Diagnosis and management of von Willebrand disease

Diagnosis of von Willebrand disease requires an understanding of the classification of the condition.

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Erik von Willebrand first described inherited von Willebrand disease (vWD) in 1926, when he documented an autosomal-dominant pattern of inheritance of excessive bleeding (as opposed to X-linked transmission that characterises the common 2 types of haemophilia) in a family from the Åland Islands in the Gulf of Bothnia. vWD is caused by a decreased level or function of von Willebrand factor (vWF) and may be inherited or acquired. While we have come a long way in characterising the disorder, much remains to be clarified regarding both diagnostic assessment and pathophysiology and, to a lesser extent, clinical management of this common bleeding disorder.

Structure and function of von Willebrand factor

vWF is a glycoprotein that is synthesised in both endothelial cells and megakaryocytes (in the bone marrow). This large gene, of approximately 178 kilobases, is situated on chromosome 12 (with a pseudogene located on chromosome 22). The protein undergoes extensive post-translational modification and homodimerisation, followed by formation of disulfide-linked large multimers in the circulation. This form of the protein is highly active and is rapidly degraded into smaller multimers by ADAMTS13. It may be either secreted constitutively, or stored in Weibel-Palade bodies in the endothelial cells or α-granules of platelets for later secretion.

vWF has two major functions:

- To enable platelet–subendothelial and platelet–platelet adhesion via its collagen and (platelet) GPIb binding domains. This is particularly important under conditions of high shear stress, such as that found in the arterial circulation. Platelet interaction is also facilitated by adhesion to the platelet receptor GPIIb-IIIa ($\alpha_{IIb}\beta_3$ integrin) on activated platelets.
- To bind and protect factor VIII from premature proteolysis with a shortened half-life in the circulation. The association with vWF also helps locate factor VIII at the site of vascular injury.

The level of vWF in the circulation is variable and may be affected by inherited factors such as ABO blood group (people with blood group O having levels reduced by 25%), race (studies in the USA show that black women have higher levels than white women) and environmental factors such as age (young infants have higher levels), oestrogen and thyroid hormone levels (deficiencies may cause lower levels) and stress.

Table I. Classification of von Willebrand disease

Quantitative deficiency of vWF
Type 1: Partial (mild to severe)
Type 3: Complete
Qualitative deficiency of vWF
Type 2A: Decreased platelet-dependent function with absent high molecular weight multimers
Type 2B: Increased affinity with platelet GP1bα, with thrombocytopenia
Type 2M: Decreased platelet-dependent function with normal high molecular weight multimers
Type 2N: Decreased affinity for factor VIII, with low circulating factor VIII levels

Classification of von Willebrand disease

The most recent classification was proposed in 1994: vWD is divided into 3 major groups – 2 quantitative deficiencies and 1 qualitative deficiency (with 4 major subgroups). Further subdivisions have been proposed, but are not relevant for this review. The classification is presented in Table I.

Type 1 is thought to represent 80% of all cases and may be present in 0.8% of the general population – the majority of these cases are mild, but it should be noted that type 1 may be severe, with levels so low that they approach those found in severe type 3. In many recent trials it has also been found that type 2 has been misdiagnosed as type 1, further contributing to the general difficulty of accurately classifying this disorder in clinical practice.

Diagnosis of von Willebrand disease

To diagnose vWD the following general features should be present:

- a significant bleeding history that generally dates back to childhood
- a low level of vWF or its activity
- a family history (autosomal dominant or rarely recessive) – this criterion need not be filled in case of a new mutation.

Clinical assessment

Up to 25% of the general population may respond positively to a question regarding excessive bleeding or bruising; for this reason attempts have been made to standardise the history, as well as to provide an objective, quantitative score and correlate this with a significant positive predictive value. The predominant bleeding sites in vWD are mucous membranes and skin. An approach to significant bleeding symptoms is outlined below:[1]

- **Nose bleeding**. Two or more episodes (without a history of trauma) not stopped by short compression of < 10 min, or one or more episode requiring blood transfusion.
- **Cutaneous haemorrhage and bruising** with minimal or no apparent trauma – as a presenting symptom or requiring medical treatment.
- **Prolonged bleeding from trivial wounds**, lasting ≥ 15 min or recurring spontaneously during the 7 days after wounding.
- **Oral cavity bleeding** that requires medical attention, such as gingival bleeding, or bleeding with tooth eruption or bites to lips and tongue.
- **Spontaneous gastrointestinal bleeding** requiring medical attention or resulting in acute or chronic anaemia, unexplained by ulceration or portal hypertension.
- **Tooth extraction** or other oral surgery such as tonsillectomy and adenoidectomy followed by heavy, prolonged, or recurrent bleeding requiring medical attention.
- **Menorrhagia** resulting in acute or chronic anaemia, or requiring medical treatment, not associated with structural lesions of the uterus.
- Bleeding from other **skin or mucous membrane surfaces** (e.g. eye, ear, respiratory tract, genitourinary tract other than uterus) requiring medical treatment.

Criteria for bleeding symptoms

A significant mucocutaneous bleeding history requires:

- at least two symptoms in the absence of a blood transfusion history, or
- one symptom requiring treatment with blood transfusion, or
- one symptom recurring on at least 3 distinct occasions.

Criteria for family history

A positive family history compatible with vWD type 1 requires that

- at least 1 first-degree relative, or
- at least 2 second-degree relatives have a personal history of significant mucocutaneous bleeding and laboratory tests compatible with vWD type 1. A more rigorous and validated questionnaire with a bleeding score may be found at: http://www.med.unc.edu/isth/SSC/collaboration/Bleeding_Type1_VWD.pdf [2]

The level of vWF in the circulation is variable and may be affected by inherited factors such as ABO blood group.

It can be seen from the above that the history remains an integral and essential part of the diagnostic strategy that should not be glossed over, particularly in the light of difficulties in interpreting von Willebrand assays, which are outlined below. A strong history should prompt ongoing investigation despite initial normal results; conversely, false-positive laboratory results may result in a wrong diagnosis of vWD in a patient with a weak history of bleeding.

A drug history is also vitally important, especially relating to antiplatelet agents and non-selective NSAIDs – a history of worsening bleeding after ingestion of these drugs provides a useful clue to the presence of vWD, but is not at all specific. The use of oestrogen-containing oral contraceptives should also be noted; low-dose preparations may not affect diagnosis, but high doses may elevate vWF and give a false-negative result.

Laboratory diagnosis

A few baseline investigations should always be performed in the workup of an unexplained bleeding disorder – these are tabulated and the likely findings in vWD noted:

- FBC (and more particularly platelet count) – normal (except type 2B – low)
- aPTT – normal, or borderline to moderately elevated
- prothrombin time (INR) – normal
- fibrinogen – normal.

The bleeding time is a commonly performed screening test for vWD – however, it suffers from a number of problems in that it is neither sensitive nor specific; aspirin should be avoided for 10 days and NSAIDs for 3 days prior to the test. It also requires an experienced technologist and standardised equipment. A normal bleeding time does not exclude the diagnosis of vWD.

An alternative new assay is the use of the PFA-100 analyser, which mimics high shear stress conditions *in vitro*, and produces a reading called the platelet closure time. This is prolonged in vWD and appears to be more sensitive (although not specific); however, its utility is still debated and it is not widely available in South Africa.

The standard von Willebrand assays are (requiring a citrated blood sample):

- von Willebrand antigen level (vWF:Ag)
- measure of function – ristocetin co-factor activity (vWF:Rco) (note that other functional assays such as the collagen-binding assay have now also been described)
- factor VIII level (usually determined by functional assay)
- multimer assay (for use in difficult cases)
- factor VIII binding assay for type 2N (Normandy).

Using a combination of these tests it is possible to diagnose and classify vWD – if the VWF:Ag and vWF:RCo show concordance, then the diagnosis is either type 1 or 3 (depending on levels); if there is a less than 0.7 ratio between vWF:Ag and vWF:RCo (i.e. VWF:RCo is disproportionably low), then the diagnosis is likely to be type 2.

Not infrequently the assays give either normal, borderline or conflicting results. In the situation of a strong bleeding history, it is useful to repeat the tests a number of times: in women of childbearing age, the sample should be taken in the first week of the menstrual cycle. An assessment of thyroid function as well as ABO blood group should be performed (although it is debatable whether to correct normal ranges for blood group O).

If the sample has to be transported from a remote clinic or practice, it should either be transported at room temperature as whole blood, or centrifuged and the plasma supernatant frozen for transport – refrigeration or freezing of whole blood renders the sample useless for evaluation.

Genetic diagnosis is still problematic, particularly for the common type 1. Mutations for the various type 2 and 3 variants have been well described and localised with good structure-function relationships. In the MCMDM-1VWD study, 150 families with type 1 vWD were analysed for mutations, and only 70% of patients had demonstrable mutations in the vWF gene.[3] In 19 families, there was no demonstrable linkage to the vWF gene at all, suggesting that alternative factors (such

as blood group O) may be contributing to the von Willebrand bleeding phenotype. The majority of mutations in this study, and also in the UK and Canadian series, are mis-sense mutations and many are novel and private. Together with the incomplete penetrance and variable expressivity, genetic diagnosis for type 1 vWD is still not feasible at this time.

Therapy

Effective therapy is available for people living with vWD; this may be required for frequent ongoing complications such as epistaxis or menorrhagia, or more significant but rare stressors such as surgical intervention. The first aspect that should be stressed is avoidance of all aspirin-containing medication, including low-dose prophylactic doses; aspirin irreversibly inhibits platelet cyclo-oxygenase and the platelet is non-functional for its entire lifespan. NSAIDs are relatively contraindicated, but may be given in short courses (note that the newer COX-2 selective agents have a far less anti-platelet effect and are safer).

A Medic-Alert disc should be obtained, and the patient data entered into the confidential national database, the South African Haemophilia Register (Professor C Karabus, Red Cross Children's Hospital, ckarabus@ich.uct.ac.za, or Sr A-L Cruickshank, Groote Schuur Hospital).

Anti-fibrinolytics

Tranexamic acid (and to a lesser extent epsilon-aminocaproic acid) inhibits plasminogen activation to plasmin, and thus prevents clot breakdown. They are highly effective agents, particularly in menorrhagia, epistaxis and oral cavity bleeds, which are common in vWD, and may be used as single agents or in combination with other modalities. When used for menorrhagia, they should be taken for the first 3 - 4 days of the menstrual cycle. The usual dose for tranexamic acid is 1 g 6 - 8 hourly as an oral formulation; an intravenous preparation is also available. It is also highly effective when used as a mouthwash – the tablet may be crushed and placed in water, or the effervescent formulation, if available, may be used for this purpose.

Desmopressin

Desmopressin (DDAVP) is a synthetic analogue of arginine vasopressin, and was originally developed for use in diabetes insipidus. It releases vWF, factor VIII and plasminogen activator from storage sites, as well as causing mild platelet activation and adhesion to sites of injury. Both nasal and intravenous preparations are available; the IV dose is 0.3 µg/kg given as an infusion over 20 minutes; facial flushing and headache are commonly reported symptoms. The nasal preparation is a much higher dose than the standard intranasal DDAVP used in the therapy of diabetes insipidus (viz. 300 µg versus 10 µg bd). The high-dose nasal preparation is currently not easily obtainable in South Africa.

DDAVP is useful for patients with type 1 disease where there is still a significant circulating level of functional protein; it may occasionally be of benefit in type 2A, and is theoretically contraindicated in type 2B (where it may worsen the thrombocytopenia). All patients for whom DDAVP is considered should have a diagnostic trial of this agent with blood levels determined after infusion to ensure that adequate elevation of vWF is achieved. Patients in whom the elevation is not satisfactory may still derive some benefit owing to the platelet activation obtained. It is considered good practice to add an antifibrinolytic (owing to the concomitant release of plasminogen activator) when using DDAVP.

Caution is advised with multiple repeat doses owing to the water retention and subsequent hyponatraemia; and in older individuals where the risk of thrombotic events is increased.

Factor VIII concentrate

Most plasma-derived factor VIII concentrates have equimolar or higher concentrations of vWF; this does not apply to recombinant factor VIII concentrates. The preparations vary in the amount of vWF as well as the amount of active high molecular weight multimers. All preparations are now carefully screened for infections, contain viral inactivation steps in the manufacture, and are considered safe. These should be used in types 2 and 3, as well as severe type 1 with an inadequate response to DDAVP. Dosages should be discussed with clinicians familiar with the use of these products.

Conclusion

vWD is a common but significantly under-diagnosed bleeding entity in the general population. Diagnosis may be problematic, but the standard tests are widely available and should be utilised more frequently in patients who have a strong personal and family history of a mucocutaneous bleeding disorder. Effective therapy is widely available, and is in all likelihood being used to good effect in patients who have the disorder, but have not been diagnosed as such. Much more work is required to elucidate the genetic underpinnings of the common type 1 disorder and its pathophysiology, and this may hopefully translate into better diagnostic strategies in the future.

References

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2. Tosetto A, Castaman G, Rodeghiero F. Assessing bleeding in von Willebrand disease with bleeding score. *Blood Rev* 2007; 21(2): 89-97.
3. Goodeve A, Eikenboom J, Castaman G, *et al*. Phenotype and genotype of a cohort of families historically diagnosed with type 1 von Willebrand disease in the European study, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD). *Blood* 2007; 109(1): 112-121.

A very good and easily readable reference by Carol Kasper for those who require more detail is found at: http://www.med.unc.edu/isth/publications/vwd_monogaph/VWD_monograph_2005.pdf

In a nutshell

- Mild type 1 vWD is common and significantly underdiagnosed.
- A detailed history of mucocutaneous bleeding (epistaxis, mouth, menorrhagia, bruising) since childhood is an essential tool in the diagnosis of vWD.
- In women in whom the tests are not diagnostic the best time to sample blood is during the first week of the menstrual period.
- Aspirin should be avoided in patients with vWD, and NSAIDs prescribed with caution.
- Tranexamic acid is very effective in controlling most minor bleeds as well as menorrhagia (for which the combined oral contraceptive pill is also effective).
- DDAVP should be considered in type 1 disease, but access to the intranasal preparation is limited.
- Patients should be registered with Medic-Alert and the data sent to the South African Haemophilia Register.