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Diversified and transforming von Willebrand disease

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Progress in diagnostics and treatment

Diversified and transforming von Willebrand disease

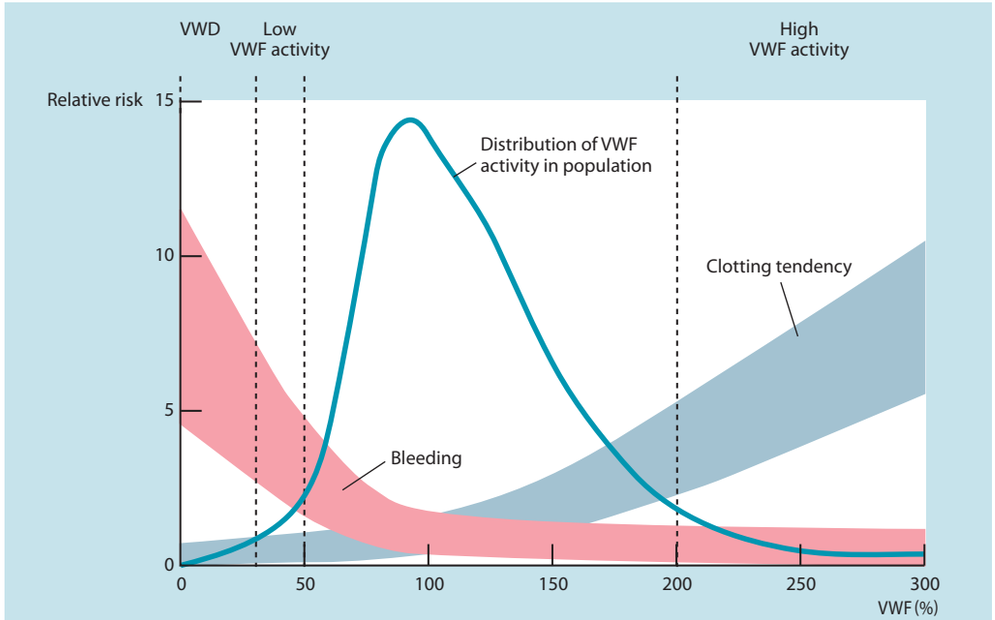
Von Willebrand disease (VWD) is the most common hereditary condition in both men and women characterized by mucosal bleeding tendency ranging from mild to very severe. The condition is caused either by a deficiency or dysfunction of the vW factor (VWF). Understanding of the diversity of VWD has increased. It is important to evaluate how laboratory test abnormalities correlate with the clinical condition, lead to a diagnosis and guide the treatment. With ageing, VWF activity increases and a mild disease may resolve. The clinical picture of the disease varies, and on the other hand, the diagnostic criteria for the actual VWD have become more stringent. Therefore, especially in patients who have earlier been diagnosed with a mild type 1 disease, VWF activity and the clinical bleeding tendency should be determined and the appropriateness of the diagnosis evaluated before any surgeries or other procedures, at the latest.

Von Willebrand (vW) factor is critical in blood coagulation, both in primary and secondary haemostasis (1). The vW factor (VWF) is needed at vascular injuries as a "glue protein" for adhesion of platelets and also as a carrier of coagulation factor VIII (FVIII). Deficiency of VWF results in a bleeding tendency, the severity of which depends primarily on VWF and FVIII activities. The prevalence of VWD is about 1%, but the condition is clinically relevant and symptomatic in about 0.01%.

Scoring of bleeding symptoms may be useful when evaluating the connection between phenotype and genotype, because the bleeding tendency and VWF activity do not entirely correlate with each other. Symptoms and laboratory test results in VWD patients and the rest of the population are partially overlapping (**PICTURE 1**) (2,3). In recent years, there has been an increasing tendency to re-evaluate the accuracy and permanence of earlier diagnoses of mild type 1 VWD. Also new tests for more accurate diagnostics of VWD and its variants have been developed.

VWF in coagulation

VWF is a large multimeric and adhesive plasma glycoprotein which is produced by endothelial cells and megakaryocytes (4). Fully functional large multimers are formed in a multiphasic reaction from propeptide, a precursor of VWF, via dimerisation (**PICTURE 2**) (5,6). Normal plasma also contains ADAMTS13 protease which cleaves large multimers. In blood circulation, VWF is usually present in inactive form. The main function of VWF, which is activated by an endothelial injury and which binds to collagen, is to support platelet adhesion, especially under conditions of rapid flow. Binding of VWF to the platelet GPIb receptor activates platelets, and binding of VWF to GPIIb/IIIa receptors supports platelet aggregation. The bleeding problem develops when platelets cannot form a secure plug either due to a quantitative or qualitative defect in VWF. Also, the clot will remain weaker as there is not enough VWF to protect FVIII and because the half-life of FVIII is short without VWF (**PICTURE 3**) (6).



PICTURE 1. Relationship between von Willebrand factor (VWF) activity and bleeding risk (3). The thick turquoise line describes the distribution of VWF activity in the population. The reddish area describes the relative bleeding risk and the blue-grey area describes relative clotting tendency. VWF activity less than 20% to 30% indicates VWD, activity of 30% to 50% indicates a bleeding risk, and activity of >200% indicates an increased clotting risk. The relative risk has been defined to be 1.0 when the mean VWF activity in the population is expected to be 100%. VWD = von Willebrand disease

Symptoms

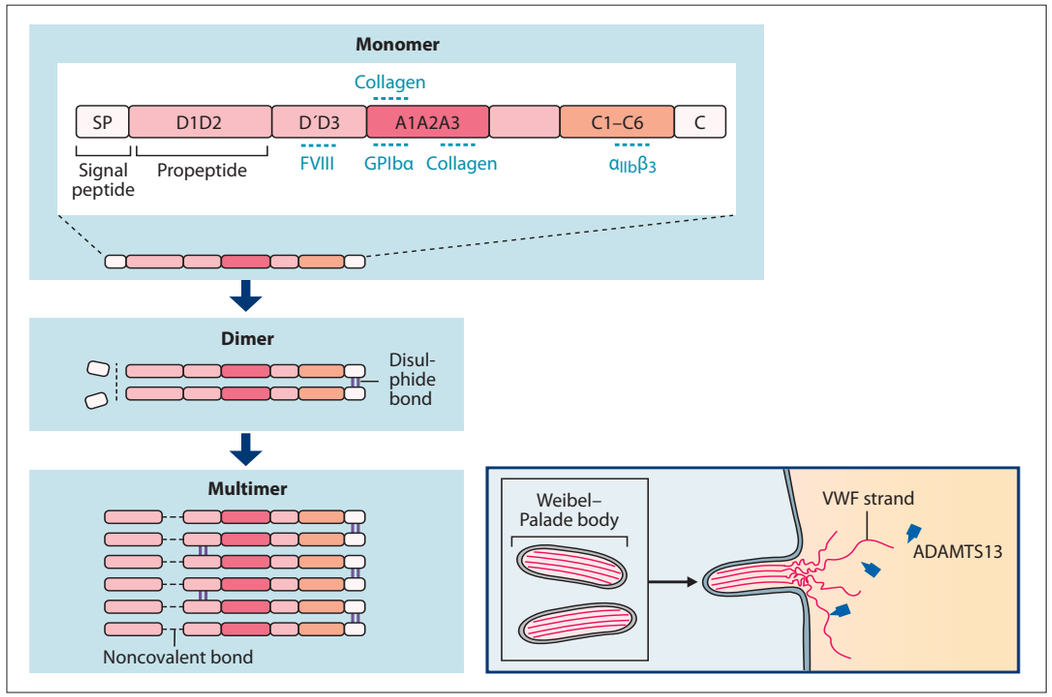
Symptoms affecting the skin and mucous membranes are typical in primary haemostatic disorders, i.e. thrombocytopenia, platelet function disorders and VWD. The list of symptoms is worth going through while taking the history of bleedings (**TABLE 1**) (7–9). The bleeding questionnaire and the scoring instructions based on the international ISTH Bleeding Assessment Tool (ISTH BAT) can be found at veripalvelu.fi and huslab.fi (8,9).

The history of bleedings is partly subjective, and symptoms can change and even resolve with ageing. Typical symptoms include epistaxis, easy bruising, bleedings in connection with procedures on mucous membranes, and in women, menorrhagia and bleedings related to childbirth. With ageing, the tendency for intestinal bleeding increases. Usually, bleeding symptoms are mild in type 1 VWD and increase gradually from type 2 to type 3

Diagnosis and classification

The VWD diagnosis is based on the patient's history of bleedings, bleeding tendency of close relatives and low VWF or FVIII activities in laboratory tests (6). VWD is classified into three main types based on the quantitative (types 1 and 3) or qualitative (types 2A, 2B, 2M and 2N) defect (**TABLE 2**).

About 70% to 80% of all VWD cases involve type 1 VWD which is inherited as an autosomal dominant disease. In these patients, VWF activity is abnormally low (less than 30%) and laboratory tests reveal an equivalent decrease in VWF and FVIII activities. The normal range of VWF activity is from 50% to 150%. Nowadays, type 1 disease is diagnosed when VWF activity is repeatedly less than 30%. Patients with VWF activity ranging from 30% to 50%, are classified into groups of "low VWF activity" or "VWD tendency" in which the bleeding tendency may be increased, even though the diagnostic criteria of VWD are not met (**PICTURE 1**) (3).



PICTURE 2. Synthesis of von Willebrand factor (VWF) (5,6). VWF is produced by endothelial cells and megakaryocytes. It is initially a monomer which then undergoes dimerisation in connection with the cleavage of a signal peptide and is stored as a helical multimer in Weibel-Palade bodies of endothelial cells and alpha-granules of platelets. Upon release into blood circulation, VWF unfolds from its coiled form into long strands which ADAMTS13 then cleaves shorter. The dotted lines mark the binding sites of various factors in VWF. ADAMTS13 = A Disintegrin-like And Metalloprotease domain with a Thrombospondin type 1 motifs, member 13, FVIII = coagulation factor VIII, GPIbα = glycoprotein Ibα

Of the four subtypes of type 2 VWD, 2A, 2B and 2M are inherited as an autosomal dominant disease and 2N as an autosomal recessive disease. The bleeding tendency is often moderate. VWF does not work properly which shows in laboratory tests as normal or somewhat reduced VWF concentration and as a simultaneous severe reduction in VWF activity. **TABLE 2** presents the main features of the current classification (3).

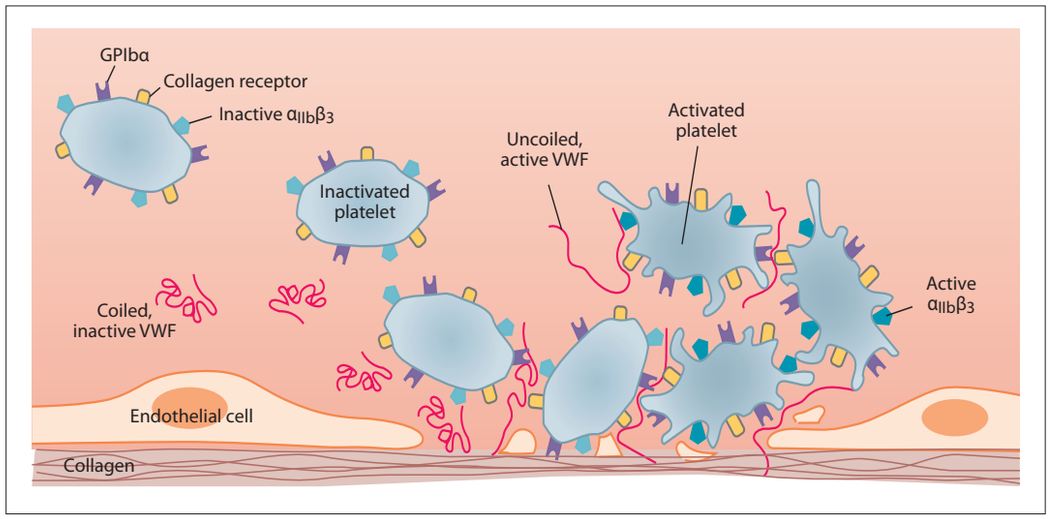
The total VWF deficiency typical of type 3 VWD results in a severe disease form and spontaneous bleedings, also joint bleedings. In Finland, there are about twenty patients with type 3 VWD. Inheritance is recessive and for most patients the close relatives have no signs of VWD nor any knowlegde of carriers of the mutation. When ten Finnish type 3 VWD patients were examined, two dominant mutations were detected; the patients were either doubly heterozygous or homozygous (10).

Mutation testing is not helpful in the diagnostics of type 1 disease as the disease penetrance varies and the mutation type does not affect the disease phenotype.

TABLE 1. Assessment of bleeding symptoms (7–9)

Epistaxis (bilateral, duration over 10 min)
Bruises (more than 5 at a time, large)
Bleeding from minor cuts (duration over 10 min)
Bleeding from mouth cavity (other than gingivitis)
Tooth extraction (prolonged bleeding)
Gastrointestinal bleeding (spontaneous)
Muscle and joint bleedings (without a trauma)
Surgeries (need for blood transfusion)
Menorrhagia (since menarche)
Lochia (over 6 weeks)

The bleeding questionnaire and scoring instructions modified based on the international ISTH Bleeding Assessment Tool (ISTH BAT) (http://c.ymcdn.com/sites/www.isth.org/resource/resmgr/ ssc/isth-ssc_bleeding_assessment.pdf) can be found at veripalvelu.fi and huslab.fi.



PICTURE 3. Role of von Willebrand factor (VWF) in haemostasis (6). VWF is present in blood circulation in an inactive, coiled form. It attaches to collagen filaments exposed due to an endothelial injury and uncoils when activated, exposing the binding site of glycoprotein GPIbα in VWF. The binding of VWF to platelet GPIbα results in platelet adhesion to the site of injury and platelet activation. Along with it, platelets bind to VWF via GPIIb/IIIa receptor and aggregate, forming the primary haemostatic plug.

In some cases VWF production is lower, and in some cases the loss of VWF is accelerated. The clinical penetrance of type 2 VWD is complete (except in type 2N) and the detection of mutations is more reliable when they are limited to a specific domain of the VWF.

Laboratory tests

Mild VWD cannot be excluded if results from haemostatic screening tests (TT/INR and APTT) are within the reference range. The platelet count is usually normal, or may sometimes be reduced in type 2B disease. Basic tests include antigen concentration of VWF (VWF:Ag) and VWF activity (VWF:Act) as well as FVIII activity. Today, VWF activity is measured as binding to platelet GPIb receptor attached to the surface of latex particles. Previously, the reference method was to investigate the ability of VWF to agglutinate platelets in the presence of ristocetin (VWF:RCo).

In healthy individuals, VWF activity is 40% to 200% (11). VWF activity may be lower in blood group O, which is at least partially due to different kind of glycosylation of ABO blood group antigens. There is an abundance of carbohydrates on the surface of VWF, some of which are ABO blood group antigens. Individuals with blood type O do not have any antigens of blood group A or B on the surface of erythrocytes or VWF, which is why VWF is cleared from blood circulation more rapidly than in individuals with blood type A, B or AB (4).

VWF activity is increased by pregnancy, infections and physical and mental stress. The mean half-life of VWF is 10 hours in blood group O and 25 hours in the other blood groups (3,4). Especially in the diagnostics of type 1 disease, the examinations should be repeated at least once after a couple of months, because VWF activity may be temporarily normal for the reasons mentioned above. VWF determines the half-life of FVIII, which is why FVIII activity in VWD patients is often reduced. Platelet function test with a PFA analyser reveals type 2 and 3 VWD but less reliably type 1 VWD.

Reduced binding of VWF to collagen (VWF:CB) suggests a qualitative VWF change caused by certain gene defects as well as a deficiency of large multimers and type 2A and 2B disease. Although tests for VWF activity and binding to collagen exhibit different things in the functioning of VWF, they both are sensitive to the loss of large multimers. Therefore a reduction in the activity-to-antigen ratio (VWF:Act/VWF:Ag less than 0.6) supports the diagnosis of type 2 disease (11,12).

TABLE 2. Classification of von Willebrand disease

Type and subtypes		Proportion of cases	Bleeding tendency
1	Partial VWF deficiency	70–80%	Usually mild
2	Qualitative defect of VWF	20–30%	Moderate
	2A Various structural injuries in VWF which weaken interaction with platelets. Large and intermediate multimers are missing.		
	2B Aberrant VWF increases binding to platelet GPIb receptors so also thrombocytopenia can occur. Large multimers are missing.		
	2M Structural injury, which weakens adhesion to platelet GPIb receptor. Large multimers are present.		
	2N Structural defect, considerable reduction in binding to FVIII. Resembles haemophilia A.		
3	Total VWF deficiency	1–2%	Severe

VWF = von Willebrand factor

Type 1 VWD – variability of clinical picture and laboratory values

Taking into account the prevalence of subjective bleeding tendency, VWF activities measured when investigating bleeding symptoms are often within the lower end of the reference range. Consequently, a definite history of bleedings and repeatedly reduced VWF activity are required for a diagnosis. Nevertheless, it is known that even VWF activity of less than 20% is not always associated with an abnormal bleeding history (12,13).

VWF activity increases physiologically with age which may result in resolution of type 1 disease. In healthy individuals, VWF activity and antigen concentrations have been described to increase by 15% and 17%, respectively, within a period of ten years (14,15). When VW complex (VWF:Act, VWF:Ag, FVIII) values were followed-up for 11 years on average in 31 patients diagnosed with type 1 VWD at adult age, VWF activity was found to have increased by 20%, antigen concentration by 30% and FVIII activity by 20%. The VW complex was normalised in 18 of the 31 patients (14).

Therefore re-evaluation of the diagnosis of type 1 disease is recommended as the patient grows older. If there has been no bleeding symptoms and the VW complex values have normalised, VWD disease can be considered resolved. However, the bleeding tendency in patients aged over 65 years and with type 1 disease has been shown to persist despite normalisation of laboratory test results.

It seems that earlier normalisation of low VWF activity does not always abolish the bleeding tendency (15). Definitive age-specific reference ranges for VWF antigen concentration or activity have not been determined (16).

In terms of differential diagnosis, it is worth keeping in mind that if low VWF activity is no longer detected in individuals earlier diagnosed with a mild VWD but the bleeding tendency persists, the patient may have a platelet function disorder. It has been proposed that the VWD diagnosis should be made only after VWF activity has twice been measured to be less than 30% and the patient has a bleeding tendency considered to be abnormal (17). The concept of "low VWF activity" could be applied in cases in which VWF activity is more than 30% but below the lower end of the reference range (most frequently 50%) (**PICTURE 1**) (3). Even the majority of these patients have mild bleeding symptoms without a significant bleeding risk. This has recently been found to be due to reduced VWF production, in particular, and a good treatment response is achieved with desmopressin (18). However, there is no ICD code for the diagnosis of "low VWF activity", and if the actual VWD diagnosis cannot be made, patients will not get reimbursement for medication used in the treatment of VWD.

TABLE 3. Medication of adults with von Willebrand disease

Type	Alternatives for medication	Alternative/adjunctive medication
Low VWF activity	Desmopressin (one dose, can be repeated after 12–24 hours) For patients weighing >50 kg, 300 microg intranasally (150 microg/nostril), For patients weighing <50 kg, one spray of 150 microg intranasally 0.3 microg/kg intravenously	Tranexamic acid 1 g × 3–4
1	Desmopressin[1]	Tranexamic acid
2	Desmopressin[1] FVIII/VWF combination product or VWF product alone	Tranexamic acid
3	FVIII/VWF combination product or VWF product alone	Tranexamic acid

[1] After the response to the medication has been tested

Due to the diversity of VWF, low activity is in some patients due to the accelerated loss of VWF, rather than due to reduced VWF production. This may have a significance especially when setting the target plasma concentration in the treatment of bleedings.

Also, when assessing the efficacy of desmopressin, it is useful to know whether VWF released by desmopressin is functionally normal or abnormal.

Even though determination of VWF activity before elective procedures is often warranted, routine monitoring of the VW complex activity is not considered necessary.

Treatment

The treatment of VWD is either prophylactic or symptomatic treatment of bleedings (**TABLE 3**) (19,20). The aim is to increase VWF and FVIII activity in plasma with desmopressin or by intravenous administration of either the FVIII/VWF combination or VWF alone. Tranexamic acid is an antifibrinolytic medicine and as such critical in the prophylaxis and treatment of bleedings in VWD patients. Monotherapy with tranexamic acid may be sufficient in connection with mucous bleedings, e.g. menorrhagia and epistaxis, and its role in supporting desmopressin treatment is crucial. Tranexamic acid is not recommended for the treatment of macroscopic haematuria due to the risk of an obstructive clot in the urinary tract.

Desmopressin increases VWF and FVIII concentrations by increasing the release of endogenous VWF from Weibel–Palade bodies in the endothelium and alpha granules of platelets (**PICTURE 3**) (6). Desmopressin also enhances platelet adhesion and releases plasminogen activator into blood circulation. Due to the individual variation in the effect, it is recommended to test the response to the medication (a blood sample 30–60 min after administration of desmopressin) and the duration of the response (a blood sample after four hours) by measuring the activities of VWF and FVIII. Desmopressin can be administered intravenously, subcutaneously, or as a nasal spray (**TABLE 3**). Usually, VWF activity increases about 3- to 5-fold and the response lasts for 6 to 8 hours. In repeated desmopressin administration, the response declines and the risk of adverse effects (fluid retention, increase in blood pressure, hyponatraemia) increases. The dose can be repeated after 12 to 24 hours, but it is not recommended to use desmopressin longer than this. It is also important to limit the daily fluid intake to a maximum of 1,500 ml. Rapidly developing hyponatraemia can be particularly dangerous, which is why instructions for the desmopressin treatment should preferably be given only by a physician who is familiar with the patient's overall situation. Desmopressin is not recommended for patients under the age of two years because of the risk of hyponatraemia. Desmopressin may be used when performing minor procedures, e.g. tooth extraction or tonsillectomy in adults, if an increase in the coagulation factor concentration for 1 to 2 days is considered sufficient. Desmopressin is most useful in type 1 VWD patients whose VWF and FVIII activities

TABLE 4. Need for and dosing of coagulation products (6)

Indication	Dose[1] (IU/kg)	Target activity (VWF:Act and FVIII)	Treatment duration (days)
Bleeding			
Minor or moderate	20–40	Day 1: maximum of >50–80% After Day 1: minimum of >30%	1–3
Severe	50	Day 1: maximum of >100% After Day 1: minimum of >50%	7–10
Procedure			
Tooth extraction	25	Day 1: maximum of >50%	1
Minor surgery	30–60	Day 1: maximum of >50% After Day 1: minimum of >30%	1–5
Major surgery	50–60	Day 1: maximum of >80-100 % After Day 1: minimum of >50–80%	7–10 7–14
Childbirth	40–50	Day 1: maximum of >100% After Day 1: minimum of >50%	3–7

[1] The dose is based on the expected recovery and the FVIII/VWF ratio of the product used. One unit of FVIII increases FVIII activity by two percentage points, and one unit of VWF increases VWF activity by 1.5 to 2 percentage points. FVIII and VWF are given to patients with type 3 VWD and those with type 1 or 2 VWD who have not responded to desmopressin treatment or in whom desmopressin is contraindicated.

exceed 10 to 20% (**TABLE 4**) (5). If desmopressin is not effective enough or if it is contraindicated, replacement therapy with VWF and often also with a coagulation product containing FVIII is warranted. The FVIII/VWF ratio of products varies. VWF and FVIII activities should preferably be monitored also after the procedure, especially when the patient needs treatment for several days (1).

Usually, coagulation products are given if VWF activity and FVIII activity need to be maintained over 50% for a couple of days (**TABLE 4**). This may however increase also FVIII activity by more than 150%, and the risk of thrombosis can increase. Consequently, monitoring of both FVIII activity and VWF activity is warranted.

Usually, prophylactic treatment with coagulation products is needed in severe type 3 VWD and occasionally also in type 2 VWD, especially during pregnancy and in patients with a tendency for joint or intestinal bleedings. Development of alloantibodies against VWF is rare. Prophylactic treatment with a VWF product has not been shown to predispose to the development of antibodies (21).

Characteristics of female patients

VWD is diagnosed twice as often in women as in men. The relevance of a mild disease is greater in women because the bleeding tendency manifests in connection with menstruation and childbirths. In fact, the most significant bleeding problem in women with VWD is menorrhagia (32% to100%) (22). On the other hand, the prevalence of VWD among women with menorrhagia is 5% to 20%, and VWD has been described in 5% to 36% of adolescents with menorrhagia (23,24).

The treatment goal is to prevent or correct anaemia and to improve the quality of life (24,25). The most common treatment is a combined oral contraceptive; a hormone-releasing intrauterine device can also be used. As regards non-hormonal alternatives, tranexamic acid alone or combined with a desmopressin nasal spray may be useful.

No special treatment is needed in connection with a childbirth in women with type 1 VWD whose VWF activity during pregnancy increases to over 50% and whose bleeding symptoms are not particularly severe. In women with type 2 or 3 VWD, the need for replacement therapy with coagulation products during childbirth and the need for follow-up should be assessed and planned in advance if VWF activity during pregnancy does not increase to over 50% or if the patient has a history of severe bleeding symptoms (24,26).

Paediatric patients

If one of the parents has autosomal dominant type 1 or 2 VWD, the child has a 50% chance of inheriting the disease. Usually, there is no need to determine VWF concentrations in small children with no bleeding symptoms, because physiologically, in type 1 VWD at least, VWF activity is often within the reference range in children aged less than one year. Occasionally, VWF activity is normal even in neonates with type 2 VWD. In case of a known gene mutation (type 2 VWD) in the family, a genetic test can be done if the neonate has bleeding symptoms or if a procedure is being planned. As low VWF activity in childhood may however be taken for VWD, the patient needs to be re-assessed later and the diagnosis removed, if needed.

Usually, the diagnostics of a suspected VWD in basically healthy children with only mild bleeding symptoms can be postponed until preschool age if no surgical procedures are planned.

Acquired von Willebrand disease

Acquired VWD is a rare condition in which bleeding symptoms and laboratory findings consistent with VWD manifest themselves in elderly individuals who themselves, or whose close relatives, have not had any bleeding symptoms before. In acquired VWD, VWF is formed normally but its function is reduced or inhibited altogether. Bleeding symptoms vary but the tendency for intestinal bleeding is pronounced in the elderly.

There is no accurate estimate on the incidence of acquired VWD. The condition is probably underdiagnosed because bleeding symptoms may occur in connection with many diseases. In an international registry of 186 patients, 48% of cases were related to lymphoproliferative diseases and 15% to myeloproliferative diseases, 21% to cardiovascular diseases, 2% to autoimmune diseases and 9% to other conditions (27). Acquired VWD may resemble type 1 or 2 VWD. Autoantibodies form immune complexes with VWF, which are rapidly cleared from blood circulation. VWF may also attach to the surface of cancer cells. In aortic valve stenosis, large multimers break down at rapid vortical flow. In acquired VWD, treatment of the underlying disease corrects the bleeding tendency (28).

KEY POINTS

- The diagnostic criteria of VWD include a bleeding symptom, low VWF activity (less than 30%) and bleeding tendency in close relatives.
- Mild bleeding tendency and VWF activity of 30% to 50% suggest susceptibility to VWD but do not meet the diagnostic criteria of VWD.
- Bleeding symptom questionnaire helps to determine the clinical bleeding tendency.
- VWF activity increases with ageing.
- The nature and relevance of a VWD diagnosed in childhood should be re-evaluated at adult age.

To conclude

Increased understanding of the biological properties of VWF and its effect on haemostasis have also changed VWD diagnostics and clinical evaluation. Appropriate use of various treatment possibilities requires assessment of the patient's overall situation. Removal of a prior VWD diagnosis, that has been proven groundless in the light of the current criteria, can relieve the patient's concern and also reduce unnecessary treatment. As an increasing number of procedures on VWD patients will in future be performed on an outpatient basis, appropriate treatment should be planned and the risk of post-procedural bleedings assessed well in advance of the actual procedure. ■

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DECLARATION OF INTERESTS
Presentation/expert fee (Bayer, CSL Behring, Shire, SPR Blood service), congresses and seminars (Octapharma, Pfizer)

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SUMMARY

Diversified and transforming von Willebrand disease – progress in diagnosis and treatment

Von Willebrand disease (vW disease) is the most common hereditary condition causing especially mucosal bleeding and affecting both males and females, in which the bleeding tendency may range from mild to very severe. Either a deficiency or a dysfunction of the vW factor is involved. Understanding of the diversity of the vW disease has increased. It is important to evaluate how laboratory abnormalities correlate with the clinical state, lead to diagnosis and guide treatment. Upon ageing of the patient, a mild disease may resolve as the activity of the vW factor increases. The clinical picture of the disease varies, and on the other hand, the diagnostic criteria for the actual vW disease have become more stringent. Therefore, especially for those with mild type 1 disease, the activity of the vW factor and clinical bleeding tendency should be checked, and appropriateness of the diagnosis evaluated before any procedures at the latest.

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