Blood group O and black race are independent risk factors for thrombotic thrombocytopenic purpura associated with severe ADAMTS13 deficiency

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BACKGROUND: It has been postulated that blood group O subjects may be partially protected against thrombotic thrombocytopenic purpura (TTP) because they have lower plasma levels of von Willebrand factor.
STUDY DESIGN AND METHODS: The Oklahoma TTP Registry enrolled 301 consecutive patients from November 13, 1995 (when systematic ADAMTS13 measurements began), through 2009; 281 (93%) patients had ADAMTS13 measurements. Patients were designated as having severe ADAMTS13 deficiency when the activity measurement by either method was less than 10%. ABO blood group was determined in all 281 patients. The observed frequency of blood group O was compared to the expected frequency. The association between severe ADAMTS13 deficiency and blood group, race, sex, and age were analyzed by logistic regression.
RESULTS: The frequency of blood group O was unexpectedly and significantly greater than the race-ethnicity–adjusted expected frequency in 65 patients with severe ADAMTS13 deficiency (60.0% vs. 47.4%, $p = 0.042$) but not in 216 patients without severe ADAMTS13 deficiency (44.9% vs. 46.5%, $p = 0.639$). Blood group O and race-ethnicity were independently associated with severe ADAMTS13 deficiency among patients with TTP. The probability for severe ADAMTS13 deficiency was 45.8% with O and 32.1% with non-O blood groups for black patients and 24.1% with O and 15.1% with non-O blood groups for white patients.
CONCLUSION: Among patients with TTP and severe ADAMTS13 deficiency the relative frequency of patients with blood group O was greater than expected, suggesting that blood group O may be a risk factor for TTP associated with severe ADAMTS13 deficiency.

Subjects with blood group O have been postulated to be partially protected against the occurrence of thrombotic thrombocytopenic purpura (TTP) and therefore it was predicted that the observed frequency of blood group O among patients with TTP would be less than the expected frequency.[1,2] This postulate was based on previous observations that 1) plasma von Willebrand factor (VWF) levels are lower in subjects with blood group O compared to subjects with non-O blood groups;[3-7] 2) the clearance of VWF from plasma is faster in subjects with blood group O compared to subjects with non-O blood groups;[7] 3) the rate of proteolysis

ABBREVIATIONS: ANC(s) = absolute neutrophil count(s); HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura; ULVWF = ultralarge multimers of von Willebrand factor.

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of VWF by ADAMTS13 is greater in subjects with blood group O compared to subjects with non-O blood groups;[6,8] and 4) the level of ADAMTS13 activity in plasma in inversely related to the plasma VWF level.[9] Since the pathogenesis of TTP associated with severe ADAMTS13 deficiency is related to VWF-mediated microvascular thrombosis,[10] partial protection from TTP among subjects with blood group O was predicted because there may be less VWF in subjects with group O to contribute to VWF-mediated thrombosis and the greater rate of proteolysis of VWF by ADAMTS13 in group O subjects may serve to partially protect these subjects from VWF-mediated thrombosis. This postulate of partial protection against TTP is consistent with previous observations that blood group O may provide protection against myocardial, cerebral, and peripheral vascular thrombosis.[11,12]

The two previous studies that investigated this postulate both failed to detect a difference between the observed and expected frequencies of blood group O in patients with TTP.[1,2] Therefore, we investigated this postulate to determine if we could detect a difference between the observed and expected frequencies of blood group O in a large cohort of consecutive patients with TTP with and without severe ADAMTS13 deficiency.

MATERIALS AND METHODS

Patients

The Oklahoma TTP Registry is a population-based inception cohort of consecutive patients with a diagnosis of TTP or hemolytic uremic syndrome (HUS) begun January 1, 1989. Patients are identified by a request to the Oklahoma Blood Institute for plasma exchange treatment.[13,14] The Oklahoma Blood Institute is the sole provider of plasma exchange treatment for all hospitals in the 58 of Oklahoma's 77 counties that comprise the Registry region. Since standard practice in this region is to treat all adults who are diagnosed with either TTP or HUS, as well as all children who are diagnosed with TTP, with plasma exchange, the Registry is a population-based inception cohort of consecutive patients in whom a diagnosis of TTP or HUS is made and plasma exchange treatment is requested.[13,14] All identified patients have consented to be enrolled. The Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

ADAMTS13 activity and inhibitor measurements

The Registry enrolled 301 consecutive patients with an initial episode of clinically diagnosed TTP or HUS from November 13, 1995 (when systematic ADAMTS13 measurements began), through December 31, 2009; 281 (93%) patients had ADAMTS13 measurements. ADAMTS13 activity was measured in all 281 patients at the time of initial diagnosis on serum samples obtained immediately before the first plasma exchange treatment. Measurements were all performed in the Central Hematology Laboratory of the Inselspital (Berne, Switzerland) by both quantitative immunoblotting of degraded, plasma-derived VWF substrate[15,16] and a fluorogenic assay using FRETS-VWF73 substrate.[17,18] 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride (Pefabloc SC, Boehringer, Mannheim, Germany), 1 mmol/L, was present in all assay buffers to irreversibly block serine proteases, including thrombin and plasmin.[18] To examine the reliability and validity of these methods, ADAMTS13 activity in serial dilutions of normal plasma with plasma from patients with congenital TTP was measured by both methods in a blinded fashion.[19] Since serum, rather than plasma, has been used for all ADAMTS13 assays, ADAMTS13 activity was measured by both immunoblotting and FRETS-VWF73 methods on serum and plasma simultaneously obtained from 13 patients with TTP who had different levels of ADAMTS13 activity. ADAMTS13 levels in serum and plasma correlated for both methods ($r = 0.983$ immunoblotting, $r = 0.996$ FRETS-VWF73); agreement was good (mean paired difference $\pm$ standard deviation: immunoblotting, $3.6 \pm 6.0\%$; FRETS-VWF73, $5.3 \pm 6.5\%$).[14] Patients were designated as having severe ADAMTS13 deficiency when measurement by either method was less than 10%. ADAMTS13 activity less than 10% was selected as the level to identify patients with severe deficiency because this level provides a clinically important distinction related to risk for relapse.[14] ADAMTS13 functional inhibitor activity was measured on samples with ADAMTS13 activity of 20% or less by determination of residual ADAMTS13 activity of normal human plasma after 1:1 (vol/vol) incubation for 2 hours at 37°C with heat-inactivated patient's serum by the FRETS-VWF73 method. Assays of ADAMTS13 activity and inhibitors were performed without knowledge of the patients' clinical data.

Additional patient data

Patients' race-ethnicity was determined by observation at the time of hospitalization; Native Americans were also identified by their medical home (Indian Health Service). ABO blood group was determined by routine hospital blood bank methods in all 281 patients in whom ADAMTS13 activity was measured. White blood cell counts from the day of the initial plasma exchange treatment have been systematically collected since June 8, 1999. Data were available from 192 (96%) of 201 patients through December 31, 2009. VWF levels were not measured and VWF molecular size distribution was not analyzed.

Statistical analysis

Patients with ADAMTS13 activity less than 10% and 10% or more were analyzed as separate groups because we initially postulated that blood group O would only be protective in patients with TTP associated with severe ADAMTS13 deficiency who have VWF-mediated thrombosis. Only data from each patient's first episode were analyzed. To compare observed and expected frequencies of patients with blood group O, one-way exact chi-square analysis was performed. Expected blood group frequencies were calculated using US data specific for race-ethnicity[20] and the race-ethnicities of our patients. Wilcoxon analysis was used to compare the absolute neutrophil counts (ANCs) in TTP patients with and without severe ADAMTS13 deficiency. Chi-square analysis and logistic regression analyses were used to determine if the variables, blood group, race-ethnicity, sex, and age were associated with the presence of severe ADAMTS13 deficiency among patients with TTP. Interactions among the four variables were also assessed. An α of 0.05 was used. Analyses were performed using computer software (SAS, Version 9.2, SAS Institute, Cary, NC).

RESULTS

Patients

ADAMTS13 deficiency

Sixty-five (23%) of the 281 patients who had ADAMTS13 activity measurements were defined as having severe ADAMTS13 deficiency by activity less than 10%. Fifty-five (85%) of the 65 patients with severe ADAMTS13 deficiency had a demonstrable ADAMTS13 inhibitor at the time of their initial episode; nine of the 10 patients who did not have a demonstrable inhibitor at the time of their initial episode did have an inhibitor at the time of a relapse and/or had increased ADAMTS13 activity measured during clinical remission. The one patient without a demonstrable ADAMTS13 inhibitor died before the first plasma exchange was begun; she was 51 years old with no history of hematologic disorders and no apparent condition triggering an acute episode of TTP. Therefore, all 65 patients were considered to have acquired ADAMTS13 deficiency.

Sixteen (6%) of the 281 patients had received plasma infusions before the sample for ADAMTS13 measurement was collected; four had ADAMTS13 activity of less than 10% and 12 had ADAMTS13 activity of 10% or more. In one patient who had ADAMTS13 activity of 11%, the previous plasma infusion may have caused her to be misclassified as not severely deficient. The other 11 patients had ADAMTS13 activities of 24 to 100%.

Race-ethnicity

Among all 281 patients, the race-ethnicity distribution was 203 (72%) white, 58 (21%) black, and 20 (7%) other race-ethnicities. Among the 20 patients with other race-ethnicities, there were 11 Native Americans, four Hispanic nonblacks, and three Asians, and two patients were biracial (one black/Native American, one black/white). Among the 65 patients with severe ADAMTS13 deficiency, the race-ethnicity distribution was 39 (60%) white, 23 (35%) black, and three (5%) Native Americans. The racial-ethnic distribution was different between patients with (60% white, 35% black, 5% other race-ethnicity) and without severe ADAMTS13 deficiency (76% white, 16% black, 8% other race-ethnicity; $p = 0.003$).

ANC

The median ANC level among all 192 patients who had ANC measurements was 8774×10^6/L. ANC levels were not different between patients with and without severe ADAMTS13 deficiency ($p = 0.390$).

Frequency of severe ADAMTS13 deficiency among all 281 patients with TTP related to blood group, race-ethnicity, sex, and age

Surprisingly, the frequency of blood group O among the 65 patients with severe ADAMTS13 deficiency (60.0%) was significantly greater than the expected frequency (47.4%, $p = 0.042$) (Table 1). Among the 216 patients without severe ADAMTS13 deficiency, the frequency of blood group O (44.9%) was not different from the expected frequency (46.5%, $p = 0.639$). Among all 281 patients, the frequency of blood group O was significantly greater among patients with severe ADAMTS13 deficiency (60.0%) than among patients without severe ADAMTS13 deficiency (44.9%, $p = 0.033$).

Blacks have a higher frequency of blood group O than whites[20] and we have previously documented that black race is a risk factor for TTP associated with severe ADAMTS13 deficiency.[21,22] Therefore, because the data in this study suggested that blood group O may also be a risk

TABLE 1. Frequency of blood group O in 281 patients with TTP, with and without severe ADAMTS13 deficiency

		Blood group O*		
Patients	Number	Observed	Expected	p value
ADAMTS13 < 10%	65	39 (60.0%)	47.4%	0.042
ADAMTS13 ≥ 10%	216	97 (44.9%)	46.5%	0.639
p value		0.033		

* The percentage of patients with blood group O was compared to the expected frequency based on the patients' race-ethnicities.[20]

TABLE 2. Logistic regression models to determine the association of blood group, race-ethnicity, sex, and age with severe ADAMTS13 deficiency (<10% activity) among patients with TTP

	Logistic OR with 95% CIs for presence of ADAMTS13 < 10%	
Patient groups (number)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Blood group		
O (136)	1.84 (1.05-3.24)†	1.87 (1.03-3.40)†
Non-O (145)	1.0	1.0
Race-ethnicity‡		
Black (58)	2.76 (1.47-5.20)†	2.55 (1.29-5.05)†
Other (20)	0.74 (0.21-2.66)	0.82 (0.21-3.18)
White (203)	1.0	1.0
Sex		
Female (192)	2.45 (1.23-4.86)†	2.66 (1.28-5.54)†
Male (89)	1.0	1.0
Age (years)		
<16 (13)	0.8 (0.09-7.19)	1.01 (0.11-9.71)
16-65 (205)	3.75 (1.53-9.17)†	3.14 (1.24-7.95)†
>65 (63)	1.0	1.0

* Each variable was adjusted for the other three variables.
† $p < 0.05$.
‡ Other race-ethnicities were Native American, 11; Hispanic, non-black, 4; Asian, 3; and mixed race, 2 (black/white, black/Native American).

TABLE 3. Predicted probabilities for presence of severe ADAMTS13 deficiency by sex among patients 16 to 64 years with TTP related to blood group and race-ethnicity from a logistic regression model*

	Blood group (%)	
Patient groups (number)†	O	Non-O
Females, 16-64 years old		
Black (33)	57.3	41.8
White (106)	34.5	22.0
Other (6)	30.1	18.8
Males, 16-64 years old		
Black (20)	33.5	21.3
White (33)	16.5	9.6
Other (7)	14.0	8.0

* These probabilities were calculated from the fully adjusted logistic model presented in Table 2. Only 12 of 36 predicted probabilities are presented (probabilities for those <16 years and >65 years are not presented).
† Other race-ethnicities were Native American, 11; Hispanic, non-black, 4; Asian, 3; and mixed race, 2 (black/white, black/Native American).

factor for TTP associated with severe ADAMTS13 deficiency, we investigated the possibility that black race and blood group O may be dependent, interacting variables. We also added the variables of sex and age to the final logistic regression model because these are also risk factors for TTP associated with severe ADAMTS13 deficiency.[21,22] The crude (unadjusted) and adjusted odds ratios (OR) for an association of each of these four variables with TTP associated with severe ADAMTS13 deficiency were significant (Table 2). Interactions among these four variables were not significant. In a preliminary analysis with the 192 (68%) of the 281 patients who had ANC levels measured, ANC levels were included in a logistic regression model together with race-ethnicity, blood group, sex, and age group. ANC levels were not significantly associated with the occurrence of severe ADAMTS13 deficiency and they did not interact or confound the relationship between the other variables in the model with the occurrence of severe ADAMTS13 deficiency. Therefore, ANC was not included in the final multivariable logistic regression model.

Based on the logistic regression model the predicted probability of severe ADAMTS13 deficiency among patients with TTP was greater for patients with blood group O compared to patients with non-O blood groups, for blacks compared to whites, and for females compared to males (Table 3). The predicted probability of severe ADAMTS13 deficiency among black females, 16 to 64 years of age, was 57.3% for those with blood group O and 41.8% for those with non-O blood groups. The predicted probability of severe ADAMTS13 deficiency among black males 16 to 64 years of age was 33.5% for those with blood group O and 21.3% for those with non-O blood groups.

Survival and relapse were not affected by blood group. Among all 281 patients, mortality was not different between patients with blood group O (36 [26%] of 136 died) and patients with non-O blood groups (47 [32%] of 145 died; $p = 0.275$). Among the 65 patients with severe ADAMTS13 deficiency, survival was also not different between patients with blood group O and patients with non-O blood groups: seven [18%] of 39 patients with blood group O and six [23%] of 26 patients with non-O blood groups died during their initial acute episode of TTP ($p = 0.613$). Among the 52 survivors the median number of plasma exchange treatments required to achieve remission was not different among patients with blood group O (17.5 treatments) and patients with non-O blood groups (18.0 treatments; $p = 0.687$). Relapse is essentially restricted to patients with severe ADAMTS13 deficiency.[14] Among the 52 survivors with severe ADAMTS13 deficiency, relapse was not different among patients with blood group O (12 [38%] of 32 patients relapsed) and patients with non-O blood groups (6 [30%] of 20 patients relapsed; $p = 0.580$).

DISCUSSION

Our data document that in patients with TTP associated with severe ADAMTS13 deficiency, the frequency of blood group O was significantly greater than the expected fre-

quency. In patients with TTP who did not have severe ADAMTS13 deficiency, the frequency of blood group O was not different from the expected frequency. These data suggest that blood group O is a risk factor for TTP associated with severe ADAMTS13 deficiency, a result that is opposite to our initial postulate that patients with blood group O would be partially protected from TTP associated with severe ADAMTS13 deficiency. Although the risk for TTP associated with severe ADAMTS13 deficiency was greater among patients with blood group O, the presence of blood group O did not affect the clinical course of patients with TTP. There was no significant increased risk for death among patients with blood group O. There was also no significant increased risk for relapse for patients with blood group O among surviving patients with severe ADAMTS13 deficiency.

There are two possible explanations for why our data are different from the two previous studies that failed to detect a difference between the observed and expected frequency of blood group O in patients with TTP.[1,2] First, the previous studies were retrospective reviews of available data in medical records at the participating hospitals;[1,2] this methodology could have created issues of patient selection. In contrast, our study was based on the prospective analysis of a population-based inception cohort of consecutive patients.[13,14] Second, our observation that the observed frequency of blood group O was greater than the expected frequency was limited to patients with severe ADAMTS13 deficiency. The previous studies may have failed to detect a difference because ADAMTS13 activity was measured in only five of 74 patients[2] and 38 of 76 patients.[1] The inclusion of patients without severe ADAMTS13 deficiency would diminish the opportunity to detect an increased frequency of blood group O in patients with severe ADAMTS13 deficiency.

Previously we have shown with population data that the incidence of TTP associated with severe ADAMTS13 deficiency is greater among blacks than nonblacks.[21,22] Since the frequency of blood group O is increased among blacks compared to nonblacks,[5,20] it was considered that blood group O and black race may be dependent and/or interacting risk factors. Logistic regression analysis demonstrated that blood group O and black race were independently associated with severe ADAMTS13 deficiency among patients with TTP and that there was no significant interaction between these two risk factors. Our data, together with previously published population data for blood group frequencies,[20] demonstrate that the relative frequency of blood group O is increased among patients with TTP associated with severe ADAMTS13 deficiency in all race categories. We have also previously documented that female sex and ages 16 to 65 years are risk factors for TTP associated with severe ADAMTS13 deficiency;[21,22] these risk factors were also determined to be independent of both blood group and race, without significant interactions. We examined the ANC because blacks have lower baseline ANCs than nonblacks[23] and neutrophil proteases may have a disease modifying role in TTP by proteolysis of VWF.[24] However, ANC levels were not associated with risk for TTP associated with severe ADAMTS13 deficiency and did not interact with other variables in the logistic regression model.

Greater frequency of blood group O in patients with TTP and severe ADAMTS13 deficiency suggests that the higher basal levels of normal VWF multimers in patients with non-O blood groups, documented in multiple previous studies,[3-7] may protect against TTP. This interpretation may seem paradoxical, since it may be assumed that higher basal levels of VWF would be associated with greater risk for VWF-mediated thrombosis. However, the pathologic thrombosis in patients with TTP associated with severe ADAMTS13 deficiency may be primarily dependent on newly secreted "ultralarge" multimers of VWF (ULVWF) that result from ADAMTS13 deficiency, rather than "normal" VWF multimers. Non-O patients could have partial protection from ULVWF-mediated thrombosis if higher basal levels of normal-sized VWF could compete with ULVWF for platelet (PLT) binding, reducing the risk for ULVWF-mediated formation of PLT thrombi in the microvasculature. This hypothesis is consistent with previous observations that elevated plasma VWF levels are not a risk factor for the occurrence of the features of TTP in *Adamts13*$^{-/-}$ mice.[25] Further experimental studies are required to determine whether higher basal levels of normal-sized VWF multimers are actually protective against development of TTP associated with severe ADAMTS13 deficiency.

One strength of our study is that we analyzed a population-based inception cohort of consecutive patients over 15 years, without risk of referral or selection bias.[13,14] Another strength of these observations is the measurement of ADAMTS13 activity by two independent methods in a single laboratory. Potential limitations of this study were the possible misclassification of race-ethnicity and the absence of analysis of VWF levels. Another potential limitation was the use of hospital-reported blood groups; AA and BB were not distinguished from AO and BO. The VWF levels of patients with blood group genotypes AO and BO are less than in patients with genotypes AA and BB, but greater than in patients with blood group O.[4] Inclusion of genotype data may allow for more sensitive analysis of the relation between blood groups and the risk for severe ADAMTS13 deficiency among patients with TTP.

In conclusion, our data demonstrate that blood group O is an independent risk factor for TTP associated with severe ADAMTS13 deficiency, suggesting a hypothesis that higher levels of normal VWF multimers may provide partial protection against microvascular thrombosis caused by pathologic ULVWF. These observations provide

a basis for further investigations on the mechanisms of VWF-mediated microvascular thrombosis in patients with TTP.

AUTHORSHIP CONTRIBUTIONS

DRT, DGM, JNG, and SKV analyzed the patient data; JAKH and BL measured the ADAMTS13 activities; and all authors interpreted the data and contributed to writing the manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest with the topic or data of this manuscript. DRT, JAKH, BH, and JNG are consultants for Baxter, Inc., for rADAMTS13 development. DGM and SKV have no conflicts.

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