# Acquired von Willebrand Disease

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**Acquired von Willebrand disease (AvWD) is a relatively rare acquired bleeding disorder that usually occurs in elderly patients, in whom its recognition may be delayed. Patients usually present predominantly with mucocutaneous bleeding, with no previous history of bleeding abnormalities and no clinically meaningful family history. Various underlying diseases have been associated with AvWD, most commonly hematoproliferative disorders, including monoclonal gammopathies, lymphoproliferative disorders, and myeloproliferative disorders. The pathogenesis of AvWD remains incompletely understood but includes autoantibodies directed against the von Willebrand factor (vWF), leading to a more rapid clearance from the circulation or interference with its function, adsorption of vWF by tumor cells, and nonimmunologic mechanisms of destruction. Laboratory evaluation usually reveals a pattern of prolonged bleeding time and decreased levels of vWF antigen, ristocetin cofactor activity, and factor VIII coagulant activity consistent with a diagnosis of vWD. Acquired vWD is distinguished from the congenital form by age at presentation, absence of a personal and family history of bleeding disorders, and, often, presence of a hematoproliferative or autoimmune disorder. The severity of the bleeding varies considerably among patients. Therapeutic options include desmopressin and certain factor VIII concentrates that also contain vWF. Successful treatment of the associated illness can reverse the clinical and laboratory manifestations. Intravenous immunoglobulins have also shown some efficacy in the management of AvWD, especially cases associated with monoclonal gammopathies. Awareness of AvWD is essential for diagnosis and appropriate management.**

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**AvWD = acquired von Willebrand disease; GP = glycoprotein; IVIG = intravenous immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance; vWD = von Willebrand disease; vWF = von Willebrand factor**

In contrast to congenital von Willebrand disease (vWD), which has a prevalence of about 1% in the general population,[1] acquired von Willebrand disease (AvWD) is believed to be rare. Since the initial description,[2] fewer than 300 cases of AvWD have been reported,[3] and there are no accurate estimates of its prevalence. This apparent rarity has contributed to the lack of recognition of AvWD in the older patient with unexpected bleeding. We summarize the pathophysiology, laboratory evaluation, and management options for this clinically important bleeding disorder that may be more prevalent than has been appreciated.

## HISTORICAL ASPECTS AND PREVALENCE ESTIMATE

In 1968, Simone et al[2] described the first case of AvWD in a 7-year-old boy with systemic lupus erythematosus. Although Ingram et al[4] in 1971 initially described the association between monoclonal gammopathy and AvWD, Handin et al[5] coined the term *acquired von Willebrand's disease* in their report of a patient with an autoantibody against the von Willebrand factor (vWF) and provided one of the first descriptions of the mechanism of AvWD.

To date, a total of 211 cases of AvWD have been reported to an international registry.[6] Our recent experience suggests that up to 4.5% of patients with a clinical and laboratory diagnosis of vWD may have the acquired form.[7] Based on our experience, the estimated prevalence of AvWD ranges from 0.04% to 0.13% of the general population.

## PATHOPHYSIOLOGY AND ASSOCIATED DISORDERS

The vWF protein circulates in plasma as a spectrum of multimers ranging in size from approximately 800,000 to more than 12,000,000 d.[8] The binding of vWF to nonendothelialized surfaces in the high shear milieu of the microcirculation induces conformational changes in the vWF molecule that make it attractive for platelets that adhere by means of their glycoprotein (GP) Ib-IX receptor complexes, the principal platelet vWF receptor. Therefore, surface-bound vWF induces platelet adhesion and aggregation, leading to formation of a platelet hemostatic plug in regions of disrupted vascular endothelium. The larger, or high-molecular-weight, vWF multimers are hemostatically the most active in this process, and quantitative abnormalities of this form are seen in varying severity with all types of vWD.

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Table 1. **Disease States and Other Factors Associated With Acquired von Willebrand Disease***

| Associated disorder or factor | References |
|---|---|
| Lymphoproliferative disorders | |
| Chronic lymphocytic leukemia | 9-11 |
| Hairy cell leukemia | 12 |
| Non-Hodgkin lymphoma | 13-15 |
| Plasma cell proliferative disorders | |
| MGUS | 4, 16, 17 |
| Waldenström macroglobulinemia | 17, 18 |
| Multiple myeloma | 19-21 |
| Myeloproliferative disorders | |
| Chronic myeloid leukemia | 22-24 |
| Essential thrombocythemia | 25, 26 |
| Polycythemia vera | 27, 28 |
| Neoplastic disorders | |
| Wilms tumor | 29-31 |
| Adrenocortical carcinoma | 32 |
| Lung cancer | 33 |
| Peripheral neuroectodermal tumor | 34 |
| Gastric carcinoma | 19 |
| Acute myeloid leukemia | 35 |
| Acute lymphoblastic leukemia | 35 |
| Autoimmune states | |
| Systemic lupus erythematosus | 2, 36, 37 |
| Scleroderma | 19 |
| Mixed connective tissue disease | 38 |
| Felty syndrome | 39 |
| Autoimmune hemolytic anemia | 40 |
| Endocrine disorders | |
| Hypothyroidism | 17, 41, 42 |
| Diabetes mellitus | 43 |
| Drugs | |
| Ciprofloxacin | 44 |
| Valproic acid | 45 |
| Hydroxyethyl starch | 46, 47 |
| Recombinant factor VIII infusion | 48 |
| Griseofulvin | 49 |
| Others | |
| Embryonal adenoma of kidney | 50 |
| Amyloidosis | 51 |
| Angiodysplasia | 52, 53 |
| Hemoglobin E β-thalassemia | 54 |
| Ehlers-Danlos syndrome | 55 |
| Excessive fibrinolysis | 56 |
| Epstein-Barr virus infection | 57 |
| Allogeneic bone marrow transplant | 58 |
| Hydatid disease | 59 |
| Pesticide ingestion | 60 |
| Reactive thrombocytosis | 61 |
| Glycogen storage disease | 62, 63 |
| Uremia | 64 |
| Mitral valve prolapse | 65 |
| Congenital heart disease | 66, 67 |

*MGUS = monoclonal gammopathy of undetermined significance.

The pathophysiology of AvWD has been defined in a few cases, but its occurrence with benign and malignant hematologic disorders, which has been described extensively, may point to several mechanisms of development of AvWD. The most frequently observed association is with dysproteinemias (Table 1). These range from monoclonal gammopathy of undetermined significance (MGUS), a common scenario,[4,16,27,68] to plasma cell proliferative disorders such as Waldenström macroglobulinemia[17,18,68] and multiple myeloma.[19-21] The presence of a monoclonal protein is not always essential, as seen in certain low-grade lymphoproliferative disorders such as chronic lymphocytic leukemia,[9,10] hairy cell leukemia,[12] and non-Hodgkin lymphoma.[13,14] In fact, of the 211 patients with AvWD in the international registry, 47% had an underlying lymphoproliferative disorder or plasma cell proliferative disorder. However, the occurrence of AvWD in association with myeloproliferative disorders (chronic granulocytic leukemia,[22-24] polycythemia vera,[27,28] essential thrombocythemia[25,69]) and other benign disorders is evidence of a diverse etiopathogenesis. An asymptomatic decrease in the large vWF multimers has been noted in patients with myeloproliferative disorders,[70,71] and this decrease correlates with the platelet count. In addition, isolated case reports have described AvWD associated with acute myeloid and lymphoblastic leukemia.[35]

Approximately 8% of patients (4/50) with Wilms tumor have had coexisting AvWD,[29-31] and there are rare associations with other solid tumors (adrenocortical carcinoma,[32] lung carcinoma,[33] gastric carcinoma,[19] and primitive neuroectodermal tumor[34]).

Although the occurrence of AvWD with benign disorders such as hypothyroidism[17,41] and autoimmune disorders (systemic lupus erythematosus,[2,36,37] scleroderma,[19] and mixed connective tissue disease[38]) could be considered coincidental, the observed resolution of AvWD with thyroid hormone replacement or immunosuppressive therapy, respectively, implies a pathogenetic role.

Drug-induced AvWD has been reported with ciprofloxacin,[44] valproic acid,[45] and griseofulvin.[49] Resolution of AvWD when use of the drug is discontinued suggests a pathogenetic role. Use of hydroxyethyl starch, a plasma expander, has been associated with the development of low levels of vWF, possibly related to nonimmunologic precipitation.[46,47]

Antibodies directed against functional domains of vWF have been identified in patients with AvWD and multiple myeloma,[21,72] Waldenström macroglobulinemia,[18] chronic lymphocytic leukemia,[10] angiodysplasia,[52] polycythemia vera,[28] chronic myeloid leukemia,[23] MGUS,[19,73] antiphospholipid syndrome,[36] postpartum state,[74] and non-Hodgkin lymphoma.[15] The presence of these antibodies was shown through inhibition (with the patient's plasma) of the ristocetin cofactor activity of normal plasma.

Although most of the described inhibitory antibodies recognize the factor VIII:vWF complex, antibodies have

also been reported that bind to vWF alone; they result in normal factor VIII coagulant activity but no measurable vWF activity.[28] Antibodies with more restricted specificity, affecting ristocetin cofactor activity without interfering with platelet aggregation, have also been described.[73] van Genderen et al[15] described a unique IgM antibody directed against the collagen-binding epitopes of vWF, resulting in an isolated defect in collagen-binding activity and a severe bleeding tendency. Although the monoclonal protein in some patients appeared to have specificity against vWF,[75,76] most patients had a demonstrable autoantibody that was distinct from the monoclonal protein. The majority of these patients had a selective decrease in the high-molecular-weight multimers of vWF (type II pattern) and a shortened survival of infused vWF.[10] Most of the identified autoantibodies usually have belonged to the IgG class, although IgM[77] and IgA[9] autoantibodies have also been described.

With antibodies directed against the nonfunctional region of vWF, the mechanism of shortened survival of vWF is likely increased clearance of the antigen-antibody complex despite normal biologic activity of the vWF.[10] Although this mechanism remains to be proved conclusively, the presence of such inhibitors resulted in bleeding in 1 study.[35]

A reduction in the rate of synthesis of vWF has been postulated in patients with hypothyroidism[78] and those given valproate,[45] whereas accelerated proteolysis of the large vWF multimers has been shown with the use of ciprofloxacin[44] and in patients with congenital cardiac[66] and valvular[67] diseases. Increased proteolysis may also play a role in the vWF abnormalities noted in diabetic patients with poor glycemic control,[79] probably because endothelial damage and glycosylation of vWF result in increased susceptibility to proteolysis.[80] Increased proteolysis has also been reported after thrombolytic therapy for acute myocardial infarction.[81]

Nonimmunologic binding and precipitation of vWF antigen have been noted in patients receiving hydroxyethyl starch.[47] Interference with the normal functioning of the factor VIII:vWF complex may be responsible for the AvWD noted with nephroblastoma in children.[29]

Selective adsorption of the vWF antigen by tumor cells on their surface provides another mechanism for depletion of vWF from the circulation. This phenomenon has been shown in patients with non-Hodgkin lymphoma,[14] multiple myeloma,[82] adrenocortical carcinoma,[32] Waldenström macroglobulinemia,[83] and MGUS.[84] Similar adsorption by activated platelets may play a role in the development of this syndrome associated with essential thrombocytosis. Aberrant expression of platelet GPIb on the tumor cell surface[14,84] has been shown, but its molecular basis remains unexplained. In a patient with macroglobulinemia, monomeric IgM expressed on the surface of lymphocytes was responsible for adsorbing vWF.[83] Platelet-associated vWF may be quantitatively and qualitatively normal,[68] and this feature may contribute to the lack of symptoms in some patients.[85] Thus, AvWD is apparently a syndrome of multiple etiologies and diverse pathophysiology, but it has a common clinical presentation (Table 2).

Table 2. **Pathogenetic Mechanisms in Acquired von Willebrand Disease***

| |
|---|
| Specific inhibitory antibodies to vWF function |
| Non-neutralizing autoantibodies to vWF (immune complexes) |
| Adsorption of vWF by malignant cells |
| Increased vWF proteolytic degradation |
| Decreased vWF synthesis |

*vWF = von Willebrand factor.

## DIAGNOSIS

Because of its rarity, AvWD may not be considered in a patient with a bleeding disorder. The best hemostatic screen is the patient's medical history. Thus, a detailed hemostatic history should be obtained to confirm the acquired nature of the bleeding disorder. As in congenital vWD, bleeding symptoms are typically mucocutaneous (epistaxis, gastrointestinal, ecchymosis) or postoperative. Hemorrhage into soft tissue is less common. The identification of a coexisting, potentially pathogenetically linked disorder, such as dysproteinemia, a lymphoproliferative or myeloproliferative disorder, an autoimmune disorder, or hypothyroidism, can provide a diagnostic clue to the presence of AvWD.

Laboratory testing typically includes the bleeding time test, screening tests of coagulation (prothrombin time and activated partial thromboplastin time), and specific tests for vWD (vWF antigen and ristocetin cofactor activity) and factor VIII activity, with reflexive vWF multimer analysis. Although the bleeding time is prolonged in most patients with AvWD, a normal result does not exclude the diagnosis. Conversely, given the lack of sensitivity and specificity of the bleeding time test, a prolonged result does not always imply the presence of AvWD. In the absence of coexisting factors (eg, liver disease or use of warfarin), the prothrombin time is typically normal. The activated partial thromboplastin time is often prolonged, reflecting reduced factor VIII activity that accompanies the deficiency of its carrier vWF molecule. However, a normal result does not exclude AvWD.

The most specific tests for vWD are measurements of plasma vWF antigen and ristocetin cofactor activity. Ristocetin, an antibiotic, facilitates GPIb-mediated platelet binding of vWF and provides a functional assessment of vWF. Although this test lacks the precision of vWF antigen

measurement, it is the single most sensitive and specific test for vWD. The test for vWF antigen is performed by an immunologic method such as enzyme-linked immunosorbent assay. Of note, persons with blood group O have been reported to have 20% to 30% lower levels of vWF antigen and ristocetin cofactor activity compared with those with other blood groups,[86,87] and this finding should be considered in making a diagnosis of AvWD.

Of importance, distinguishing between congenital and acquired vWD with laboratory testing alone is difficult. A clinical hemostatic history is crucial in distinguishing between the 2 disorders. However, measurement of vWF propeptide may be useful in making this distinction.[88,89] von Willebrand factor propeptide, or von Willebrand antigen II, results from endoproteolytic cleavage of vWF in the endothelial cells before its release, has a half-life of 2 hours in the circulation, and is believed to provide a reliable estimate of the rate of vWF synthesis.

Abnormal results of vWF assays should prompt reflexive analysis of the vWF multimers with use of agarose gel electrophoresis. In our coagulation laboratory, we have used Roman numerals (I, II, III) to describe the general pattern of vWF multimers. The pattern most commonly seen is a selective decrease in the high-molecular-weight multimers (type II multimer pattern) similar to that observed in type IIA or IIB congenital vWD. A normal (type I) multimer pattern may be observed, as may its apparent absence (type III multimer pattern). A multimer analysis demonstrating a selective decrease in the high-molecular-weight vWF multimers helps confirm the diagnosis of vWD in patients in whom levels of vWF antigen may be discordantly normal compared with decreased ristocetin cofactor activity. Occasionally, because of the interference by some monoclonal immunoglobulins with electrophoretic migration of vWF, AvWD associated with MGUS or dysproteinemia can be suspected based on vWF multimer analysis.

Up to 16% of patients with AvWD may have inhibitors of ristocetin cofactor activity.[6] Screening for the inhibitor is typically performed by mixing patient and normal plasma, followed by comparison of observed and expected ristocetin cofactor activity. However, antibodies directed against the nonfunctional domains of vWF are not detected by these methods. Diagnostic use of staphylococcal protein A[77,90] and crossed immunoelectrophoresis[91] has been explored. In our experience,[7] an inhibitor of vWF ristocetin cofactor activity is rarely shown in AvWD.

## MANAGEMENT

Clinical management of AvWD has 2 components: (1) symptomatic treatment of bleeding or prevention of bleeding in patients having invasive procedures and (2) treatment of the underlying pathogenetically associated disease when such can be identified.

Agents for the treatment of bleeding in patients with AvWD include desmopressin and concentrates containing vWF. Although rich in vWF, plasma-derived cryoprecipitate is not currently used because of the risk of transfusion-transmitted diseases. However, it may still have a role when appropriate concentrates are not available.

Currently available purified concentrates containing vWF and factor VIII are considerably less likely to transmit infection and are the mainstay of therapy for AvWD. Concentrates containing vWF that are currently available in the United States include Humate-P, Koate-DVI, and Alphanate. Most patients with AvWD respond with an increase in factor VIII and vWF levels, but in these patients the factors may have a shorter survival than in those with congenital vWD, especially patients with AvWD who have demonstrable inhibitors.

Desmopressin induces release of preformed vWF from the endothelial cells. A therapeutic trial of desmopressin should be performed in all patients newly diagnosed with AvWD because it may provide a pharmacologic alternative. However, the response is typically minimal or brief,[35,68] probably because of decreased vWF survival. Desmopressin can be administered intravenously in doses of 0.3 μg/kg or intranasally at 300 μg. However, nasal administration typically does not yield as great an increment of vWF and factor VIII as does intravenous infusion, and the latter route is probably preferable for a treatment trial in patients with AvWD.[92,93] Advantages of desmopressin include absence of transfusion-transmitted disease, lower cost, and ready availability. Adverse effects typically include flushing, water retention (especially with repeated use), and occasional tachycardia. However, the increment of increase in vWF concentration is typically not equivalent to that obtained with administration of vWF concentrates; thus, desmopressin use is precluded in patients with severe deficiency, those undergoing major surgery, or those with severe trauma. Predictors of beneficial effect include presence of the type I (normal) vWF multimer pattern,[94] but patients with inhibitors will likely not have sustained benefit.[35]

Intravenous immunoglobulin (IVIG) has been used in patients with AvWD[35,36,90] and seems to be useful in some patients with an MGUS; it can produce a more sustained response than desmopressin or factor concentrates.[16,95] However, patients with IgM-MGUS appear to be less responsive to IVIG than those with IgG-MGUS.[16] The mechanism of action of IVIG in this setting is unclear but may be related to its effect on the clearance of the vWF-antibody complex,[95] such as blocking reticuloendothelial Fc receptors in the spleen and increasing catabolism of

autoantibodies, as is observed in other conditions in which IVIG is effective. In several situations in which use of desmopressin or factor concentrates did not control bleeding, IVIG was effective.[96,97] Responses lasting up to a month have been observed after treatment with a single dose of IVIG, and this agent has been used repeatedly every 3 to 4 weeks to maintain normal hemostasis in patients with AvWD who are not responding to desmopressin or vWF concentrates.[16,97,98] The high cost of IVIG limits routine use.

Other treatment modalities reported to be successful in patients with AvWD include plasma exchange[20] and extracorporeal immunoadsorption,[99] procedures that would lead to removal of inhibiting pathogenetic antibodies from the plasma.

The aforementioned options may lead to symptomatic and laboratory improvement in patients with AvWD. However, permanent reversal of the bleeding disorder may occur occasionally with treatment of the associated disease. Since the early and subsequent reports of such an improvement with treatment of underlying systemic lupus erythematosus,[2,4,100] such reversibility has been reported with treatment of hypothyroidism[78,101] and with some malignancies, including multiple myeloma,[72] lymphoma,[14] hairy cell leukemia,[12] chronic granulocytic leukemia,[22] and Wilms tumor. A reduction in the platelet count with cytapheresis and cytotoxic agents has been associated with partial correction of the abnormalities in 1 patient with AvWD associated with postsplenectomy thrombocytosis and myeloproliferative disorder.[70] Thus, a reasonable search for an associated disease should be undertaken in a patient with AvWD (Table 1).

## CONCLUSION

A high degree of suspicion of AvWD should lead to an appropriate investigation in a patient with an acquired bleeding disorder. Laboratory evidence of vWD should prompt a reasonable investigation into the presence of an associated underlying disease. Management includes therapies to increase the level of associated vWF and treatment of the associated pathogenetic disorder, when indicated.

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