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Original Article

Value of ABO blood group in predicting the severity of children with Crimean-Congo hemorrhagic fever

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Abstract: Purpose: The aim of this study was to assess the role of ABO blood groups in predicting disease severity and bleeding potential in children with Crimean-Congo hemorrhagic fever (CCHF). Methods: One hundred fifty-one hospitalized patients with CCHF were enrolled in this retrospective study. The patients were divided according to O- and non-O- (A, B and AB) blood groups (n=91 and n=60, respectively). They were also classified into two groups (severe and non-severe) based on disease severity (n=29 and n=122, respectively). Demographic characteristics, clinical findings, and hematologic and biochemical parameters of all patients were recorded on admission and discharge. Results: Although, in all cases, compared to the non-O blood group, the ratio of the blood group O was considerably higher (60% vs. 40%) and similarly so in severe cases (58.6% vs. 41.4%), this difference was not statistically significant (p>0.05). The aPTT at discharge and fever duration of the O-blood group were significantly higher than those of the non-O-blood group (p=0.042, p=0.034, respectively). The factor VIII level of the O-blood group was significantly lower than that of the non-O-blood group (p=0.040). Although the ratios of bleeding and severity were higher in the O-blood group compared to the other group, statistical significance was not reached (p>0.05). Conclusions: Consideration of the ABO blood group is important during diagnostic follow-up to assess the severity of CCHF. In clinical practice, pediatric CCHF patients with the O blood group need to be followed closely for tendency to bleed.

Keywords: CCHF, children, disease severity, bleeding, blood groups

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a fatal viral hemorrhagic fever caused by a genus Nairovirus of the family Bunyaviridae and is usually transmitted to humans via a tick bite, or exposure to infected blood or tissues of infected livestock or humans. The average mortality rate of the disease is 3-30%. CCHF is characterized by a short incubation period and then, generalized pain, myalgia, fever, nausea, abdominal pain, diarrhea, bleeding, and laboratory findings such as elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels, and leukopenia and thrombocytopenia [1, 2]. Since severe cases have to be managed early with a well-arranged treatment protocol, prediction of the clinical course and categorization of the patients according to the severity of the infection is a first step toward saving the life of patients [3, 4].

Previous studies demonstrated that ABO antigens are associated with vulnerability to a wide variety of infections, such as *Helicobacter pylori*-group O, *Salmonella typhi*-group B and *Pseudomonas*-group A. Furthermore, increased frequency of certain cancers, such as rectal, cervical, gastric, breast, and ovarian cancer, are associated with the blood group A [5]. Blood groups might also be associated with coagulation proteins, and this association is clinically significant in certain states. For example, blood group O individuals have significantly (about 25%) lower plasma levels of factor VIII (FVIII) and von-Willebrand factor (vWF). Low plasma levels of either FVIII or vWF have been reported to be causes of excessive bleeding [6].

Table 1. Demographic characteristics and distribution of blood groups of the study population

Characteristics		Severe group (n=29)	Non-severe group (n=122)	p
Age (years)		11.5±3.9	11.7±4.8	0.478
Gender (male/female)		19/10	73/49	0.654
Days from symptoms to admission		6.8±3.3	6.2±3.6	0.586
Rh Positive	A	8 (28%)	33 (27%)	0.437
	B	2 (7%)	6 (5%)	0.300
	AB	0 (0%)	3 (2%)	0.847
	0	16 (55%)	67 (55%)	0.803
Rh Negative	A	0 (0%)	4 (3%)	0.886
	B	2 (7%)	1 (1%)	0.848
	AB	0 (0%)	1 (1%)	0.845
	0	1 (3%)	7 (6%)	0.848

Rh, Rhesus.

There are several studies investigating the relationship of venous thromboembolism and bleeding and the course of infectious diseases with the blood groups; however, there is no study evaluating the effect of the ABO blood group on clinical course and coagulation tests in children with CCHF, as far as we know. Therefore, we purposed to assess the role of ABO blood groups in predicting disease severity and bleeding potential in children with CCHF.

Material and methods

This retrospective study included all patients with CCHF (n=151) who had been hospitalized in the pediatric unit between 2009 and 2013. The patients were divided according to blood groups as 0 and non-0 blood groups (A, B and AB) (n=91 and n=60, respectively). They were also classified into two groups based on the severity of the disease as severe and non-severe groups (n=29 and n=122, respectively). The criteria of the severity of disease were reported by Cevik et al. Patients with at least one of the following were considered severe cases: somnolence, melena, activated partial thromboplastin time (aPTT) ≥60 s, and thrombocyte count ≤20x10^9/L during their hospital stay [7].

The suspected diagnosis of CCHF infection was based upon typical clinical and epidemiological findings. In addition, diagnosis was confirmed by serological tests with ELISA (anti-CCHF IgM and IgG antibodies) or of genomic segments of the CCHF virus by reverse transcription-polymerase chain reaction (RT-PCR) either in the acute and/or convalescent phase of the disease. ELISA and RT-PCR analysis were done by the Virology Laboratory of Refik Saydam Hygiene Central Institute (Ankara, Turkey) which refers to the country's laboratory used for microbiological testing of the CCHF virus infection.

The blood samples of the study population were typed by slide method, using ABO and Rh (D) Typing Antisera (Ortho Clinical Diagnostics, Part of the Johnson-Johnson Family of Companies, New Jersey, United States).

Demographic characteristics, duration between onset of symptoms and admission, clinical findings, and laboratory tests (ABO and Rhesus blood groups and FVIII levels on admission, and in addition, white blood cell [WBC], platelet [PLT], AST, ALT, lactate dehydrogenase [LDH], creatine phosphokinase [CPK], and aPTT on admission and discharge) of all patients were recorded.

Statistical analysis

The data were evaluated with the SPSS 16.0 for Windows program. Mean values were shown as "arithmetic mean ± standard deviation". Data were analyzed with the t test or chi-square tests as appropriate. A *p* value of $p<0.05$ was considered significant.

Results

Mean age was 11.6±4.1 years and 92 (61%) patients were male. The severe and non-severe CCHF groups were found to be comparable with regard to the age and days from symptoms to admission, and the ratios of gender and ABO

Table 2. Clinical and laboratory characteristics of the study population

Parameters	O-blood group	Non-O blood group	p
WBC (x10^9/L)			
Admission	3.5±2.3	4.1±3.2	0.430
Discharge	5.1±1.6	4.7±1.5	0.377
PLT (x10^9/L)			
Admission	113.6±57.0	116.2±61.7	0.833
Discharge	271.4±125.6	249.2±116.5	0.378
AST (IU/L)			
Admission	168.5±275.4	119.4±112.5	0.171
Discharge	58.3±30	61.6±50	0.722
ALT (IU/L)			
Admission	66.2±84	57.5±62.7	0.522
Discharge	72.2±41.5	64.7±43.9	0.411
LDH (IU/L)			
Admission	497.4±480.7	412.3±226.2	0.195
Discharge	289.3±60.6	308.3±81.9	0.302
CK (IU/L)			
Admission	1095±2945.21	424.93±809.52	0.070
Discharge	286.85±1076.2	138.2±344.7	0.352
aPTT (sec)			
Admission	41.47±11.13	38.38±8.63	0.095
Discharge	34.76±4.65	27.70±4.80	0.042
Factor-VIII levels (IU)	92.80±33.75	99.76±27.08	0.040
Hospitalization period (day)	10.02±2.65	9.45±3.42	0.345
Bleeding (n)	16	10	0.614
Severe patient (n)	17	12	0.839
Non-severe patients (n)	74	48	0.614
Duration with fever (day)	3.42±2.10	2.18±1.61	0.034

WBC, white blood cell; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; aPTT, activated partial thromboplastin time; sec, second; FVIII, factor VIII.

blood types (p>0.05). There was no mortality and all were healed and discharged after a median of 9 (7-10) days. Although, in all cases, the ratio of the blood group O was considerably higher compared to that of the non-O blood group (60% vs. 40%) and in severe cases, the ratio of the blood group O was also considerably higher compared to that of the non-O blood group (58.6% vs. 41.4%), there was no significant difference between the severe and non-severe groups with regard to the ratio of the blood group O (p>0.05). The demographic, clinical and blood group data of the severe and non-severe CCHF cases are shown in **Table 1**.

The aPTT at discharge and duration with fever of the O-blood group were significantly higher than those of the non-O-blood group (p=0.042, p=0.034, respectively). The FVIII level of the O-blood group was significantly lower than that of the non-O-blood group (p=0.040). There was no significant difference between the O- and non-O-blood groups with regard to the WBC, PLT, AST, ALT, LDH, and CPK levels at admission and discharge; aPTT at admission; and hospitalization period (p> 0.05). Although the ratios of bleeding and severity were higher in the O-blood group compared to the non-O-blood group, these did not reach statistical significance (p>0.05). Results of the clinical and laboratory characteristics of the O- and non-O-blood group are listed in **Table 2**.

Discussion

CCHF involves the multi-organ systems in which severe cases of CCHF are characterized by hemorrhagic manifestations, disseminated intravascular coagulation, vascular dysfunction, and shock [1-3, 7]. Although knowledge about the CCHF virus has increased considerably, the specific mechanisms underlying the pathogenesis of CCHF infection have not been clearly explained [1, 2]. It has been reported that mononuclear phagocytes, hepatocytes, and endothelial cells are major targets of the CCHF virus during the course of the infection [8].

The ABO phenotype is found as related to the severity of infection in several infectious diseases [9], although the mechanism underlying this association is unknown. No study has yet investigated the relationship between the ABO blood group and CCHF. During the *Escherichia coli* O157 outbreak in Scotland in 1996, patients with the blood group O were more susceptible to hemolytic uremic syndrome (64.3%)

and 87.5% of these patients died [10]. Harris et al. [11] epidemiologic study reported that once an individual is infected with *V. cholerae* O1 and O139, the O blood group renders a larger possibility of severe infections than the non-O blood group. In a study related to the cholera outbreak in Bangladesh, the prevalence of the blood group O was meaningfully lower although the prevalence of the blood group B was considerably higher [12]. However, there is a predominance of the blood group O in malaria endemic regions and evidence supporting the view that the blood group O provides a selective advantage against severe malaria has been recently reviewed [13, 14]. In addition, Wolofsky et al. [14] provide the first evidence that ABO blood group antigens influence macrophage clearance of *P. falciparum*-infected erythrocytes and they suggested an additional mechanism by which the blood group O might confer resistance to severe malaria. In our study, the number of pediatric CCHF patients is relatively higher in the O-blood group compared to the other groups; however, the study groups were found similar with regard to the severity of CCHF although hemorrhagic findings are relatively higher in the O-blood group.

The plasma coagulation proteins FVIII and vWF play a crucial role in normal hemostasis. Previous studies showed that non-O subjects have greater levels of vWF and FVIII and these subjects are also predisposed to arterial and venous thromboembolism compared to the subjects with the O blood group. Controversy, decreased plasma levels of either FVIII or vWF, was seen in group O subjects. These decreased plasma levels have long been established as causes of excess bleeding [6, 9, 15]. In a recent article in the literature, Dentali et al. [16] conducted a meta-analysis to review the clinical association between the ABO blood type and the risk of bleeding. They noted that the overall data derived from the qualitative analysis of the published literature were rather inconclusive. The results of their quantitative systematic review (i.e., meta-analysis), which was performed on 22 studies, including 9,468 bleeding cases, evidenced a slighter (OR = 1.33; 95% CI = 1.25 to 1.42) but statistically more significant ($p<0.001$) increase in bleeding risk in O blood group patients, compared to non-O blood group subjects.

The clearance of FVIII from the plasma is not clear; however, recent reports have suggested a role for the low-density lipoprotein-related receptor (LRP), a member of the LDL receptor family of endocytic receptors, in FVIII clearance [17]. It can bind a wide variety of ligands, including many glycoproteins involved in hemostasis, and mediates transport of such ligands from the cell surface to an endosomal degradation pathway. FVIII can bind to purified LRP in-vitro, and be internalized by fibroblasts expressing LRP. Sarafanov et al. [18] suggested another LRP-independent pathway of FVIII catabolism. This pathway involves binding of the A2 domain of FVIII to heparan sulphate (HS) proteoglycans. These cell surface HS proteoglycans act as receptors, providing the initial FVIII binding site on the surface of hepatic cells. Guven et al. [19] noted that CCHF increased the serum and urine HS levels. They concluded that the increase of the serum and urine levels of HS was related to vascular endothelium damage and to liver injury. The data from the studies mentioned above can contribute to the understanding of the lower levels of FVIII and longer aPTT in this study.

There are limitations to this study that merit mentioning. First, this study included cases from only one tertiary care center. Second, prospective studies from childhood to adolescence are necessary to describe more accurately the longitudinal relationship between the ABO blood group and CCHF in studies with a large sample size, that is, providing a distribution of patients in adequate numbers into the study subgroups according to the ABO blood group.

In conclusion, in pediatric CCHF patients, consideration of the ABO blood group is important during the diagnostic follow-up to assess the severity of CCHF. In clinical practice, pediatric CCHF patients with the blood group O need to be followed closely since they may have a tendency for bleeding.

Disclosure of conflict of interest

None.

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