von Willebrand disease Update

Von Willebrand disease (vWd) is an inherited blood clotting disorder caused by either a deficiency or a dysfunction of the von Willebrand factor (vWf) protein which resides in the blood plasma, platelets and subendothelial matrix. Von Willebrand disease is the most common of the inherited bleeding disorders and occurs in about 1 out of every 100 to 1,000 people. It affects both males and females, unlike hemophilia, which mainly affects males.

Von Willebrand factor has a dual role in that it mediates adhesion and aggregation of platelets at sites of vascular injury, which is crucial for hemostasis and thrombosis, and it is also the carrier of Factor VIII in the plasma. The Von Willebrand protein binds to, stabilizes, and protects factor VIII. Thus, a severe deficiency or defect in vWf can lead to low levels of plasma Factor VIII and bleeding events similar to hemophilia A may be present.

There are three major types of vWd. Type 1 vWd is the most common, representing about 80% of cases. Type 1 is due to a decreased quantity of normal functioning vWf. Type 1 is considered to be the most mild in terms of bleeding symptoms and may also have low levels of factor VIII. Type 2 vWd is due to a vWf functional defect and is subdivided further into type IIA, IIB, IIM, and IIN.

- Type IIA vWd is the most common type II variant and causes a reduction in platelet binding because of a deficiency of specific von Willebrand factor subunits.
- Type IIB vWd causes an increase in binding of vWf to platelets which results in the platelets and vWf subunits being removed from the bloodstream too quickly.
- Type IIM is a rare type of vWd characterized by a decreased affinity of the Willebrand factor for platelets.
- Type IIN causes a large decrease in binding of vWf to factor VIII.

Type 3 vWd is very rare and the most severe form, with a marked decrease or absence of detectable vWf. Type 3 disease includes severe bleeding as well as significantly decreased factor VIII function. Type 3 has a frequency of 1 case per 1 million persons.

In addition to the three major types discussed above, there are two less common types as well. Pseudo, or platelet-type vWd is similar clinically to von Willebrand type IIB and is caused by defects in a person's platelets rather than problems with their vWf. Finally, there is an acquired vWd which develops later in life and is not inherited from a parent. This disorder results from the development of antibodies to vWf. Typically, it is associated with an underlying and unrelated medical condition. The treatment for these two types is similar to the inherited disease.

Many individuals with vWd go undiagnosed, especially for the milder forms of the disease. In types 1 and 2 vWd, you tend to see mild to moderate mucocutaneous bleeding. In type 3, the combination of reduced factor VIII levels with very low or absent vWf levels can lead to significant bleeding. Some of the most common bleeding symptoms include nose bleeding, abnormal or easy bruising, bleeding of the gums, bleeding after surgery, gastrointestinal bleeding, heavy menstrual bleeding and bleeding after childbirth. Pediatric-specific bleeding that may occur in children with vWd include umbilical stump bleeding, cephalohematoma, cheek hematoma, conjunctival bleeding, post-circumcision bleeding and post-venipuncture bleeding.

Management of vWd can vary widely depending on the type of vWd, severity and location of bleeding. The primary goal is the prevention of bleeding episodes. Typically for Type 1 and some type 2 vWd, the recommended treatment option is desmopressin (DDAVP) for minor surgical procedures and minor bleeding, provided the patient showed an adequate response to a DDAVP trial. A DDAVP response

requires an increase of at least >2 times the baseline vWf activity. Desmopressin is a synthetic hormone which helps the body release more vWf than it would normally, and also helps increase the level of factor VIII in the blood. In moderate to severe type 2 and type 3 vWd, desmopressin is not recommended due to lack of response. In type 2B vWd, desmopressin is contraindicated because of possible thrombocytopenia induced by DDAVP.

For those with a demonstrated response, DDAVP can be administered by several routes (i.e., intravenous, subcutaneous, or intranasal spray). The subcutaneous preparation is available but not FDA approved. The intranasal formulation (Stimate®) was voluntarily recalled in mid-2020 due to packaging issues that affected potency but is predicted to be available again in the second half of 2023.

The efficacy of DDAVP has been established primarily from observational studies. For patients with type 1 disease and vWf activity above 10%, good hemostasis was observed, the same does not hold true for individuals with severe type 1. Some patients with mild type 2 vWd respond to DDAVP but this is less frequent and those with type 3, which have no vWf, do not have a response with DDAVP and it is not recommended in this group. Fluid retention and hyponatremia are common complications of DDAVP therapy. Therefore, weight-based fluid restriction and monitoring of sodium levels are recommended in patients receiving repeated doses of DDAVP.

If an individual does not respond to DDAVP or if DDAVP is not recommended, another treatment option is von Willebrand factor-containing concentrate. These products provide the missing von Willebrand factor in the body and there are two classes of concentrates, plasma-derived products (derived from human plasma) and recombinant (those made in a laboratory).

Plasma-derived products are made from human blood which is then separated into its components which are then purified to remove any potential viruses. These products contain a mixture of both von Willebrand factor and factor VIII, although the ratio varies between products.

The recombinant products may provide a safer option than plasma-derived products but they do not contain factor VIII. For these products only a single dose of factor VIII is needed because the endogenous factor VIII becomes stabilized by the vWf.

The current plasma-derived products available are Humate-P®, Alphanate® and wilate®. All three of these plasma-derived products contain both factor VIII and von Willebrand factor. Humate-P and Alphanate are indicated for both hemophilia A and von Willebrand disease. The dose of these products depends on patient's weight, severity of hemorrhage, severity of deficiency, presence of inhibitors and the desired FVIII level. Alphanate is indicated for surgical and/or invasive procedures in adult and pediatric patients when desmopressin is either ineffective or contraindicated. It is not indicated for patients with severe Type 3 vWd undergoing surgery. Humate-P is indicated in adult and pediatric patients for the treatment of spontaneous and trauma-induced bleeding episodes and prevention of excessive bleeding during and after surgery. This applies to patients with severe vWd as well as patients with mild to moderate vWd where use of DDAVP is inadequate. Wilate is indicated in children and adults for on-demand treatment and control of bleeding episodes and also for perioperative management of bleeding for minor or major surgery.

Vonvendi® is a recombinant product that is only indicated for vWd. Vonvendi was approved by the FDA in 2015 and the approval was based on a phase 3 trial that showed the recombinant product was safe and effective in treating 192 bleeds in 22 patients with vWd and stabilized endogenous FVIII:C levels. Control of bleeding was rated good or excellent, with excellent control in 96.9% (119 of 122 minor bleeds, 59 of 61 moderate bleeds, and 6 of 7 major bleeds. A single infusion was effective in 81.8% of bleeds.

Observational studies for the plasma-derived concentrates have demonstrated good to excellent efficacy in infants, children and adults with bleeding or surgery.

Deciding on which product to use depends on availability and cost. The plasma-derived and recombinant products have not been compared in head-to-head trials, but based on separate studies, efficacy and adverse effects are similar between these sources of products. One concern that may come up with plasma-derived products is the accumulation of factor VIII, which carries a risk of thrombosis.

Von Willebrand concentrates are appropriate for patients who have a vWf activity level of < 50 international units (IU)/dL when there is major or life-threatening bleeding and major surgery. Some examples include bleeding that causes a decrease in hemoglobin concentration of 2 or more g/dL, or intracranial, spinal or joint bleeding, pregnant women with Vaseline vWf activity < 50 Iu/dL during and shortly after delivery, etc. In these situations, vWf should be administered without delay until the patient is stabilized.

Continuous infusion of plasma-derived vWf concentrates has also been used for individuals who have an inhibitor or acquired von Willebrand syndrome. Continuous infusion has been shown to decrease the total dose needed for treatment by 20% to 50%, and this in turn decreases the total cost of treatment.

Other therapies used in vWd include antifibrinolytic agents such as aminocaproic acid and tranexamic acid. These therapies are used adjunctively or as standalone treatment, depending on the site and severity of bleeding. Typically they are useful as standalone treatment for heavy menstrual bleeding, postpartum bleeding or for minor dental and gynecologic procedures.

Von Willebrand disease is the most common inherited bleeding disorder, yet diagnosis and management remain a challenge. This in part is due to the fact that plasma von Willebrand factor levels vary over a wide range in the normal populations. Advances in bleeding assessment tools and new assays for vWf activity may help alleviate some of these challenges. People with mild cases may not require any treatment, but should avoid certain medications that could aggravate bleeding, such as aspirin and ibuprofen. For the more serious cases, the available therapies include DDAVP, and plasma-derived or recombinant-derived vWd concentrates.

The new vWd guidelines for the diagnosis and management of von Willebrand disease were released in January 2021 and the key recommendations of these guidelines include the role of bleeding-assessment tools in the assessment of patients suspected of vWd, diagnostic assays and laboratory cutoffs for type 1 and type 2 vWd, how to approach type 1 vWd patients with normalized levels over time and the role of genetic testing vs. phenotypic assays for types 2B and 2N. Because of the nature of the disease and the many different subtypes, individualized treatment based on specific diagnosis and bleeding phenotype are crucial in the successful treatment of patients.

1. https://www.cdc.gov/ncbddd/vwd/facts.html#:~:text=Von%20Willebrand%20disease%20(VWD)%20is,von%20Willebrand%20factor%20(VWF).
2. https://emedicine.medscape.com/article/206996-overview
3. https://www.uptodate.com/contents/pathophysiology-of-von-willebrand-disease?search=von%20willebrand%20disease&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2702526/
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6174185/
6. https://etha.eu/wp-content/uploads/2018/03/vwd_in_brief.pdf

7. https://www.ncbi.nlm.nih.gov/books/NBK559062/
8. https://www.ihtc.org/types-of-von-willebrand-disease
9. https://www.aafp.org/pubs/afp/issues/2009/1201/p1261.html
10. https://www.hemophilia.org/bleeding-disorders-a-z