HLA-B51 Impact on Clinical Symptoms in Behcet's Disease

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ABSTRACT

Objective: To investigate the association of HLA-B51-positivity to clinical manifestations of Behçet's disease (BD).
Study Design: Descriptive study.
Place and Duration of Study: Clinic of Rheumatology, Dıskapi Education and Research Hospital, Health Sciences University, Turkey, from December 2018 to December 2020.
Methodology: Patients who had HLA-B5 genetic results and fulfilled the international criteria for BD were included in the study. HLA-B51 status was determined and compared with the symptomatology.
Results: Mean age of 204 cases was 39.9±11.4 years. There were 52.5% female and 47.5% male patients. One hundred (61.7%) patients were HLA-B51-positive. The frequency of papulopustular lesions (PPL), ocular involvement, neurologic involvement, and vascular involvement was significantly higher in HLA-B51-positive patients compared to HLA-B51 negative patients (p=0.044, 0.012, 0.039, and 0.022 respectively). HLA-B51-positivity was found to be a significant risk factor for PPL (OR and 95% CI:1.946 and 1.044-3.629), ocular involvement (OR and 95% CI:2.399 and 1.165-4.938), and neurological involvement (OR and 95% CI:5.404 and 1.119-26.093). Significant risk factors for vascular involvement were male gender (OR and 95% CI:2.810 and 1.403-5.627) and low age of disease onset (OR and 95% CI:0.935 and 0.894-0.979).
Conclusion: Ocular, vascular, and neurological involvements are more common in patients with BD with HLA-B51-positive. HLA-B51 was found to be an independent risk factor for papulopustular lesion, ocular and neurological involvement, while the male gender was found to be an independent risk factor for vascular involvement.

Key Words: *Behcet syndrome / genetics, HLA-B51, Neurologic involvement, Ocular involvement, Vascular involvement, Vasculitis* / diagnosis.*

How to cite this article: Pamukcu M, Duran TI, Demirag MD. HLA-B51 Impact on Clinical Symptoms in Behcet's Disease. *J Coll Physicians Surg Pak* 2022; **32(07)**:904-908.

INTRODUCTION

Behçet's disease (BD) is a chronic multisystemic disease characterized by recurrent mucocutaneous ulceration, arthralgia/arthritis, ocular, nervous and cardiovascular system involvement.[1] It has been defined as 'variable type vasculitis' in the Chapel Hill consensus conference nomenclature of vasculitides.[2] BD shows a different geographical distribution pattern that is more common on the ancient Silk Road. BD typically begins in the third and fourth decades and a lower age of onset has a more severe disease course, and a higher mortality rate. The disease affects both genders equally, but young male BD patients suffer from a relatively more serious disease.[1]

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Received: August 11, 2021; Revised: November 01, 2021; Accepted: December 16, 2021
DOI: https://doi.org/10.29271/jcpsp.2022.07.904

The etiology of BD has not been fully clarified, but it has been suggested that immunological, microbiological, environmental, and genetic factors such as human leukocyte antigen (HLA-B51).[3] Many endogenous and exogenous factors are thought to play a role in the development of BD. Because most HLA-B51-positive individuals do not appear BD in their lifetime, and also about half of the patients with BD are HLA-B51 negative.[3]

Although many authors have attempted to identify possible relationships between genetic factors, particularly HLA-B51 and BD, it is not yet clear whether the HLA-B51 gene itself is pathogenic. The relationship of HLA-B51 with specific symptoms of BD or severe course of the disease has previously been studied with conflicting reports, especially on its relationship with uveitis and disease severity.[4,5] The aim of this study was to investigate the influence of HLA-B51-positivity to clinical manifestations in BD patients.

METHODOLOGY

Medical records of 250 BD patients, who visited the Rheumatology clinic, from December 2018 to December 2020 were

analysed retrospectively. Two hundred and four patients who had HLA-B51 genetic results and fulfilled the international criteria for BD (ICBD) were included in the study.[6] Demographic, medical and laboratory findings were obtained from the medical records. Major organ involvement was defined as involvement of the vessels, neurologic, eyes, or gastrointestinal system (GIS). Vascular manifestations were confirmed by Doppler sonography or angiography. Neurologic involvement was diagnosed by international consensus recommendation criteria for Neuro-BD diagnosis. Ocular involvement was diagnosed by the ophthalmologist. GIS involvement was confirmed by gastroduodenoscopy or colonoscopy. We described joint involvement as joint swelling or/and pain or articular damage on conventional radiography.

SPSS (Statistical Package for Social Sciences) version 22.0 software was used for statistical analysis. Descriptive data were presented as frequency (percentage), number, and mean±SD. The distribution characteristics of numerical variables were evaluated using the Kolmogorov–Smirnov test. Independent-Samples-T test was used for intergroup comparisons of numerical variables with normal distribution, while the Mann–Whitney-U test was used for those without normal distribution. Chi-square/Fisher's exact test was used for evaluating categorical data. Logistic regression analysis was used to determine risk factors. A value of $p<0.05$ was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the patients and their distribution by gender are given in Table I. The frequency of ocular and vascular involvement, deep vein thrombosis (DVT), and dural sinus thrombosis was significantly higher in male patients.

Mean age at disease onset was significantly lower in HLA-B51-positive patients compared to HLA-B51-negative patients. The frequency of papulopustular lesions (PPL), ocular involvement, and neurologic and vascular involvement were significantly higher in HLA-B51-positive patients (Table II).

Risk factor analysis results are shown in Table III. While HLA-B51-positivity was observed to increase the risk for PPL development, the presence of ocular involvement was found to reduce the risk. Similarly, HLA-B51-positivity was determined as a significant risk factor for neurological involvement, while male gender and lower age of onset were significant risk factors for vascular involvement.

DISCUSSION

In the present study, we examined the frequency of clinical characteristics of the disease and the relationships of each clinical characteristic with HLA-B51 and gender status in BD; the male/female ratio was 0.9. In the Turkish patients with BD, the male/female ratio was reported to be 1.03.[7] In BD, differences in the ratio of gender may occur depending on the geographical region. The male/female ratio was reported as 1.3 in Iran,[8] 0.7 in Japan, and 1.2 in China.[8-10]

In Turkish patients with BD, it was observed that the age of symptoms onset was between the ages of 26-27, and the age of diagnosis was between the ages of 30-33.[11,12] In this study, the age of disease onset was found to be 28.3±8.9 years and it was lower in male patients and HLA-B51-positive patients. Alli *et al*. reported that the age of disease onset in Turkish patients with BD was similar in both genders.[11] Ryu *et al*. reported similar results, HLA-B51-positive patients had a lower age of disease onset.[13]

The frequency of HLA-B51 in the Turkish population with BD was reported between 54%-82%.[14,15] In this study, the frequency of HLA-B51 was found to be 61.7%. Although the frequency of HLA-B51 was higher in males, this difference was not statistically significant. The frequency of HLA-B51 in BD may vary according to different geographical regions and different ethnicities. The frequency of HLA-B51 was reported to be 44.5% in Japan,[9] and 48.9% in Iran.[8] A meta-analysis has shown that the pooled OR of HLA-B51/B5 allele carriers was 5.78. The estimated prevalence of HLA-B51-positivity was 34.2% in North America, 39.0% in Eastern and Northern Europe, 55.0% in East Asia, 60.6% in Southern Europe, and 63.5% in North Africa and Middle East.[16]

Mucocutaneous involvements are the most common manifestations of BD.[17] In this study, at least one mucocutaneous finding was present in all patients included and the most common mucocutaneous involvement was oral ulcers (99%). Other mucocutaneous involvements were genital ulcers (GU) (67.2%), PPL (58.8%), and erythema nodosum-like lesions (36.8%). Pathergy reaction positivity was present in 41.2%. Among the mucocutaneous involvement, it was found that only the frequency of GU was significantly higher in female patients. In addition, only the frequency of PPL was significantly higher in HLA-B51-positive patients. The frequency of mucocutaneous involvement in Turkish BD patients was reported: oral aphthae 100%, GU 88.1%, PPL 54%, erythema nodosum 47.6%, and pathergy reaction positivity 56.1%.[7] In addition, they found that the frequency of GU and erythema nodosum was significantly higher in women, while the frequency of PPL was significantly higher in male patients. On the other hand, they found no significant difference in the frequency of pathergy reaction positivity according to gender.[7] In a meta-analysis, HLA-B51/B5 carrier was found to increase the risk of skin involvement in BD.[18]

Ocular involvement is one of the most important causes of morbidity in BD. In this study, the frequency of ocular involvement was found to be 29.4% in all patients. The incidence of ocular involvement was significantly higher in male patients and in HLA-B51 positive patients. In addition, HLA-B51-positivity was determined as an independent risk factor for ocular involvement. Tursen *et al*. reported the frequency of ocular involvement was 29.1%, and the incidence of ocular involvement was significantly higher in male patients.[7] Consistent with this study, the meta-analysis results revealed that HLA-B51/B5 carriage was an independent risk factor for ocular involvement.[18]

Table I: Distribution of clinical and demographic characteristics in the whole study group and by gender status.

Parameters	Patients (n=204)	Gender		P
		Female (n=107)	Male (n=97)	
Age, years, mean ± SD	39.9±11.4	40.8±11.8	38.9±10.9	0.230
Age at disease onset, years, mean ± SD	28.3±8.9	29.4±8.8	26.9±8.5	**0.043**
HLA-B51-positive	126 (61.7)	60 (56.1)	66 (68.0)	0.079
Family History	29 (14.2)	15 (14.0)	14 (14.0)	0.933
Mucocutaneous involvement	204 (100)	107 (100)	97 (100)	-
Oral ulcer	202 (99.0)	107 (100)	95 (97.9)	0.136
Genital ulcer	137 (67.2)	81 (75.7)	56 (57.7)	**0.006**
Papulopustular lesions	120 (58.8)	57 (53.3)	63 (64.9)	0.091
Erithema nodosum – like lesions	75 (36.8)	43 (40.2)	32 (33.0)	0.287
Pathergy reaction	84 (41.2)	39 (36.4)	45 (46.4)	0.150
Joint involvement	45 (22.1)	20 (18.7)	25 (25.8)	0.223
Ocular involvement	60 (29.4)	25 (23.4)	35 (36.1)	**0.046**
Gastrointestinal involvement	5 (2.5)	1 (0.9)	4 (4.1)	0.155
Cardiac involvement	2 (1.0)	-	2 (2.1)	0.225
Neurologic involvement	15 (7.4)	7 (6.5)	8 (8.2)	0.641
Vascular involvement	55 (27.0)	17 (15.9)	38 (39.2)	**<0.001**
Superficial thrombophlebitis	15 (7.4)	6 (5.6)	9 (9.3)	0.316
Deep vein thrombosis	40 (19.6)	12 (11.2)	28 (28.9)	**0.002**
Posttrombotic syndrome	4 (2.0)	1 (0.9)	3 (3.1)	0.348
Dural sinus thrombosis	10 (4.9)	1 (0.9)	9 (9.3)	**0.006**
Pulmonary artery aneurysm	2 (1.0)	1 (0.9)	1 (1.0)	0.999
Extrapulmonary artery aneurysm	1 (0.5)	1 (0.9)	0 (0)	0.999
İnferior vena cava thrombosis	6 (2.9)	3 (2.8)	3 (3.1)	0.999
Superior vena cava thrombosis	2 (1.0)	0 (0)	2 (2.1)	0.225
Hepatic vein thrombosis	2 (1.0)	2 (1.9)	0 (0)	0.499
Arterial thrombosis	3 (1.5)	2 (1.9)	1 (1.0)	0.999

*Unless otherwise stated, values are presented as n (%). *p-values were obtained from comparisons between gender groups.*

Table II: Distribution of clinical and demographic characteristics according to HLA-B51 status.

Parameters	HLA-B51-positive (n=126)	HLA-B51 negative (n=78)	P
Age, years, mean ± SD	39.7±11.5	40.2±11.3	0.748
Age at disease onset, years, mean ± SD	26.9±8.1	30.3±9.2	**0.008**
Gender, Female	66 (52.4)	31 (39.7)	0.079
Family History	18 (14.3)	11 (14.1)	0.971
Mucocutaneous involvement	126 (100)	78 (100)	
Oral ulcer	125 (99.2)	77 (98.7)	0.731
Genital ulcer	86 (68.3)	51 (65.4)	0.672
Papulopustular lesions	81 (64.3)	39 (50.0)	**0.044**
Erithema nodosum–like lesions	50 (39.7)	25 (32.1)	0.272
Pathergy reaction	49 (38.9)	35 (44.9)	0.399
Joint involvement	24 (19.0)	21 (26.9)	0.187
Ocular involvement	45 (35.7)	15 (19.2)	**0.012**
Gastrointestinal involvement	5 (4.0)	0 (0)	0.159
Cardiac involvement	1 (0.8)	1 (1.3)	0.999
Neurologic involvement	13 (10.3)	2 (2.6)	**0.039**
Vascular involvement	41 (32.5)	14 (17.9)	**0.022**
Superficial thrombophlebitis	11 (8.7)	4 (5.1)	0.338
Deep vein thrombosis	28 (22.2)	12 (15.4)	0.232
Posttrombotic syndrome	3 (2.4)	1 (1.3)	0.999
Dural sinus thrombosis	7 (5.6)	3 (3.8)	0.583
Pulmonary artery aneurysm	1 (0.8)	1 (1.3)	0.999
Extrapulmonary artery aneurysm	1 (0.8)	0 (0)	0.999
İnferior vena cava thrombosis	6 (4.8)	0 (0)	0.084
Superior vena cava thrombosis	2 (1.6)	0 (0)	0.525
Hepatic vein thrombosis	1 (0.8)	1 (1.3)	0.999
Arterial thrombosis	3 (2.4)	0 (0)	0.288

Unless otherwise stated, values are presented as n (%).

Table III: Logistic regression analysis for risc factors.

OR (95 % CI)	Papulopustular lesions	Ocular involvement	Neurologic İnvolvement	Vascular involvement
HLA-B51 positivity	1.946 (1.044 - 3.629)	2.399 (1.165 - 4.938)	5.404 (1.119 - 26.093)	1.534 (0.720 - 3.271)
Male gender	1.622 (0.884 - 2.976)	1.735 (0.896 - 3.360)	1.397 (0.450 - 4.339)	2.810 (1.403 - 5.627)
Age at disease onset	0.994 (0.960 - 1.029)	0.979 (0.941 - 1.019)	1.035 (0.969 - 1.104)	0.935 (0.894 - 0.979)
Papulopustular lesions	-	0.409 (0.211 - 0.790)	0.824 (0.262 - 2.595)	1.213 (0.593 - 2.479)
Ocular involvement	0.413 (0.214 - 0.797)	-	0.661 (0.185 - 2.365)	1.311 (0.630 - 2.729)
Neurologic involvement	0.841 (0.274 - 2.582)	0.688 (0.199 - 2.375)	-	0.873 (0.234 - 3.264)
Vascular involvement	1.252 (0.615 - 2.549)	1.342 (0.654 - 2.753)	0.926 (0.256 - 3.348)	-

In this study, the frequency of neurological involvement was found 7.4%. While the frequency of neurological involvement was similar in both genders, it was significantly higher in HLA-B51-positive patients and HLA-B51-positivity was noted as an independent risk factor for the development of neurological involvement. In the literature, the frequency of neurological involvement was reported between 2.3% – 6.19%.[7,11,12,19] While the frequency of neurological involvement was higher in men in two of these studies,[7,12] no significant difference was found in terms of distribution by gender in the other studies.[11,19] Demirseren *et al*. showed that neurological involvement was more common in Turkish patients with positive HLA-B51 and HLA-B51-positivity was an independent risk factor for the development of neurological involvement.[14]

In this study, the frequency of vascular involvement was 27%, and it was found that male patients were significantly more affected. Among all vascular involvement subtypes, we found that DVT and dural sinus thrombosis were more common in male patients. Although we found that the frequency of vascular involvement was higher in HLA-B51--positive patients, HLA-B51-positivity was not a significant risk factor for vascular involvement. It was also found that male gender and early onset of the disease were significant risk factors for vascular involvement. The frequency of vascular involvement was reported between 5.7% – 29% and male patient dominance was reported.[7,11,19] In a large cohort study from China, it was reported that the male gender significantly increased the risk of vascular involvement in BD.[10] Similarly, a significant relationship was found between the male gender and vascular involvement in BD patients in the German registry.[20]

The frequency of other clinical characteristics in this study was as follows; arthralgia/arthritis 22.1%, GIS involvement 2.5%, and cardiac involvement 1%. The distribution of these three forms of involvement by gender and HLA-B51 was similar. The frequency of joint involvement and GIS involvement in Turkish BD patients was reported between 5%, 51%, 0.8%, and 6% respectively.[7,11,12,19] Both joint involvement and GIS involvement were seen with similar frequency in both genders.[7,12] Demiresen *et al*. reported that the frequency of articular involvement was not differed according to HLA-B51 status.[14] Maldini *et al*. showed that HLA-B51/B5 carriage did not have a significant effect on joint involvement and reduced the risk of GIS involvement.[18]

The key limitations of this study were its retrospective design, the inclusion of patients whose HLA results could be accessed, and availability of data from a single center. These findings are thought to have implications for the speculations discussed about the clinical course of the disease and treatment choice. It is not possible to predict which patient will experience attacks when and how often, but these findings highlight the points that should have been paid attention to about the follow-up of a patient.

CONCLUSION

The most feared complications of BD are ocular, vascular, and neurological involvement. While these 3 findings were found to be higher in HLA-B51-positive BD, ocular and vascular involvement was found higher in male patients. On the other hand, HLA-B51 was found as an independent risk factor for PPL, ocular and neurological involvement, while the male gender was found an independent risk factor for vascular involvement.

ETHICAL APPROVAL:

This study was conducted in accordance with the Helsinki Declaration. The study was approved by the local Ethics Committee (Approval No. 106/19).

PATIENT'S CONSENT:

All participants were informed and their consent was obtained.

COMPETING INTERESTS:

The authors declared no competing interest.

AUTHORS' CONTRIBUTIONS:

MP, TID, MDD: Contributed to the study conception, design, material preparation, data collection, analysis, and manuscript writing.

All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All co-authors take full responsibility for the integrity of the study and the final version of the manuscript.

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