (p=0.001, p=0.011, p=0.013, p=0.001, p=0.038, respectively). Smoking was also effective on BSAS, EN, articular, ocular and neurological involvements (p=0.001, p=0.001, p=0.013, p=0.042, p=0.027, respectively). There was a strong association between positive HLA-B51 with smoking (p=0.004). Smoking and HLA-B51 were effective on articular involvement, smoking was effective on EN, and HLA-B51 and smoking were effective on ocular and neurological involvements (p=0.039, p=0.040, p=0.001, p=0.028, p=0.037, respectively).

Conclusion: Our findings indicate that smoking and HLA-B51 influence severity and systemic involvements of BD with a positive relationship in between. We recommend that smoking and HLA-B51 should be considered simultaneously in BD since this relationship may lead to incorrect inferences.

Keywords: Behçet's disease; human leukocyte antigen-B51; smoking.

Behçet's disease (BD) is an autoimmune inflammatory disorder characterized by recurrent oral aphthous ulcers, genital ulcers, and the involvement of musculoskeletal and other systems. Clinical features of BD are affected by both genetic and environmental factors and may vary between individuals and societies.[1,2]

Human leukocyte antigen (HLA)-B51 has been recognized as the strongest genetic predisposing factor for BD. In the literature, a relationship has been reported between HLA-B51 and different manifestations of BD which varies according to regions and ethnic backgrounds.[1,3,4]

Smoking which is the most widespread addiction in the world is an environmental factor associated with many diseases. Toxic components in the cigarette which stimulate vasospasm and platelet aggregation while decreasing the antioxidants in blood damage the vascular and immune systems.[2] There are different speculations about the relationship between BD and smoking. While some authors claim that

Received: February 26, 2015 ***Accepted:*** June 12, 2015 ***Published online:*** August 21, 2015

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smoking can activate, others claim that smoking cessation can activate several manifestations of BD. However; the general consensus is that smoking alleviates oral aphthous lesions but aggravates other manifestations of BD.[5-8]

In the literature, there are studies which investigated the effect of HLA-B51 or smoking on the manifestations of BD. However, to our knowledge, there is no other study that investigated the cumulative effects of both on the clinical manifestations of BD. Therefore, in this study, we aimed to investigate the separate and cumulative effects of smoking and HLA-B51 on the severity and clinical manifestations of BD.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 209 patients with BD (119 males, 90 females; mean age 42.97±10.44 years; range 23 to 75 years) who were examined in Physical Medicine and Rehabilitation, Dermatology and Ophthalmology Department of Medical Faculty of Akdeniz University between January 2010 and October 2014. Patients older than 18 years of age and who met the 1990 International Study Group classification criteria for BD were included.[9] Patients who had other inflammatory diseases such as rheumatic diseases, infectious diseases (hepatitis B virus, hepatitis C virus, human immunodeficiency virus), and malignancy were excluded. Informed consents were obtained from patients in accordance with the Declaration of Helsinki.

All patients were evaluated for their smoking status and separated into a smoking group (smoking or smoking cessation patients, n=103) and non-smoking group (never smoking patients, n=106). Patients were also classified as HLA-B51 positive (n=62) or negative (n=147). In the last stage, patients were divided into four groups: Group 0 (HLA-B51 negative and non-smoking), Group 1 (HLA-B51 positive and non-smoking), Group 2 (HLA-B51 negative and smoking), and Group 3 (HLA-B51 positive and smoking).

Behçet's Syndrome Activity Scale (BSAS)[10] scores were noted for all patients. The manifestations of BD and articular- extra-articular involvements were noted. Patients with articular involvement were classified as monoarticular, oligoarticular, and polyarticular.

Statistical analysis

The IBM SPSS version 20.0 software program (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Chi-square tests were used for comparing nominal variables. Shapiro-Wilk test was used for testing normality. Multivariate analysis was performed using binary logistic regression with forward conditional method. Four groups were compared using Kruskal-Wallis test, later the groups were compared with each other using Mann-Whitney U test and Bonferroni correction. Alpha significance level less than 0.05 was considered as statistically significant.

RESULTS

The demographic and clinical characteristics of patients are summarized in Table 1. Smoking rate was significantly higher in male sex than female sex. Demographic and clinical characteristics of patients with BD according to sex are summarized in Table 2.

A comparison of demographic and clinical characteristics of HLA-B51 positive and -negative patients with BD revealed that rate of smokers, BSAS scores, EN, articular, ocular and neurological involvements were significantly higher in HLA-B51 positive patients than HLA-B51 negative patients ($p<0.05$) (Table 3).

A comparison of demographic and clinical characteristics of smoking group and non-smoking group with BD showed that male sex, HLA-B51 positive patients, BSAS scores, EN, articular, ocular and neurological involvements were significantly higher in smoking group than non-smoking group ($p<0.05$) (Table 4).

An investigation of the effect of consumed cigarette amount on articular and extra-articular involvement in BD demonstrated that the smoking pack/years did not affect articular, ocular or neurological involvement, or EN ($p=0.434$, $p=0.371$, $p=0.476$, $p=0.839$, respectively). Also, there was no correlation between these and BSAS scores.

Table 1. Demographic and clinical characteristics of 209 patients with Behçet's disease

	n	%	Mean±SD	Min.-Max.
Age (years)			42.97±10.44	23-75
Disease duration (years)			8.46±6.05	1-36
Gender				
Female	90	43.1		
Male	119	56.9		
Smoking				
+				
Current	65	31.1		
Cessation	38	18.2		
Total smokers	103	49.3		
Tobacco per day			16.02±7.587	2-50
Duration (years)			12.88±8.21	2-40
Pack (years)			11.01±9.62	0.20-40
–				
Non-smokers	106	50.7		
Human leukocyte antigen-B51 (+)	62	29.7		
Behçet's Syndrome Activity Scale scores			5.34±2.05	2-14
Articular involvement				
Monoarticular	78	37.3		
Oligoarticular	46	22.0		
Poliarticular	15	7.2		
Total	139	66.5		
Extra-articular involvement				
Mucocutaneous				
Oral ulcer	205	100		
Genital ulcer	190	90.9		
Papulopustular lesions	153	73.2		
Erythema nodosum	90	43.1		
Gastrointestinal system	5	2.4		
Cardiovascular system	35	16.75		
Ocular	73	34.93		
Neurological	8	38.3		

SD: Standard deviation; Min.: Minimum; Max.: Maximum.

Three binary logistic regression models were performed to analyze factors affecting articular, ocular involvements, and EN. Both smoking and HLA-B51 were effective on articular involvement. Smoking was effective on EN. While smoking or HLA alone was not effective, HLA-B51 with smoking was effective on ocular and neurological involvements (Table 5).

When four groups were compared to investigate the effects of smoking and/or HLA-B51 on BSAS scores, a significant difference was shown. The BSAS scores of group 1 and 2 were significantly higher than in group 0 and the BSAS scores of group 3 were significantly higher than in group 0, 1 and 2; however, there was no significant difference between groups 1 and 2. Both smoking

Table 2. Demographic and clinical characteristics of patients with Behçet's disease according to sex

	Female			Male			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Gender	90	100		119	100		
Human leukocyte antigen-B51 (+)	24	26.7		38	31.9		0.409
Smoking	36	56.3		67	40.0		0.020*
Articular involvement	66	73.3		73	61.3		0.069
Erythema nodosum	44	48.9		46	38.7		0.139
Ocular involvement	29	32.2		44	37.0		0.475
Neurological involvement	2	2.2		6	5.0		NA
Behçet's Syndrome Activity Scale			5.01±1.95			5.59±2.10	0.028*

SD: Standard deviation; NA: Not applicable (2 cells have expected count less than 5); *: $p<0.05$.

Table 3. Demographic and clinical characteristics of human leukocyte antigen-B51-positive and -negative patients with Behçet's disease (n=209)

	HLA-B51 (+) (n=62)			HLA-B51 (–) (n=147)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Gender							
Male	38	61.3		81	55.1		0.400
Female	24	38.7		66	44.9		
Smoking	40	64.5		63	42.9		0.004*
Behçet's Syndrome Activity Scale scores			6.61±2.145			4.80±1.762	0.001*
Articular involvement							
Monoarticular	20	32.3		58	39.5		
Oligoarticular	20	32.3		26	17.7		
Poliarticular	9	14.5		6	4.1		0.001*
Total	49	79.0		90	61.2		0.013*
Extra-articular involvement							
Mucocutaneous							
Genital ulcer	53	85.5		137	93.2		0.076
Papulopustular lesions	49	79.0		104	70.7		0.217
Erythema nodosum	35	56.6		55	37.4		0.011*
Gastrointestinal system	3	4.8		2	1.4		NA
Cardiovascular system	14	22.6		21	14.3		0.142
Ocular	35	56.5		38	25.9		0.001*
Neurological	5	8.1		3	2.0		0.038*

HLA-B51: Human leukocyte antigen-B51; SD: Standard deviation; *: p<0.05; NA: Not applicable (2 cells have expected count less than 5).

and HLA-B51 were effective on BSAS scores, but HLA-B51 with smoking was significantly more effective on BSAS scores (Table 6).

DISCUSSION

In this study, both smoking and positive HLA-B51 were found to be effective on BSAS, EN, articular, ocular and neurological involvements. Surprisingly, smoking rate was higher in the patients with positive HLA-B51 than in patients with negative HLA-B51.

In the literature, many studies have shown that HLA-B51 and smoking are factors associated with clinical manifestations of BD.[2,5,7,11] Gür et al.[12] have reported that HLA-B51 rate

Table 4. Demographic and clinical characteristics of smoking and non-smoking patients with Behçet's disease (n=209)

	Smoking (n=103)			Non-smoking (n=106)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Gender							
Male	67	65.0		52	49.1		0.020*
Female	36	35.0		54	50.9		
Human leukocyte antigen-B51 (+)	40	38.8		22	20.8		0.004*
Behçet's Syndrome Activity Scale Scores			6.23±2.07			4.47±1.63	0.001*
Articular involvement							
Monoarticular	37	35.9		41	38.7		
Oligoarticular	31	30.1		15	14.2		
Poliarticular	9	8.7		6	5.7		0.012*
Total	77	74.7		62	58.5		0.013*
Extra-articular involvement							
Mucocutaneous							
Genital ulcer	91	88.3		99	93.4		0.205
Papulopustular lesions	72	69.0		81	76.4		0.288
Erythema nodosum	60	58.3		30	28.3		0.001*
Gastrointestinal system	3	2.9		2	2.9		NA
Cardiovascular system	18	17.5		17	16.0		0.781
Ocular	43	41.7		30	28.3		0.042*
Neurological	7	6.8		1	0.9		0.027*

SD: Standard deviation; *: p<0.05; NA: Not applicable (2 cells have expected count less than 5).

Table 5. Three different binary logistic regression models for analyzing factors affecting articular, ocular involvements, and erythema nodosum

	Predictors	Outcome	*p*	Exp (B)	95% CI
Model 1	Smoking	Articular	0.039*	2.11	1.04-4.30
	HLA-B51 (+)		0.040*	1.88	1.03-3.43
	HLA-B51 (+) and smoking		0.405		
Model 2	Smoking	Erythema nodosum	0.001*	3.54	1.99-6.29
	HLA-B51 (+)		0.076		
	HLA-B51 (+) and smoking		0.129		
Model 3	Smoking	Ocular	0.153		
	HLA-B51 (+)		0.266		
	HLA-B51 (+) and smoking*		0.028*	2.19	1.09-4.41

Exp: Exponentiated logistic coefficients; CI: Confidence interval; HLA-B51: Human leukocyte antigen-B51; * Statistically significant.

in Behçet's patients with articular involvement was significantly higher than patients without articular involvement, but smoking rates were not significantly different among them. In our study, both HLA-B51 and smoking were shown to be effective, but both of them when they are together were not more influential on articular involvement.

In the literature, an association between HLA-B51 with clinical involvement and prognosis of BD has been reported.[13-16] Results of these studies partially support our findings, but they have not examined whether patients smoke or not. Bilgin et al.[2] have also reported that cystoid macular edema among current smoking patients with BD was significantly higher than non-smoking patients, but smoking was inefficient on other ocular involvement. They have not examined HLA-B51. Their finding might seem to be partially different at first glance from our finding; however, they have accepted their patients who quit smoking in the not smoking category. Hirohata[17] reported that positive HLA-B51 rate was higher in patients with neurological involvement than patients without neurological involvement in BD.

According to our results, smoking is a risk factor for ocular and neurological involvements in patients with positive HLA-B51. Therefore, we may recommend that both HLA and smoking habits should be evaluated in patients with BD as well as studies on clinical findings of BD.

Another relationship referred to in the literature is between poor prognosis and severe complications of BD with male sex.[18] The results of some studies have shown that systemic involvements, disease severity and poor prognosis of BD were associated with male sex.[19,20] Moreover, Hirohata[17] has affirmed that HLA-B51, smoking, and male sex is strongly associated with chronic progressive BD with neurological involvement.

Table 6. Effects of positive human leukocyte antigen-B51 and/or smoking on Behçet's Syndrome Activity Scale scores (n=209)

	n	Median	25-50 percentile	*p*	Test
Group 0	84	4.0	3.0-5.0	0.001*	
Group 1	22	5.5	3.75-7.0		
Group 2	63	5.0	4.0-7.0		
Group 3	40	7.0	6.0-8.0		Kruskal-Wallis
Group 0-1			0.004*		
Group 0-2			0.001*		
Group 0-3			0.001*		
Group 1-2			0.788		
Group 1-3			0.004*		
Group 2-3			0.001*		Mann-Whitney U

Group 0: HLA-B51-negative and non-smoking; Group 1: HLA-B51-positive and non-smoking; Group 2: HLA-B51-negative and smoking; Group 3: HLA-B51-positive and smoking; * Statistically significant, according to p<0.008 level after Bonferroni correction.

Male sex was not associated with BD manifestation in our study. Also, there was no significant difference between males and females in terms of HLA-B51. In studies associating systemic involvements and disease severity of BD with male sex, HLA-B51 frequency was generally higher in males than females. Besides, when taking into account that males generally smoke more than females, as in our study, this relationship may be due to direct smoking and/or indirect positive HLA-B51.

In their meta-analysis, Maldini et al.[21] have reported that HLA-B51 was significantly associated with male sex, and ocular and skin involvements including EN. In our study, EN seems to be associated with both HLA-B51 and smoking, but the influence factor was smoking on EN. The increased EN in patients with positive HLA-B51 may be due to the association of positive HLA-B51 with smoking. Also, the relationship between male sex with positive HLA-B51 and smoking may indicate that males smoke more because they have higher HLA-B51 frequency than females.

A relationship between smoking and severity of BD has been shown in the literature.[22] However, there are conflicting results about the relationship between HLA-B51 and smoking with severity of BD.[23-25] In our study, both smoking and HLA-B51 were found to be effective on BD. In addition, their concurrent presence was demonstrated to be more effective on BD activity scores.

The limitation of this study is that there was no control group. There is need for further studies in this regard.

In conclusion, we may say that smoking and HLA-B51 are influential factors on severity and systemic involvements of BD and there is a positive relationship between them. This relationship affects severity and same clinical manifestations of BD, sometimes leading to incorrect inferences. Therefore, we recommend that smoking and HLA-B51 should be considered simultaneously in BD with clarifications by further studies.

Acknowledgements

The authors are greatly indebted to Mehmet İhsan Arman and Kemal Hakan Gülkesen for his help during preparation of this work.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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