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Effect of Blood Groups on Clinical Presentations and Treatment Outcomes in Immune Thrombotic Thrombocytopenic Purpura Patients with Severe ADAMTS13 Deficiency: A Multi-Center Experience

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ADAMTS13 · ABO blood group · Thrombotic thrombocytopenic purpura

Abstract

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy caused by accumulation of ultra-large von Willebrand factor (vWF) due to the significantly reduced activity ADAMTS13. Limited studies have been published examining the blood group as an epidemiological factor that can contribute to development of TTP. It has been suggested that due to low vWF levels, the distribution of the "O" blood group among TTP patients may be lower than anticipated compared to the blood group distribution rates in the normal population. The aim of this study was to explore the relationship between blood groups and the clinical outcome of immune TTP (iTTP). ***Methods:*** Thirty patients with iTTP with severe ADAMTS13 deficiency were enrolled. Data collection commenced in January 2011 and was completed by June 2020. It was analyzed whether there was a difference between the blood groups in terms of frequency of iTTP, response to treatment, frequency of relapse, and clinical and laboratory results. ***Results and Conclusions:*** The distribution of group "A" among patients with iTTP was higher than expected. Although not statistically significant, patients with blood group "O" required more TPE for the treatment and relapse rate was statistically higher than other blood groups. Mortality rate in all patients was 6.7%. Although blood group "A" is a risk factor for iTTP, the frequency of relapse is higher in the blood group "O."

Introduction

A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) is a protease that allows the ultra-large von Willebrand factor (ULvWF) to be functional by cleaved in shorter vWF multimers. Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) caused by accumulation of ULvWF with platelets due to the significantly reduced activity ADAMTS13.

The annual incidence of TTP is 3 per million in adulthood and 1 in 10 million in childhood. The typical patient profiles are young, nonpregnant adult women. Children and pregnant women can be rarely affected [1]. Many patients do not have a prominent TTP clinical signs, until microthrombosis-related specific organ damage symptoms occur. So, many clinicians have difficulty diagnosing TMA/TTP at first admission [2, 3].

Immune TTP (iTTP) is characterized by a severe deficiency of ADAMTS13 (typically activity <10%), which caused by immunoglobulin-G-type antibody that inhibits proteolytic activity and/or accelerates the opsonization/

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plasma clearance of the protease. ADAMTS13 is mainly synthesized in hepatic stellate cells and endothelial cells of the liver. The human ADAMTS13 gene is encoded in 29 exons covering about 37 kb in chromosome 9q34. Also, "ABO" blood group genes are encoded in chromosome 9q34.2. Deletion of guanine at position 258 near the N-terminal of the protein creates a frameshift mutation, causing the "O" blood group, an almost completely different protein form. Individuals with the A, B, and AB allele contain glycosyltransferase activities that convert the H antigen to the A or B antigen. It is still uncertain whether the presence of ADAMTS13 and ABO blood group in the same gene region has an effect on the pathophysiology of the disease [4].

The relationship between ABO blood group and plasma vWF levels has been known for a long time [5]. Serum levels of vWF vary according to 30% ABO blood group, and 70% genetic reasons [5]. People with the "O" blood group have been shown to have lower levels of vWF than other blood groups (O < A < B < AB, respectively), as well as for those with A and B blood groups the concentration of vWF from homozygotes (AA or BB) (AO or BO) has been shown to be slightly higher. It was reported that the incidence of von Willebrand disease (vWD) was higher in patients with "O" blood group and 77% of type 1 von Willebrand cases were composed of "O" blood group patients. In this context, it is considered that the frequency of TTP in patients with the "O" blood group should be lower than expected in patients in the "AB" and "B" blood groups [5, 6].

Also, the rate of ADAMTS13 proteolysis of vWF is faster for the "O" blood group compared to other blood groups, and the pathophysiology of this relationship is not fully understood. However, it is thought that different translational modification patterns in the glycosylation regions of N-linked ABO (H) antigen oligosaccharide chains due to ABO blood group cause change in the chemical and 3-dimensional structures of the sugars and the change of steric or electrical charge effects. As a result of these changes, vWF shows a different sensitivity to proteolysis [7].

Our aim is retrospectively to examine the relationship between ABO blood group, PLASMIC score, ADAMTS13 level, the number of applied plasmapheresis, and the treatment response. Our study could provide additional information that could potentially increase the knowledge of the pathophysiology of such rare diseases.

Materials and Methods

Patients

The data of patients diagnosed as iTTP and referred to the three different apheresis centers for total plasma exchange (TPE) between 2011 and 2020 were obtained retrospectively. Thirty patients (10 males, 20 females) over 18 years old were included in the study.

All patients were diagnosed by a hematologist after clinical and laboratory evaluation before TPE. The diagnosis of iTTP was based on laboratory evidence of microangiopathic hemolytic anemia (presence of fragmented erythrocytes on peripheral blood smear), thrombocytopenia. The other clinical features of the disease (i.e., fever, neurological symptoms, acute renal failure) were also evaluated and noted separately for each patient. Only subjects who were categorized as iTTP were included in this study, and subjects with congenital TTP or suspected secondary TMA were excluded. The data were collected retrospectively from patient registration files of the centers where the patients were followed up.

Demographic Data and Laboratory Results

Demographic data such as age, gender, and blood group ABO were recorded. Additionally, laboratory results that included platelet counts, hemoglobin/hematocrit, mean corpuscular volume (MCV), lactate dehydrogenase (LDH), total reticulocyte count, and serum creatinine were also recorded.

To exclude autoimmune hemolytic anemia, direct coombs screening test, to exclude DIC, activated prothrombin time, prothrombin time, and fibrinogen levels were measured from all patients included in the study, but these results were not included in the evaluation. The calculated PLASMIC scores of all patients at the time of admission were noted separately.

TPE Procedure

TPE procedures were performed with Fresenius COM.TEC and Spectra Optia apheresis systems. TPE continued according to the clinical and laboratory response. Response status determined total TPE count, session interval, and length of hospital stay. For this purpose, clinical findings, platelet count, and LDH levels were followed daily. TPE continued daily until the platelet count exceeded 150,000/mm^3 for two consecutive days, and LDH levels decreased to the normal range (<240 U/L). After complete clinical and laboratory recovery, TPE frequency reduced (initially every other day, then 2 days a week) and discontinued. ABO type-specific fresh frozen plasma used as a replacement fluid in all procedures and at least one total plasma volume (1–1.5) of the patient was changed in each procedure.

ADAMTS13 Activity and Antibody

Since TPE treatment was initiated without waiting for the result of ADAMTS13 activity, just before the first TPE started samples were taken into blue cap tubes (3.2% Na citrate) and sent to the reference laboratory in a few hours for ADAMTS13 activity measurement. None of these samples were visibly hemolyzed, or serum bilirubin levels were above 10 mg/dL. ADAMTS13 activity was measured using FRET. ADAMTS13 activity levels were classified as serious (below 10% of normal) or moderately (between 10% and 60%) reduced. The ADAMTS13 antibody was serologically detected in all samples by enzyme-dependent immunosorbent analysis (ELISA not by functional Bethesda-like assay) ≥15 U/mL antibody level was considered as positive. But this technique is unable to determine whether these antibodies are functional inhibitors or not.

Definitions

Treatment response criteria are defined as response: normalization of the platelet count and LDH < 1.5 times ULN with no clinical evidence of new or progressive ischemic organ injury; remission: normal platelet count for 30 days after stopping TPE and anti-vWF therapy, or with attainment of ADAMTS13 remission (partial or complete), whichever occurs first; exacerbation: recur-

rent thrombocytopenia with or without clinical evidence of new or progressive ischemic organ injury within 30 days of stopping TPE or anti-vWF therapy; relapse: after a clinical remission recurrent thrombocytopenia with or without clinical evidence of new ischemic organ injury. A clinical relapse must be confirmed by documentation of severe ADAMTS13 deficiency [8].

Statistical Analysis

Standard incidence rate (SIR) was calculated to compare frequency of blood groups in TTP patients, and in Turkish population, SIR was calculated as the ratio of observed blood group to expected blood group (O/E). After calculating 95% confidence intervals for SIR, "Poisson distribution" was accepted as appropriate and "*p*" values were calculated. In the literature, it has been reported that parametric tests lose their strength in small sample sizes. Nonparametric tests, like permutation tests, are not affected by the assumptions and produce more reliable results in small sample sizes [9].

In the analysis, the permutation test equivalents were used instead of ANOVA, *t* test, or χ^2 tests for binary or multiple comparisons of continuous and categorical variables. In calculations, type 1 error rate alpha 0.05 was accepted. Statistical analyses were performed using R 3.5.0 (R Core Team, 2018) software. Tables were created with Microsoft Excel.

Results

Demographic and Laboratory Data of All TTP Patients

Thirty patients (10 males, 20 females; median age 45 years; range 23–74 years) followed up with diagnosis of iTTP were retrospectively evaluated. PLASMIC score was evaluated for all patients before the diagnosis. Two patients (6.7%) had moderate score [5] and 28 patients (96.6%) had high PLASMIC score (≥6).

Fever (≥38.3°C) was detected in 16 (53.3%) patients. Fourteen patients (46.6%) had thrombocytopenia-related skin findings as petechiae, purpura, ecchymosis, and no life-threatening bleeding were observed in any of the patients. Thus, none of the patients were given platelet transfusions. Neurological symptoms and signs varied from headache and dizziness to ataxia, paresthesia, confusion, and coma, observed in 18 (60%) patients. Although the renal and cardiac system are less affected, it was observed in 7 and 3 patients, respectively. While two of the patients had acute coronary syndrome and arrhythmia observed in 1 patient, acute kidney failure (increase in serum creatinine ≥0.5 mg/dL per day) occurred in 7 patients; however, the creatinine values were below 2 mg/dL and there was no need for hemodialysis.

Only 2 patients (6.7%) died, other patients were alive, the median number of TPE treatment was 20.5, and the median length of hospital stay was 27.5 days. High-dose methyl prednisolone (intravenous methylprednisolone 1,000 mg daily for 3 days) was given in 3 severely affected patients (serious neurological involvement such as stupor or coma), while the other 30 patients were treated with standard dose prednisone (1 mg/kg per day orally).

Table 1. Blood group frequency comparison in iTTP

Blood groups	*n*	Observed (O)	Expected (E)	Standardized incidence ratio	*p* value
O	6	20.00	32.70	0.61	0.99
A	17	56.67	42.80	1.32	**0.03**
B	5	16.67	16.50	1.01	0.58
AB	2	6.67	8.00	0.83	0.80
Rh (+)	26	86.67	89.90	0.96	0.67
Rh (–)	4	13.33	10.10	1.32	0.21

Rituximab (375 mg/m^2 intravenously once a week for four consecutive weeks) was added for totally 13 patients (43.3%), 5 relapsed and 8 exacerbated under TPE treatment. Other therapeutic approaches were recorded much less frequently, and only 1 patient received vincristine treatment before rituximab in 2011. However, upon the lack of response, rituximab was added. The median follow-up period was 42 months.

Comparison of Groups

Distribution of patients according to blood groups and comparison of frequencies according to normal population are shown in Table 1. In our study, the most common blood group detected for iTTP was "A" and it was found statistically more frequently than the frequency in the healthy population. In addition, although the frequency of group "O" was lower, it was not statistically significant.

The results of the laboratory tests and ADAMTS13 activity and antibody levels according to blood groups at the time of admission are presented in Table 2. There was no statistical difference between blood groups in terms of Hb, Hct, MCV, LDH, total and indirect bilirubin, platelet counts, and ADAMTS13 antibody levels at the time of admission. ADAMTS13 activity level was found higher and statistically significant in blood groups "O" and "B." It was considered that ADAMTS13 level was found statistically higher coincidentally before the treatment in "O" and "B" blood groups, compared to the other groups.

When the clinical response rates of TPE therapy were compared according to the blood groups of patients, it was determined that although the blood group "O" was not statistically significant, the number of TPE administered was higher and the frequency of relapse was statistically significant. No statistically significant difference was observed between the blood groups in terms of fever, neurological symptoms, renal involvement frequencies. Cardiac clinical findings were observed in only 3 patients, so statistical evaluation could not be performed (Table 3).

Table 2. Comparison of the laboratory results according the blood groups

Variable median (min-max)	O (*n* = 6)	A (*n* = 17)	B (*n* = 5)	AB (*n* = 2)	Overall (*n* = 30)	*p* value
Hb (13.5–17.5), g/dL	9.2 (7.4–12.8)	8.1 (5.5–11.5)	7.6 (5.3–10.7)	10.0 (8.3–11.8)	8.5 (5.3–12.8)	0.47
Hct (36.6–44), %	28.2 (22.1–35.1)	23.7 (16–32.9)	22.8 (15.5–30.5)	29.4 (25.3–33.6)	24.5 (15.5–35.1)	0.06
MCV (82.9–98), fL	88.7 (88–104)	88 (76.6–95.9)	84.5 (82–129.3)	88.5 (84.9–92)	88 (76.6–129.3)	0.25
LDH (0–247), U/L	1,065 (488–2,587)	1,125 (595–2,226)	745 (311–3,200)	1,367.5 (1,246–1,489)	1,119 (311–3,200)	0.86
PLT (150,000–450,000), /mm^3	11,000 (10,000–20,000)	11,000 (3,000–55,000)	14,000 (9,000–74,000)	11,500 (9,000–14,000)	11,000 (3,000–74,000)	0.09
Total bilirubin (0.3–1.0), mg/dL	2.6 (1.9–2.9)	2.8 (1.2–7.7)	2.7 (1.5–3.3)	4.2 (3.1–5.1)	2.7 (1.2–7.7)	0.43
Indirect bilirubin (0–0.8), mg/dL	2.2 (1.3–2.6)	2.2 (0.4–7.0)	1.9 (1.1–2.2)	3.5 (2.4–4.6)	2.2 (0.4–7.0)	0.40
ADAMTS13 activity (40–130), %	2.6 (0.2–5)	0.2 (0.2–1.9)	2.2 (0.4–7.0)	0.1 (0–0.2)	0.2 (0–7.0)	**0.04**
PLASMIC score	6	6	6	6.5	6	0.46
Creatinine (0.74–1.25), mg/dL	1.1 (0.9–2.1)	1.1 (0.6–5.6)	1 (0.7–1.2)	1 (0.9–1.1)	1.1 (0.7–5.6)	0.60
INR (0.8–1.2)	1.1 (1.0–1.2)	1.0 (0.9–1.6)	0.9 (0.9–1.5)	0.9 (0.8–0.1.0)	1 (0.9–1.6)	0.66
ADAMTS13 antibody (<12), U/mL	58.5 (36.9–90)	51.2 (22.8–90)	71.8 (55–90)	25.2 (50.3–65)	55.5 (22.8–90)	0.30

Table 3. Comparison of the clinical findings and responses according the blood groups

Variable	O (*n* = 6)	A (*n* = 17)	B (*n* = 5)	AB (*n* = 2)	Overall (*n* = 30)	*p* value
Frequency of fever, *n* (%)	3 (50)	11 (64.7)	2 (40)	0	16 (53.3)	0.31
Frequency of neurological symptom, *n* (%)	4 (66.6)	10 (58.8)	4 (80)	0	18 (60.0)	0.26
Count of TPE	24 (13–35)	20 (3–56)	8 (6–22)	30.5 (28–33)	20.5 (3–56)	0.21
Relapse rate, *n* (%)	4 (66.6)	2 (11.7)	1 (20)	0	7 (23.3)	**0.04**
Mortality rate, *n* (%)	0	1 (5.8)	1 (20)	0	2 (6.7)	0.56
Length of hospital stay, day	32 (10–51)	28 (2–62)	21 (11–29)	39.5 (32–47)	27.5 (2–62)	0.30

Discussion

There is a discrepancy between the results of a limited number of studies on the effects of ABO blood group on laboratory results, treatment responses, and clinical outcomes of iTTP patients associated with severe ADAMTS13 deficiency. The aim of our study was revealing whether the blood group really had an impact on the risk of disease and whether it was also a risk factor in determining the response to treatment and the frequency of relapse. vWF expression and clearance vary according to the blood group, and previous studies have shown that the "O" blood group has a lower vWF level than other blood groups [5, 6, 10, 11].

Theoretically, the frequency of "O" blood group observed in patients with TTP is anticipated to be less than the expected frequency. Unlike previous studies, the frequency of blood group "A" was found to be statistically higher in iTTP patients compared to other blood groups first time in our study. In addition, although the frequency of blood group "O" decreased, it was not statistically significant. Interestingly, the number of TPE and duration of hospitalization for the first attack in the "O" blood group is higher than other blood groups, although it is not statistically significant. In addition, the frequency of relapse in these patients was 66.6%, and it was found that the frequency of relapse increased significantly compared to other blood groups. Although the frequency of TTP decreases, we have some assumptions to understand the need for long-term treatment and increased relapse rate in patients in the blood group "O."

Low vWF production may explain the decrease in ULvWF formation and lower iTTP frequency in blood group "O." Higher baseline levels of normal-size vWF observed in "non-O" blood groups may compete with ULvWF multimers for platelet binding, ultimately reducing the risk of vWF-mediated microvascular thrombosis. Due to low production of vWF in the "O" blood group, the competition with ULvWF multimers will decrease, so recurrence rate will increase and longer TPE will be required in patients with "O" blood group.

Our data are concordant and give additional support to the findings of Hussein et al. [12]. They found the distribution of blood group "O" among patients with iTTP was lower than expected and patients with blood group "O" required more sessions to achieve remission than did those with blood group "B." They emphasized the similar mechanism to explain this result. Another study by Tuncer et al. [13] found that patients of blood group "O" showed a trend toward more relapses. However, Behtaj et al. [14] reported the opposite to be this condition and found that among patients with ADAMTS13 deficiency, "non-O" patients required a significantly greater number of TPE compared to blood group "O" patients but no difference

in frequency between blood groups. In other studies, there was no difference between the blood groups in terms of number of TPEs per episode and response to TPE or relapse of the disease in the univariate analyses [13, 15].

In terms of comparison of blood group frequencies, more studies were found to detect no difference between the frequencies of blood groups "O" and non-O [13–20]. The only study reporting that the frequency of TTP increased in blood group "O" was performed by Terrel et al. [18], and they found that 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.

Although hereditary TTP cases were an exclusion criterion in our study, interestingly, it was noteworthy that the 2 patients in our follow-up were blood group "O." The presence of both the genes encoding the blood group and the genes encoding ADAMTS13 on the arm of chromosome 9 at position 34.2 (chromosome 9q34.2) raises the question whether there is a relationship between blood groups and hereditary TTP and ADAMTS13 mutations are affecting the blood groups. Unfortunately, hereditary TTP is very rare, making it difficult to conduct large cohort studies to show this relationship. There is an international registry of patients with hereditary TTP (www.ttpregistry.net). In the article in which the data were published, the relationship between blood group and hereditary TTP was not mentioned [19].

In our study, the demographic data of the patients were similar to the previous studies and the median age was 44 years; it was found more frequently in women (66.7%) [20, 21]. Fever was the most common clinical finding as expected and observed in 53.3% of patients. Although the rate of renal involvement in TTP reported in previous studies ranged between 10 and 76%, we observed in 11.7% of our patients [20, 22, 23]. In addition, neurological involvement was observed in 52.9% of patients ranging from headache to coma. Neurological symptoms are often known to be associated with intravascular microthrombi. It has been stated in some studies that the basal vWF level is high in blood groups other than the "O" group and the frequency of thromboembolism and therefore neurological symptoms are more common. However, contrary to these studies, in our study, no statistically significant difference was found between the blood groups in terms of TTP clinical findings. Cardiovascular involvement, one of the rare clinical findings, was recorded in 11.7% of patients in our registry. Previous reports found 3–40% of TTP cases presenting with cardiac symptoms [24, 25].

No statistically significant difference was found between the blood groups at the time of admission when compared to laboratory findings and PLASMIC score. As our study, Staropoli et al. [15] reported that their results did not show statistically significant differences between group "O" and non-O patients: age, platelet count, and LDH concentration at presentation. Furthermore, we did not find any statistically significant difference between ADAMTS13 antibody levels among the blood groups. According to ADAMTS13 activity level, there was a statistically significant increase in "O" blood group, since only iTTP patients were included and patients' ADAMTS13 activities were generally below 5%. In addition, no statistically significant difference was found in the clinical response to treatment. Although ADAMTS13 measurement was recommended at regular intervals during treatment and remission for early prediction of subclinical disease reactivation and recurrence, this was not possible in our clinical practice because measurements were made at the external reference laboratory [26]. In the routine, one ADAMTS13 measurement was made before plasmapheresis or fresh-frozen plasma replacement to support the diagnosis in patients suspected of iTTP in all three centers.

The main treatment of iTTP is TPE, which has reduced the mortality from 90% to <10% [27]. In patients who cannot start TPE in the early disease period, high-dose plasma infusion may be an alternative treatment for TTP. Since TPE could be started within hours for all patients, no patients needed high-dose plasma infusion. While TPE alone may be sufficient for most idiopathic TTP patients, steroid therapy is added to the treatment by all three centers due to antibody positivity. Despite these treatments, rituximab treatment due to exacerbation and relapse was applied in 43.3% of the cases.

TTP is a disease in which mortality can be prevented with effective plasmapheresis. At our center, relapse rate was similar and 30-day mortality rate was significantly lower than previously published data. In most studies, TTP-related mortality rates due to severe ADAMTS13 deficiency were found above 10% [28–31]; however, as in our study, there are few studies with mortality below 10% with treatment and exacerbation of acute TTP occurred in 26.6% rate [32–34]. In only 2 patients who died despite proper treatment, mortality is thought to be due to the patient's late admission to the hospital for more than 72 h after the appearance of neurological symptoms. As shown in previous studies, delay in starting treatment is associated with treatment failure [28, 31, 35]. In addition, when the patient first admitted to the hospital, she did not have a fever, and the findings of kidney failure and hypertension (systolic 210 mm Hg; diastolic 120 mm Hg) were more prominent. Three-day double total plasma volume TPE and additional intravenous methylprednisolone 1,000 mg daily were administered; however, the patient died on the 4th day of treatment.

Conditions that are limiting our study are as follows: iTTP is an orphan disease, and this limits it from being a large-scale study, although it was a multi-center study. Some of statistical analysis limited depending on the

number of patients. Second, some patients were excluded from the study due to lack of data and ADAMTS13 antigen and activity measurement. This also limited the number of patients.

In conclusion, although blood group "A" appears to be associated with the development of iTTP, the number of TPE required and relapse frequency in blood group "O" was higher than the other groups. In addition, in our study, there was no statistically significant difference between the blood groups in terms of age, fever, and neurological findings, ADAMTS13 antibody levels, and other laboratory parameters.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (Etlik Zubeyde Hanım Educational and Research Hospital [2020/109]).

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Murat Yıldırım and Selim Sayın contributed to the writing of the article, Ahmet Kürşat Güneş and Merih Reis Aras contributed to the collection of patient data, Esra Şafak Yılmaz contributed to the statistical analysis, Murat Albayrak and Gülsüm abstracted, and Meltem Aylı contributed to the determination of the subject and the final evaluation of the article.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (Selim Sayın), upon reasonable request.

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