

Acquired von Willebrand syndrome 2004: International Registry

Diagnosis and management from online to bedside

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Keywords

Acquired von Willebrand syndrome, von Willebrand factor, lymphoproliferative disorders, myeloproliferative disorders, solid tumours

Summary

The acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder with laboratory findings similar to those for congenital von Willebrand disease. Unlike the congenital form, AVWS usually occurs in individuals with no personal or family history of bleeding. Large studies on AVWS are not available, diagnosis remains difficult and treatment empirical. Acquired von Willebrand syndrome is especially frequent in lympho- or myeloproliferative disorders. It is associated with solid tumours, immunological and cardiovascular disorders as well as other miscellaneous conditions. Diagnosis of AVWS is based on assays measuring ristocetin cofactor activity or collagen binding, which are usually abnormally low, while factor VIII coagulant activity is sometimes within the reference range. FVIII/VWF inhibiting activities are found in only a minority of cases. Bleeding episodes in patients with AVWS are mostly of the mucocutaneous type and can be managed with desmopressin, plasma-derived factor VIII/von Willebrand factor (FVIII/VWF) concentrates and intravenous immunoglobulin. Recombinant activated factor VII can be useful in cases unresponsive to standard therapy. In conclusion, the AVWS, although rare, is certainly underestimated in clinical practice: The actual clinical impact of AVWS should be evaluated by prospective studies. The authors are co-ordinating an updated version of the International Registry on AVWS that will allow data to be entered directly online.

Schlüsselwörter

Erworbenes von-Willebrand-Syndrom, von-Willebrand-Faktor, lymphoproliferative Erkrankungen, myeloproliferative Erkrankungen, solide Tumoren

Zusammenfassung

Das erworbene von-Willebrand-Syndrom (VWS) ist eine seltene Erkrankung, die sich laboranalytisch nicht vom angeborenen VWS unterscheiden lässt. Eindeutig different von der angeborenen Form sind das meist deutlich spätere Manifestationsalter sowie die negative Familienanamnese. Größere Studien, die sich mit allen Formen des erworbenen VWS befassen, sind nicht publiziert, die Diagnose ist oftmals schwierig und die Behandlungsmodalitäten sind mehr oder weniger empirisch aufgrund der unbefriedigenden Datenlage. Die Literatur und eine weltweite Umfrage finden die meisten Fälle bei Patienten mit lympho- und myeloproliferativen Erkrankungen. Daneben tritt es noch bei soliden Tumoren und immunologischen Erkrankungen auf, häufiger bei kardiovaskulären Erkrankungen und assoziiert mit einer Reihe anderer, untereinander nicht verwandter klinischer Situationen. Diagnostisch sind erniedrigte funktionelle Parameter des von-Willebrand-Faktors (VWF:RCo und VWF:CB) wegweisend, nicht selten mit normalem oder wenig erniedrigtem VWF:Ag. Häufig liegt die FVIII-Aktivität im Referenzbereich. Die Suche nach Antikörpern gegen den von-Willebrand-Faktor (VWF) ist selten erfolgreich. Die Blutungssymptome ähneln denen von Patienten mit angeborenem VWS. Sie können erfolgreich mit Desmopressin, FVIII/VWF-Konzentraten oder intravenösen Immunglobulinen therapiert werden. Ist hiermit die Situation nicht beherrschbar, bleibt aktivierter rekombinanter FVII. Derzeit ist davon auszugehen, dass das erworbene VWS zwar selten, jedoch eindeutig unterdiagnostiziert ist. Daher sind weitere prospektive Studien notwendig, die sich mit den klinischen Folgen des erworbenen VWS befassen. Die Autoren werden Anfang 2004 eine aktualisierte Fassung des International Registry on AVWS auflegen, das eine direkte Online-Eingabe neu entdeckter Fälle ermöglichen soll.

Erworbenes von-Willebrand-Syndrom 2004:
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The acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder similar to inherited von Willebrand disease in terms of laboratory findings and clinical severity, being characterized by a prolonged bleeding time (BT) and variably low plasma levels of factor VIII von Willebrand factor (FVIII/VWF) measurements. The syndrome usually occurs in individuals with no personal or family history of bleeding. Since the original description in 1968 of a patient with systemic lupus erythematosus (50), about 300 cases of AVWS have been reported. Several review articles have been published in the preceding ten years (3, 18, 20, 26, 35, 39, 47, 54, 57, 59) and the data in an international registry on AVWS are also available (17). Six categories of underlying disorders have been reported to be frequent in both an international registry and recent reviews (3, 17, 18, 20, 35, 39, 54, 59):

- lymphoproliferative disorders,
- myeloproliferative disorders,
- solid tumours,
- immunological disorders,
- cardiovascular disorders,
- miscellaneous.

Lympho- and myeloproliferative disorders appear most frequently (about 50 and 60% in both the literature and the registry).

Pathophysiology

VWF is synthesized normally in most patients (17, 31), except for those with hypothyroidism, who are characterized by de-

creased VWF synthesis or release (3, 17, 18, 20, 31, 35, 39, 54, 59). When VWF is synthesized normally, the low levels are due to accelerated removal from plasma by five possible pathogenetic mechanisms:

- specific auto-antibodies that inactivate VWF,
- nonspecific antibodies that form circulating immune complexes with VWF and are cleared by Fc-bearing cells,
- absorption of VWF onto malignant cell clones,
- increased proteolytic degradation of VWF,
- loss of high VWF multimers under conditions of high shear stress.

However, none of the proposed mechanisms appears to be disease-specific: The same mechanism can be responsible for AVWS in different underlying disorders known to be associated with this syndrome (17).

General diagnosis and management

Diagnosis of AVWS is usually based on the laboratory parameters typical for VWD in the absence of a family history of bleeding. Bleeding time, VWF ristocetin cofactor activity (VWF:RCo) or collagen binding assay (VWF:CB) in plasma compared with VWF antigen (VWF:Ag), ristocetin induced platelet agglutination (RIPA), multimeric analysis in plasma and platelets, and VWF antigen II have been used to identify patients suffering from AVWS (17, 31, 56). Anti-FVIII/VWF antibodies should be always searched for, because the presence of these inhibitors is of clinical significance (36). A diagnostic flow chart to be used in case of excessive bleeding or before surgery in patients with underlying disorders known to be associated with AVWS that has been recommended by the members of the Scientific Standardization Committee on VWF of the International Society of Thrombosis and Haemostasis is shown (17).

There are three goals of treatment of AVWS:

- control current bleeding episodes,
- prevent bleeding when an invasive procedure is necessary,
- remove, when possible, the underlying disease.

In several disorders associated with AVWS, surgery (1, 7, 13, 16, 40, 42, 46, 49, 60, 61), chemotherapy (6, 15, 38, 55), radiotherapy (27) and discontinuation of the responsible drugs (9, 14) can sometimes control the underlying disease, with resolution of the bleeding diathesis and normalization of the laboratory abnormalities. In patients with AVWS and lymphoma, the prolonged bleeding time and low plasma VWF levels were normalized when remission of lymphoma was obtained after chemotherapy. Later, the lymphoma relapsed together with the features of the AVWS (55).

Unfortunately, in some cases of AVWS, the underlying disorders can not be identified (24, 39). In others, such as the AVWS associated with a monoclonal gammopathy of uncertain significance (MGUS), the underlying disease is usually not treated. Hence the best approach to stop bleeding episodes and/or to prevent bleeding during surgery must be identified (19). A variety of therapeutic approaches have been used for AVWS, including desmopressin, factor VIII/VWF concentrates, high-dose intravenous immunoglobulin (iv:Ig), plasmapheresis, glucocorticosteroids and immunosuppressive drugs (20). Recently, recombinant activated factor VII has been also used in patients with AVWS who were unresponsive to standard therapy (21).

Lymphoproliferative disorders and AVWS

MGUS is the condition most frequently associated with AVWS (3, 17, 18, 35, 59). The first case was described by Ingram et al. in 1971 (25). Acquired VWS is also associated with multiple myeloma (9%), Waldenström macroglobulinaemia (9%), non-Hodgkin's lymphomas (4%), and chronic

lymphocytic leukaemia (3%). There is a single case report of AVWS with acute lymphocytic leukaemia (17). The AVWS associated with lymphoproliferative disorders is slightly more frequent (63%) in adult men (median age 64 years) than women. The majority of patients were alive at the time of enrollment in the registry (55%) suggesting that in these disorders the AVWS may mirror the relatively indolent course of the underlying disorder (17). While AVWS was accompanied by bleeding symptoms in the majority of patients (87%), in the remainder, the syndrome was diagnosed on the basis of laboratory abnormalities found in asymptomatic patients (13%). The main laboratory findings for the patients in the registry are as follows.

- The bleeding time (BT) was often prolonged, with median values of 15 min and a wide range (3-35 min): the slight prolongation of aPTT (expressed as ratios) was consistent with the mildly reduced levels of FVIII:C.
- FVIII:C levels were reduced in many patients but were normal in some.
- VWF antigen was generally reduced with median values of 17 U/dL but a wide range of values was observed (4-80 U/dL).
- Assays for VWF activity, measured either as ristocetin cofactor activity (VWF:RCo) or by collagen binding assay (VWF:CB), appeared to be the most sensitive for the diagnosis of the VWF defect of AVWS, with median values of both assays of 8 U/dL (range 3-45 U/dL).
- The calculated ratios of VWF:RCo or VWF:CB to VWF:Ag were 0.57.

Only 5/186 (3%) patients in the registry were tested for VWF:Ag II, for which a role in the diagnosis of AVWS was proposed (56) all with MGUS: Levels were always within the reference range (median 75, range 60-121) even in the presence of reduced VWF:Ag. Plasma VWF multimers were analyzed in approximately two thirds of the patients and the larger multimers were missing in the majority of cases tested (76%). VWF was measured in platelets only in 12/89 cases (13%) and was within the reference values. The methods most often used

to search for inhibitory activity against FVIII/VWF based upon the measurement of the FVIII/VWF properties in plasma after mixing patient's plasma with normal plasma. This assay was carried out for 80/89 (90%) cases. But inhibitory activity was constated in only a minority of them: 10/89 (11%). The prevalence of anti-FVIII/VWF activities found in the registry is similar to that reported in the literature (38/226, 14%).

Several therapeutic approaches were used for AVWS associated with lymphoproliferative conditions in the registry. Desmopressin (DDAVP) was given to 59/89 patients (66%) and stopped bleeding in 26 (44%) of them by restoring normal levels of FVIII/VWF in plasma. DDAVP is relatively inexpensive and carries no risk of blood borne infections. However, its usefulness in AVWS is limited by the short half-life of endogenous FVIII/VWF that is released. A DDAVP infusion test, with BT and FVIII/VWF measured pre- and post-infusion, is advisable for every new diagnosis of AVWS (19).

FVIII/VWF concentrates were used for 56/89 patients with AVWS (63%) and they were clinically effective in 28 cases (50%). High dose i. v. immunoglobulin (iv:Ig) was tried for 48/89 patients (54%) and proved as effective only for 18 (37%), mainly in MGUS (15/18). It has been proposed that iv:Ig would be more effective in those AVWS cases characterized by the presence of anti-FVIII/VWF activities. Although prospective data are not available, data in the registry show that 13/21 (62%) AVWS patients responsive to iv:Ig had anti-FVIII/VWF activities. Because of the high cost of this treatment, iv:Ig should be reserved for AVWS patients unresponsive to DDAVP and FVIII/VWF concentrates and for cases with anti-FVIII/VWF inhibitors (17).

30/89 patients were treated with plasmapheresis or extracorporeal immunoadsorption and these procedures were effective in 6/30. A total of 31/89 patients were given glucocorticosteroids to treat the AVWS associated with lymphoproliferative disorders and this therapy was effective in 10/31 (32%). In patients who were receiving immunosuppressive agents and chemothera-

py for their lymphoproliferative disorders – 47/89 (53%) were treated in this way – a beneficial on the AVWS was observed in 17/47 (36%) cases.

Recently, recombinant factor VIIa was successfully used in a bleeding patient with AVWS and IgG-MGUS who was unresponsive to treatment with DDAVP, FVIII/VWF concentrates and iv:Ig (21).

Myeloproliferative disorders and AVWS

Since the first description of AVWS in a patient with chronic myelogenous leukaemia (15), several studies have described AVWS in myeloproliferative disorders (MPD) (4, 5, 8, 36, 44, 53, 58). More recently, Mohri et al. reported a prevalence of 11.6% (17/147 AVWS cases) in MPD (36), very similar to the distributions observed in the literature and the registry. The features of the AVWS associated with essential thrombocythaemia (ET) have been extensively evaluated by the work of Budde et al. and Michiels et al. (3-5, 35, 57), who demonstrated that the clinical syndrome and recurrent bleeding are associated with very high platelet counts and that improvement of the platelet count is associated with a decrease in the frequency of bleeding episodes (6, 58).

The associated MPDs in the registry are essential thrombocythaemia (11%), chronic granulocytic leukaemia (3%), myelofibrosis (1%) and polycythaemia vera (1%) (17). Acquired VWS associated with MPD is observed more frequently (65%) in adult women (45 years) than in men. Only 24% of the cases were still in follow-up at the time of enrolment in the registry: Most of them were lost to observation or had died. Only 48% of the patients with AVWS in MPD underwent laboratory investigation because bleeding symptoms. Low VWF:Ag levels were detected only in few cases (mean 70 U/dL), but VWF:RCo or VWF:CB levels were always lower than VWF:Ag so that RCo/Ag or CB/Ag ratios were always <0.7 (mean 0.52). There was an absence of larger multimers in most cases (86%), in agreement with previously re-

ported data showing a significant loss of high molecular weight multimers and increased VWF proteolysis in MPD (4, 36). Anti-FVIII/VWF activities were measured in only a few cases and no inhibitory activity was found.

DDAVP was tested in MPD in 14/29 (48%) and was effective in 3/14 (21%) while FVIII/VWF concentrates were also used in 14/29 (48%) but were effective in only 2/14 (14%) cases. The use of iv:Ig, plasmapheresis and glucocorticoids in MPD were not reported by any of the participants in the registry. Immunosuppressive or chemotherapy was used in 14/29 (48%) and they corrected AVWS abnormalities in 5/14 (36%).

Patients with solid tumours and AVWS

Acquired VWS was first associated with solid tumours in a patient with neuroblastoma or Wilm's tumour (40), after which additional cases were reported (13, 49). Chemotherapy was successful in reducing both tumour mass burden and the features of the AVWS. Removal of the Wilm's tumour was followed by the return of levels of FVIII:C, VWF:Ag and VWF:RCo within the reference ranges in most cases (13, 40, 49).

Other solid tumours associated with AVWS are carcinomas (23) and peripheral neuroectodermal tumours (41). Surgical removal brought remission of the AVWS. Data in the registry showed that 75% of the cases were investigated because of excessive bleeding. Evidence for anti-FVIII/VWF antibodies was found in 22%. Also, high molecular weight multimers were absent. VWF:RCo/Ag, VWF:CB/Ag ratios and FVIII:C levels were low. Besides surgery, all of the therapeutic approaches to reduce bleeding, including DDAVP, factor VIII/VWF concentrates and iv:Ig, were highly effective in these patients.

Immunologic disorders and AVWS

The first description of this association was reported in 1968 in a patient with systemic lupus erythematosus (SLE) (50). Since then, several other cases have been reported, as recently reviewed by Michiels et al. (35). There may be a bias toward disproportionately fewer cases of AVWS reported in association with immunologic disorders in the registry, perhaps because the registry was organized by haematologists and oncologists with few participants coming from immunology or rheumatology clinics (17). The data from the literature and the registry indicate that these disorders affect more women than men. Several cases were asymptomatic, while others had mild and moderate bleeding symptoms. Bleeding times and FVIII:C levels were relatively normal, with decreased levels of VWF:RCo. Multimeric analyses of the VWF in those cases evaluated generally showed a type 2 pattern.

The response to DDAVP was apparently good in one patient of the five tested. The response to FVIII/VWF concentrates was not always determined. In other cases there was a slight recovery and very short half-life. The response to iv-Ig was tested for two cases with AVWS associated with SLE. Only one patient showed a transient correction of FVIII/VWF activities lasting for a few weeks, suggesting that there is an immune-mediated aetiology of AVWS in SLE. Unfortunately, there are no data concerning the relationship between the relative highly percentages of anti-FVIII/VWF antibodies found in this group of patients and the responses to iv-Ig because only a few patients received this treatment.

In the literature treatment with prednisolone (30-40 mg/d or 1-2 mg/kg body weight per day) is reported, which was effective in several cases of AVWS associated with SLE. In a few cases, with adjuvant treatment with single intravenous doses of cyclophosphamide (700 mg/m²), there was complete correction of both FVIII:C and VWF levels to reference values (35).

Besides SLE, other immunologic disorders have been associated with AVWS.

Meyer et al. described patients with AVWS associated with autoimmune disease and found the presence of auto-antibodies against FVIII/VWF (34). A case of AVWS has been reported to be associated with mixed connective tissue disease (62), graft versus host disease (30) and Ehlers-Danlos syndrome (11).

Cardiovascular disorder and AVWS

Gill et al. were the first to describe the loss of large VWF multimers from plasma of patients with congenital cardiac defects (22). Other authors reported similar abnormalities in patients with multiple congenital and cardiac defects (3, 43, 45). Recently, VWS type 2A was described in a study of 50 consecutive patients with aortic stenosis, 42 of whom underwent valve replacement (60). VWF abnormalities were present in most patients and correlated significantly with the severity of valve stenosis. In this situation, the underlying mechanisms of AVWS are related to a high shear rate of flowing blood which induces degradation of large VWF multimers in plasma.

Most of these patients are identified because of excessive bleeding before or during surgery. After surgery, once cardiac defects are corrected, the bleeding symptoms disappear and laboratory parameters normalize. During the AVWS phase, bleeding time may be prolonged, FVIII:C reduced, VWF:RCo or VWF:CB always lower than VWF:Ag with a relative loss of the high molecular weight multimers.

Therapeutic approaches, such as DDAVP, FVIII/VWF concentrates or iv-Ig attempted to stop bleeding tendency are seldom effective. Removal of cardiac defects by cardiac surgery usually correct the typical abnormalities of the AVWS (1, 3). However, in one study, the haemostatic abnormalities tended to recur after six months, especially when there was a mismatch between patient and prosthesis (60).

Miscellaneous disorders

Acquired VWS has been described in association with drugs. These include repeated administration of hydroxyethyl starch (14, 52), valproic acid (29), griseofulvin (12), and ciprofloxacin (10). Furthermore, AVWS has been described with hydatid disease of the spleen. After splenectomy factor VIII/VWF activities normalized (46). Additionally, AVWS was described in association with Epstein-Barr virus infection (28). Infective colitis and sarcoidosis have also been reported in the international registry (17).

Acquired VWS has been described in other systemic diseases including hypothyroidism (48), where some of the patients were asymptomatic while others presented with mild-to-moderate bleeding symptoms. Two such cases have been reported in the registry with factor VIII/VWF activities similar to those of the literature: Anti-FVIII/VWF antibodies were not identified in these two patients, who responded well to DDAVP.

FVIII/VWF abnormalities suggestive of AVWS have also been reported in diabetes mellitus (51), uraemia (32), haemoglobinopathies (2), and teleangiectasia (33). The VWF defects of these conditions were corrected by using DDAVP or FVIII/VWF concentrates.

Several cases of AVWS without any associated conditions or known aetiologies have been reported in the literature (3, 17, 18, 20, 35, 39, 54, 59). The responses to DDAVP and iv-Ig were not tested in six of seven cases. Only one case, with AVWS and the presence of anti-FVIII/VWF antibody, responded poorly to DDAVP and FVIII/VWF concentrates: only iv-Ig were effective to correct the VWF defects.

Conclusions, perspectives

The data from the literature and international registry indicate that AVWS occurs in association with a variety of underlying disorders, most frequently in lymphoproliferative disorders, cardiovascular disease

and myeloproliferative disorders. Acquired VWS is remarkably heterogeneous and its basic mechanisms remain undefined in many cases. Functional assays of VWF in patients' plasma are essential for making a firm diagnosis. While assays for anti-FVIII/VWF activities should be performed to identify patients with inhibitors, these tests usually yield negative results.

Management of bleeding in AVWS relies mainly on DDAVP, FVIII/VWF concentrates and high-dose iv:Ig. But no single drug is effective for all AVWS cases. As bleeding episodes are sometimes life-threatening and require prolonged hospitalization with the infusion of large doses of blood products, the organization of large prospective interinstitutional studies are required. The authors are currently establishing an updated version of the International Registry on AVWS (www.intreavws.com) with the aims

- to promote a direct registration of new cases,
- a better understanding of the basic mechanisms of AVWS by new assays,
- the limits of standard therapies and
- the success or failure of novel and experimental therapeutic approaches.

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