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Acquired von Willebrand factor abnormalities in myeloproliferative disorders and other hematologic diseases: a retrospective analysis by a single institution

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Background and Objectives. Acquired von Willebrand syndrome (AVWS) is a rare acquired disorder. In most cases it is associated with lymphoproliferative disorders and monoclonal gammopathies, while less frequently myeloproliferative disorders (MPD) are involved. Although bleeding is the most important symptom, thrombotic complications have also been observed in cases associated with MPD. Our aim was to review the clinical and laboratory findings in AVWS patients from a single institution.

Design and Methods. The records of 99 patients with AVWS were reviewed to identify the underlying diseases, the symptoms and the laboratory parameters.

Results. In 75% of cases the AVWS was associated with MPD. The most frequent pattern was type 2 (67.7%). Abnormalities of bleeding time, factor VIII levels or platelet retention to glass beads were observed in 83.8% of cases. Bleeding was present in 38.4% of patients, more frequently in the not-MPD-associated (58.3%) vs. MPD-associated cases (32%) (p=0.022), with a significant predominance in females, irrespective of the underlying disease (p=0.0007). In 32% of patients with MPD, thrombotic manifestations, mostly microvascular and arterial episodes, were observed.

Interpretation and Conclusions. AVWS in MPD seems to be mainly a laboratory diagnosis, without clinical symptoms in most cases, although bleeding as well as ischemic events can be present. In contrast, AVWS in not-MPD-associated cases is most frequently associated with severe bleeding symptoms. Performing appropriate laboratory tests may be useful for screening for AVWS.

Key words: von Willebrand factor, acquired abnormalities, myeloproliferative disorders, bleeding, thrombosis

Acquired von Willebrand syndrome (AVWS) is a rare acquired bleeding disorder, with 186 cases having been reported to the International Registry of AVWS.[1] The mechanisms involved remain difficult to characterize, but three main ones have been postulated: 1) the presence of circulating antibodies that inactivate functional domains of von Willebrand factor (VWF) or form a complex with VWF which is rapidly cleared from the circulation,[2-4] 2) selective adsorption of VWF onto abnormal cells,[5] and 3) increased proteolysis of VWF induced by enzymes not clearly identified, although platelet proteases could be involved.[6,7] In myeloproliferative disorders (MPD), an increased platelet count may favor the adsorption of VWF multimers onto the platelet membrane, resulting in their removal from the circulation and subsequent degradation.[7] AVWS has been reported in association with lymphoproliferative disorders, monoclonal gammopathies, kidney neoplasms, autoimmune disorders, myeloproliferative syndromes, several congenital heart diseases, angiodysplasia, hypothyroidism, drugs and other diseases.[1,3,6-19]

In this paper we present a retrospective study of 99 patients with AVWS, mainly associated with MPD, from a single institution. We evaluated the prevalence of different hematologic disorders related to AVWS and the risk factors linked to clinical manifestations.

Design and Methods

Patients

We reviewed the records of 99 patients studied in the Hemostasis and Thrombosis Department between January 1980 and December 2000 who presented acquired VWF abnormalities associated with different hematologic disorders. Details of symptoms (bleeding and/or thrombosis), surgical procedures, referral causes (routine work-up, bleeding, laboratory abnormalities), and family history of bleeding were recorded. The underlying diseases were: MPD-75 patients (polycythemia vera [PV], 29 patients; essential thrombocythemia [ET], 19 patients; chronic myeloid leukemia [CML], 17 patients; myelofibrosis [MF], 6 patients; *unclassified* myeloproliferative disorder [UMPD], 4 patients), myelodysplastic syndrome (MDS)-7 patients, lymphoproliferative disorders-5 patients (chronic lymphocytic leukemia, 2 patients; Waldeström's macroglobulinemia, 2 patients; Hodgkin's disease, 1 patient), Gaucher's disease-5 patients, systemic lupus erythematosus-4 patients, and monoclonal gammopathies-3 patients [1 multiple myeloma and 2 monoclonal gammopathy of uncertain significance (MGUS)]. The diagnosis of CML was confirmed by the Philadelphia chromosome on cytogenetic analysis; PV and ET were diagnosed by criteria described elsewhere.[20] The diagnosis of plasma cell dyscrasias was made by classical criteria.[21-22] The diagnosis of lymphoproliferative disorders was based on clinical, morphologic, histopathologic and immunophenotypic criteria as described in the literature.[23] The MDS were defined by morphologic, histopathologic and cytogenetic analyses.[24] Systemic lupus erythematosus was diagnosed by the American Rheumatism Association criteria.[25] The diagnosis of Gaucher's disease was made according to the revised criteria.[26]

Laboratory studies

The platelet blood count was measured by a Thrombocounter (Coulter Electronics Inc). The bleeding time (BT) was measured by the modified method of Ivy[27] using an automatic template device (Simplate) (normal value [nv] 4-9 minutes). Platelet retention to glass beads was determined using the Hellem II method (28) (nv: 26-70%). Activated partial thromboplastin time (APTT) was measured using home-made rabbit brain cephalin and kaolin.[29] The factor VIII levels (FVIII:C) were assayed applying the one-stage method (nv: 50-150 U/dL).[30] The VWF antigen (VWF:Ag) was measured by the Laurell technique[31] (nv: 50-150 U/dL). The von Willebrand ristocetin cofactor (VWF:RCo) was assayed with formalin-fixed platelets as described elsewhere.[32] The standard pool was periodically calibrated for FVIII:C, VWF:Ag and VWF:RCo against the International Standard from the National Institute for Biological Standards and Control, UK.

Inhibitors of VWF were investigated by incubating 1 volume of pooled normal plasma with 1 volume of patient's plasma for 30 minutes at 37°C.[2] Controls were determined by mixing normal plasma (1 volume) with phosphate-buffered saline (PBS) (1 volume). Patient's and normal plasma were also incubated under the same conditions. The expected values of the mixture were calculated from the values for the patient's plasma and normal plasma incubated and assayed separately

Criteria and classification of AVWS

Patients included for analysis were those with reduced levels of VWF, i.e. decreased VWF:Ag and/or VWF:RCo, with or without bleeding symptoms, but with exclusion of features of congenital VWD.

As in congenital disease, the classification adapted from Sadler[33] was applied to the AVWS: type 1: partial, quantitative deficiency of VWF (VWF:RCo/VWF:Ag ratio ≥ 0.7), type 2: those patients with discordant levels of VWF:RCo and VWF:Ag (ratio < 0.7) and type 3, that is the virtually complete deficiency of VWF.

Statistical analysis

Values are expressed as percentages, means and ranges. Results were compared using the χ^{-2} test or Fisher's exact test, as appropriate. Odds ratios (OR) as estimators of relative risk with their 95 percent confidence interval (CI) were computed by the Mantel-Haenzsel method. Statistical significance was set at p values <0.05. All the analyses were performed with SPSS 10.0 package for Windows and Epi Info, 6.04 version from the Center for Disease Control and Prevention (CDC), Epidemiology Program Office, USA.

Results

Patients' characteristics

AVWS was diagnosed in 99 patients with a mean age of 47.7 years (range 7-84). There were 57 females (57.6%). Patients were referred because of bleeding symptoms in 38.4% (38/99) of the cases and abnormalities in routine hemostasis laboratory tests in 61.6% (61/99) of the cases. AVWS was associated with MPD in 75.7% of cases (75/99), MDS in 7.1%, lymphoproliferative disorders and Gaucher's disease in 5.1% each, SLE in 4% and monoclonal gammopathies in 3% (Table 1).

Table 1. Characteristics of patients and type of AVWS according to underlying disease.

		Underlying disease						
	no.	MPD	MDS	LD	GD	SLE	MG	Total
Female/male	57/42							
Age Mean (range, yrs)	47.7 (7-84)							
Cases (n)		75	7	5	5	4	3	99
AVWS type 1 (n)		20	3	1	3	3	2	32
AVWS type 2 (n)		55	4	4	2	1	1	67

Abbreviations: MPD: myeloproliferative disorder, MDS: myelodysplastic syndrome, LD: lymphoproliferative disorders, GD: Gaucher's disease, SLE: systemic lupus erythematosus, MG: monoclonal gammopathies, AVWS: acquired von Willebrand syndrome.

Table 2. Mean values of laboratory parameters in each type of AVWS.

	FVIII:C U/dL Mean (SD) NV: 50-150	VWF:Ag U/dL Mean (SD) NV: 50-150	VWF:RCo U/dL Mean (SD) NV: 50-150
Type 1	45.5 (21)	34 (15)	39.4 (18)
Type 2	64.5 (35)	105 (52)	33 (11.4)

Abbreviations: FVIII:C: factor VIII, VWF:Ag: von Willebrand antigen, VWF:RCo: ristocetin cofactor, VWF: von Willebrand factor, SD: standard deviation, NV: normal values.

Classification of AVWS

The frequency of type 2 disorder was 67.7% (67/99) and that of type 1 was 32.3% (32/99) (Table 1). There were no differences in sex distribution between types of AVWS. Table 2 shows the mean values of FVIII:C and VWF in each type of disease. The bleeding time was abnormal in 30.5% of patients, platelet retention to glass beads in 67.4% and low FVIII:C levels were found in 50%. Overall, one of these abnormalities was found in 83.8% of patients (83/99).

In the group with type 1 AVWS, five cases had severe VWF deficiency (levels of VWF:Ag and VWF:RCo below 10%). Four of these cases with an inhibitory mechanism were associated with bleeding symptoms. The search for inhibitory activity against FVIII/VWF was carried out in 22/99 (22.2%) cases but inhibitory activity was detected by the mixture tests in only four of them, 2 with lymphoproliferative disorders (1 CLL and WM), 1 with SLE and 1 with monoclonal gammopathy (4/22, 18%). The patient with WM and the other with monoclonal gammopathy were lost from follow-up. The others were hospitalized because of bleeding. Both were treated with plasma FVIII/VWF concentrates. The patient with CLL stopped bleeding after transfusion of cryoprecipitates but he died because of sepsis. The patient with SLE died because of severe digestive tract hemorrhage and lupus nephritis. The fifth patient who presented with a severe type 1 deficiency had ET as the underlying disease. He had digital ischemia without any bleeding complaint.

Table 3. Bleeding symptoms according to the underlying disease.

Underlying disease	Number of patients	%
GD	4/5	80%
MG	2/3	66.7%
MDS	4/7	57.1%
SLE	2/4	50%
LD	2/5	40%
MPD	24/75	32%
Total	38/99	34.4%

Abbreviations: GD: Gaucher's disease, MG: monoclonal gammopathies, MDS: myelodysplastic syndrome, SLE: systemic lupus erythematosus, LD: lymphoproliferative disorders, MPD: myeloproliferative disorder.

Bleeding symptoms

Bleeding manifestations were present in 38/99 (38.4%) patients, with a significant predominance in females irrespective of the underlying disease (n=30/38, p=0.0007; OR 4.72, CI: 1.73-13.73). Symptoms were more frequent in patients with not-MPD-associated diseases: 14/24 (58.3%) vs. 24/75 MPD patients (32%) (p=0.022; OR 2.97, CI: 1.04-8.6). There were no differences in frequency of bleeding among types of AVWS (type 1: 46.9% (15/32), type 2: 34.3% (23/67); p=0.09). The frequency of bleeding complaints by underlying disease and the sites of bleeding are shown in Tables 3 and 4.

Thrombotic symptoms in MPD

There were 24 MPD patients (32%) with thrombotic symptoms. There were no differences in the frequency of symptoms according to sex or type of AVWS. The related diagnoses were: 11 PV, 8 ET, 1 CML, 2 MF and 2 UMPD. PV and ET were associated with a higher risk of thrombosis compared to the other MPD (p=0.05; OR 2.88, CI: 0.83-10.49).

The symptoms were more frequently vasomotor (62%) and transient: distal paresthesias, visual disturbances, Raynaud's phenomenon, dizziness, vertigo and headaches. Other less frequently observed thrombotic events were: myocardial infarction,

Table 4. Sites of bleeding.

Ecchymoses/bruises	21/38	55.3%
Nose/gum bleeding	19/38	50%
After tooth extraction	7/38	18.4%
Low gastrointestinal tract	4/38	10.5%
Post-surgery	3/38	7.9%
Menorrhagia	8/30 women	26.7%

Table 5. Prophylaxis and management of bleeding.

Underlying disease	*Type of bleeding/surgery*	*Age (yrs)*	*PS*	*Basal values of VWF:Ag/RCo*			*DDAVP*	*CRYO*	*Resp.*
CLL	Epistaxis	45	No	60	45	18	Yes	Yes	Good
ET	Hernioplasty	36	Yes	98	162	27	Yes	–	Good
GD	Tonsillectomy	25	Yes	–	–	–	Yes	–	Good
GD	Cesarean section	23	Yes	48	34	45	Yes	–	Good
PV	Gall bladder resection	44	No	28	62	18	Yes	–	Good
SLE	Breast tumor biopsy	17	Yes	8	41	33	Yes	–	Good
UMPD	Anal fistula correction	65	Yes	90	100	46	Yes	–	Good
GD	Splenectomy	16	Yes	8	49	30	–	Yes	Good
PV	Heart valve replacement	65	No	70	36	46	–	Yes	Good
PV	Orthopedic hip surgery	75	No	28	40	44	–	Yes	Good
SLE	Dig. tract hemorrhage	46	Yes	12	10	5	–	Yes	NR

Abbreviations: PS: previous symptoms; DDAVP: desmopressin; CRYO: plasma cryoprecipitates; Resp.: response; CLL: chronic lymphocytic leukemia; ET: essential thrombocythemia; GD: Gaucher's disease: PV: polycythemia vera; SLE: systemic lupus erythematosus; UMPD: unclassified myeloproliferative disorder; NR: no response.

cerebrovascular accidents, digital ischemia and spleen infarction.

Factors related to symptoms in MPD

Patients with symptoms (n=35), i.e. bleeding or thrombosis, were significantly older than asymptomatic ones (n=40), (51 vs. 45.77 years-old, p=0.000).

The mean platelet count was significantly higher in patients with thrombosis (n=11) (1,935×10^9/L, p=0.005) or hemorrhage (n=11) (2,466×10^9/L, p=0.000) than in asymptomatic patients (1,096×10^9/L). There was no difference in FVIII:C, VWF:Ag levels or VWF:RCo levels between different categories of patients.

Treatment

The patients' characteristics, indications for treatment and type of treatment are detailed in Table 5. Transfusion therapy was selected because of advanced age and coronary risk factors (2 patients), presence of inhibitor to VWF (2 patients) or severe VWF deficiency (1 patient). In one patient the transfusion was combined with desmopressin (DDAVP) to improve the response. DDAVP was given without any adverse events, and indeed one patient with Gaucher's disease safely delivered two children. In a 65-year old patient the response to DDAVP was evaluated prior to surgery, and after normal myocardial stress perfusion study results. Only one SLE patient did not respond to immunosuppressive therapy and she died despite transfusion treatment.

Outcome

Thirty patients were studied twice or more. The VWF abnormalities normalized in 9 of them: 7 MPD patients (5 PV, 2 ET) between 1 to 5 years after diagnosis of AVWS, 1 patient with Gaucher's disease following substitutive enzyme treatment and 1 SLE patient who presented a mild deficiency of VWF and whose levels of VWF normalized after 1 year of treatment. VWF levels changed variably in 21 patients but the abnormalities tended to be corrected with adequate therapy: 16 MPD (8 PV, 5 ET, 1 MF, 2 CML), 2 Gaucher's disease patients, who were followed before the enzyme therapy was available and 3 patients with monoclonal gammopathy. The mean follow-up of this group was 3.23 years (range 1-15). In all cases the clinical symptoms were mild and similar to those of congenital VWD.

Discussion

AVWS is a rare acquired bleeding disorder whose clinical and laboratory findings are similar to those of the congenital disease. We report the experience of AVWS at our center over 20 years. Although AVWS has been said to be associated most frequently with monoclonal gammopathies and lymphoproliferative disorders,[1-5,8-9] we found MPD to be the underlying condition in 75% of cases. They presented with a prolonged bleeding time or activated partial thromboplastin time, low levels of FVIII:C or platelet retention that gave rise to an extensive work up for AVWS. This finding highlights the importance of considering the diagnosis of AVWS in certain hematologic diseases, regardless of symptoms. The most common laboratory features were indicative of type 2 AVWS. Although several authors have established a relationship between increased platelet count and a decrease in large VWF multimers,[7,34] we did not find any correlation between platelet count and levels of VWF in MPD (data not shown). Type 1 AVWS was found in 32.3% of cases. Five cases had severe VWF deficiency and four of them, produced by an inhibitory mechanism, had bleeding symptoms. The other case with ET pre-

sented digital ischemia without any bleeding complaint. A mechanism of consumption of VWF related to the ischemic event may be considered.[35] The 18% prevalence of anti-FVIII/VWF inhibitors is similar to that reported in the literature,[1] suggesting either that the techniques available to measure anti-FVIII/VWF are not sensitive enough or that the reduction of factor VIII/VWF in AVWS occurs through other mechanisms (e.g. increased clearance due to immunologic or non-immunologic mechanisms).

The more frequent bleeding complaints were mucocutaneous and post-surgical. There was no difference in age or type of AVWS between the symptomatic/asymptomatic cases. A significant number of non-MPD patients had bleeding symptoms (p=0.022). As in the congenital disease,[36] there was a significantly higher frequency of hemorrhagic symptoms in females (p=0.0007). There was no correlation between symptoms and laboratory findings, except for MPD.

The MPD are a group of diseases characterized by a chronic clinical course, in many cases complicated by thrombotic or hemorrhagic events, even in the same patient.[34] Although older age had been described as a risk factor for thrombosis,[37] we found that it was also significantly related to hemorrhage. All thrombotic events in our cases were arterial, microvascular, non-embolic and transitory. Although to date no firm correlation has been made linking the development of vascular or hemorrhagic complications to laboratory findings in MPD,[37] the proliferative activity of ET, expressed by higher platelet counts, has been associated with thrombotic diatheses.[38-39] In MPD only a significant higher platelet count was seen in patients with thrombosis or hemorrhage. VWF abnormalities have been described by some authors in patients with MPD and thrombosis[35,40-41] but not included as part of an AVWS. Van Genderen *et al.*[35] proposed that changes in VWF levels could have been involved in the occurrence of thrombotic and bleeding complications in six cases of ET. The high prevalence and the heterogeneity of manifestations of AVWS in MPD suggest that screening for VWF abnormalities could be useful not only prior to surgical procedures but also as a thrombotic risk marker. In those cases with thrombosis, evaluation of AVWS could influence therapy and favor prompt control of MPD, and perhaps the use of small doses of aspirin, too.[42] A prospective study could help to define the complete spectrum of AVWS manifestations associated with MPD.

Several regimens of treatment have been used in AVWS,[5,8-9,43-47] most on a empirical basis. DDAVP may be useful, although its effect is transient. The advanced age of patients should be considered before using it and coronary disease should be ruled out. Severe cases and those with an inhibitor mechanism usually require FVIII/VWF concentrates and/or immunoglobulin infusions to correct the defective VWF. The primary disease must, of course, also be treated.

Our evaluation demonstrates two main groups of patients with AVWS. Those with an immunologic pathogenesis usually have severe bleeding symptoms and require aggressive tratment. The other group, composed mainly of patients with MPD, has minor bleeding and occasional ischemic events; therapy is generally required for surgical procedures.

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AS-L: responsible for patients, collection of clinical and laboratory data, statistical analysis and interpretation of data and preparation of the manuscript; SSM: responsible for patients' referral to our Department and contribution to the revision of the manuscript; AIW: laboratory tests and contribution to the data analysis and revision of the manuscript; ANB: laboratory tests and contribution to the data analysis and revision of the manuscript; ACK: laboratory tests and contribution to the data analysis and revision of the manuscript; PC: responsible for patients' referral to our Center and contribution to the data analysis and revision of the manuscript; MJS: laboratory tests and contribution to the data analysis and revision of the manuscript; MAL: contribution to the conception, design and interpretation of study and revision of the final version of the manuscript.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Vicente Vicente, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Professor Vicente and the Editors. Manuscript received October 9, 2001; accepted January 3, 2002.

What is already known on this topic

Acquired von Willebrand's syndrome (AvWS) has been associated with several blood disorders.

What this study adds

This study confirms that AvWS is frequently related with myeloproliferative syndromes (MPS), however the bleeding manifestations were not relevant.

Potential implications for clinical practice

In contrast with other blood disorders the AvWS in MPS seems to be mainly a laboratory diagnosis without clinical symptoms.

Vicente Vicente, Deputy Editor