ABO blood groups and increased risk for the development of vascular involvement in Behçet's disease

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Abstract

Objective

Inflammatory endothelial activation is a prominent feature of vascular involvement in Behçet's disease (BD), which is usually accompanied by a thrombotic tendency. Recent studies suggest an association between ABO blood groups and thrombotic vascular disease in those carrying non-O (A, B, and AB) groups. This study aimed to analyse the contribution of ABO blood groups to the vascular involvement in BD.

Method

In this retrospective study, BD patients with available ABO blood group data and meeting the ISG criteria were included in the study. The presence of vascular involvement, its clinical characteristics, and the data about other manifestations were recorded from the patient charts.

Results

This study was conducted in 411 patients; 143 (34.8%) were carrying O and 268 (65.2%) were carrying non-O groups. The vascular involvement was significantly more frequent and the risk for overall vascular and venous events was up to 2-fold higher in the patients with non-O groups. After adjustments for age, sex, and comorbidities, the risk for arterial disease was also found to be increased in association with non-O groups. ABO blood groups were shown to be independent risk factors for vascular BD by multiple regression models based on known predisposing factors. Compared with other non-O blood groups, the patients carrying blood group B had a higher risk for vascular events.

Conclusion

The results of this preliminary study show the potential contribution of ABO blood groups to the vascular-BD phenotype and suggest an increased risk for vascular BD in association with non-O blood groups.

Key words

Behçet's disease, ABO blood group, vascular disease, thrombosis

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Received on April 9, 2024; accepted in revised form on September 18, 2024.

Funding: this study was partially supported by Istanbul University Research Fund (TSA-2023-39471).

Competing interests: none declared.

Introduction

Behçet's disease (BD), a multi-systemic inflammatory disease of unknown aetiology, is characterised by recurrent mucocutaneous, ocular, articular, vascular, gastrointestinal system, nervous system involvement, and less often other organ systems manifestations. BD has a multifactorial pathophysiology, and the interaction of environmental factors with the immune system is considered to trigger inflammatory findings in genetically susceptible individuals (1). A strong association of HLA-B*51 with BD has long been known, and recent genome-wide association studies (GWAS) revealed additional associations with several non-HLA genes, including ERAP1, which shows an epistatic interaction with HLA B*51 (2). The phenotype of BD is heterogeneous, and it is classified as a variable vessel vasculitis affecting both veins and arteries of all sizes (3). Inflammatory changes in endothelial cells are mainly responsible for the tendency for thrombosis in BD patients, and genetic factors such as factor V Leiden may provide additional contributions to the prothrombotic state (4, 5). The phenotypes of ABO(H) blood groups are determined by the specific carbohydrate structures, which is regulated by the *FUT1*, *FUT2*, *FUT3,* and *ABO* genes, in red blood cells, vascular endothelial cells, and other tissues (6). A close relationship between the ABO blood group antigens and vascular disease has been shown in numerous studies. Recent investigations have shown that individuals with blood group O in particular, have a lower risk of some vascular events, such as venous thromboembolism (VT) and arterial disease (7). This association has been confirmed in several studies in which the ABO blood subgroups were determined serologically or by haplotype analysis (8, 9). We, therefore, aimed to analyse the potential association between the vascular manifestations of BD and ABO blood group antigens in this exploratory study.

Patients and methods

Patients and data collection

This was a descriptive, retrospective study from a single centre. A total of 411 consecutive patients aged ³18 whose ABO blood group information determined by standard agglutination test was already available from their charts and followed up between 1978 and 2022 enrolled in the study. All patients met the International Study Group's 1990 criteria for diagnosis (ISG-1990) except for three patients, who were diagnosed with BD based on their typical organ involvements (10). Demographic, clinical, and blood group data of the patients were obtained from their medical records and were noted on a standard form. Blood groups were routinely asked and recorded in patient charts since 2020, and data were noted as A, B, AB, O, and Rhesus (Rh) antigen positive or negative. For the analysis, blood groups were classified as "non-O" group for A, B, AB blood types and "O" group. The vascular phenotype of the patients was specified as venous and/or arterial involvements, and the involved sites were also noted. This study was approved by the Istanbul University Istanbul Faculty of Medicine Ethics Committee (2022-801627).

Statistical analysis

The quantitative variables were described as the mean with standard deviation (SD) or median with interquartile range (IQR), while the categorical variables were presented as a number and percentage. The Kolmogorov-Smirnov test was performed to determine the normality of the data. Student's t-test or Mann-Whitney U-test was used to compare quantitative variables according to the distribution of the data. Chi-square or Fisher's exact tests were used for categorical comparisons where appropriate. Logistic regression was performed to estimate crude odds ratios (ORs) of vascular involvement according to blood types. Multivariate logistic regression models were adjusted for sex, age at diagnosis, comorbid diseases (diabetes mellitus, hypertension, hyperlipidaemia, cardiovascular disease), malignancy, and smoking. Adjusted ORs were estimated by considering logistic models. Chi-square risk analysis was used for detecting vascular involvement risk of patients with A, B, or AB blood types compared individually with the patients with O blood type. Missing

data were not included in the statistical analyses. All analyses were performed by using SPSS v. 26 (IBM Corp, USA), and the two-tailed *p*-value <0.05 was considered significant.

Results

The study group consisted of 411 patients with available ABO blood group data; 143 (34.8%) were classified in the "O" group and 268 (65.2%) were in the "non-O" group [171 (41.6%) were "A", 65 (15.8%) were "B", 32 (7.8%) were "AB" blood types]. Rh antigen data were available in 408 patients and Rh antigen was positive in 354 (86.8%). ABO and Rh antigen distribution of our study population was compared with the data of a previously reported cohort of the Turkish population, and no statistically significant difference was found (p=0.634, p=0.393, respectively) (11). The age at BD diagnosis was 31.38±10.13 years, the follow-up period was 167 (107-251) months, and 83 (58%) were male among the "O" group, while 30.70±8.40, 148 (92-204) and 161 (60.1%) among the "non-O" group, respectively. Age at diagnosis, sex, family history, HLA-B51 frequency, smoking, history of comorbidities which pose a risk factor for vascular disease, and available data for genetic thrombophilia (factor V Leiden and prothrombin G20210A gene mutation) were similar between "O" and "non-O" groups (Table I). Comparing the "O" group with the "non-O" group, the frequencies of mucocutaneous, articular, ocular, neurologic, pulmonary, and cardiac manifestations were similar, except for the frequency of gastrointestinal (GI) involvement, which was 3 (2.1%) in the "O" group and 0 (0%) in the "non-O" group (p=0.042) (Supplementary Table S1). The frequency of overall vascular involvement was 39 (27.3%) in the "O" group and 109 (40.7%) in the "non-O" group (p=0.007), and the frequency of venous involvement was 35 (24.5%) in the "O" group and 95 (35.4%) in the "non-O" group (p=0.023). There was a numerical difference in arterial involvement between the two groups, but it did not reach statistical significance [11 (7.7%) in the "O" group and 38 (14.2%) in the "non-O" group, p=0.053]. In the evaluation of the involved sites, only inferior vena cava thrombosis was found significantly different between the two groups (p=0.009) (Suppl. Table S2). The "O" and "non-O" groups were compared according to overall vascular involvement (crude OR 1.8 %95 CI 1.2-2.8, p=0.007), venous involvement (crude OR 1.7 %95 CI 1.1-2.7, p=0.023), arterial involvement (crude OR 2.0 %95 CI 0.98-4.0, p=0.057) and adjusted ORs with logistic models in the multivariate logistic regression analysis were shown in Table II. When the O blood group was taken as the reference point, the patients with B blood group had the highest risk for vascular events among "non-O" group (Table III).

Table I. The characteristics of the patients.

	All patients (n=411)	O Group (n=143)	non-O Group (n=268)	p (χ^2)
Age at diagnosis, y, mean ± SD	30.94 ± 9.03	31.38 ± 10.13	30.70 ± 8.40	0.469
BD duration, m, median (IQR)	153 (98-219)	167 (107-251)	148 (92-204)	**0.047**
Sex, male, n (%)	244 (59.4)	83 (58.0)	161 (60.1)	0.689
HLA B51, n (%)	57[‡] (53.3)	20[ᵅ] (50.0)	37[§] (55.2)	0.600
Smoking, n (%)	131[¥] (31.9)	44[†] (41.5)	87[¶] (39.4)	0.711
Comorbidity, n (%)				
Diabetes mellitus	22 (5.4)	9 (6.3)	13 (4.9)	0.536
Hypertension	34 (8.3)	16 (11.2)	18 (6.7)	0.117
Hyperlipidaemia	20 (4.9)	7 (4.9)	13 (4.9)	0.984
CVD	16 (3.9)	9 (6.3)	7 (2.6)	0.066
Malignancy	12 (2.9)	3 (2.1)	9 (3.4)	0.555
Genetic thrombophilia, n (%)				
FVL	22[Œ] (37.3)	6[ᵉ] (42.9)	16[ᶠ] (35.6)	0.622
Prothrombin gene	10[Œ] (16.9)	1[ᵉ] (7.1)	9[ᶠ] (20.0)	0.425
Combined	4[Œ] (6.8)	1[ᵉ] (7.1)	3[ᶠ] (6.7)	1.000

BD: Behçet's disease; CVD: cardiovascular disease; FVL: factor V Leiden; y: years; m: months; n: number of patients.
([‡] n=107, [ᵅ] n=40, [§] n=67, [¥] n=327, [†] n=106, [¶] n=221, [Œ] n=59, [ᵉ] n=14, [ᶠ] n=45).

Discussion

The vascular phenotype of BD has peculiar features with the affection of all types and sizes of blood vessels, a predilection for the venous side, and a tendency for thrombosis associated with inflammatory endothelial activation (3). Previous studies documented the contribution of procoagulant mutations such as factor V Leiden to the development of vascular involvement in at least in Turkish BD patients (4, 5). The current study has provided preliminary data for ABO blood groups as an additional risk factor for vascular manifestations of BD in those carrying non-O type.

Non-O types of ABO blood group were suggested to be associated with a tendency to vascular thrombotic disease compared to O blood type, and especially the risk of venous thrombosis was found to be increased up to 1.5–2-fold in large cohorts (7, 9). The association between the ABO blood group and vascular disease was documented previously in various serologic, genetic, and epidemiological studies. Although the mechanism of the thrombotic tendency associated with non-O blood groups has not been fully clarified yet, increased plasma concentrations of factor VIII and von Willebrand factor in patients with A1 and B blood groups and association of ICAM-1 levels with A1 blood group have been suggested as potential mechanism (8, 9, 12, 13). None of them directly associated with inflammation, but they can contribute to the thrombotic tendency associated with inflammatory endothelial activation or other risk factors.

Results of the current study provided a similar tendency for non-O blood types and vascular disease of BD, especially for venous thrombosis. A similar contribution to the thrombotic tendency of BD was previously demonstrated for the carriers of factor V Leiden mutation in Turkish patients (4, 5). Multivariate logistic regression analysis suggested that ABO blood groups may act as an independent risk factor

Table II. Univariate and multivariate logistic regression analyses to estimate unadjusted and adjusted risk for vascular events comparing the "O" group with the "non-O" group.

	Overall vascular involvement		Venous involvement		Arterial involvement	
	p	OR (CI %95)	*p*	OR (CI %95)	*p*	OR (CI %95)
Model 1	0.007	1.828 (1.176-2.842)	0.023	1.694 (1.074-2.674)	0.057	1.983 (0.980-4.010)
Model 2	0.007	1.917 (1.196-3.071)	0.024	1.739 (1.075-2.812)	0.062	1.977 (0.967-4.039)
Model 3	0.005	1.983 (1.226-3.207)	0.022	1.765 (1.085-2.871)	0.038	2.213 (1.044-4.689)
Model 4	0.006	1.967 (1.216-3.183)	0.023	1.757 (1.079-2.860)	0.046	2.156 (1.014-4.583)
Model 5	0.029	1.859 (1.066-3.240)	0.038	1.828 (1.035-3.226)	0.102	1.984 (0.873-4.512)

Model 1: ABO blood group; Model 2: Model 1 plus age at diagnosis and sex; Model 3: Model 2 plus comorbidities (diabetes mellitus, hypertension, hyperlipidaemia, cardiovascular disease); Model 4: Model 3 plus malignancy; Model 5: Model 4 plus smoking (missing value for 84 patients).
OR: odds ratio; CI: confidence intervals.

Table III. Chi-square risk analyses to estimate risk for vascular events while using "O" blood group as a reference to compare with "A", "B", and "AB" blood groups individually.

	Overall vascular involvement			Venous involvement			Arterial involvement		
	n (%)	*p* (χ^2)	OR (CI %95)	n (%)	*p* (χ^2)	OR (CI %95)	n (%)	*p* (χ^2)	OR (CI %95)
AB (n=32)	12 (37.5%)	0.349	1.600 (0.716-3.578)	12 (37.5%)	0.200	1.851 (0.823-4.165)	4 (12.5%)	0.597	1.714 (0.509-5.777)
A (n=171)	66 (38.5%)	0.034	1.676 (1.037-2.708)	56 (32.7%)	0.108	1.503 (0.914-2.471)	23 (13.5%)	0.146	1.865 (0.876-3.971)
B (n=65)	31 (47.6%)	0.004	2.431 (1.321-4.476)	27 (41.5%)	0.013	2.192 (1.175-4.090)	11 (16.9%)	0.078	2.444 (1.000-5.975)
O (n=143)	39 (27.2%)		1.00 (reference)	35 (24.5%)		1.00 (reference)	11 (7.7%)		1.00 (reference)

n: number of patients; OR: odds ratio; CI: confidence intervals.

for vascular BD with the elimination of confounding factors. Although the difference between the "O" and "non-O" groups was not statistically significant, the risk for arterial involvement was numerically higher in the "non-O" group. Arterial involvement of BD usually results in aneurysm formation, and mural thrombosis is seen in almost all, and much rarely, arterial occlusions can also occur. Therefore, it is likely that ABO blood groups may contribute to the thrombotic complications of arterial involvement in BD.

The suggested mechanisms for the association of ABO blood groups with vascular disease include the FUT2 gene, one of the genes encoding the galactoside 2-L-fucosyltransferase enzyme. FUT2 is involved in the soluble ABO blood group synthesis pathway, and responsible for secretion of ABO antigens into the gastrointestinal fluids including saliva. Non-secretory FUT2 variants were associated with an increased risk for BD and inflammatory bowel disease, and it was usually considered to play a role through alterations in intestinal microbiota (14, 15). Association of FUT2 non-secretory variants with BD was not related to any phenotypic subsets, and potential relationship between FUT2 polymorphisms, ABO blood groups and vascular phenotype needs to be investigated in a larger group of patients with genotype data along with detailed clinical features.

On the other hand, one of the major limitations of this exploratory study was its relatively small sample size, which may have affected the results due to selection bias in tertiary referral centres. Therefore, the findings related to arterial disease, gastrointestinal involvement, and the highest risk associated with blood type B compared to type O need to be replicated in a larger group. Other limitations of this study include its retrospective and single-centre design, use of only serological methods for ABO blood typing, which are expected to be clarified with the analysis of genetically determined subtyping data in a multicentre cohort.

In conclusion, the current exploratory study provides preliminary evidence for the contribution of ABO blood groups, in particular non-O blood types to the complex nature of the vascular involvement and thrombotic tendency of BD. Further investigations are required to confirm this association and explain the underlying mechanism(s).

References

1. YAZICI Y, HATEMI G, BODAGHI B *et al.*: Behçet syndrome. *Nat Rev Dis Primers* 2021; 7(1): 67. https://doi.org/10.1038/s41572-021-00301-1
2. GÜL A: Genetics of Behçet's disease: lessons learned from genomewide association studies. *Curr Opin Rheumatol* 2014; 26(1): 56-63. https://doi.org/10.1097/bor.0000000000000003
3. EMMI G, BETTIOL A, SILVESTRI E *et al.*: Vascular Behçet's syndrome: an update. *Intern Emerg Med* 2019; 14(5): 645-52. https://doi.org/10.1007/s11739-018-1991-y
4. GUL A, OZBEK U, OZTURK C, INANC M, KONICE M, OZCELIK T: Coagulation factor V gene mutation increases the risk of venous

thrombosis in Behçet's disease. *Br J Rheumatol* 1996; 35(11): 1178-80. https://doi.org/10.1093/rheumatology/35.11.1178
5. CHAMORRO AJ, MARCOS M, HERNÁNDEZ-GARCÍA I *et al*.: Association of allelic variants of factor V Leiden, prothrombin and methylenetetrahydrofolate reductase with thrombosis or ocular involvement in Behçet's disease: a systematic review and meta-analysis. *Autoimmun Rev* 2013; 12(5): 607-16. https://doi.org/10.1016/j.autrev.2012.11.001
6. LIU J, WANG D: ABO(H) and Lewis blood group substances and disease treatment. *Transfus Med* 2022; 32(3): 187-92. https://doi.org/10.1111/tme.12820
7. VASAN SK, ROSTGAARD K, MAJEED A *et al*.: ABO blood group and risk of thromboembolic and arterial disease: a study of 1.5 million blood donors. *Circulation*. 2016; 133(15): 1449-57; discussion 1457. https://doi.org/10.1161/circulationaha.115.017563
8. WU O, BAYOUMI N, VICKERS MA, CLARK P: ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. *J Thromb Haemost* 2018; 6(1): 62-9. https://doi.org/10.1111/j.1538-7836.2007.02818.x
9. GOUMIDI L, THIBORD F, WIGGINS KL *et al*.: Association between ABO haplotypes and the risk of venous thrombosis: impact on disease risk estimation. *Blood* 2021; 137(17): 2394-2402. https://doi.org/10.1182/blood.2020008997
10. INTERNATIONAL STUDY GROUP FOR BEH-ÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335(8697): 1078-80.
11. AHMET E, YARDIMCI S: Türkiye genelinde ABO kan grupları ve Rh faktörünün dağılımı. *J Ankara Univ Fac Med* 1993; 46: 527-33.
12. WARD SE, O'SULLIVAN JM, O'DONNELL JS: The relationship between ABO blood group, von Willebrand factor, and primary hemostasis. *Blood* 2020; 136(25): 2864-74. https://doi.org/10.1182/blood.2020005843
13. KIECHL S, PARE G, BARBALIC M *et al*.: Association of variation at the ABO locus with circulating levels of soluble intercellular adhesion molecule-1, soluble P-selectin, and soluble E-selectin: a meta-analysis. *Circ Cardiovasc Genet* 2011; 4(6): 681-86. https://doi.org/10.1161/circgenetics.111.960682
14. XAVIER JM, SHAHRAM F, SOUSA I *et al*.: FUT2: filling the gap between genes and environment in Behçet's disease? *Ann Rheum Dis* 2015; 74(3): 618-24. https://doi.org/10.1136/annrheumdis-2013-204475
15. HU M, ZHANG X, LI J, CHEN L, HE X, SUI T: Fucosyltransferase 2: A genetic risk factor for intestinal diseases. *Front Microbiol* 2022; 13: 940196. https://doi.org/10.3389/fmicb.2022.940196