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Original Article

The association of ABO blood group and rh factor with recurrent aphthous ulceration

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Abstract

Aim: In this study we aimed to investigate effects of blood group and Rh factor on recurrent aphthous ulceration (RAS).

Material and Methods: A total of 350 persons were included in the study, 175 with RAS and 175 as the healthy control group. Medical histories and laboratory findings of the patients presenting to the outpatient clinic were evaluated. Patients that had aphthae lesions more than three times a year were studied. Haemoglobin (Hb), vitamin B12, ferritin, folic acid, and iron levels were measured and the blood groups were recorded.

Results: Of RAS patients, 16.8% had a deficiency in Hb, 16.3% in vitamin B12, 18.5% in ferritin, 6.4% in folic acid and 28.2% in iron. The patient blood groups were distributed as follows 33.7% Group A, 20% Group B, 8.6% Group AB and 33.1% Group O. Of RAS patients were 92% Rh(+) and 8% Rh(-). No statistically significant difference was found between the distribution of blood groups and RAS. However, the risk of RAS was found to be six times higher in B Rh(+) patients compared to B Rh(-) patients and three times higher in AB Rh(+) patients com-pared to AB Rh(-) patients.

Conclusions: Rh factor may have an effect on the etiology of RAS disease. Anemia and vitamin B12 deficiency are common in RAS patients, making a hematological evaluation a necessity for RAS patients.

Keywords: Recurrent Aphthous Ulceration (RAS); Blood Group; Rh Factor; Anemia; Etiology.

INTRODUCTION

Aphthous ulcers are one of the common diseases of the oral mucosa, affecting about 10–25% of the population (1,2). Recurrent aphthous ulceration (RAS) is more common in women than in men, and it usually starts in childhood and adolescence. RAS is an inflammatory condition of unknown etiology. RASs are recurrent, painful and ulcerative lesions surrounded by a shallow and erythematous halo and are most commonly found on the cheek mucosa and tongue. According to the first classification described by Stanley, RASs have three different variants: minor (less than 10 mm in diameter), major (larger than 10 mm in diameter) and herpetiform (2–3 mm in diameter). Minor RAS is the common variety, affecting about 80% of RAS patients (1).

The ABO blood system was first discovered by Karl Landsteiner in 1901, and it has gained a paramount importance in medicine (3,4). The genes that determine the A and B phenotypes are found on chromosome 9p and are expressed in a Mendelian codominant manner (5,6). Gene frequencies for the blood groups vary among societies and create a risk factor for many diseases, with several studies demonstrating an association between diseases and blood groups (7,8,9,10). It was shown in a study by Woolf that the probability of illness could increase up to 39% based on the blood group (8).

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The objective of this study was to measure the prevalence of RAS based on blood group to shed light on its etiology because the cause of this disease is still not known despite its common nature and the number of studies conducted.

MATERIALS AND METHODS

This study included patients presenting to the otorhinolaryngology clinic between 2016 and 2017 with the complaint of RAS. A total of 350 people were included in the study, 175 (50%) patients and 175 (50%) control subjects, consisting of 37.1% men and 62.9% women (age range: 18–70 years). Patients were diagnosed as having RAS after they had at least three episodes of oral ulcerations. Venous blood samples were collected from the control and patients group. They were studied haemoglobin (Hb), serum iron, vitamin B12, folic acid and blood group in the patient and control group. The blood group of the cases and controls was collected by a single trained and calibrated investigator using finger prick method and blood typing done by tube method. Patients were classified according to blood group (A, B, AB and O) and Rh status (+ or −). The other blood samples were measured (Sysmex XE-2100; Kobe, Japan).

Selection criteria for RAS included the elimination of other possible oral mucosal disorders. All patients were systemically healthy under normal conditions. Patients with impaired blood outcomes were referred to the Internal Medicine Clinic. The control group consisted of 175 healthy participants that referred to the Department of Internal Medicine and Physical Medicine and Rehabilitation Clinic. The healthy control group consisted of those without RAS who volunteered to participate. Among the patients excluded in the study, such as, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, pemphigus vulgaris, Behcet's syndrome, celiac disease, gluten-sensitive enteropathy, inflammatory bowel diseases and cyclic neutropenia. In this study was excluded ulceration after local injury, poor oral hygiene and smoking tobacco with patients.

The approval of the local ethics committee was obtained (Protocol No. 40-03). All patients and healthy control subjects signed the informed consent forms before entering the study.

Statistical Analysis

In evaluating the data, normality was analyzed using the Kolmogorov–Smirnov test. The Mann-Whitney U test was used for the comparison of non-normally distributed variables. The median (Q1-Q3) was used as the statistical parameter. The chi-square test and Fisher exact test were used to compare the categorical variables. The positive and negative presence of the Rh gene was given using an ODDS ratio. A $p < 0.05$ value was considered statistically significant in the comparisons. All statistical analyses were carried out using SPSS package, software version 22.

RESULTS

According to the results of the analyses, the difference between the patient and control groups in terms of median age was found to be statistically significant ($p < 0.05$). The median age was 36.00 years (26.00–47.00) in the patient group and 40.00 (27.00–53.00) in the healthy control group. Aphthous ulcers were observed to be more common at younger ages. We found that 66.2% (n=116) of the RAS patients were women. The median blood concentrations of iron, Hb, ferritin, folic acid and vitamin B12 in RAS patients and the healthy control subjects are shown in Table 1. The percentage of serum iron, Hb, ferritin, folic acid and vitamin B12 levels in RAS patients and the healthy control subjects are shown in Table 2. Of the RAS patients, 28.2% had a deficiency in iron deficiency, 6.8% in Hb, 18.5% in ferritin, 6.4% in folic acid and 16.3% in vitamin B12. There was a statistically significant difference between the patient and control groups in terms of Hb levels (p=0.034). The difference between the patient and control groups in terms of median vitamin B12 levels was also found to be statistically significant (p=0.005).

Table 2. The persentage of serum iron, Hb, ferritin, folic acid and vit B12 levels in patients with RAS and control groups

		Group			
		Patient		Control	
		n	%	n	%
Iron (lg/dl)	Low	48	28.2	60	34.3
	High	122	71.8	115	65.7
Hb (g/dl)	Low	29	16.8	25	14.3
	High	144	83.2	150	85.7
Ferritin (ng/ml)	Low	31	18.5	24	13.7
	High	137	81.5	151	86.3
Folic Acid (ng/ml)	Low	11	6.4	27	15.5
	High	160	93.6	147	84.5
Vit B12 (pg/ml)	Low	28	16.3	12	6.9
	High	144	83.7	163	93.1

Mann-Whitney U Test; α:0.05; *Difference is statistically significant

Table 2. The persentage of serum iron, Hb, ferritin, folic acid and vit B12 levels in patients with RAS and control groups

	Patient		Control		
	Median	(Q1-Q3)	Median	(Q1-Q3)	p
Age	36.00	(26.00-47.00)	40.00	(27.00-53.00)	0.011*
Iron (lg/dl)	71.00	(47.00-93.00)	60.00	(42.00-90.00)	0.216
Hb (g/dl)	13.50	(12.60-14.70)	13.90	(12.80-15.30)	0.034*
Ferritin (ng/ml)	38.47	(11.74-70.54)	36.70	(15.50-79.10)	0.462
Folic Acid (ng/ml)	8.81	(6.92-10.71)	8.12	(5.91-11.00)	0.107
Vit B12 (pg/ml)	286.65	216.80-366.70)	322.00	(257.00-404.00)	0.005*

Low: Below the reference limit, High: over the reference limit

In this study, the blood group distributions of the RAS patients were as follows: 37.7% group O (n=66), 33.7% group A (n=59), 8.5% group AB (n=15) and 20% group B (n=35). Of these RAS patients, 92% (n=161) were Rh(+) and 8% (n=14) were Rh(−). In the control group, the blood group distributions were as follows: 33.1% group O (n=58), 45.7% group A (n=80), 6.3% group AB (n=11) and 14.9% group B (n=26). Of these healthy controls, 88% (n=154) were Rh(+) and 12% (n=21) were Rh(−) (Table 3). The 175 RAS patients were further divided into 23 (13.2%) major-type, 133 (76.4%) minor-type and 18 (10.3%) herpetiform patients.

Table 4 shows a comparison of the gender distribution, ABO blood group types and the Rh factor between RAS patients and the control group.

There was no significant difference between patients with RAS and the control group in terms of the distribution of ABO blood groups and the Rh factor. However, considering Rh genes, the incidence of the disease was 3.111 times more common in Rh(+) people than in Rh(−) ones among the AB blood group. Among the patients in the B blood group, the risk of the disease was 6.182 times higher in Rh(+) people than in Rh(−) ones.

Table 3. Comparison of ABO/Rh blood groups between RAS and control groups

ABO Blood	Patient group (n/%)	Control group (n/%)
O	66 (%37.7)	58 (%33.1)
A	59 (%33.7)	80 (%45.7)
AB	15 (%8.6)	11 (%6.3)
B	35 (%20)	26 (%14.9)
RH+	161(%92)	154 (%88)
RH-	14 (%8)	21 (%12)
Total	175 (%100)	175 (%100)

Table 4. Comparison of ABO blood groups, Rh factor and gender between RAS and control group

Blood Groups*		Patient		Control				
		n	%	n	%	OR(%95CI)	X2	P
O[a]	RH+	60	34.3	52	29.7	1.154(0.351-3.796)	0.056	0.814
	RH-	6	3.4	6	3.4			
AB[b]	RH+	14	8.0	9	5.2	3.111(0.245-39.540)	0.824	0.556
	RH-	1	0.6	2	1.2			
A[a]	RH+	53	30.2	71	40.5	1.120(0.376-3.339)	0.041	0.839
	RH-	6	3.4	9	5.2			
B[b]	RH+	34	19.5	22	12.6	6.182(0.648-59.003)	3.111	0.054
	RH-	1	0.6	4	2.2			
Gender								
Male		59	33.8	71	40.6	0.745(0.482-1.151)	1.762	0.184
Female		116	66.2	104	59.4			

*No Difference between patient and control; a Chi-Square test; b Fisher exact test; OR:ODDS Ratio

DISCUSSION

RAS is a very common oral mucosal disorder of unknown etiology. Local and systemic conditions together with genetic, immunologic and microbiological factors have been shown to be possible etiological factors. ABO blood group types have been frequently associated with some diseases. The first evidence of the link between blood group polymorphism and disease was the association of peptic ulcers with the O blood group (10,11). Case studies have demonstrated the significant associations of particular human leukocyte antigens and ABO blood groups with various autoimmune diseases, such as juvenile diabetes, multiple sclerosis, rheumatoid arthritis, psoriasis, Crohn's disease, and Celiac disease (12,13). In our study, the incidence of RAS was significantly higher among patients with AB and B blood who were Rh(+). We believe that this result is noteworthy for the Rh antigen, which has the highest antigenicity following the A and B blood group antigens.

Genetic studies have demonstrated that individuals with the A blood group are more resistant to the influenza virus despite having a higher risk profile for acute rheumatism. In addition, although it has been reported that several forms of cancer are associated with subtypes of ABO blood groups, the exact mechanism of this association remains to be elucidated (14,15). Some studies have also demonstrated that in certain infections the severity of the infection is associated with ABO phenotypes. Rowe et al (16). compared Malian patients with blood group to the other blood groups and found that Plasmodium falciparum was less common in children with that blood type. Another study showed that people in group O who are infected by Vibrio cholera are more severely affected by the infection (17). In another study from Scotland conducted in 1996, it was shown that 87.5% of people who died of the Escherichia coli epidemic had the O blood group, and the O phenotype is more influenced by cholera pandemics (7).

The mechanism for the relation of ABO blood groups with some diseases has not yet been clarified. However, this association has shed some light on various aspects of the etiopathogenesis of certain disorders. In recent studies, ABO blood group antigens have been found in many epithelial cells and mucosal secretions (18,19). Alterations in the release of ABO antigens from the epithelium have been found to be associated with epithelial differentiation, such as wound tissue healing, oral mucosal cancers and the maturation of cells (18,19) Helicobacter pylori, which causes gastric cancer and peptic ulcers, is known as a gastric pathogen, and studies have shown the ability of strains to bind to the O blood group (20).

Studies conducted on haematological diseases have shown that, oral mucosa is also affected by existing diseases (21). Oral epithelial cells have a high turnover rate. Folic acid and iron are required for all body cells, such as in the healing and regeneration of injured oral mucosal epithelium. These deficiencies may cause oral epithelial atrophies. In addition, studies have shown that deficiencies in vitamin B derivatives, folic acid, zinc and iron are among the most significant causes of 5–12% of RAS cases (21,22). In our study, 16.8% of RAS patients had anemia, 16.3% a deficiency in vitamin B12, 18.5% in ferritin, 6.4% in folic acid and 28.2% in iron. Burgan et al (23). have showed that 26.6% a deficiency in vitamin B12, 16.8% % in ferritin, 4.9% in folic acid in RAS patients. Compilato et al (24). have also reported of 15.6% a deficiency in vitamin B12, 8.8 % in folic acid, 40.6% in ferritin.

RAS typically occurs in patients between 10–30 years of age and recurs at varying intervals throughout life (25,26). Similarly, in our study, RAS was more common at younger ages. Despite being commonly seen today, RAS is still not clearly understood, and treatments only address the symptoms, making this disease a serious problem for many people. Because stress and psychological disorders may induce the onset of RAS episodes, this disease is currently difficult to diagnose and control, and its treatment will remain non-specific and for the symptoms only until a principal causal factor can be isolated. Topical agents are currently the preferred treatments due to their limited side effects. Treatments to reduce pain and prevent secondary infections are sometimes necessary, as well. Even though various immune modulators, topical and systemic steroids, topical analgesics and topical antibiotics have been shown to be successfully applied, the prevention of recurrences has not been successful (27).

CONCLUSION

Precise haematological evaluation is a requirement for RAS patients and is very important in the diagnosis and treatment of these deficiencies. Our results show that the status of the Rh factor should be considered in the blood groups of RAS patients. Further large-scale studies are required to investigate the effects of blood groups on RAS.

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