Von Willebrand disease

Key facts

- Von Willebrand disease (VWD) is the most common heritable bleeding disorder in humans.
- The condition is caused by a low or absent levels of von Willebrand factor (VWF), a clotting protein important for forming blood clots.
- VWD is an autosomal condition, and so men and women have an equal chance of being affected.
- Females are more likely to present with symptoms, as they can be affected by heavy periods and bleeding during childbirth.

Clinical features

- Individuals with mild forms of VWD may not suffer any symptoms in daily life, and only exhibit increased bleeding after trauma or a surgical procedure.
- The most common symptoms are nosebleeds, oral bleeding, bleeding or bruising after minor trauma and heavy menstrual bleeding in women.
- Affected individuals may notice that cuts take longer than normal to stop bleeding.
- When VWF is completely absent, factor VIII (FVIII), another blood-clotting protein, is also very low, and patients may suffer bleeding into joints (as is typical of haemophilia), or severe internal bleeding.

Diagnosis

- Unexplained or unusual bleeding in the clinical history, or a family history of bleeding.
- A similar clinical picture may also arise from disorders of platelet number or function.
- A clotting screen and full blood count usually present normally when tested.
- Patients with a suggestive history should be referred to a haematologist for laboratory testing, as these tests are mostly done in specialist coagulation units and may not be requestable in primary care.
- Laboratory tests are performed to establish:
  - » the amount of VWF present;
  - » the ability of the present VWF to bind to platelets and collagen;
  - » the amount and binding activity of present FVIII; and
  - » the presence of high molecular weights of WVF multimers that are essential for normal activity.
- These tests can be used to determine the type of VWD, and to distinguish between VWD and haemophilia A

Types of VWD

- There are six types of VWD as well as the category ‘low VWF’.

- The diagnostic classification is shown in the following table (Table 1):

Table 1: Classification of VWD

Type	Description	Comments	Inheritance
1	Partial quantitative deficiency of VWF.	Mostly heterozygous missense variants. Genetic tests fail to detect a variant in ~40% of cases. Includes VWF variants causing rapid VWF clearance and requires function: antigen ratio >0.6.	Mostly autosomal dominant inheritance when VWF <0.3 iu/mL. VWF variants in kindred with levels >0.3 iu/mL show variable penetrance.
2	**Qualitative VWF defects**		
2A	Decreased VWF-dependent platelet adhesion, with selective deficiency of high-molecular-weight multimers.	Variants specifically affecting multimerisation.	Mostly autosomal dominant
2B	Increased affinity for platelet GPIb.	Gain of function variants in the platelet-binding region. Should be distinguished from platelet type pseudo-VWD (PT-VWD), which is due to variants in the platelet GPIb gene.	Autosomal dominant
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of HMW multimers.	Loss of function variants in the platelet or collagen-binding regions. May be combined quantitative/qualitative defect.	Autosomal dominant
2N	Markedly decreased binding affinity for FVIII.	Loss of function variants in the FVIII-binding regions. Should be distinguished from mild haemophilia A.	Reduced VWF: FVIII binding defects are more commonly identified in a compound heterozygote state with a VWF null allele, rather than the classical homozygous.
3	Rarest and most severe form of VWD, with virtually complete deficiency of VWF, and a consequently low level of FVIII.	Variants resulting in null alleles, for example, nonsense, frameshifts or deletions. VWF levels are <0.03 iu/mL in most assays	Autosomal recessive; carriers are usually asymptomatic. Prevalence is approximately 1 in 10^6, but is higher where consanguinity is common.

Low VWF

- Many people with a VWF level below the normal range do not have any increased tendency to bleed, and so cannot be said to have VWD due to this level alone.
- From large population studies, it appears that the VWF level must fall below approximately 0.3 iu/mL (normal range 0.5-1.5) before an increased bleeding tendency becomes very likely. However, investigations also show that bleeding is more frequent in those who have 0.3-0.5 u/mL of VWF activity, suggesting that in these patients, bleeding may be due to a combination of low VWF and another factor, such as impaired platelet function.
- Patients with VWF activity between 0.3 and 0.5 are classified as having 'low VWF', but not VWD.

Genetic basis

- The gene for VWF (*VWF*) lies on the short arm of chromosome 12 and is therefore subject to autosomal inheritance, which helps to distinguish it from haemophilia, which is X-linked.
- Although most cases of VWD arise from genetic variants in *VWF,* there are many other loci which have a quantitative effect on plasma VWF. The most notable of these is the ABO locus; group O individuals have a mean VWF level that is between 25% and 40% lower than other blood groups.
- The mature VWF protein consists of multiple polypeptide chains, which makes it susceptible to the effects of dominant negative variants; the more severe forms of type 1 VWD have a dominant inheritance.
- Type 2 VWD is indicated by a significant discrepancy between the amount of VWF antigen present and one of the measures of function. The ratio of function to antigen is ≤0.6 in type 2, whereas it is >0.6 in types 1 or 3. In type 2 VWD, the variants are usually localised to a particular functional site in the molecule.

Acquired von Willebrand syndrome

- As well as being inherited, a phenotype similar to VWD, called acquired von Willebrand syndrome (AVWS), exists. In these cases, low levels of VWF can occur as a result of a variety of factors.
- Careful attention to the patient's history and any associated potential causes should allow most cases to be identified without recourse to genetic analysis.

Clinical management

- Milder forms of VWD can be managed with tranexamic acid which does not affect VWF levels. Instead, it improves bleeding symptoms by inhibiting fibrinolysis.
- When surgery is required, or in cases of more significant bleeding, it may be necessary to elevate VWF levels. This can be achieved with desmopressin, which is usually administered by subcutaneous injection.
- The more severe forms of VWD require factor levels to be increased with VWF-containing factor concentrates. These are plasma derived, but a recombinant version has recently been licensed.

Direction to further reading, guidelines and patient groups

- Information for doctors: http://www.ukhcdo.org/
- Information for patients: https://haemophilia.org.uk/ and https://www.wfh.org/

This information is intended for educational use and was current in January 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and the Genetics Working Party of the UK Haemophilia Centre Doctors Organisation.