Comment on Roach et al, page 4264

Superficial venous thrombosis: recognizing the risk

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Although superficial venous thrombosis was originally perceived as a benign disease with a self-limited clinical course, it is now recognized that this condition is often associated either with concomitant venous thromboembolism or with early development of deep vein thrombosis and pulmonary embolism. Further, Heit et al reported in 2000 that individuals with previous superficial venous thrombosis were more than 4 times more likely to develop future deep vein thrombosis or pulmonary embolism, and this finding has subsequently been confirmed by several investigators. However, because most individuals with superficial venous thrombosis do not develop venous thromboembolism, it has been difficult to know how best to use this information to risk stratify patients.

Prior research has shown that genetic thrombophilias only minimally increase the risk of venous thromboembolism in patients with a history of superficial venous thrombosis. In the report published in this issue of Blood, Roach et al use data from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) population-based case control study that enrolled 4956 consecutive patients between 18 and 70 years of age with a first symptomatic objectively confirmed deep vein thrombosis or pulmonary embolism, together with 6297 age- and sex-matched controls, to examine the risk of venous thromboembolism in individuals with a self-reported history of superficial venous thrombosis and various clinical risk factors. Acquired risk factors included in this analysis were surgery, pregnancy, plaster casting and hospitalization within 3 months of venous thromboembolism diagnosis or study enrollment, oral contraception or hormone replacement therapy within the preceding 1 month, and malignancy in the 5 years prior to the index event.

Clinical risk factors were categorized as mild (smoking or overweight), strong (surgery, hospitalization, plaster casting, or malignancy), or reproductive (oral contraceptive use, postmenopausal hormone replacement therapy, or pregnancy and the postpartum period). Consistent with previous reports, individuals with prior superficial venous thrombosis had a 6-fold increase in the risk of venous thromboembolism compared with those without a similar history. The odds ratio for venous thromboembolism was increased to 9 with the addition of a mild clinical thrombotic risk factor and to approximately 30 in those with a major risk factor and in women with reproductive risks. The highest risks in the latter 2 categories were seen in patients with previous superficial venous thrombosis undergoing surgery or requiring hospitalization and those using oral contraceptives. Although one cannot directly infer absolute risks from a case-control study, the authors use previously established background incidences to determine the impact of their findings on the thrombotic risks associated with various clinical risk factors. In individuals with prior superficial venous thrombosis, the calculated risks were 1 in 32 in those undergoing surgery, 1 in 27 for those requiring hospitalization, and 1 in 51 in oral contraceptive users.

Although this study has several strengths, including its large size, objective diagnosis of the index venous thromboembolic event, and similar method of data collection for patients and controls, there are important limitations. Most importantly, the 95% confidence intervals for many of the risk estimates are wide; the diagnosis of superficial venous thrombosis and occurrence of clinical risk factors are based solely on patient self-report, and no information was obtained on the location of the superficial venous thrombosis or on the temporal relationship between it and the various clinical risk factors or the diagnosis of venous thromboembolism.

The results of this study are not sufficient to allow physicians to confidently modify standard recommendations for thrombosis prophylaxis in patients with a history of superficial venous thrombosis undergoing surgery or requiring hospitalization or to recommend against oral contraceptive therapy in affected women. How best to incorporate a history of superficial venous thrombosis into prophylaxis risk stratification schemes and decision making about the use of hormonal therapy in these patients has yet to be determined. However, in the interim, individuals with prior superficial venous thrombosis and their treating clinicians should have a heightened awareness of the potential for developing venous thromboembolism in these clinical settings.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Factor VIII inhibitor epitopes and an enigma

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In this issue of Blood, Walter et al provide an x-ray crystallographic structure of the factor VIII C2 domain in complex with 2 antibodies that illuminates how inhibitory antibodies complicate hemophilia A therapy.1

Inhibitory antibodies against factor VIII thwart effective treatment of hemophilia A. Nearly half target the C2 domain, underscoring the importance of its interactions. Mapping of antibody epitopes is a fruitful approach to understanding function of factor VIII and strategies to avoid hindrance by inhibitory antibodies.

Only membrane-bound, activated factor VIII can form an efficient complex with factor IXa to produce factor Xa and quench bleeding. The C2 domain of factor VIII participates in membrane binding. Factor VIII also binds to von Willebrand factor (vWF) via the same surfaces that bind membranes. Antibodies that block binding to vWF and to membranes are dubbed “classical” inhibitors.

The C2 domain also contains a thrombin and factor Xa recognition motif, a factor IXa contact site, and possibly a factor Xa contact site. Inhibitory antibodies that prevent activation by thrombin or factor Xa or assembly with factor IXa and factor X are dubbed “nonclassical” inhibitory antibodies. Walter et al report the radiograph crystallographic structure of the factor VIII C2 domain in complex with the Fab fragments of mAb 3E6, a classical inhibitor, and mAb G99, a nonclassical inhibitor.1

Recent biochemical studies indicate that function of the C2 domain is more complicated than expected. For example, the isolated C2 domain does not compete with factor VIII for membrane binding and does not interfere with the factor VIIIa–factor IXa complex.2 Furthermore, factor VIII engineered to lack the C2 domain, retains functional activity, although with a requirement for a higher concentration of phospholipid vesicles with a high density of negative charge.3 In short, recent biochemical studies suggest that the C2 domain could have only marginal importance. It is the clinical anti-C2 antibodies that remind us that the function of the C2 domain is critically important and may provide insight that reconciles biochemical data with clinical facts.

The structure reported by Walter et al identifies the epitope recognized by thrombin or factor Xa. It provides more insight into the surface that contacts vWF. In addition, there are 2 surprises. First, the epitope of 3E6 does not include any of the 3 clusters of membrane–interactive amino acids established by site-directed mutagenesis and x-ray crystallography (see figure).4,7 Second, the epitope of 3E6 is not on, or adjacent to, the plane of factor VIII that contacts a membrane.6 Thus, the structure poses an enigma for factor VIII biochemistry.
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