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Acquired von Willebrand disease in chronic myeloproliferative disorders: a prospective single-center study

Muhammed Aslanboğa[1], Ömer Ekinci[2]*

Abstract

Objective: The rate of acquired von Willebrand disease (aVWD) among myeloproliferative patients is substantial enough to merit serious consideration, as it is thought to play a role in hemorrhage. We aimed to investigate the rate of acquired von Willebrand disease (aVWD) in chronic myeloproliferative disorders (MPD)

Materials and Methods: The present study was conducted prospectively on 70 patients admitted to hematology clinic. Complete blood count, PT, aPTT, vWF:Ag level, vWF:RCoF test, and factor VIII levels were analyzed for all patients. A finding of vWF:RCoF / Ag < 0.7 was accepted as predisposition to aVWD.

Results: Of the patients, 33 (47.1%) were male, 37 (52.8%) were female, and the mean age was 50 ± 16.25. We detected aVWD in 19 (vWF:RCoF / Ag test < 0.7) (28%) of the 70 patients in the study group. Predisposition to aVWF was present in 7 of the 16 patients in the ET group(43.7%), in 4 of the 11 PV patients (36%), and in 8 of the 43 CML patients (18.6%). There was no statistically significant difference in the presence of aVWD between the three disease groups (p: 0.079).

Conclusion: The underlying mechanism of aVWD is still not fully resolved. Myeloproliferative diseases are one of the few diseases that can cause avWS. It should be kept in mind that aVWD may play a role in pathogenesis in people with chronic myeloproliferative disease, especially in cases of hemorrhage occurring in ET and PV patients.

Keywords: Acquired von Willebrand disease, chronic myeloproliferative disorders, hemorrhage

Introduction

Acquired von Willebrand disease (aVWD) is a bleeding diathesis disorder associated with von Willebrand factor (VWF) deficiency or functional failure as a result of underlying disease. These underlying diseases have been found to be primarily monoclonal gammopathies, lymphoproliferative diseases, myeloproliferative diseases, autoimmune disorders, solid tumors, infectious diseases, heart valve diseases, or other unidentifiable conditions (1). People diagnosed with aVWD do not have a family history of the disease and have complaints of bleeding that develops subsequent to other conditions. The type of underlying disease is closely related to the severity of VWF deficiency and the general condition of the patient (2).

Chronic myeloproliferative disorders (CMD) such as polycythemia vera (PV), essential thrombocytosis (ET), and chronic myeloid leukemia (CML) may co-occur with aVWD, although such cases are rare. In aVWD, which develops secondary to chronic myeloproliferative disorders, critical deficiencies in the molecular structure of VWF are seen; this is thought to cause bleeding problems (3). CMDs are characterized by normal factor VIII (FVIII) and VWF antigen (VWF:Ag) levels; however, ristocetin cofactor activity (VWF:RCoF) and collagen binding activity (VWF:CBA) are decreased. The increased cell burden in CMD patients predisposes them to aVWD. In CMD, the normally large multimeric and functional VWF structure is either absorbed by malignant of hyperproliferative cells or undergoes proteolysis. The result is the development of VWF structures separated into small fragments that are less functional in the hemostatic system (4).

CMD is also implicated in a number of developing antibodies as well as increased clearance and proteolysis resulting from degeneration in the VWF structure. In people with aVWD, the structure of VWF in the multimeric structure has been observed to decrease.

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1 YüzüncüYıl University, Faculty of Medicine, Department of Hematology, TR
2 Firat University, Faculty of Medicine, Department of Hematology, TR
*** Corresponding Author:** Ömer Ekinci **E-mail:** dromere@hotmail.com **Phone:** +90 531 792 62 06

These antibodies increase the breakdown of large VWF multimers in circulation or lead to proteolysis by making them more sensitive. This situation is related to VWF production and the reduction in binding of the VWF produced to cells. As a result of this extensive paucity of production, malfunctioning, and proteolysis, aVWD develops (5). This is also encountered in cases of clonal lymphoproliferative and autoimmune diseases (e.g., systemic lupus erythematosus). Although laboratory findings resemble the hereditary type of von Willebrand disease, the absence of bleeding abnormalities in patients' pasts and the lack of a family history support a diagnosis of aVWD (6).

Only a few studies have reported on the association of aVWD with myeloproliferative diseases. In this study, we aimed to identify the presence of acquired von Willebrand disease in patients diagnosed with chronic myeloproliferative disease.

Materials and methods

This single-center study was conducted prospectively at the department of hematology. Patients diagnosed with CMD who agreed to participate were recruited into the study. Informed consent was obtained in writing from all participants. Ethical approval was granted by medical faculty clinical research ethics board (07/03/2017, decision no: 002). The present study was supported by the university scientific research projects department (SRP). Patients diagnosed with bleeding disorders prior to CMD diagnosis were not included in the study. Complete blood count (CBC), prothrombin time (PT), active partial thromboplastin time (aPTT), VWF:Ag level, VWF:RCoF test, and FVIII levels were analyzed for all patients. A finding of VWF:RCoF / Ag < 0.7 was accepted as predisposition to aVWD.

For complete blood count, venous blood was placed in tubes containing ethylenetetraacetic acid and analyzed using an Abbot Cell-Dyn 3700 automated blood count machine. For analysis of VWF:Ag, PT, and aPTT levels, venous blood samples were placed into tubes containing sodium citrate. STA-Compact and STA-R Evolution brand autoanalyzer commercial kits were used to test VWF:Ag and FVIII levels. PT and aPTT levels were analyzed using the Dade Behring BCS XP system. Ristocetin cofactor levels were tested using the ELISA method and the Helena AggRAM analyzer.

Statistical Method: Descriptive statistics for continuous variables in the study were expressed as mean, standard deviation, minimum, and maximum values, while categorical variables were expressed as number and percentage. One-way analysis of variance (ANOVA) was performed to compare group averages in terms of continuous variables. Following analysis of variance, the Duncan test was used to identify the different groups. Pearson correlation coefficients were calculated separately for the groups in determining the relationship between these variables. The Chi-square test was conducted to determine the relationship between groups and categorical variables. A p value lower than 0,05 was accepted as statistically significant, and the SPSS statistical package program (version 20.0) was used for the calculations.

Results

The median age of all 70 patients studied was 51.18 ± 16.47. Of the patients, 33 (47.2%) were male (mean age 50.67 ± 15.13) and 37 (52.8%) were female (mean age 49.56 ± 17.31). Sixteen (22.8%) of the patients had a diagnosis of ET, 11 (15.8%) had PV, and 43 (61.4%) had CML. No significant difference in age with respect to the type of diagnosis was found (p: 0.082). There was no statistically significant difference in age between the sexes when mean ages of all patients were compared on the basis of gender (p: 0.79) (Table I). In terms of gender distribution, no statistically significant difference between the overall disease groups was observed (p = .498) except PV group that number of female patients were higher (p: 0.009). In the present study, predisposition to aVWD was found in 7/16 (43.7%) of the ET patients, in 4/11 of the PV patients (36.3%), and in 8/43 of the patients with CML (18.6%). There was no statistically significant difference between the three disease groups with regard to the presence of aVWD (p: 0.079). The distribution of the red blood cell numbers(RBCs), hemoglobin levels, platelets numbers, mean corpuscular volume (MCV), and hematocrit values in the patients hemogram samples were evaluated for all three disease groups (PV, ET, and CML). RBCs were significantly higher in PV patients than in ET and CML patients (p: 0.01). Hemoglobin values were significantly higher in PV patients compared with CML patients (p: 0.004). The difference in hematocrit levels between the three disease groups was also significant; the highest hematocrit value was found in PV and the lowest value was observed in CML patients (p: 0.001). Platelets values were higher in ET patients than in PV and CML (p: 0.001), significantly. Similar MCV values were obtained for all three groups (p: 0.320).

Values for VWF:Ag, VWF:RCoF, RCoF/VWF (ratio), aPTT and FVIII (%), are showed in Table II. The VWF:RcoF was significantly lower in ET and PV than in CML patients (p: 0.009). Values for aPTT were significantly higher in the ET and PV groups compared with CML (p: 0.001). For other values, no significant difference between the disease groups was found (p< 0.05). Correlation relationship between VWF:Ag, aPTT, FVIII (%), RCoF, RCoF/VWF ratio measurements and hemogram parameters values are shown in Table III. There was a statistically significant negative correlation between platelets levels and RCoF measurements (p< 0.01). There was a significant positive correlation between VWF:Ag and FVIII (%) (p< 0.001), and a significant negative correlation was found between VWF:Ag and RCoF/VWF (p< 0.01). The negative correlation between the RCoF/VWF:Ag ratio and FVIII was statistically significant (p< 0.05). A significant negative correlation was observed between FVIII and RBCs, aPTT, and RCoF/VWF:Ag measurements, the positive correlation between FVIII and VWF:Ag was significant (p: 0.01). There was no significant correlation between FVIII and hemoglobin, hematocrit, platelets, and RCoF measurements (p> 0.05).

Table 1. Patients characteristics and distribution of disease subtype to gender and age

Parameters	Number of patients, (%)	Mean Age ± SD	Range	*P* value
CMD patients, n	70	50.18 ± 16.47	23 - 86	0.082
ET	16 (22.8)	53.19 ± 17.40	23 - 77	
PV	11 (15.8)	58.45 ± 8.75	24 - 86	
CML	43 (61.4)	47.07 ± 16.63	40 - 68	
Gender				0.79
Male	33 (47.2)	50.67 ± 15.13	23 - 86	
Female	37 (52.8)	49.56 ± 17.31	26 - 86	

CMD: Chronic Myeloproliferative Disorders, PV: Polycythemia Vera, ET: Essential Thrombocytosis, CML: Chronic Myeloid Leukemia

Table 2. Analysis of VWF:Ag, VWF:RCoF, RCoF/VWF, aPTT, FVIII (%) values by disease group

Parameters	Mean	St. Dev.	Min- Max.	p value
Von Willebrand Ag (%)				0.57
ET	116.06	71.767	31 - 328	
PV	123.00	58.346	47 - 253	
CML	116.06	49.377	20 - 258	
FVIII (%)				0.76
ET	80.75	55.213	15 - 254	
PV	70.36	43.470	4 - 156	
CML	81.49	41.838	27 - 242	
Von Willebrand ristocetin cofactor (%)				**0.009**
ET	78.90a*	35.01	33 - 177	
PV	72.54a*	23.05	46 - 126	
CML	102.30b*	35.27	44 - 232	
Ristocetin cofactor / von Willebrand Ag (%)				0.078
ET	0.808	0.401	0.32 - 1.99	
PV	0.729	0.448	0.27 - 1.86	
CML	1.313	1.160	0.33 - 6.26	
Activated partial thromboplastin time (s)				**0.001**
ET	34.44a*	4.052	25.9 - 40.3	
PV	33.49a*	2.767	29.9 - 38.8	
CML	30.37b*	1.850	26.4 - 33.8	

PV: Polycythemia Vera, ET: Essential Thrombocytosis, CML: Chronic Myeloid Leukemia ***There is a significant difference between patient groups with different letters, but no significant difference between groups assigned the same letter.***

Table 3. Correlation relationship between VWF:Ag, aPTT, FVIII (%), RCoF, RCoF/VWF ratio measurements and hemogram parameters

Parameters	r
Platelets - aPTT	0.427**
Platelets - VWF:Ag	0.015
Platelets - FVIII	-0.062
Platelets - RCoF	-0.383**
Platelets - RCoF/VWF:Ag	-0.210
VWF:Ag - aPTT	-0.13
VWF:Ag - FVIII	0.630**
VWF:Ag - RCoF	0.154
VWF:Ag - RCoF/VWF:Ag	-0.549**
RCoF/VWF:Ag - WBCs	-0.15
RCoF/VWF:Ag - RBCs	-0.16
RCoF/VWF:Ag - hemoglobin	-0.15
RCoF/VWF:Ag - hematocrit	-0.19
RCoF/VWF:Ag - aPTT	-0.072
RCoF/VWF:Ag - FVIII	-0.243*
FVIII - WBCs	-0.15
FVIII - RBCs	-0.243*
FVIII - aPTT	-0.374**
FVIII - RCoF	0.161

**: $p < .01$, *: $p < .05$, *r: correlation coefficient*

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Discussion

The von Willebrand factor is a factor in the construction of large multimeric glycoproteins, which have two important functions in the hemostatic process. The first of these is to function as a bridge for thrombocyte adhesion in places where there is vascular damage, while the second is to support thrombocyte aggregation. At the same time, VWF also contributes to hemostasis by transporting FVIII in the circulation and prolonging its half-life (7). Acquired von Willebrand disease is a bleeding diathesis caused by a deficiency of VWF or functional impairment due to disease. Although rare, aVWD may be associated with PV, ET, and CML. The most common subtype of aVWD in myeloproliferative disorders is ET (8). Tests for routine VWF deficiency should be performed in such cases. These tests are VWF:Ag, VWF activity, VWF:RCoF, multimer analysis, and collagen binding activity tests (9). In the present study, patients were evaluated by comparing the ratios calculated from VWF:Ag and VWF: RcoF test values and other parameters.

The VWF multimers test is considered the gold standard for diagnosing aVWD. When VWF:RCoF/Ag or VWF:CB/Ag values are at normal levels, the quality of this test as an indicator is enhanced. Under normal conditions, VWF:RCoF and VWF:Ag are in proportion; in this case their ratios are generally accepted as "1". However, change in the multimeric structure results in a decrease to levels below 0.6 or 0.7 due to inhibitors that could not be completely immobilized, thus leading to aVWD (5). Castaman et al. conducted a study of 10 PV, 11 ET, and 8 CML patients. For PV patients they reported the following mean values: platelets were 568×103/μL, VWF:Ag was 167%, VWF:RCoF was 103%, and a VWF: RcoF/Ag ratio was of 0.66. The mean platelet for ET patients were 997×103/μL, VWF:Ag was 138%, VWF:RcoF was 85%, and the VWF:RcoF/Ag ratio was 0.61 (10). Their findings for CML patients were a mean platelets of 334×103/μL, VWF:Ag 248%, VWF:RcoF 157%, and the VWF:RcoF/Ag ratio was 0.64 (10). In our study, for patients diagnosed with PV (11 cases), the mean platelets were 337×103/μL, VWF:Ag was 110%, VWF:RCoF was 72%, and VWF:RcoF/Ag was 0.77. The mean platelets for our patients with ET (16 cases) were 572×103/μL, VWF:Ag was 116%, VWF:RCoF was 78%, and the VWF:RcoF/Ag ratio was 0.80, while those values for patients with CML (43 cases) were 222×103/μL, 104%, 102%, and 1.31, respectively.

According to our findings, an increase in platelet counts showed a significant negative correlation with VWF:RCoF levels ($p< 0.01$). The VWF:RcoF/Ag ratios were 0.77 and 0.80 for the PV and ET patient groups, respectively. Although not to a statistically significant extent, the ratios were found to negatively correlate with the platelets and RBCs parameters. These findings are similar to those of Castaman et al. (10), Franchini et al. (11), Fabris et al. (12), and Tatewaki et al. (13). In their study of 142 PV patients, Mital et al. determined that VWF:RcoF/Ag ratios supported a diagnosis of aVWD in 17 (12%) patients (VWF:RcoF/Ag ratio < 0.7) (3).

In the present study we found that 4 of the 11 PV patients (36%) had VWF:RcoF/Ag ratios suggesting aVWD. According to a study by Mital et al., of 160 ET patients (mean platelets 700×103/μL), 32 patients (20%) had a mean VWF:RcoF/Ag ratio of 0.62 (4). In patients with low VWF:RcoF/Ag, FVIII levels were found to be considerably lower than normal ($p< 0.01$) (4). In the present study, the mean VWF:RcoF/Ag ratio was 0.52 in 7 out of 16 (43%) ET patients (mean platelets 781×103/μL). Seven patients with low VWF:RcoF/Ag in our study were also found to have significantly lower FVIII levels than normal ($p< 0.05$).

In our literature search on CML, we found case studies but not any studies consisting of large patient groups. Of the 43 CML patients in our study, 8 (18.6%) had a VWF:RcoF/Ag ratio of less than 0.7 (mean: 0.48). For those 8 patients, the mean platelets were 237×103/μL, RBCs were 4.69×106/μL, and WBCs were 6.81×103/μL. The reason that these values were normal, however, because those patients were being treated with drugs. In spite of their normal hemogram values, the fact that a VWF:RcoF/Ag ratio < 0.7 was detected in 18.6% of this patient group suggests that not only the number of cells but also different mechanisms had an effect on the current condition of the CML patients. We believe that the details of these mechanisms could be revealed by further studies incorporating greater numbers of patients and more advanced tests.

Acquired von Willebrand disease is frequently reported in ET patient groups (5-30%) (14). In our study, aVWD (defined as VWF:RCoF/Ag < 0.7) frequency was 43% in the ET patient. The fact that similar results have been reported in other studies indicates that newly developing aVWD should be considered in ET patients with complaints of bleeding, except in disorders of plateletes function or drug-induced diseases. ADAMTS13 activity has been shown to increase the clearing of von Willebrand multimers proportional to the increase in platelets count, especially in ET patients (15, 16).

Although the situation in PV patients is not as clear as that in ET patients, the pathophysiology is thought to be similar to that of ET, and includes multimer deficiencies, absorption by over-produced cells, and specific and non-specific antibody systems. The possibility of aVWD as the underlying pathology should be considered, although it is less common in bleeding cases in PV patients than in cases of ET.

As a result of our findings, we determined the presence of aVWD based on low VWF:RCoF/Ag ratios in patients with CMD. However, we should note the weaknesses of the present study. The first is the fact that due to the inability to analyze VWF:CB at the medical center where we conducted our study, the VWF:CB/vWF:Ag ratio could not be checked; this test provides confirmation of the VWF:RCoF/Ag test, thus eliminating the margin of error. The second weakness is that the VWF multimer structure could not be analyzed. This test, by identifying a reduction in the multimeric structure, represents the gold standard for aVWD diagnosis, as it may help to confirm aVWD even in cases where the VWF:RCoF/Ag ratio is normal (> 0.7).

Conclusion

This study aimed to determine the presence of von Willebrand disease in patients with chronic myeloproliferative diseases. Acquired von Willebrand disease (VWF:RcoF/Ag < 0.7) was detected in 19 (28%) of the 70 patients in the study group. A value of 0.7 or greater indicating a normal VWF:RcoF/Ag ratio was in accordance with the literature. Eight of the 43 CML patients (18.6%) in the present study were diagnosed with aVWD, but due to insufficient data on this patient group in the literature, no comparisons could be made with our findings. In light of our study, in CML, aVWD may also develop by means of a mechanism similar to other chronic myeloproliferative diseases. We believe that this pathogenesis can be better elucidated through further studies with more patients. Underlying acquired von Willebrand disease should be considered in cases of acquired bleeding occurring in patients with chronic myeloproliferative disorders.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits.

Author's Contributions: Aslanboga M and **Ekinci O**, analyzes and interpretation of the data, preparation of the manuscript, application of the statistical analyses.

Consent: Written informed consent form was obtained from the patients who participated in this study.

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