is remarkably similar to the phenotypes of mice with low levels of tissue factor, fII and fX. Pharmacological inhibition of tissue factor in mice also leads to hemorrhage in the heart and brain. These studies support the idea that hemostasis is not equal in all tissues.

Anticoagulant therapy is designed to reduce thrombosis without affecting hemostasis. However, not surprisingly, the major side effect of anticoagulant drugs is hemorrhage. New anticoagulants have been developed that selectively target thrombin or fXa. The current study demonstrates that pharmacologic reduction in thrombin activity below a critical threshold could compromise cardiac and brain hemostasis.

Conflict-of-interest disclosure: The author serves as a consultant for Daichi-Sankyo.

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Comment on Federici et al, page 526

At least Type VWD2B is a discrete variant of VWD, isn’t it?

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In this issue of Blood, Federici and colleagues demonstrate that some characteristics of VWD2B may be less than universal in identifying all patients diagnosed with the disease.

Type 2B von Willebrand Disease (VWD2B) is generally characterized as including patients with bleeding symptoms whose laboratory studies demonstrate (1) reduced von Willebrand factor (VWF), (2) loss of high-molecular-weight (HMW) VWF multimers, (3) thrombocytopenia, and (4) platelet aggregation of patient platelet-rich plasma to low concentrations of ristocetin (usually ≤ 0.6 mg/mL). The article by Federici et al is critical because it demonstrates the phenotypic diversity of laboratory tests in patients diagnosed with VWD2B. While clinical laboratory studies using ristocetin have recognized laboratory to laboratory differences, this collaborative group includes laboratories of excellence that are recognized for their precision in VWD diagnosis.

Looking at each of these key components separately, Federici et al made some interesting observations. There were 11 mutations identified as causing VWD2B. In 6 of the families with these mutations, some members had plasma von Willebrand ristocetin cofactor (VWF:RCO) assays greater than 50 U/dL. In a separate analysis of people with mutations and VWD2B, 6 of 16 had plasma VWF:RCO levels above 50 U/dL. Thus, not all patients with VWD2B will have recognized reduction of plasma VWF:RCO.

While most had abnormal VWF multimers, VWF multimers were normal in 5 families with 3 different VWD2B mutations. Only 30% of the subjects had platelet counts, although many of those, but not all, with normal platelet counts exhibited thrombocytopenia following stress or DDAVP. They also demonstrated that those subjects with the combination of VWD2B and thrombocytopenia have significantly higher bleeding scores. Twenty-one of 67 had bleeding scores of less than 4. Thus, VWD2B patients do not all exhibit thrombocytopenia, loss of high-molecular-weight VWF multimers in their plasma, or even abnormal bleeding scores.

While all subjects exhibited heightened ristocetin-induced platelet aggregation, many of those identified in their study required more than 0.6 mg/mL of ristocetin to demonstrate this heightened interaction—a dose higher than many laboratories use to identify this interaction.

Thus, the clinical lab phenotypes that we have accepted for this disorder are not universally present, even in patients with defined type 2B VWF mutations. Assumptions that many of us have had for years about VWD2B and its diagnosis now need to be reexamined in light of this important study. While some might question whether the patients with normal VWF multimers, VWD New York and VWD Malmo, should be included in VWD2B, these investigators demonstrate much greater diversity in the laboratory studies, even in patients with abnormal multimers.

Since platelet VWF (and presumably endothelial) VWF multimers are normal sized in patients with VWD2B, more studies may be necessary to understand the reason in some subjects for the loss of high-molecular-weight multimers without concomitant thrombocytopenia. Some, but not all, of this might be explained by heightened cleavage of type 2B VWF by ADAMTS13.

It seems that the more we learn about VWD, the more challenges we uncover to our accepted dogmas about it. Our work and learning continue!

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