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Von Willebrand disease

CLINICAL REVIEW

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Von Willebrand disease is the most common inherited bleeding disorder and is characterised by bleeding from the skin and mucous membranes. The severity of the disease can vary, and women are often more severely affected than men. Patients with von Willebrand disease can require multidisciplinary follow-up, and special precautions need to be taken during surgery and invasive procedures. We present a clinical review of von Willebrand disease in order to raise awareness of this patient group among doctors in Norway.

At the time of writing, it has been 100 years since Dr Erik von Willebrand published his paper on hereditary pseudohaemophilia (the original paper, in Swedish, was entitled *Hereditär pseudohemofili*) in the Finnish medical journal *Finska Läkaresällskapets Handlingar* (1). He wrote about Hjördis from the Åland Islands and several of her family members, who were affected by an unidentified, severe bleeding disorder that had caused the death of three of her elderly siblings. Hjördis died at the age of 14 during her fourth menstrual period.

Today, it is estimated that 1 in 1000 people in the general population have symptomatic von Willebrand disease requiring treatment (2). Oslo University Hospital's national haemophilia register includes just under 500 people, with varying disease severity. Given Norway's population of 5.6 million, the relatively low number of recorded cases suggests substantial underdiagnosis, and according to the register, most of those with mild disease are not identified until adulthood.

The aim of this article is to raise awareness of von Willebrand disease among doctors in Norway, to ensure more patients are accurately diagnosed and receive optimal follow-up and treatment. The evidence base for this article consists of international and Nordic guidelines, supplemented by a selective review of articles from a literature search in PubMed and the authors' clinical experience.

Von Willebrand factor

Von Willebrand factor is a glycoprotein produced in endothelial cells and megakaryocytes (3). It is composed of monomers that are bound together into dimers and subsequently into multimers of varying sizes. The largest forms are the most haemostatically active and consist of long multimers, which are cleaved by the enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). This cleavage prevents spontaneous intravascular platelet aggregation, as seen in thrombotic thrombocytopenic purpura.

Von Willebrand factor binds to glycoprotein Ib on platelets, facilitating platelet adhesion to the damaged vessel wall in the event of tissue injury (Figure 1). Platelets attach directly to von Willebrand factor in the subendothelium, as well as indirectly to collagen via circulating von Willebrand factor. In addition, von Willebrand factor contributes to platelet aggregation and serves as a carrier protein for coagulation factor VIII, protecting it from rapid degradation in the circulation.

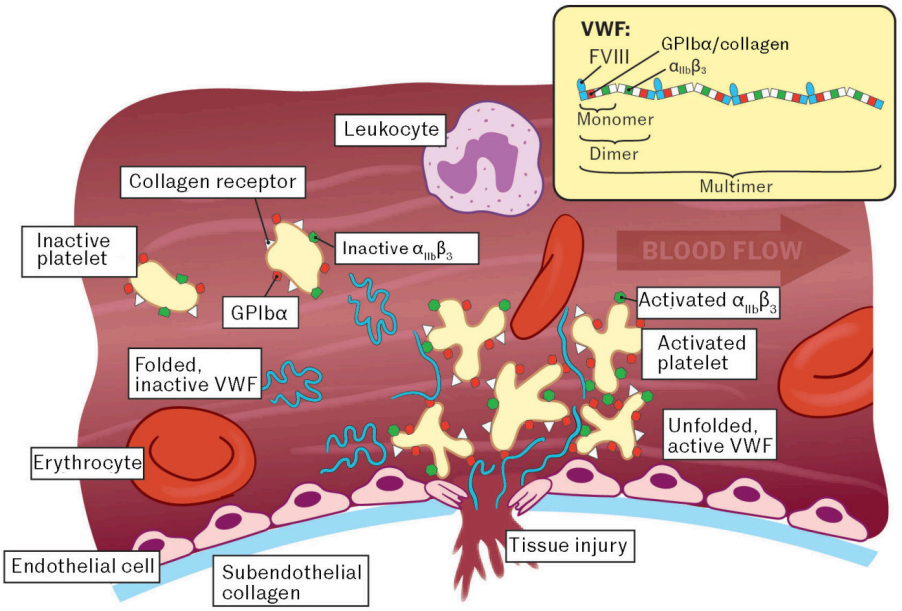

Figure 1 Von Willebrand factor in haemostasis. Abbreviations: FVIII, coagulation factor VIII; GPIbα, glycoprotein Ibα; VWF, von Willebrand factor. Illustration: Jeanette Engqvist/Illumedic.

Von Willebrand factor also has significance beyond haemostasis. Its levels rise in connection with inflammation and pregnancy, which can mask milder forms of von Willebrand disease. In preclinical trials, von Willebrand factor has shown anti-angiogenic properties, and low levels are thought to cause vascular proliferation, contributing to the development of angiodysplasias and gastrointestinal bleeding, which can present clinical challenges (4, 5).

Clinical presentation

Von Willebrand disease is characterised by bleeding from the skin and mucous membranes due to defects in primary haemostasis. The bleeding phenotype varies considerably and depends on the activity levels of von Willebrand factor and coagulation factor VIII (6). Women are generally more severely affected than men due to heavy menstrual bleeding and obstetric bleeding complications, but the diagnosis is nevertheless often under-recognised in milder cases. Mucosal bleeding can lead to iron deficiency anaemia requiring intravenous supplementation, and heavy menstrual bleeding can be particularly challenging in patients with severe disease, as illustrated by Hjördis' tragic outcome.

In surgical settings, patients experience increased perioperative bleeding, and even minor procedures, such as tooth extraction, should be planned in consultation with a haematologist. In type 3 disease, which is also associated with severely reduced factor VIII activity, joint bleeds leading to arthropathy can occur, as in haemophilia (7). Patients with a severe bleeding phenotype may also experience reduced health-related quality of life (8).

Diagnosis

Von Willebrand disease is diagnosed based on three criteria: an increased bleeding tendency, a family history and laboratory assays showing reduced von Willebrand factor activity (< 35 IU/dL) on repeated testing (9, 10). A thorough clinical history, including bleeding history and family background, should therefore always guide laboratory investigations. A standardised bleeding assessment tool has been developed for the systematic evaluation of bleeding tendency, but it is extensive and highly detailed. Nordic guidelines recommend that it only be used by trained personnel in the specialist health service (9, 11).

The disease is subdivided into categories according to severity and whether the reduced von Willebrand factor activity is the result of a quantitative deficiency or a qualitative dysfunction (Figure 2). Activated partial thromboplastin time is usually normal but may be prolonged if coagulation factor VIII is also reduced.

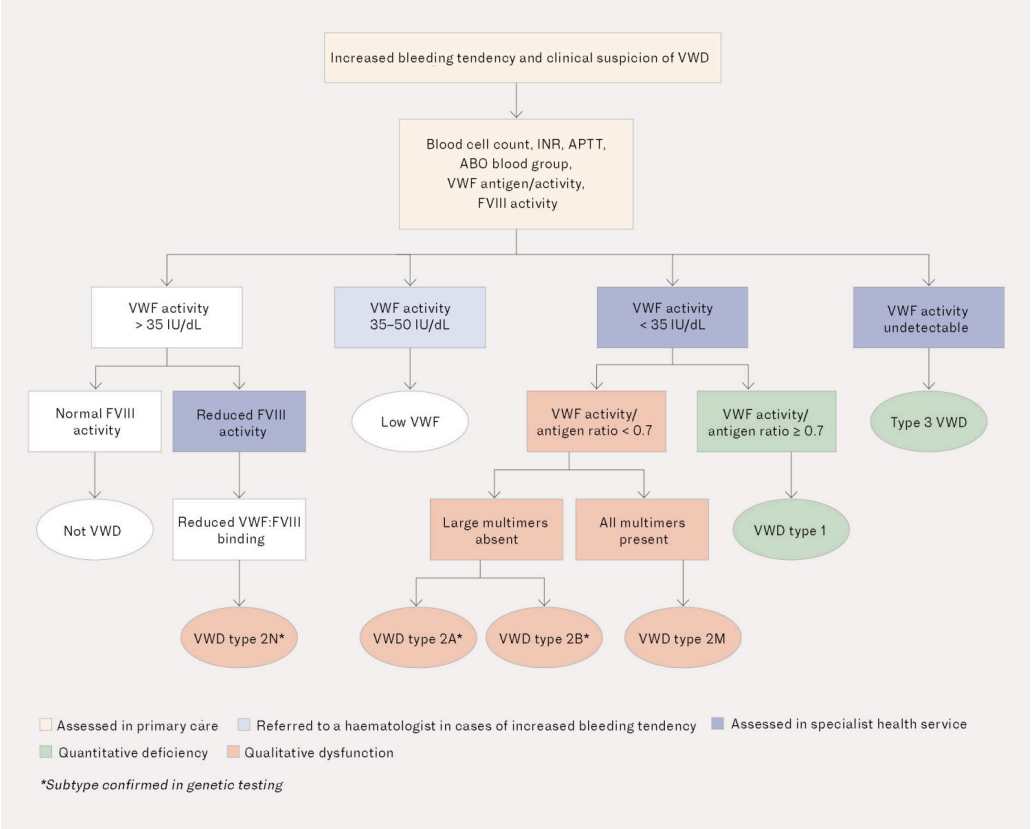

Figure 2 Investigation of increased bleeding tendency and suspected von Willebrand disease, based on Nordic guidelines (9). Abbreviations: APTT, activated partial thromboplastin time; INR, International Normalised Ratio; FVIII, coagulation factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.

Type 1 von Willebrand disease is the most common form, accounting for 70–80 % of cases (12). It is characterised by a quantitative deficiency of von Willebrand factor, with activity levels < 35 IU/dL.

Type 2 accounts for approximately 20 % of cases and comprises several subtypes, all characterised by a qualitative dysfunction of von Willebrand factor (12). Functionally, this is indicated by a reduced ratio of von Willebrand factor activity to antigen (< 0.7), and both platelet-binding and collagen-binding von Willebrand factor activity should be assessed. In types 2A and 2B, the largest von Willebrand factor multimers are absent, while type 2M usually exhibits a normal multimer pattern. Type 2B is also characterised by increased binding of von Willebrand factor to platelets, accompanied by thrombocytopenia. In type 2 N, there is reduced binding of von Willebrand factor to coagulation factor VIII, resulting in decreased factor VIII activity, which can be mistaken for mild haemophilia A. The Section for Haemostasis and Thrombosis in the Department of Medical Biochemistry at Oslo University Hospital has national responsibility for these specialised coagulation assays.

Type 3 von Willebrand disease is characterised by a severe quantitative deficiency, with von Willebrand factor being virtually undetectable (< 5 IU/dL). Coagulation factor VIII is therefore also markedly reduced (< 10 IU/dL). Type 3 is rare (< 5 %) (12), but this was the variant originally described by von Willebrand (1).

Von Willebrand disease is usually inherited in an autosomal dominant pattern, except for types 2 N and 3, which are inherited in an autosomal recessive pattern. Genetic analyses to identify underlying mutations are performed at the Section for Medical Genetics in the Department of Laboratory Medicine at Telemark Hospital Trust.

Low von Willebrand factor

A modestly increased bleeding tendency may also be observed at von Willebrand factor activity levels of 35–50 IU/dL. Internationally, views differ on whether patients in this group who bleed more than expected should be classified as having von Willebrand disease. According to Nordic guidelines, alternative explanations for the bleeding tendency – such as platelet dysfunction – should be sought in these cases. Patients with blood group O may have mildly reduced levels of von Willebrand factor due to decreased glycosylation of this and other proteins, resulting in increased clearance and a shorter half-life of von Willebrand factor (13).

Acquired von Willebrand disease

This is a condition that can occur in association with other disorders, such as severe aortic stenosis and mechanical heart valves (leading to physical destruction of von Willebrand factor), lymphoproliferative and myeloproliferative disorders (via adsorption of von Willebrand factor to cells), or autoimmune disease (immune-mediated) (14). Management is generally aimed at addressing the underlying condition. In cases of bleeding, desmopressin or factor concentrate is administered as in inherited von Willebrand disease; however, the effect is usually short-lived.

Management of bleeding

Most cases of von Willebrand disease are type 1 with mild severity. In this patient group, treatment may be indicated for individual bleeding episodes or administered prior to surgery and invasive procedures to prevent bleeding complications. Less severe bleeding can often be managed by the patient, either independently or in collaboration with their general practitioner (GP) or an out-of-hours clinic. Nordic guidelines for von Willebrand disease have been developed in line with international recommendations (9, 15). In the following, key aspects of disease management are outlined.

In women with menorrhagia, hormone therapy – either combined oral contraceptives (oestrogen/progestogen) or a levonorgestrel-releasing intrauterine system (progestogen) – can reduce menstrual blood loss.

Antifibrinolytic treatment with tranexamic acid can be beneficial in all forms of von Willebrand disease, either as monotherapy in less severe bleeding or in combination with other treatments. Tranexamic acid solution for injection can also be used topically in mucosal bleeding from the nose or mouth. This can often be administered by the patient, for example as a moistened compress or nasal pledget, or diluted with a small amount of water for use as a mouthwash. Systemic tranexamic acid is used for more severe bleeding or in the perioperative setting but should be avoided in urinary tract bleeding to prevent clot formation that could obstruct drainage.

Management of von Willebrand disease can otherwise involve stimulating endogenous haemostasis with desmopressin in milder disease (type 1), or replacement therapy with factor concentrate in more severe disease (types 2 and 3). These treatments are usually administered in the specialist health service.

Desmopressin is a vasopressin analogue that promotes the release of von Willebrand factor from Weibel–Palade bodies in endothelial cells, resulting in a temporary increase in coagulation factor VIII activity (2–5-fold increase). The response to desmopressin varies between patients, and its effect should therefore be tested in each patient. Levels of von Willebrand factor and coagulation factor VIII should also be checked before, and one and four hours after administration. The effect of desmopressin diminishes rapidly after a few doses as endothelial stores are depleted. Fluid retention and hyponatraemia are possible adverse effects, and no more than three consecutive doses at twelve-hour intervals should be administered. In type 2B disease, desmopressin can exacerbate thrombocytopenia and should be avoided in this patient group.

Factor replacement therapy is the mainstay of treatment for types 2 and 3 von Willebrand disease, although some patients with type 2A or 2M may also respond to desmopressin. Replacement therapy primarily involves plasma-derived products containing both von Willebrand factor and coagulation factor VIII, although the relative concentration of each component varies. Recombinant von Willebrand factor is also available, but it requires regular administration to maintain adequate circulating levels of factor VIII and is primarily used prophylactically (16).

Prophylactic factor replacement

In patients with a severe bleeding phenotype, regular prophylactic replacement therapy with factor concentrate may be indicated. This is particularly relevant for patients with type 3 disease in order to prevent joint bleeds, as seen in haemophilia, and for women with menstrual bleeding that leads to anaemia and does not respond sufficiently to hormone therapy and tranexamic acid. Prophylaxis may also be indicated for type 2 and the most severe forms of type 1 disease, for example in recurrent gastrointestinal bleeding (5, 17). However, this applies to very few patients, and there are limited data and no international guidelines on optimal administration of this treatment. Nevertheless, prophylaxis can improve quality of life in patients with recurrent bleeding

episodes. Replacement therapy with factor concentrate is administered by intravenous infusion, and those requiring regular treatment are trained in home infusion so that they can self-administer. Developing neutralising antibodies in response to von Willebrand factor replacement therapy is very rare.

Clinical follow-up

Patients with severe forms of von Willebrand disease should be followed up by a haematologist or a paediatrician with specialised expertise in bleeding disorders. In Norway, this responsibility is centralised at Oslo University Hospital, where most patients attend for annual check-ups. However, patients with von Willebrand disease may also require follow-up by other specialties, such as gynaecology, otolaryngology, gastroenterology and orthopaedics. Surgical procedures require bleeding prophylaxis and should always be carried out in close collaboration with Oslo University Hospital.

The article has been peer-reviewed.

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