Acquired von Willebrand Syndrome

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KEYWORDS

- Acquired von Willebrand • Essential thrombocythemia
- Waldenström macroglobulinemia • Mechanical circulatory support • Aortic stenosis
- Shear forces • Mucocutaneous bleeding
- Gastrointestinal arteriovenous malformations

KEY POINTS

- Diagnosis should be suspected in patients with mucocutaneous bleeding and a predisposing condition.
- Myeloproliferative neoplasms, plasma cell dyscrasias (PCD), and cardiovascular disease, including aortic stenosis and mechanical circulatory support, are the most common causes.
- Treatment should be focused on the underlying disease when possible.

INTRODUCTION

Although von Willebrand factor (VWF) was initially characterized in the setting of an inherited bleeding disorder, individuals may also develop a deficiency of VWF during their lifetime, termed acquired von Willebrand syndrome (AVWS). AVWS may arise from a heterogenous group of mechanisms, but share a common set of features (Table 1).

In 1958, Dr Edward Heyde first reported a link between aortic and gastrointestinal (GI) bleeding.[1] Nearly 30 years later, this association was proven[2] and the presence of low VWF was noted in certain cardiac surgery patients with bleeding,[3] but it was several more years before AVWS was proposed as the link between these observations.[4] Since that time AVWS has gained recognition and been shown to be associated with several cardiac, hematologic, and autoimmune disorders.

EPIDEMIOLOGY

The exact frequency of AVWS is difficult to ascertain, because it is underdiagnosed and increasing in incidence and prevalence.[5,6] Underdiagnosis is likely driven by attribution of bleeding to comorbidities and lack of consideration of this rare diagnosis,

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Table 1
Causes of Acquired von Willebrand Syndrome

Causes	Examples and Prevalence of AVWS in Each Condition if Available
Shear forces	Aortic stenosis (Heyde syndrome): prevalence 67%–92% by laboratory criteria; bleeding seen in 21%[25] Congenital heart defects: prevalence 20.8% by laboratory criteria[33] Other structural defects: mitral regurgitation, hypertrophic obstructive cardiomyopathy Extracorporeal membrane oxygenation: prevalence up to 100% by laboratory criteria; bleeding seen in 68.8%–94.4%[11,17] Ventricular assist device: prevalence up to 100% by laboratory criteria; bleeding seen in 19%–59%[38,39,43,45,46] Short-term microaxial pumps: prevalence 95.2% by laboratory criteria[47]
Myeloproliferative neoplasms	Essential thrombocythemia: prevalence 20%–70% by laboratory criteria; bleeding in <50% of laboratory diagnoses[7,54–56] Polycythemia vera: prevalence 12%–30% by laboratory criteria; bleeding in <50% of laboratory diagnoses[7,54,57] Chronic myelogenous leukemia
Lymphoproliferative disorders	Monoclonal gammopathy of undetermined significance Waldenström macroglobulinemia: prevalence 14% by laboratory criteria[9] Multiple myeloma AL amyloidosis Chronic lymphocytic leukemia Other lymphomas
Autoimmune disorders	Systemic lupus erythematosus Rheumatoid arthritis Graft-versus-host disease Isolated von Willebrand factor inhibitor
Other	Wilms tumor Other solid tumors Hypothyroidism Medications: griseofulvin, ciprofloxacin, valproic acid, hydroxyethyl starch

and the existence subclinical AVWS.[7–13] However, better recognition is not solely responsible for increasing diagnosis, because the true prevalence is rising, caused by the aging of the population leading to a great prevalence of age-related conditions, such as monoclonal gammopathy of undetermined significance (MGUS)[14] and aortic stenosis[15,16] and caused by the use of mechanical circulatory support, such as ventricular assist devices (VADs) and extracorporeal membrane oxygenation (ECMO).[6,10,11,17–21] We group the etiologies as arising from shear forces, myeloproliferative neoplasms (MPNs), plasma cell dyscrasias (PCD) and other lymphoproliferative disorders, autoimmune disorders, and other conditions.

Shear Forces

Mechanical shearing leads to AVWS by activation of high-molecular-weight (HMW) VWF multimers and subsequent removal from circulation.[11,22–24] There is also evidence of increased cleavage by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) and mechanical destruction of VWF.[19] Increased shear forces can arise from structural heart disease, prototypically

aortic stenosis, or from the use of mechanical circulatory support. The rate of AVWS is 67% to 92% of patients with severe aortic stenosis, although only a smaller proportion of patients (21%) have bleeding manifestation.[25] The valve gradient has been shown to be correlated with the degree of disturbance in multimer patterns and likelihood of bleeding.[26,27] The causal link was proven by the observations that correction of aortic stenosis is associated with resolution of bleeding and normalization of VWF multimers.[25,28]

In addition to aortic stenosis, other structural defects that have been associated with AVWS include mitral regurgitation, hypertrophic obstructive cardiomyopathy, and congenital heart defects, and are well documented to correct with repair of the structural defect.[29–37] The rates for AVWS in congenital heart defects vary widely by defect: one study of 192 patients seen in an adult congenital heart defect clinic found an overall AVWS prevalence of 20.8% with a range of 9.4% in patients with less complex defects and 38.6% in patients with the most complex defects in the cohort.[33] Another series that focused on congenital heart defects with a stenotic component found AVWS rates of 50% in those with a significant gradient (mean, 80; range, 52–130 mm Hg), as compared with no children with a gradient less than 20 mm Hg,[34] further emphasizing the role of shear forces.

Mechanical circulatory support is increasing in prevalence and increasingly recognized to cause AVWS. Venovenous and venoarterial ECMO have been shown to cause AVWS.[10,11,17–19,21] One series of 18 venovenous ECMO patients found laboratory evidence of ECMO in all 18 patients with 17 of the 18 showing clinical signs of bleeding,[11] whereas another series of 32 venoarterial ECMO patients found laboratory evidence in 31 and bleeding in 22 patients, respectively.[17] Similarly, laboratory evidence of AVWS in VAD patients was seen in all 102 patients in one series.[38] Bleeding represents the most common complication of VAD implantation and is impacted by, although not exclusively caused by, AVWS with rates varying from 19% to 59% depending on the study.[23,39–46] Newer devices with lower shear stress seem to have lower rates of AVWS.[19] AVWS can also occur with short-term microaxial pumps with laboratory evidence in 20 of 21 patients in one series.[47–49] AVWS caused by mechanical circulatory support typically resolves with decannulation or device removal.[11,40,50]

Myeloproliferative Neoplasms

The markedly increased platelet counts that are see with MPNs are thought to underly the association with AVWS in most cases. This is most commonly reported with essential thrombocythemia but also in patients with polycythemia vera and chronic myelogenous leukemia when the platelet count is concurrently elevated.[7,51,52] The likelihood of AVWS is correlated with the degree of thrombocytosis and is unusual without a platelet count of greater than 1000×10^9/L, although cases have been reported at lower platelet counts, because the mechanism is adsorption on the surface of excessive platelets, which preferentially impacts HMW multimers.[7,8,53,54] Estimates for AVWS are 20% to 70% in essential thrombocythemia and 12% to 30% in polycythemia vera by laboratory criteria, but clinically significant bleeding is much less common, at 4% to 7% in some studies and affecting fewer than half of those with a laboratory-based diagnosis.[7,54–57]

Plasma Cell Dyscrasias and Other Lymphoproliferative Disorders

AVWS has been associated with PCD through adsorption by paraproteins and acquisition of an autoantibody to VWF, which is termed a VWF inhibitor.[9,51,58–61] PCD includes AL amyloidosis, MGUS, multiple myeloma, and Waldenström macroglobulinemia. In a

series of 72 patients with Waldenström macroglobulinemia, 10 patients (14%) met laboratory criteria for AVWS.[9] Rates for multiple myeloma and MGUS are not well characterized, but occur with IgG and IgM subtypes.[5,51,58] Likewise, AVWS is a rare complication of AL amyloidosis, but can occur with kappa and lambda subtypes.[60,61] Although the proportion of PCD patients with AVWS is likely low, because of the prevalence of these disorders, PCD accounts for a large proportion of identified cases, as high as 48% in a registry of 211 patients.[5] Rarely other lymphoproliferative disorders including chronic lymphocytic leukemia and other lymphomas have been associated with AVWS.[5,51]

Autoimmune Disorders

Autoimmune AVWS can occur in the setting of PCD. Autoimmune AVWS has also been documented to occur in the setting of systemic autoimmune disorders. This is most commonly in association with systemic lupus erythematosus,[62–69] but has also been reported with rheumatoid arthritis[70,71] and graft-versus-host disease.[72] AVWS as an isolated inhibitor without evidence of other autoimmunity or systemic disease has also been reported.[73,74]

Other Etiologies

Rare cases of AVWS have also been reported with several other conditions. Solid tumors, including most notably Wilms tumor, have been associated with rare cases.[5,51,75] Hypothyroidism has been associated with AVWS with a normal multimer pattern and resolution with administration of L-thyroxine, implying diminished synthesis can occur in this setting.[76–78] Rarely, AVWS has been associated with medications including griseofulvin,[79] ciprofloxacin,[80] valproic acid,[81] and hydroxyethyl starch.[82–84] Drug-induced AVWS can involve loss across all multimer forms (eg, hydroxyethyl starch, valproic acid) or be limited to HMW multimers (eg, ciprofloxacin).

EVALUATION

Diagnosing Acquired von Willebrand Syndrome

Patients with suspected AVWS based on either clinical symptoms or a predisposing condition should have VWF testing (**Table 2**). This testing should include VWF antigen levels and ristocetin cofactor assay or equivalent test of VWF platelet binding activity. Normal results for VWF antigen levels and VWF ristocetin cofactor assay effectively

Table 2
Laboratory Profile of Acquired von Willebrand Syndromes

Laboratory Parameter	Type 1 AVWS	Type 2A AVWS
VWF:Ag	Low	Low, normal, or high
VWF:RCo	Low, in proportion to VWF:Ag	Low, out of proportion to VWF:Ag
VWF multimer analysis	Normal distribution	HMW multimer diminished or absent
Testing to distinguish from inherited VWD	Genetic testing or VWFpp[a]	Genetic testing, elevation of VWF:Ag if present, VWFpp

Abbreviations: HMW, high molecular weight; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor antigen levels; VWF:RCo, von Willebrand factor ristocetin cofactor assay; VWFpp, von Willebrand factor propeptide.

[a] Rare this may misidentify type 1C VWD as acquired and hypothyroidism-associated type 1 AVWS as congenital.

rule out AVWS. If either is abnormal, VMF multimer analysis can distinguish the AVWS subtype. A global decrease with a normal multimer pattern is equivalent to type 1 von Willebrand disease (VWD) (or type 3 if sufficiently severe), whereas selective loss of HMW multimers is analogous to type 2A VWD. When suspicion is high or diagnosis is time sensitive, it may be appropriate to send multimer testing with the initial evaluation. Multimer analysis is helpful not only in establishing the diagnosis, but also in selection of therapy (discussed later).

Distinguishing Acquired von Willebrand Syndrome From von Willebrand Factor

Clinical history is often able to distinguish AVWS from inherited VWD by the abrupt onset of bleeding symptoms or the novel presence of a predisposing condition (eg, essential thrombocythemia diagnosis or VAD placement). As such, a careful bleeding history is of vital importance to rule out an occult bleeding history, particularly that of heavy menstrual bleeding, which patients may not recognize as excessive because of lack of context for comparison or may be hesitant to disclose because of historical stigmatization of menses.[85]

When clinical history is insufficient, additional testing is of use.[13] Few patients have prior VWF testing for comparison, but this would differentiate AVWS from VWD if available. Normal or elevated VWF propeptide can distinguish AVWS caused by increased clearance, which represents most AVWS, from VWD.[86,87] However, one should be cautious relying on propeptide testing without understanding the clinical context as would result in cases of AVWS caused by reduced production (eg, hypothyroidism)[76–78] being mislabeled as type 1 VWD and cases of type 1C VWD being mislabeled as AVWS. Gene sequencing to assess for mutations, inversions, and deletes associated with VWD can provide clarity when clinical context or other laboratory testing is insufficient to make the determination.

For patients in whom an autoimmune mechanism is suspected, testing directly for an inhibitor can confirm the diagnosis and help tailor therapy.

Assessing for Underlying Conditions

Most AVWS is associated with a predisposing condition[5] and that is often apparent before the diagnosis of AVWS or readily apparent from the patient's history. For those patients without a known cause, a complete blood count should be reviewed for evidence of MPN or cytopenias suggestive of an underlying disorder. A serum protein electrophoresis and free light chain ratio may be useful to screen for PCD. Patients with inhibitors should be screened for systemic lupus erythematosus and hematologic malignancies including PCD. Cardiac auscultation may reveal previously unappreciated aortic stenosis. Testing for more obscure causes should be clinically driven.

CLINICAL OUTCOMES

The clinical presentation of AVWS can vary widely in severity. Many cases with clear laboratory evidence suggesting AVWS may be clinically silent.[7,9,17,25,56,57] Cases with clinical manifestations can present with mucocutaneous bleeding including petechiae, bruising, gum bleeding, epistaxis, heavy menstrual bleeding and GI bleeding.[51] GI bleeding is the most common site of life-threatening bleeding, although bleeding can been seen at any site including airways, pericardium, pleural space, and peritoneum.[6,10,39,51]

Subtypes of AVWS where HMW multimers are preferentially impacted are most likely to manifest bleeding, because these multimers are the most hemostatically

active. Furthermore, in patients with a loss of HMW multimers, GI bleeding may be driven not only because of the hemostatic defect, but also by the development of arteriovenous malformations (AVMs). The propensity of patients with AVWS with loss of HMW multimers to form AVMs is thought to be central to the original observation linking aortic stenosis to GI bleeding in Heyde syndrome.[1,2,4] VWF, and HMW multimers in particular, play a role in regulation of angiogenesis, which may be tissue specific and account for GI AVMs.[88–90] As such, recurrent GI AVMs should prompt clinical consideration of underlying VWD or AVWS.

THERAPEUTIC OPTIONS

The most effective long-term therapy for AVWS usually addresses the predisposing condition. This has been shown to be effective in most causes,[25,28–31,35,37,50,54,55,57] but this approach is not always feasible and does not address acute bleeding (**Table 3**).

Acute Bleeding

Desmopressin, which is routinely used for type 1 VWD, generally performs poorly as a rescue therapy for bleeding with great heterogeneity across AVWS causes.[5,6,51,58,77,91] Response rates to desmopressin were 10% for cardiovascular causes, 21% for MPNs, 33% for autoimmune conditions, and 44% for PCD and lymphomas.[5] Mechanistically, low response rates are not surprising, because a transient release of endothelial stores

Table 3
Treatments for Acquired von Willebrand Syndrome

Therapy	Dosing	Considerations
VWF concentrates	Initial: 40–60 U/kg Maintenance: 40–50 U/kg daily	Fast onset; short duration of effect
Desmopressin	0.3 μg/kg, max 20 μg	Fast onset; poor efficacy; short duration of effect
Intravenous immunoglobulins	Initial: 1 g/kg q d × 2 d Maintenance: 1 g/kg q 3 wk	Fast onset; significant volume load
Antifibrinolytics		
Tranexamic acid ε-Aminocaproic acid	1–1.3 g IV or PO q 8 h IV: 4–5 g loading dose followed by 1 g/h continuous infusion or PO: 50–100 mg/kg q 6 h	Adjunctive therapy for bleeding refractory to other therapies
B-cell-directed therapy		
Rituximab	Initial: 375 mg/m^2 weekly × 4 doses Maintenance (optional): 375 mg/m^2 q 90 d or with relapse	Slow onset; may provide long treatment-free interval
Bortezomib	1.3 mg/m^2 (+dexamethasone 40 mg) on D1, 4, 8, and 11 of 21-d cycles × 6 cycles	Slow onset; response in rituximab refractory patient
Antiangiogenic therapy		
Thalidomide	50 mg PO BID	Slow onset; prothrombotic
Octreotide	Short acting: 50 μg SC BID; Depo: 20 mg SC monthly	Slow onset; gastrointestinal, cardiovascular and endocrinologic side effects

Abbreviations: IV, intravenous; SC, subcutaneous.

of VWF does not address the rapid clearance of VWF underlying most AVWS. The use of VWF concentrates may be more successful than desmopressin, although data are limited, with a response rate of 40% across underlying causes.[5,10,20,58,92] Intravenous immunoglobulin (IVIG) has shown success in MGUS, lymphoproliferative disorders, autoimmune conditions, and solid tumors with response rates ranging from 37% to 100%.[5,58,59,92,93] It is physiologically plausible that immune clearance of VWF is halted by IVIG administration, which may explain its success in this particular subset of AVWS. This theory is bolstered by the observation that high success rates in IgG MGUS are not found with IgM MGUS, where adsorption rather than targeted clearance may be underlying.[9,58,94] Plasmapheresis is effective for IgM MGUS or Waldenström macroglobulinemia.[58,59] Antifibrinolytics, such as tranexamic acid and ε-aminocaproic acid, have also been suggested to ameliorate acute bleeding, but data are lacking.[6] One series reported the successful use of recombinant activated factor VII to halt bleeding in AVWS.[95]

Prophylaxis Against Future Bleeding

Correction of the underlying condition is the optimal approach, but this may be impossible in many circumstances. For conditions discussed previously that are responsive to IVIG, including IgG MGUS, other PCD, and autoimmune causes, repeat administration every 3 weeks may provide long-term control.[93,96] If an inhibitor is identified or suspected, B-cell therapy, such as the anti-CD20 monoclonal antibody rituximab, has generated long-term responses[64,96–100]; however, rituximab failure in MGUS-associated AVWS has been reported.[101] There is a case report of successful treatment of MGUS-associated AVWS with bortezomib.[102]

Patients for whom the previously mentioned therapies are insufficient or are not expected to be effective and have developed recurrent GI AVMs may be considered for antiangiogenic therapies. This is particularly relevant to patients with VADs, because there is no expectation of resolving AVWS without heart transplantation. Factor replacement alone is likely to be insufficient, because accelerated clearance makes it difficult to maintain VWF levels. For the combination of GI bleeding and VAD, the antiangiogenic medications octreotide and thalidomide have reduced GI bleeding.[103–109]

CLINICS CARE POINTS

- Recurrent GI AVMs should prompt consideration of underlying AVWS.
- Diagnostic testing should include VWF multimer analysis to identify the decrease in HMW multimers.
- Multimer pattern, history, and clinical context can usually distinguish AVWS from VWD; however, genetic testing may be needed to distinguish AVWS from type 2A VWD.
- Treatment should target the underlying condition when possible (eg, correction of aortic stenosis, removal of mechanical circulatory support, treatment of an MPN or PCD).
- Desmopressin performs poorly in AVWS, especially when caused by underlying cardiovascular causes.
- VWF concentrates may be effective to treat acute bleeding episodes.
- IVIG is effective for rapid and long-term correction of AVWS in lymphoproliferative and autoimmune conditions.
- Patients with recurrent AVMs despite treatment may benefit from antiangiogenic therapies.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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