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Original Article

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Is There an Association Between ABO Blood Group and Microangiopathic Hemolytic Anemia?

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Abstract

Background: Several studies have reported the relationship between ABO blood groups and thrombosis and hemorrhagic disorders, most of them showing that non-O blood groups have a high risk for thrombosis and O blood groups have a high risk for hemorrhage. However, there are a few studies about the relationship between the microangiopathic hemolytic anemia (MAHA) and the ABO blood groups.

Methods: A prospective case-control study was conducted in the ICU centers of the Hasheminejhad and the Imam Reza Hospital of the Mashhad University of Medical Science in Mashhad, Iran between May 2011 and December 2012. Patients admitted to the ICU with different etiology showed symptoms and signs of microangiopathic hemolytic anemia. There were 80 patients (age: 20 - 70 years) and 100 controls in this study. Controls were selected at random from a laboratory.

Results: In this study, we show that there is a significant difference in all blood groups between patients with microangipatic hemolytic anemia and the control group (P = 0.009), with a significant difference between O and non-O blood groups (P = 0.023).

Conclusions: Previous studies confirm the historical linkage between some vascular disorders and non-O blood group status. In this study we show the significant relationship between microangiopathic hemolytic anemia and non-O blood groups; therefore, we recommended non-O blood group consider as a risk factor for this group of disease.

Keywords: ABO blood group; Microangiopathic hemolytic anemia; Risk factor

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Introduction

Several studies have reported the relationship between ABO blood groups and thrombosis and hemorrhagic disorders, most of them showing that non-O blood groups have a high risk for thrombosis and O blood groups have a high risk for hemorrhage. Limited study about some kind of microangiopathic hemolytic anemia (MAHA), such as TTP or eclapsia and ABO blood groups, shows different results. However, there are no studies about the relationship between all kinds of microangiopathic hemolytic anemia, in which patients have bleeding and thrombosis with each other, and the ABO blood groups.

Non-O blood type individuals have higher levels of Factor VIIIc (FVIII) and von Willebrand factor (VWF) [1-2], and elevated FVIII and VWF levels are risk factors for venous thromboemboly (VTE) [3], and O blood group individuals have lower levels of VWF than non-O blood group [4]. Microangiopathic hemolytic anemia is a group of diseases including: disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), as well as malignant hypertension, which the endothelial layer of small vessels is damaged with resulting fibrin deposition and platelet aggregation, leading the patients to have both thrombosis and hemorrhage. In this group of diseases, the red cells are ripped apart by physical trauma as they try to pass through vessels laden with fibrin strands, causing hemolytic anemia.

Due to the different risks for hemorrhage and thrombosis in relation to ABO blood groups in different studies, in this study we evaluate the relationship between ABO blood groups and MAHA.

Subjects and Methods

A prospective case-control study was conducted in different sections of the Hasheminejhad and the Imam Reza hospital of the Mashhad University of Medical Science in Mashhad, Iran, between May 2011 and December 2012. Patients admitted with different etiologies such as infection, collagen

Table 1. The Distribution of ABO Blood Group Among Patients With Microangiopathic Hemolytic Anemia

ABO group	Case, N (%)	DIC	TTP/HUS	Eclampsia	HELP syndrome	Control, N (%)	P value	Odds ratio
N (%)	86 (100)	45 (52)	23 (27)	14 (16)	4 (0.06)	100 (100)		
A	36 (42)	22	7	6	1	29 (29)		
B	26 (30.2)	10	7	6	3	27 (27)		
AB	6 (7)	3	3	0	0	8 (8)	< 0.009	2.7
O	18 (21)	10	6	2	0	38 (38)		
Non-O	68 (79)	35	17	11	4	64 (64)		
O/Non-O	0.26	0.28	0.35	0.18	0	0.59	< 0.023	2.3
M/F	31/55	26/19	4/19	0/14	0/4	48/52		

DIC: disseminated intravascular coagulopathy; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome; CI: confidence interval.

vascular disease and complication of pregnancy, and so on, also showed symptoms and signs of microangiopathic hemolytic anemia (hemolytic anemia, thrombocytopenia and fragmented red cells in peripheral blood smear) either initially or during their hospitalization. Patients evaluated for microangopathic hemolytic anemia including DIC, TTP, HUS, Eclampsia, and Help syndrome (hemolytic anemia, elevated liver enzyme and low platelet count) by taking a complete history and physical examination, and by measuring PT, PTT, BT, the serum level of fibrinogen, FDP, D-dimer, liver function test, BUN, creatinin, as well as by studying the peripheral blood smear for shistocyte and helmet cells.

Diagnostic criteria for TTP/HUS were as follows: 1) haemolytic anaemia; 2) three or more fragmented red cells or helmet cells per high power field in the peripheral blood smear; 3) thrombocytopenia (platelet count $< 75 \times 10^6/\mu L$) or a 50% drop compared with previous count [5] and extremely elevated serum levels of lactate dehydrogenase. Neurological symptoms, renal function abnormalities or fever were not considered as diagnostic inclusion. Prolonged PT and PTT considered as diagnostic exclusion. Diagnostic criteria for DIC were microangiopatic hemolytic anemia with PT and PTT prolongation and for pre-eclampsia with edema and hypertension. Hemolytic anemia, elevated liver enzyme and low platelet count are diagnostic criteria for Help syndrome.

Blood group of all patients and the control group were detected. There were 86 patients (age: 20 - 70 years) and 100 controls in this study. Controls were selected at random from the patients within the same geographic region who were referred to the laboratory for any reason to determine their blood groups.

To compare case and control frequencies of patients with different ABO blood groups, Wilcoxon analysis was used and significance was assumed at a P-value below 0.05. Analyses were performed using computer software SPSS version 16.

Results

Among patients with microangiopathic hemolytic anemia, Non-O group distribution was present in 68 (79%) of patients while it was 64 (64%) in the control group. The difference between these two groups was significant, with a P value less than 0.023 (odds ratio 2.3). Also the difference between all blood groups in all kind of microangiopathic hemolytic anemia were significant ($P < 0.009$) and the odds ratio was 2.7 (Table 1). The most common microangiopathic hemolytic anemia in our study was disseminated intravascular coagulopathy, and the second most common was thrombotic thrombocytopenic purpura. DIC was more common in men, but TTP was more common in women; this difference is due to their etiology. TTP in 60% of patients was followed by systemic lupus erythematosis and pregnancy. The most common cause of DIC was infection and trauma.

Discussion

Microangiopathic hemolytic anemia is defined as a non-immune hemolysis with prominent red cell fragmentation in peripheral blood smear and thrombocytopenia. It is a group of diseases with poor prognosis and high mortality rate; therefore, if we know more about the pathophysiology and the risk factor of this group of diseases, we may manage them more effectively.

Several studies showed the correlation between blood groups and bleeding, as well as thrombosis. The study performed by Jukic et al with 154 patients diagnose with thrombosis and 200 asymptomatic blood donors as a control group showed that carriers of ABO blood group non-OO genotype have a slightly elevated twofold predisposition to develop thrombosis compared to OO genotypes. Their results revealed that ABO system genotypes show a significant correlation with the development of venous and arterial thromboembolism [6]. Another study performed by Lourenço DM et al showed that there was an imbalance between blood group A and O frequencies in patients with venous thrombosis versus blood donors, with a higher frequency of A blood groups and a lower frequency of O blood groups, represented by a high A/O ratio [7]. The systematic review confirmed the historical impression of linkage between some vascular disorders and non-O blood group status [8].

In the other systematic review and meta-analysis about ABO blood group and pre-eclampsia, the author suggested that there is no clear association between any ABO (H) blood group and pre-eclampsia. However, existing data does not allow exclusion of any effect limited to those expressing the least O(H) antigen [9]. The data from Morelli et al study indicated that carriers of blood group alleles A1 and B have a 2-fold increased risk of a first deep vein thrombosis, and that the non-OO genotypes strongly influence the risk of thrombosis in factor V Leiden carriers [10]. In one study, among 28 patients with FV Leiden and venous thrombosis, 96% possessed a non-O blood group, while in another study among carriers of FV Leiden, the thrombosis risk for subjects with a non-O blood group were increased by 4-fold compared with those with an O blood group [11].

The study of Welsby IJ et al showed that patients with an O blood group may be at greatest risk of bleeding after cardiac surgery due to lower baseline levels of the Von Willebrand factor (VWF) compared to patients with other blood groups [12]. In another study, the risk factors for postoperative bleeding were evaluated in 877 patients undergoing primary non-emergent coronary artery bypass surgery; they measured perioperative in-vitro bleeding times to determine whether there were measurable differences in primary hemostasis between patients with blood type O and those with other blood groups. They showed that patients with O blood groups did not have increased bleeding after cardiac surgery compared to patients with non-O blood groups [9]. In the Reddy et al study, 1,261 Caucasians admitted with epistaxis showed that 50.44% of patients belonged to blood group O; However, it was 45.10 percent (chi-square test P = 0.008) among the control group. This concluded that compared to the control population, blood group O appears over-represented in Caucasian patients admitted with epistaxis, raising the possibility that blood group O is a risk factor for epistaxis [13]. Oral anticoagulant treatment for secondary prevention after cerebral ischaemia is associated with a higher bleeding rate than cardioembolic stroke, this can be explained by known bleeding risk factors, in which hemostatic genetic variants and ABO blood groups may be involved [14].

Meta-analysis studies on the association between vascular diseases and ABO showed the pooled Odds Ratio for venous thromboembolism to be 1.79 [8]. The other study showed that the risk of venous thrombosis associated with non-O blood groups have been estimated at 1.75-fold. ABO antigens are expressed on red blood cells and on the Von Willebrand factor. Therefore, an association between non-O blood groups and thrombosis exists, an effect that is predominantly mediated by the Von Willebrand factor [10].

There are few studies about the relationship between all microangiopathic hemolytic anemia and ABO blood groups. One study that assed the association between only TTP and ABO blood groups showed that there were no relationship between them but they revealed greater frequency of the blood group O in patients with TTP and severe ADAMTS13 deficiency [15]. Another retrospective study that compared the ABO blood group distribution in 32 patients diagnosed of thrombotic microangiopathy(TTP/HUS) showed there are no statistically significant differences in the ABO blood group distributions between patients and controls [16]. Both studies were limited to only TTP, but in this study we asses all kinds of MAHA. As we can see in table 1, the O to Non O ratio in TTP was much higher (0.36) than other MAHA, and closer than the normal value (0.59). This ratio can relatively interpret the difference between this study and previous studies.

The mechanism by which non-O blood groups contribute to the thrombosis risk in carriers of the factor V Leiden mutation is mainly explained by its effect on factor VIII levels. High levels of factor VIII are associated with a decreased responsiveness to activated protein C in the absence of factor V Leiden [17]. Factor V Leiden appeared to modify the non-O blood type association with VTE in a supra-additive fashion, with an age-, sex- and race-adjusted OR of 6.77 for having both risk factors [18]. ABO blood groups are a major determinant of plasma Von Willebrand factors and factor VIII levels, thereby mediating the effects of ABO blood groups on VTE risk. While a deficiency of VWF is responsible for a hemorrhagic diathesis (Von Willebrand Disease) [19], there is an increasing amount of evidence that proves elevated VWF levels are an important thrombotic risk factor [20]. Plasma VWF levels are 25-35% lower in subjects with

an O blood group than in subjects with a non-O blood group. Therefore the former subjects having an increased bleeding tendency are reasonable [10, 21]. Preliminary evidence suggests that blood groups may influence the venous thromboemboli risk associated with factor V Leiden [22]. Also, ABH antigens alter plasma levels of the Von Willebrand factor via clearance mechanisms, which are in turn mediated by ADAMTS13 [6, 23]. Based on this data, it is expected that Non O Blood groups should be at risk for MAHA.

This study confirms the linkage between microangiopathic hemolytic anemia and non-O blood group status, also showing that the odds ratios (about 2.3) are similar to those predicted by the effect of ABO (H) on the venous thromboembolic risk or the O blood group are protected against MAHA. These effect are especially more significant in MAHA secondary to obstetric complications, and less in TTP/HUS patients. This relationship suggest that the thrombotic event are prominent than the hemorrhagic event in most patients with MAHA.

Therefore, information on blood group genotypes may play a role in the prevention and management of the MAHA. We believe that these results will greatly contribute to making proper decisions regarding whether or not ABO genotyping should be included in the mandatory risk testing of MAHA. These data are not conclusive about the causes of the association between ABO blood groups and MAHA, and prospective studies are needed to verify whether blood typing could have a predictive value for prophylactic measures in clinics. Further work is required to assess risk prospectively and to refine the effect of increasing non-O antigen expression MAHA.

Conclusion

The main conclusion of this study is that carriers of ABO non-O blood group have elevated more than twofold predispositions to develop MAHA compared with those found in O blood groups. Results of our study defined ABO system genotypes, showing significant correlation with the development of various kinds of microangiopathic hemolytic anemia. These data can provide a valuable tool for prevention and target management of these pathologies. We believe that these results will greatly contribute to making proper decisions regarding whether or not ABO genotyping should be included in the mandatory risk testing in MAHA. However, our study has some limitations, such as the relatively small number of patients due to the non-existence or low frequency of MAHA.

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Disclosure Statement

The author declares no conflict of interest.

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