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Patients with a history of epistaxis, menorrhagia or excessive bleeding after dental or surgical procedures may have von Willebrand's disease. Although screening coagulation tests may be normal, many patients with this disease will have excessive bleeding after surgical procedures if the disorder has not been recognized and appropriately treated. Patients with von Willebrand's disease may be treated with a medication that stimulates an increase in von Willebrand's factor, allowing them to avoid the need for blood product support.

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Von Willebrand's Disease

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Patients with a history of epistaxis, menorrhagia or excessive bleeding after dental or surgical procedures may have von Willebrand's disease. Although screening coagulation tests may be normal, many patients with this disease will have excessive bleeding after surgical procedures if the disorder has not been recognized and appropriately treated. Patients with von Willebrand's disease may be treated with a medication that stimulates an increase in von Willebrand's factor, allowing them to avoid the need for blood product support.

Von Willebrand's disease is the most common inherited bleeding disorder. It is transmitted in an autosomal dominant fashion and has an estimated prevalence as high as 82 cases per 10,000.[1,2] Patients with von Willebrand's disease often have a history of epistaxis or excessive bleeding after surgical or dental procedures but have a normal bleeding time and activated partial thromboplastin time (APTT).[3-8] By taking a careful history for bleeding in the patient and members of the patient's family, the family physician can decide whether specialized testing for von Willebrand's disease should be performed. Recognition of this disorder permits the use of pharmacologic agents rather than blood products to prevent or treat excessive blood loss that may occur with surgical procedures.

Illustrative Case

A 17-year-old woman was referred for evaluation of a possible bleeding disorder. She was scheduled to undergo dental surgery, and she had a history of excessive bleeding following a dental extraction when she was eight years of age. She had no history of bruising or menorrhagia.

The patient's 39-year-old mother had a lifelong history of easy bruising. When she was four years old, she required a blood transfusion after a tonsillectomy. At the age of 16, she underwent extraction of her wisdom teeth and had oozing at the extraction site for three days. She experienced delayed hemorrhage after the births of all three of her children. Coagulation studies when she was 38 years old had revealed normal prothrombin time (PT), APTT, platelet count and bleeding time. However, von Willebrand's factor antigen (vWF:Ag) level was below the normal range, and she was diagnosed as having *von Willebrand's disease*.

Studies performed in the 17-year-old patient revealed a normal platelet count; a template bleeding time of four minutes (normal: two to six minutes); a PT of 13.1 seconds (normal: 11 to 14 seconds); an APTT of 34 seconds (normal: 22 to 34 seconds); a factor VIII coagulant (VIII:C) activity of 50 percent, and a vWF:Ag level of 47 percent (normal: 50 to 150 percent). The patient was diagnosed as having von Willebrand's disease, based on a second set of similar data. Coagulation studies in the patient's two siblings and her father, all of whom were asymptomatic, were normal.

In preparation for elective removal of the third molars of her upper and lower jaw, the patient received an intravenous infusion of the vasopressin analog desmopressin. In three hours, the drug had stimulated an increase in the vWF:Ag level, from 40 to 138 percent. The patient also received the antifibrinolytic agent aminocaproic acid before the procedure and for the next 48 hours. No excessive blood loss occurred during surgery or for the next five days.

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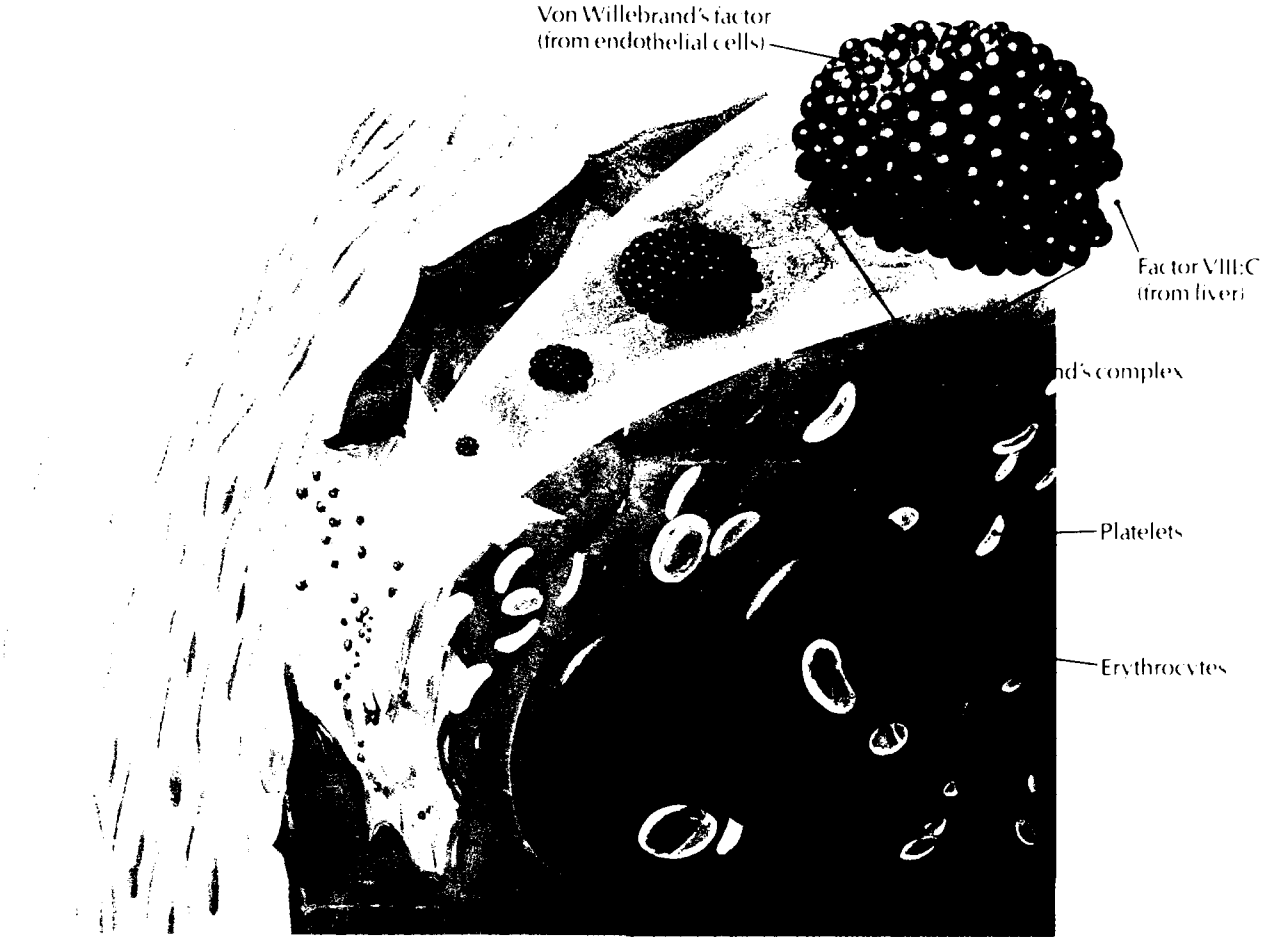

FIGURE 1. Plasma von Willebrand's factor is produced by endothelial cells and circulates as a complex with factor VIII:C, which is derived from the liver. Von Willebrand's factor consists of subunits that are assembled into high-molecular-weight multimers.

TABLE 1

Manifestations and Causes of Excessive Bleeding in 50 Patients with von Willebrand's Disease

Manifestation or cause of bleeding	*Number*	*Percentage*
Epistaxis	23	46
Dental extractions	20	40
Bruising	16	32
Menorrhagia	15	42*
Minor surgery†	15	30
Major surgery‡	13	26
Cuts or trauma	10	20
Postpartum hemorrhage	8	22*
Spontaneous oral bleeding	1	2
Gastrointestinal bleeding	1	2

*—*Percentage of female patients.*
†—*Includes breast biopsy, polypectomy, circumcision, rhinoplasty, hemorrhoidectomy, dilatation and curettage, and removal of a ganglion cyst.*
‡—*Includes tonsillectomy, laparotomy, hysterectomy, appendectomy, prostatectomy, mastoidectomy.*

Definition and Clinical Presentation

Von Willebrand's factor is produced by endothelial cells and by megakaryocytes. It circulates in plasma as a high-molecular-weight protein comprised of multimers (*Figure 1*). Von Willebrand's factor circulates in a noncovalent complex with factor VIII:C, a substance derived from the liver. Von Willebrand's factor promotes adherence of platelets to the subendothelium, thus allowing platelet thrombus formation at sites of vessel injury.[9] It also prolongs the circulation time of factor VIII:C.

Von Willebrand's disease is a mild bleeding disorder that results from a congenital or, rarely, an acquired decrease in the concentration of von Willebrand's factor or from an abnormal function of the molecule. The severity of bleeding problems varies among affected members of a family, and in a given individual, the frequency

TABLE 2

Definitions of Terms Related to von Willebrand's Disease

Von Willebrand's factor antigen (vWF:Ag): the concentration of von Willebrand's factor in plasma, as determined with immunologic techniques

Ristocetin cofactor activity: ability of the patient's plasma to agglutinate normal platelets in the presence of the antibiotic ristocetin

Ristocetin-induced platelet agglutination: ability of ristocetin to induce agglutination in the patient's platelet-rich plasma

Multimer analysis: molecular weight of the multimeric forms of von Willebrand's factor, as determined by gel electrophoresis of plasma

of bleeding episodes may decrease with age.[10-12]

We reviewed the clinical presentations and laboratory data in 50 patients (from 41 families) who were diagnosed at our institution as having von Willebrand's disease. The patients ranged in age from nine months to 68 years (mean age: 27 years) at the time of diagnosis. Epistaxis was the most common symptom in these patients. Other frequent manifestations were bruising and excessive bleeding with dental extractions (*Table 1*). Before von Willebrand's disease was diagnosed in these patients, at least 36 percent had received blood products during episodes of excessive bleeding.

Diagnosis

For a patient with a history that suggests a coagulation disorder, initial screening tests include assessment of platelet count, bleeding time, PT, APTT and, perhaps, thrombin time and fibrinogen level. The classic abnormalities in patients with von Willebrand's disease are a prolonged bleeding time (due to a decrease in or abnormal function of von Willebrand's factor) and a prolonged APTT (due to a decrease in factor VIII:C).[1,10-13] Even when screening tests are normal, the patient may have von Willebrand's disease, and further testing for factors specifically related to von Willebrand's disease is necessary (*Table 2*).

Results of the coagulation studies performed in the 50 patients in our series are shown in *Table 3*. Determinations were performed on more than one day in 27 of the 50 patients. The PT and fibrinogen level were normal in all patients.

VON WILLEBRAND'S FACTOR ANTIGEN

The most important test for the diagnosis of von Willebrand's disease is measurement of the vWF:Ag level. This is a determination of the von Willebrand's factor concentration by immunologic techniques.[14] The majority of patients with von Willebrand's disease have vWF:Ag levels

TABLE 3

Results of Coagulation Tests in 50 Patients with von Willebrand's Disease

Test	*Number of patients*	*Number of tests*	*Number (%) of patients with always normal results*	*Number (%) of patients with normal results at least once*
Bleeding time	45	56	23 (51)	29 (64)
APTT	50	102	29 (58)	33 (66)
Bleeding time and APTT	45	56	15 (33)	23 (51)
Factor VIII:C	50	102	20 (40)	30 (60)
vWF:Ag*	50	99	0 (0)	12 (24)

APTT = activated partial thromboplastin time; vWF:Ag = von Willebrand's factor antigen.

**—An abnormal vWF:Ag was required for the diagnosis of von Willebrand's disease in this series.*

that are less than 50 percent of the levels found in pooled normal plasma. For definitive diagnosis, this test should be performed on more than one occasion and/or in family members. Values may be in the normal range when patients are pregnant, are taking oral contraceptives, or have liver disease, diabetes or an acute illness. Thus, testing should be performed when such conditions are eliminated, if possible.

RISTOCETIN COFACTOR ASSAY

One measure of the functional activity of the von Willebrand's factor is determined with the ristocetin cofactor assay. Ristocetin is an antibiotic that interacts with von Willebrand's factor to agglutinate platelets. With this test, the ability of the patient's plasma to agglutinate platelets in the presence of ristocetin is compared with that of normal plasma. Plasma that does not induce agglutination has decreased or dysfunctional von Willebrand's factor.[15]

MULTIMER ANALYSIS

Some patients with von Willebrand's disease have a reduction in the size of the multimers that circulate in the plasma. The molecular weight of the multimers can be assessed by electrophoresis of plasma in an agarose gel that contains sodium dodecyl sulfate, which causes separation of the multimers by size. The multimers are then detected by incubating the gels with radiolabeled antibody to vWF:Ag.[9]

CLASSIFICATION

The results of these tests can allow classification of von Willebrand's disease into one of four types (*Table 4*). The majority of patients (80 percent) have type I disease, or a decrease in the vWF:Ag concentration with normal multimers. Some patients have type IIA, which is characterized by a low to normal vWF:Ag concentration and an abnormal multimer pattern. Patients with type IIB disease have an abnormal multimer pattern but the platelet-rich plasma shows increased sensitivity to ristocetin; that is, the platelets agglutinate in the presence of very low concentrations of ristocetin. Type III von Willebrand's disease is characterized by a prolonged bleeding time and low to undetectable levels of von Willebrand's factor, resulting in a severe bleeding disorder.[9] Type IIB and type III disease are rare.

Treatment

Until recently, the only treatment for the majority of patients with von Willebrand's disease was cryoprecipitate, which is enriched in von Willebrand's factor and factor VIII:C. Patients frequently received six to eight bags of cryoprecipitate before surgical procedures, with each bag sup-

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TABLE 4

Subtypes of von Willebrand's Disease

Type	*vWF:Ag level*	*Ristocetin cofactor activity*	*Multimers*	*Treatment*
I	↓	↓	Normal	Desmopressin
IIA	↓ or normal	↓	Abnormal	Desmopressin
IIB	↓ or normal	↓	Abnormal	Cryoprecipitate
III	↓↓	↓↓	Normal or abnormal	Cryoprecipitate

vWF:Ag = von Willebrand's factor antigen.

plied by a different donor. Infusions were then continued every eight to 12 hours for several days after the procedure.

Despite the screening of blood products for viral contamination, the current risk of developing human immunodeficiency virus (HIV) antibody after receiving seronegative blood is one in 40,000 units,[16] whereas the risk of non-A, non-B hepatitis is one in 160 units.[17] Thus, blood products carry a significant risk of viral transmission. The development of pharmacologic agents that can substitute for blood products has therefore provided a significant advance in the treatment of von Willebrand's disease as well as other bleeding disorders.

DESMOPRESSIN

One of the most useful agents is desmopressin (DDAVP, Stimate), a synthetic analog of vasopressin. An intravenous dose of 0.3 μg per kg induces an increase in factor VIII:C, which reaches maximum levels after 30 to 120 minutes and then decreases over six hours.[18-20] In most patients, treatment is also associated with a rise in the von Willebrand's factor level, which lasts approximately five hours, and a shortening of the bleeding time. Desmopressin produces the same effect when administered intranasally at a dosage of 2 to 4 μg per kg.[21] The drug should be infused slowly; rapid administration can result in flushing, tachycardia and transient hypotension.

Desmopressin has been shown to provide normal hemostasis in the majority of patients with mild von Willebrand's disease who have spontaneous or traumatic bleeding episodes or who are undergoing dental procedures or surgery. Desmopressin is not effective in patients with type III von Willebrand's disease and is not indicated for those with type IIB disease, because the drug induces thrombocytopenia.[22]

ANTIFIBRINOLYTIC AGENTS

Aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron) are antifibrinolytic agents that prevent the binding of plasminogen to fibrin clots.[23,24] This binding permits fibrin-bound tissue plasminogen activator to convert plasminogen to plasmin. Plasmin, in turn, digests the fibrin clot.

These agents are used most frequently in conjunction with desmopressin in patients undergoing dental extractions. The antifibrinolytic agent should be administered before oral surgery and for three to five days following the procedure. Use of desmopressin and antifibrinolytic agents, either alone or in combination, has almost completely eliminated the need for cryoprecipitate in patient's with von Willebrand's disease.

Aminocaproic acid can be used in oral or intravenous forms. In adults, the oral dosage ranges from 2 to 6 g four times daily.[23] Tranexamic acid is administered in a dosage of 1 to 2 g three times daily.[24] Since these drugs are excreted in the urine, the dosages should be reduced in patients with renal disease. Side effects of aminocaproic acid are primarily nausea and abdominal pain; side effects of tranexamic acid are nausea and diarrhea.

Final Comment

Since screening coagulation tests are frequently normal in patients with von Willebrand's disease, measurement of vWF:Ag levels and ristocetin cofactor

activity may be required for definitive diagnosis. Consultation with a hematologist or pathologist may be helpful in obtaining or interpreting these studies and in guiding therapy.

The opinions and assertions herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

REFERENCES

1. Holmberg L, Nilsson IM. Von Willebrand disease. Clin Haematol 1985;14:461-88.
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 1987;69:454-9.
3. Coller BS. Von Willebrand's disease. In: Colman RW, ed. Hemostasis and thrombosis: basic principles and clinical practice. 2d ed. Philadelphia: Lippincott, 1987:60-96.
4. Italian Working Group. Spectrum of von Willebrand's disease: a study of 100 cases. Br J Haematol 1977;35:101-12.
5. Lian EC, Deykin D. Diagnosis of von Willebrand's disease. A comparative study of diagnostic tests on nine families with von Willebrand's disease and its differential diagnosis from hemophilia and thrombocytopathy. Am J Med 1976;60:344-56.
6. Miller CH, Graham JB, Goldin LR, Elston RC. Genetics of classic von Willebrand's disease. I. Phenotypic variation within families. Blood 1979;54:117-36.
7. Abildgaard CF, Simone JV, Honig GR, Forman EN, Johnson CA, Seeler RA. Von Willebrand's disease: a comparative study of diagnostic tests. J Pediatr 1968;73:355-63.
8. Miller CH, Graham JB, Goldin LR, Elston RC. Genetics of classic von Willebrand's disease. II. Optimal assignment of the heterozygous genotype (diagnosis) by discriminant analysis. Blood 1979;54:137-45.
9. Ruggeri ZM, Zimmerman TS. Von Willebrand factor and von Willebrand disease. Blood 1987;70:895-904.
10. Nilsson IM. Von Willebrand's disease—fifty years old. Acta Med Scand 1977;201:497-508.
11. Bowie EJ. Von Willebrand's disease. Clinical picture, diagnosis, and treatment. Clin Lab Med 1984;4:303-17.
12. Bloom AL. The von Willebrand syndrome. Semin Hematol 1980;17:215-27.
13. Zimmerman TS, Ruggeri ZM. Von Willebrand disease. Hum Pathol 1987;18:140-52.
14. Zimmerman TS, Hoyer LW, Dickson L, Edgington TS. Determination of the von Willebrand's disease antigen (factor VIII-related antigen) in plasma by quantitative immunoelectrophoresis. J Lab Clin Med 1975;86:152-9.
15. Weiss HJ, Hoyer LW, Rickles FR, Varma A, Rogers J. Quantitative assay of the plasma factor deficient in von Willebrand's disease that is necessary for platelet aggregation. Relationship to factor VIII procoagulant activity and antigen content. J Clin Invest 1973;52:2708-16.
16. Ward JW, Holmberg SD, Allen JR, et al. Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. N Engl J Med 1988;318:473-8.
17. Ciavarella D. Transfusion-associated hepatitis and AIDS [Letter]. N Engl J Med 1988;318:184.
18. Menon C, Berry EW, Ockelford P. Beneficial effect of D.D.A.V.P. on bleeding-time in von Willebrand's disease [Letter]. Lancet 1978;2(8092 Pt 1):743-4.
19. Mannucci PM, Canciani MT, Rota L, Donovan BS. Response of factor VIII/von Willebrand factor to DDAVP in healthy subjects and patients with haemophilia A and von Willebrand's disease. Br J Haematol 1981;47:283-93.
20. de la Fuente B, Kasper CK, Rickles FR, Hoyer LW. Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. Ann Intern Med 1985;103:6-14.
21. Warrier AI, Lusher JM. DDAVP: a useful alternative to blood components in moderate hemophilia A and von Willebrand disease. J Pediatr 1983;102:228-33.
22. Holmberg L, Nilsson IM, Borge L, Gunnarsson M, Sjorin E. Platelet aggregation induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in Type IIB von Willebrand's disease. N Engl J Med 1983;309:816-21.
23. Griffin JD, Ellman L. Epsilon-aminocaproic acid (EACA). Semin Thromb Hemost 1978;5:27-40.
24. Verstraete M. Clinical application of inhibitors of fibrinolysis. Drugs 1985;29:236-61.

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