

Factsheet: von Willebrand Disease

Disease Information

von Willebrand disease (vWD) is a heterogeneous and complex disorder affecting about 1/100 people. Men and women are equally affected. It is the most common cause of excessive bleeding or bruising in the general population and is caused by a deficiency or a defect in von Willebrand factor (vWF). vWF is necessary for normal platelet function, particularly for binding to exposed collagen at sites of vascular damage. This in turn provides a phospholipid surface to facilitate the formation of a haemostatic plug. vWF also acts as a carrier protein for Factor VIII:c, preventing degradation of FVIII:c by proteolytic enzymes and inactivation by activated protein C, and localising fibrin formation. The clinical findings in vWD vary greatly due to the interaction between vWF and FVIII:c, and range from mild bruising due to decreased platelet adhesion, through to more major bleeding similar to that seen in haemophilia due to low levels of FVIII:c. Severe bleeding may occur in extreme cases. Bleeding on presentation relates directly to vWF/FVIII:c function, for example, decreased platelet adhesion seen in mild type 1 vWD results in bruising or mild bleeding of mucosal surfaces, but there is usually sufficient FVIII:c to maintain secondary haemostasis. Lower levels of FVIII:c are seen in type 2N and type 3 vWD, which may present with a bleeding picture similar to that of haemophilia, such as joint and muscle bleeds.

Treatment depends on the type of vWD. vWF concentrates are available but usually only used for severe bleeds or to treat type 2A, 2B or type 3 vWD. The usual treatment for vWD is DDAVP, this works by causing vWF to be released from endothelial cells and results in a temporary increase in plasma vWF levels. It can be given intravenously or intranasally (into the nose). Tranexamic acid may also be administered as it slows down fibrinolysis.

vWF is synthesised and stored predominately in vascular endothelial cells, and is also synthesised in megakaryocytes and stored in the platelets. When vWF is first released into the plasma it is in the ultra-large form (multimers), these ultra-large multimers are quickly processed further into smaller multimers by cleavage by the protease ADAMTS-13 (A Disintegrin And Metalloprotease with ThromboSpondin repeats), resulting in the reduction in size of the multimers. When ADAMTS-13 levels are decreased, ultra-large multimers appear in the circulation and cause platelet aggregation in vivo, often resulting in thrombotic thrombocytopenic purpura (TTP). Congenital TTP is a rare inherited disease caused by the production of non-functional ADAMTS13. Acquired TTP is caused by antibodies to ADAMTS13 that inhibit enzyme activity.



Classification

vWD is a heterogeneous and complex bleeding disorder, of which there are numerous subtypes:

Type 1 vWD

This is a partial quantitative deficiency of vWF, typically autosomal dominant in inheritance although diagnosis is complicated by variable expression. Characterised by parallel reductions in vWF antigen, vWF activity and Factor VIII:C. Multimer distribution is normal. This may be the most difficult of the subtypes to diagnose as plasma vWF levels are influenced by blood group, race, age, pregnancy, pathological conditions, exercise, stress and trauma.

Type 2 vWD

Usually an autosomal dominant disorder. It is characterised by qualitative abnormalities of vWF structure and/or function. Quantitatively vWF is mildly or moderately reduced, but may be normal. There are 4 major subtypes of type 2 vWD.

Type 2A

10-15 % of all cases of vWD. Qualitative vWF defect associated with absence of the largest multimers and low levels of vWF:Rco activity relative to vWF:Ag. Generally autosomal dominant. DDAVP has a variable effect, vWF concentrates recommended.

Type 2B

Approximately 5% of all cases of vWD. Qualitative defect with increased affinity for platelet GPIb, also associated with reduced levels of large multimers. Type 2B shows enhanced ristocetin-induced platelet agglutination (RIPA) although vWF:Rco may be normal or increased. Inheritance is autosomal dominant. Patients with Type 2B must not be treated with DDAVP as this causes severe thrombocytopenia.

Type 2M

Qualitative vWF defect associated with reduced binding of vWF to GPIb but with a normal range of multimers. Inheritance is autosomal dominant.

Type 2N (Normandy)

Qualitative vWF defect resulting from defective vWF binding to FVIII:c and consequently low levels of circulating FVIII:c. Inheritance is autosomal recessive.



Type 3 vWD

Usually autosomal recessive inheritance (or occasionally a manifestation of homozygous or compound heterozygous inheritance of type 1 vWD). Accounts for 1-5% of clinically significant vWD, has very low or undetectable levels of vWF and generally presents with severe bleeding early in life. Patients with type 3 vWD with very low FVIII:c levels can experience soft tissue and joint haemorrhage, as seen in moderate and severe haemophilia. DDAVP ineffective, vWF concentrates recommended.

Pseudo, or **platelet-type**, vWD is similar to Type 2B, but the defect is in the platelets instead of in the factor.

Acquired vWD

Caused by antibodies against vWF molecule which can lead to a variable clinical presentation. Antibody mediated usually secondary to another autoimmune disorder, such as SLE or may be associated with haematological malignancies such as myeloma. May present with severe bleeding like haemophilia A due to very low levels of FVIII:c.

Summary

VWD Classification	Description
Type 1	Partial quantitative deficiency of vWF. Typically autosomal dominant in inheritance although diagnosis is complicated by reduced penetrance and variable expressivity. Characterised by parallel reductions in vWF:Ag and Factor VIII. Multimer distribution is normal.
Type 2A	Qualitative vWF defect associated with absence of the largest multimers and low levels of vWF:Rco activity relative to vWF:Ag. Generally autosomal dominant, caused by missense mutations within the vWF A2 repeat. Group 1 (defect in intracellular transport) or group 2 (increase in proteolysis in plasma after secretion).
Type 2B	Qualitative vWF defect associated with (usually) reduced high molecular weight multimers. Also enhanced ristocetin-induced platelet agglutination (RIPA) although vWF:Rco may be normal. Inheritance is autosomal dominant.
Type 2M	Qualitative vWF defect associated with specific defects in platelet/vWF interaction but with a normal range of multimers. Inheritance is autosomal dominant.
Type 2N	Qualitative vWF defect resulting from defective vWF binding to FVIII:c and consequently low levels of circulating FVIII:c. Inheritance is autosomal recessive.
Type 3	Clinically severe quantitative disorder resulting from a markedly reduced or absent platelet and plasma vWF (less than 5U/dL). FVIII activity also reduced. Usually autosomal recessive inheritance (or occasionally a manifestation of homozygous or compound heterozygous inheritance of type 1 vWD).

Adapted from Keeney and Cumming (2001)

Laboratory Testing

Screening tests alone are not sensitive enough to exclude vWD, indeed it is not uncommon for the APTT to be within the normal range. The Bleeding Time has poor reproducibility and has been mainly superseded by testing using a platelet function analyser (PFA). The PFA simulates a damaged blood vessel to measure platelet function in primary haemostasis, again it is not specific for vWD and may be prolonged by other platelet defects.

It is possible to distinguish between vWD types by measuring vWF ristocetin cofactor activity (vWF:Rco), vWF collagen binding activity (vWF:CB), vWF antigen (vWF:Ag) and FVIII:c. The correct diagnosis is important because treatment is dependant on the subtype of vWD.

Immunoassays and functional assays are available for the measurement of vWF in plasma. Antigen levels are most commonly measured by an enzyme-linked immunosorbent assay (ELISA). vWF activity is measured by vWF:Rco assay or vWF:CB assay. Diagnosis of vWD should not be based on antigenic assays alone, because both qualitative and quantitative defects may be present. vWF:Rco measures the ability of plasma vWF to bind washed, normal fixed platelets in the presence of ristocetin. The assay is difficult to standardise and has high inter-assay and inter-laboratory variability. The main advantage of the ELISA vWF:Rco is its reproducibility. The vWF:CB assay relies on the ability of plasma vWF to adhere to collagen and is sensitive to low levels of HMW multimers. It is also available in an ELISA format. FVIII:c can be normal in type 1 vWD, so a normal assay result does not exclude vWD.

Type 2N vWD can be diagnosed with a vWF:FVIII:c Binding Assay, which is performed in just a few specialised laboratories. The defect in this subtype is on the FVIII:c binding site. FVIII:c levels are reduced with normal vWF:Ag and vWF:Rco, so gives a similar picture to mild haemophilia A but for an autosomal inheritance pattern.

If a diagnosis of vWD type 2B is suspected then Ristocetin Induced Platelet Aggregation (RIPA) testing can be performed for confirmation. In vWD type 2B platelet aggregation occurs at low ristocetin concentration (<0.8 mg/mL) that has little or no effect on platelet-rich plasma from normal controls and patients with other types of vWD. In the RIPA test the patient platelets are used rather than test platelets as in the vWF:Rco test.

Laboratory values and clinical symptoms can vary considerably, even in the same individual, and establishing a definite diagnosis of vWD is often difficult, therefore follow-up testing is advised to confirm or exclude a diagnosis of vWD.



Multimer analysis may be helpful in type 1 vWD, vWF multimer distribution is typically normal and the intensity of band staining will correlate with vWF antigen level. Multimer analysis will distinguish type 2A vWD, lack of the largest and intermediate multimers, and type 2M vWD with all multimers present. Type 2N vWD shows a normal multimer distribution, while in type 3 vWD there are no multimers present.

Investigation of TTP

Quantitation of ADAMTS13 activity has been useful in distinguishing between TTP and haemolytic uraemia syndrome or idiopathic thrombocytopenia purpura. Testing is available as a functional fluorescence resonance energy transfer (FRET) assay and in an ELISA format.

Product Information

The Axis-Shield von Willebrand Factor activity test is a quantitative direct enzyme-linked immunosorbent assay (ELISA) for the detection of vWF:Rco activity in citrated human plasma.

The Vital™ CBA ELISA is for the detection of Collagen Binding activity in citrated human plasma.

The American Diagnostica range includes FVIII:c antigen, ADAMTS13 antigen and antibody assays available as ELISA kits. The ADAMTS13 activity is available as a functional fluorescence resonance energy transfer (FRET) assay.

Ordering Information

ADI-885	IMUBIND® vWF Activity ELISA, 96 microwell plate
VD-4000040	Collagen Binding Assay, 12 x 8 tests
ADI-884CON	IMUBIND® Factor VIII ELISA, 12 x 8 tests
ADI-811	IMUBIND® ADAMTS13/FXI Complex ELISA, 96 microwell plate
ADI-812	ACTIFLUOR™ ADAMTS13 Activity Assay, 48 tests
ADI-813	IMUBIND® ADAMTS13 ELISA, 96 microwell plate
ADI-813H (half size)	IMUBIND® ADAMTS13 ELISA, 3 x 16 strip wells
ADI-814	IMUBIND® ADAMTS13 Autoantibody ELISA, 96 microwell plate
ADI-814H (half size)	IMUBIND® ADAMTS13 Autoantibody ELISA, 3 x 16 strip wells

