Alloantibodies in von Willebrand disease

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The development of alloantibodies against von Willebrand factor (VWF) represents a rare but serious complication of treatment of von Willebrand disease (VWD), occurring in ∼5% to 10% of type 3 VWD patients. Affected patients can present with a range of symptoms, including lack or loss of hemostatic response to infused VWF concentrates up to anaphylactic reactions in rare cases. It is classically reported in multitransfused patients and occurs most frequently in patients with partial or complete VWF gene deletions. A positive family history of anti-VWF antibodies also appears to be a risk factor. There is a lack of standardization of laboratory methods for antibody identification and characterization. Issues of variability in laboratory approaches as well as the rarity of the complication act as a barrier to future studies. Recombinant factor VIII as well as bypassing agents and immune tolerance have been reported as effective treatments; however, aside from case reports, little exists in the literature to guide management. The imminent clinical availability of recombinant VWF has prompted a resurgence of interest in this area. Additional study is warranted to address the deficiencies in our understanding of this treatment complication. (Blood. 2013; 122(5):636-640)

Introduction

Von Willebrand disease (VWD) is generally considered the most common inherited bleeding disorder known in humans, with a population prevalence of ∼1% and a symptomatic prevalence of ∼1 in 1000.1-3 It was originally described in 1926 by Erik von Willebrand in a Finnish medical journal.4 In this landmark publication, a young woman was reported to have bled to death at the time of her fourth menstrual period. Since then, significant advances have been made in our understanding of the disease, including the underlying physiopathology, molecular basis, and potential complications of treatment.

VWD is caused by deficiency or dysfunction of the multimeric glycoprotein, von Willebrand factor (VWF), and is clinically characterized by excessive mucocutaneous bleeding as well as musculoskeletal bleeding in type 3 VWD, the most severe form. At present, VWD classification includes 3 types: type 1 is a partial quantitative deficiency of functionally normal VWF, type 2 VWD encompasses 4 qualitative variants, and type 3 is a virtual absence of VWF.5 Treatment options include the infusion of concentrates of VWF (which also usually contain factor VIII [FVIII]) given to prevent or treat bleeding episodes. In 1974, Sarji et al first reported a case of an alloantibody against VWF in a multitransfused patient.6 This was followed quickly by additional reports from Sweden and Italy, including the description of a precipitating anti-VWF antibody by Mannucci et al.7,9 In such cases, treatment with VWF concentrates is rendered ineffective, and anaphylaxis with subsequent exposures has been described.10,11 In this review, we will discuss the epidemiology of alloantibodies against VWF including what is known about underlying risk factors, the challenges facing laboratory characterization, and the clinical presentation and treatment options.

Epidemiology

In 1984, a cross-sectional study was published describing the results of a survey of severe VWD in Western Europe and Israel, with all laboratory results confirmed in a centralized laboratory. One hundred and six patients were included from 21 countries; of those, 8 were found to have alloantibodies, resulting in a prevalence of 7.5%.12 These results are generally consistent with results of other studies, which showed prevalence estimates ranging from 5.8% to 9.5%.13,14 Thus, alloantibodies against VWF are a rare complication. It is important to highlight that all reported cases have occurred in severe or type 3 VWD; there are no reports of VWF alloantibody development in either type 1 or type 2 VWD.

Interesting comparisons can be made with the hemophilias in terms of alloantibody prevalence. In hemophilia A, the overall prevalence across the spectrum of disease (including severe, moderate, and mild hemophilia A) of inhibitory alloantibodies to FVIII is ∼6%, with the majority occurring in severe, hemophilia A (prevalence ∼15%). The incidence of inhibitors in severe hemophilia A is ∼25%, but many are transient. The development of these antibodies greatly complicates treatment.15,16 Affected patients have to be treated with bypassing agents during acute bleeding episodes, and costly immune tolerance regimens are not universally effective in eradicating inhibitors.17 Anaphylaxis has been described very rarely in patients with hemophilia A receiving FVIII, although the inciting antigen in these cases is not always clear and has been hypothesized to be concentrate components other than the FVIII molecule.18,19 Further complicating the issue, the reports of anaphylaxis do not always temporally relate to the development of an inhibitor, leaving unresolved questions about the underlying pathophysiology.

In hemophilia B, inhibitor prevalence (and incidence) is ∼4%.20,21 In contrast to inhibitors in hemophilia A, anaphylaxis is reported much more frequently (in nearly all cases) and typically coincides with the development of the inhibitory alloantibody. This certainly affects the clinical management of a hemophilia B patient with an inhibitor and necessitates that any future reexposure to factor IX occurs in a monitored setting.22 In both hemophilia A and
B, inhibitors tend to develop early in the course of treatment and the underlying gene mutation is a risk factor with deletions conferring the highest risk.16,24

Molecular pathology

The majority of the early reports of anti-VWF antibodies were all from patients with partial or complete VWF gene deletions; however, there was a patient reported in the 1970s who was subsequently determined to have a nonsense mutation.9,25-29 Subsequent publications reported patients with additional nonsense mutations as well as a frameshift plus more cases with partial or complete VWF gene deletions.30,31 A summary of reported cases and their characteristics can be found in Table 1. In many instances, individuals who developed anti-VWF antibodies were related, suggesting a heritable risk for anti-VWF antibodies, although complete penetrance of the immune phenotype is not observed in these families.26 Furthermore, not all cases of type 3 VWD caused by partial gene deletions develop alloantibodies against VWF. Mohl et al32 described 25 Hungarian type 3 VWD patients of which 5 were homozygous for a large partial gene deletion. None of these 5 patients developed anti-VWF antibodies as a complication of treatment, raising unanswered questions about additional genetic or environmental modifiers.32

Laboratory identification and antibody characteristics

There is no standard laboratory approach for the identification of anti-VWF antibodies. In general, the available assays are based on the principle of a mixing study to demonstrate the inhibition of the platelet-dependent function of VWF, although recommendations to evaluate VWF function more broadly (including collagen-binding and FVIII-binding) exist.33 The anti-VWF antibodies do not demonstrate time and/or temperature dependence and the assay is typically done at 37°C with an incubation time between 15 minutes and 2 hours. The antibody titer is reported in Bethesda units.34 Negative results from mixing studies do not necessarily rule out the presence of an anti-VWF antibody, because it may be directed against nonfunctional epitopes.35-37 Based on these

Table 1. Characteristics of patients reported with anti-VWF antibodies

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issues, a strong case can be made for centralized testing in an experienced laboratory familiar with both the screening ELISA and the functional mixing studies.

When immunoglobulin (Ig) characterization has been performed, anti-VWF antibodies are most commonly polyclonal IgG and exhibit a wide range of epitope recognition on VWF. IgG subclasses 1–4 have been identified, with IgG4 being the most common, as is also the case with anti-FVIII antibody responses.2,7,26,39 Interestingly, when an inhibitory immune response develops in either VWD or hemophilia, IgG subclass antibodies predominate. This low abundance IgG subclass (<5% of total IgG) does not activate complement and is recognized to undergo antigen binding domain switching, often resulting in monovalent and sometimes bispecific antibodies. However, the significance of these properties in the context of the anti-VWF (or FVIII) immune response is unknown. As mentioned previously, a striking feature of some, but not all, of the anti-VWF antibodies identified is their ability to precipitate VWF in normal plasma. In an Italian study, only high-titer antibodies precipitated with VWF; this phenomenon was not observed with lower-titer antibodies.40

A consistent feature of all anti-VWF antibodies to date is their specificity for VWF and lack of activity against FVIII. Interactions with plasma FVIII are possible, but likely as a result of the bound antibody causing steric hindrance of the FVIII binding site on VWF.8,39 This distinction is clinically relevant in terms of treatment options for patients with anti-VWF antibodies.

The lack of standardization of laboratory approaches for the identification of anti-VWF antibodies is a barrier to further advances of our understanding of this complication. A coordinated approach to this problem would be beneficial, perhaps organized by the VWF Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Given the rarity of both this disease and this complication, this would of course need to be a multinational, multicenter study and could involve both the evaluation of laboratory protocols on shared samples of previously identified cases and the prospective assessment of VWF alloantibody incidence and pathophysiology. Such a study is currently under way under the leadership of Federici and Mannucci, entitled 3WINTERS-IPS (Type 3 von Willebrand International Registries Inhibitor Prospective Study). This study provides the much-needed opportunity to identify correlations between antibody characteristics and clinical presentation; clinicopathologic correlations that are currently missing from the literature.

Clinical presentation and treatment

The clinical presentation of an anti-VWF antibody usually involves lack of, or loss of, hemostatic response to infused concentrates of VWF. Lower than expected VWF recoveries can also be seen.41 With regard to prophylaxis, a recently published retrospective study reports that of 59 severe VWD patients, only 1 developed an inhibitor during the reporting period.41 In another recent study reporting 32 patients receiving secondary prophylaxis for VWD, 1 developed an inhibitor following intensive exposure for an ankle bleed.42 As previously mentioned, some patients, particularly those with high-titer anti-VWF antibodies, can experience severe or life-threatening anaphylactic reactions when reexposed to VWF. These cases are characterized by complement activation as well as immune complex formation.10,11 In a detailed investigation of a patient with severe VWD, IgG alloantibodies against VWF and a history of transfusion anaphylaxis failed to identify the presence of IgE against VWF.11 As a result of these reports, and our lack of ability to definitively predict who will experience anaphylaxis with subsequent exposure, products containing VWF should be avoided or reexposure only attempted in carefully monitored settings.

Recombinant FVIII has been used successfully for hemostatic therapy in patients with anti-VWF antibodies. The resultant plasma FVIII half-life can be expected to be short (<2 hours in a reported case), because of the lack of stabilization by VWF, but by using higher doses given by continuous infusion, bleeding has been avoided in high-risk situations such as major abdominal surgery.13 Importantly, there is a case report published in 2008 of a 35-year-old woman with type 3 VWD and an alloantibody successfully treated with recombinant FVIII (rFVIII), who upon exposure to Recombinate developed an allergic response as well as an increase in antibody titer, which subsequently decreased. The authors hypothesize that the reaction was the result of trace VWF found in the final formulation of Recombinate because of the coexpression of the VWF gene with FVIII in the cell culture system used to synthesize this rFVIII product.43 Additional therapeutic options include bypassing agents such as activated FVII (rFVIIa), factor VIII inhibitor bypassing activity, and platelet infusions.44,45 The experience with rFVIIa and factor VIII inhibitor bypassing activity is much greater in patients with hemophilia A and inhibitors, and extrapolation of that experience to this setting seems reasonable; however, the lack of experience in patients with anti-VWF antibodies warrants a cautious approach. Some clinicians advocate the use of rFVIII alternating with rFVIIa, and no reports exist of thrombosis occurring with either product in this patient population. Given that the available evidence exists only as case reports and expert opinion, additional study is needed to determine the optimal approach. The rationale for the use of transfused platelets is that in contrast to the patient’s own platelets, which are devoid of VWF,46,47 VWF will be present in the α granule of the transfused platelets in normal amounts. This localized storage will protect the VWF from the alloantibody in the plasma, which when released at the site of vascular injury might have some local hemostatic benefit before the alloantibody has a chance to bind. This rationale is supported by the relatively mild bleeding phenotype seen in patients with acquired severe von Willebrand syndrome secondary to the development of autoantibodies to VWF; however, the efficacy and safety of this approach in type 3 VWD patients requires clinical evaluation.

Again extrapolating from the experience in hemophilia A and the use of immune tolerance induction to eradicate inhibitors, immune tolerance to VWF has been attempted. In 2012, the case of a 9-year-old boy whose anti-VWF antibody was successfully eradicated with immune tolerance induction was published.45 Whether or not this approach is safe, feasible, or effective in all patients with anti-VWF antibodies remains to be seen.

Source of VWF

The first patients reported with anti-VWF antibodies were sensitized by exposure to cryoprecipitate. Plasma-derived concentrates of FVIII containing VWF have also been implicated in the development of this complication. Although the data are not conclusive, significant differences in prevalence rates of anti-VWF antibodies between the 2 types of concentrate are not apparent. Currently, recombinant human VWF is in clinical trials and preliminary results regarding anti-VWF antibody development have been published in abstract form.48 Reported patients were studied using a VWF-binding ELISA plus inhibitory assays evaluating VWF
Conclusions

The development of anti-VWF antibodies in type 3 VWD is a rare complication of a rare disease, and many unanswered questions remain. What are the underlying modifiers that lead only some patients with VWF gene deletions to develop anti-VWF antibodies? What are the determinants of antibody specificity and how should these be best characterized in the laboratory? Why is there such variability in the clinical presentation of affected individuals? And finally, what is the best treatment strategy for an affected patient? It is only through coordinated, international study that we will be able to begin to address these questions.

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Authorship

Contribution: P.D.J., D.L., and P.M.M. designed and performed research and wrote the paper.

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References


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