TABLE 140-2 LABORATORY DIAGNOSIS OF VON WILLEBRAND DISEASE (VWD)

Type	aPTT	VWF Antigen	VWF Activity	FVIII Activity	Multimer
1	Nl or ↑	↓	↓	↓	Normal distribution, decreased in quantity
2A	Nl or ↑	↓	↓↓	↓	Loss of high- and intermediate-MW multimers
2B[a]	Nl or ↑	↓	↓↓	↓	Loss of high-MW multimers
2M	Nl or ↑	↓	↓↓	↓	Normal distribution, decreased in quantity
2N	↑↑	Nl or ↓[b]	Nl or ↓[b]	↓↓	Normal distribution
3	↑↑	↓↓	↓↓	↓↓	Absent

[a]Usually also decreased platelet count. [b]For type 2N, in the homozygous state, FVIII is very low; in the heterozygous state, it is only seen in conjunction with type 1 VWD.

Abbreviations: aPTT, activated partial thromboplastin time; F, factor; MW, molecular weight; Nl, normal; VWF, von Willebrand factor.

patients with type O blood overlaps that which has been considered diagnostic for VWD. A mildly decreased VWF level should be viewed more as a risk factor for bleeding than as an actual disease.

Patients with type 2 VWD have functional defects; thus, the VWF antigen measurement is significantly higher than the test of function. For types 2A, 2B, and 2M VWD, platelet-binding and/or collagen binding VWF activity is decreased. In type 2A VWD, the impaired function is due either to increased susceptibility to cleavage by ADAMTS13, resulting in loss of intermediate- and high-molecular-weight multimers, or to decreased secretion of these multimers by the cell. Type 2B VWD results from gain-of-function mutations that result in increased spontaneous binding of VWF to platelets in circulation, with subsequent clearance of this complex by the reticuloendothelial system. The resulting VWF in the patients' plasma lacks the highest molecular-weight multimers, and the platelet count is usually modestly reduced. Type 2M occurs as a consequence of a group of mutations that cause dysfunction but do not affect multimer structure.

Type 2N VWD is due to mutations in VWF that affect binding of FVIII. As FVIII is stabilized by binding to VWF, the FVIII in patients with type 2N VWD has a very short half-life, and the FVIII level is markedly decreased. This is sometimes termed *autosomal hemophilia*. Type 3 VWD, or severe VWD, describes patients with virtually no VWF protein and FVIII levels <10%. Patients experience mucosal and joint bleeding, surgery-related bleeding, and other bleeding symptoms. Some patients with type 3 VWD, particularly those with large VWF gene deletions, are at risk of developing antibodies to infused VWF.

Acquired VWD is a rare disorder, most commonly seen in patients with underlying lymphoproliferative disorders, including monoclonal gammopathies of underdetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia. It is seen most commonly in the setting of MGUS and should be suspected in patients, particularly elderly patients, with a new onset of severe mucosal bleeding symptoms. Laboratory evidence of acquired VWD is found in some patients with aortic valvular disease. Heyde's syndrome (aortic stenosis with gastrointestinal bleeding) is attributed to the presence of angiodysplasia of the gastrointestinal tract in patients with aortic stenosis. The shear stress on blood passing through the stenotic aortic valve appears to produce a change in VWF, making it susceptible to serum proteases. Consequently, large multimer forms are lost, leading to an acquired type 2 VWD, but return when the stenotic valve is replaced.

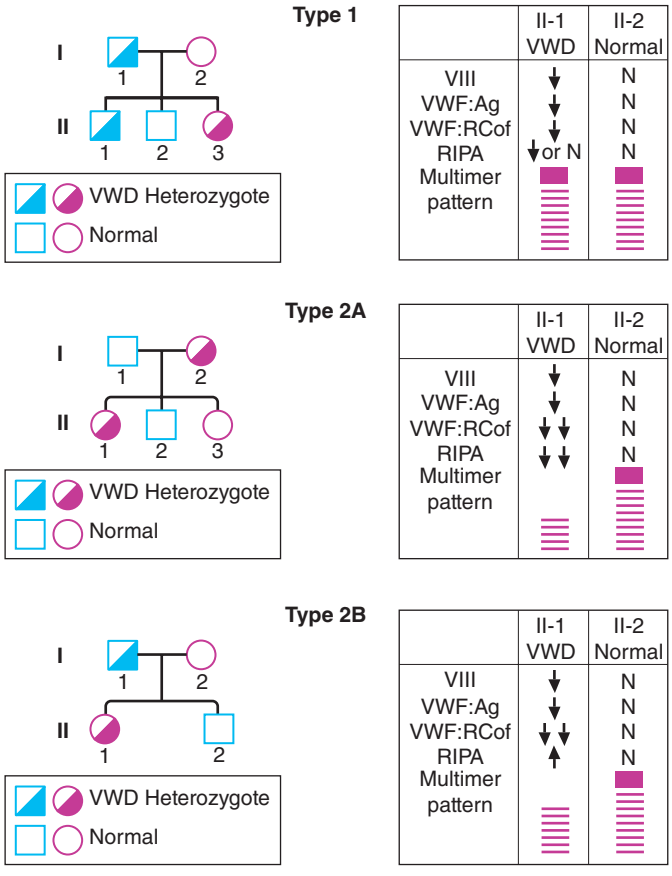

FIGURE 140-5 Pattern of inheritance and laboratory findings in von Willebrand disease (VWD). The assays of platelet function include a coagulation assay of factor VIII bound and carried by von Willebrand factor (VWF), abbreviated as VIII; immunoassay of total VWF protein (VWF:Ag); bioassay of the ability of patient plasma to support ristocetin-induced agglutination of normal platelets (VWF:RCoF); and ristocetin-induced aggregation of patient platelets, abbreviated RIPA. The multimer pattern illustrates the protein bands present when plasma is electrophoresed in a polyacrylamide gel. The II-1 and II-2 columns refer to the phenotypes of the second-generation offspring.

TREATMENT VON WILLEBRAND DISEASE

The mainstay of treatment for type 1 VWD is DDAVP (desmopressin), which results in release of VWF and FVIII from endothelial stores. DDAVP can be given intravenously or by a high-concentration intranasal spray (1.5 mg/mL). The peak activity when given intravenously is approximately 30 min, whereas it is 2 h when given intranasally. The usual dose is 0.3 μg/kg intravenously or two squirts (one in each nostril) for patients >50 kg (one squirt for those <50 kg). It is recommended that patients with VWD be tested with DDAVP to assess their response before using it. In patients who respond well (increase in laboratory values of two- to fourfold), it can be used for procedures with minor to moderate risk of bleeding. Depending on the procedure, additional doses may be needed; it is usually given every 12–24 h. Less frequent dosing may result in less tachyphylaxis, which occurs when synthesis cannot compensate for the released stores. The major side effect of DDAVP is hyponatremia due to decreased free water clearance. This occurs most commonly in the very young and the very old, but fluid restriction should be advised for all patients for the 24 h following each dose.

Some patients with types 2A and 2M VWD respond to DDAVP such that it can be used for minor procedures. For the other subtypes, for type 3 disease, and for major procedures requiring longer periods of normal hemostasis, VWF replacement can be given. Virally inactivated VWF-containing factor concentrates are safer than cryoprecipitate as the replacement product.

Antifibrinolytic therapy using either ε-aminocaproic acid or tranexamic acid is an important therapy, either alone or in an