Thrombophilia screening: whom to test?
Aisha Bruce and M. Patricia Massicotte
antibody ligation of Ly6G reduces surface, although its function is unknown. Wang et al show that Ly6G is co-localized with functions in neutrophil recruitment. Ly6G, a GPI-linked protein, is also present at high levels on the neutrophil blood

to contribute to its effects on the other extracellular binding partners that might question as to whether Ly6G associates with signal into the cell (see figure), this raises the

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The mechanism underlying this response remains to be determined. As Ly6G is a GPI-linked protein and therefore cannot directly signal into the cell (see figure), this raises the question as to whether Ly6G associates with other extracellular binding partners that might contribute to its effects on the $\beta_2$ integrins. However, while not fully delineating the mechanism, a number of issues make this an important study. At a technical level, it raises a cautionary note for researchers using anti–Gr-1 or anti-Ly6G to identify neutrophils in vivo to be vigilant in their assessment of potential artifacts associated with their imaging methodology. Secondly, it raises the question as to the existence of a yet-unidentified endogenous ligands that might mediate similar effects to the anti-Ly6G antibody used here. Finally, it reveals a novel function for this poorly understood molecule that, if it could be translated to human biology, may be therapeutically relevant. Ly6G is only present in mice, but human neutrophils express the structurally related molecule CD177, a member of the Ly6/uPAR (urokinase plasminogen activator receptor) family. Interestingly, antibodies against CD177 have been shown to inhibit neutrophil transmigration across an endothelial monolayer, potentially by interfering with an interaction between Ly6G and PECAM-1. While murine Ly6G and human CD177 are unlikely to function identically, the findings from the murine and human systems identify these molecules as worthy of further investigation for their potential as novel therapeutic targets.

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**REFERENCES**


**THROMBOSIS & HEMOSTASIS**

Comment on Holzhauer et al, page 1510

**Thrombophilia screening: whom to test?**

**Aisha Bruce and M. Patricia Massicotte UNIVERSITY OF ALBERTA**

In this issue of Blood, Holzhauer et al have determined a novel method of identifying patients with protein C, protein S, and antithrombin deficiency who are at increased risk of developing venous thromboembolism (VTE; see figure). Children with VTE and their relatives were screened for inherited thrombophilia including proteins C and S and antithrombin deficiency; and Factor (F)V G1691A and FII G20210.A. Their study demonstrates that relatives with proteins C and S and antithrombin deficiency are at a significantly higher risk of developing VTE compared with those without inherited thrombophilia.
Within the population at large, there are at least 2 groups of inherited thrombophilias based on prevalence; those with a higher prevalence, 3% to 11% (FV G1691A and FII G20210A) and those with a lower prevalence, <1% (protein C, protein S, and antithrombin deficiency). Diagnosis of a child with venous thromboembolism can be used to identify first-degree relatives with inherited thrombophilia who are at increased risk of venous thromboembolism; most notably protein C, protein S, and antithrombin deficiency, and to a much lesser extent FV G1691A and FII G20210A. PC indicates protein C deficiency; PS, protein S deficiency; AT, antithrombin deficiency; VTE, venous thromboembolism; IT, inherited thrombophilia; and combined IT, combined inherited thrombophilia (rare). See also Figure 2 in the article by Holzhauer et al that begins on page 1510.1 Professional illustration by Marie Dauenheimer.

Previous studies have demonstrated that VTE risk in families is dependent on the type of thrombophilia.2 The importance of identifying patients at risk for VTE cannot be overstated because of associated mortality, morbidity, and increased costs to society. However, mass screening for these inherited thrombophilias in the healthy population is not warranted as the prevalence of a deficiency in proteins C and S and antithrombin is less than 1%.3 In addition, thrombophilia testing is expensive and has ethical ramifications. There is a paucity of studies demonstrating the utility of testing or the safety and efficacy of prophylaxis.

There are numerous factors that increase the likelihood of the development of VTE, including blood stasis, abnormal vascular endothelium resulting from surgery, trauma, immobility, sepsis, and others; as well as abnormalities in hemostasis. Hemostasis, the normal ongoing process that repairs damaged vascular endothelium, relies on normal protein components.4 Abnormalities in proteins involved in clot formation, such as FV G1691A and prothrombin G20210A polymorphisms, as well as dysfunctional changes (low level or decreased activity) to hemostatic modulating proteins, proteins C and S and antithrombin deficiency, can result in VTE.4

Preventive strategies for VTE in established high-risk populations are supported by studies demonstrating safety and effectiveness; for example, hip and knee arthroplasty,5 trauma, surgery,6 and hospitalized nonsurgical patients.7 However, currently there are no studies supporting VTE prophylaxis in the setting of low-risk scenarios, even in a patient with a documented inherited thrombophilia but who has never been diagnosed with VTE. In fact, Holzhauer and colleagues found transient risk factors (not defined in the study) to be present in most children with VTE who were identified to have inherited thrombophilia.4 This information may provide data supporting studies using targeted preventive strategies in certain cohorts of patients with inherited thrombophilia who have additional risk factors.

Increasing age is a known risk factor for VTE.8 Supporting this fact, Holzhauer et al demonstrated that the incidence of VTE in relatives 15 years of age and older was increased relative to those younger than 15 for all study participants, those with and without inherited thrombophilia.1 Children have a lower incidence of VTE than adults but higher-risk groups exist, with the presence of a central line being the most common.9 Using a child with VTE as an index case to identify relatives that may have inherited thrombophilia presents challenges that involve the following areas: developmental hemostasis, current laboratory testing methods for inherited thrombophilia, and ethical considerations. Children have physiologic differences in hemostasis compared with adults, including lower levels of proteins C and S and antithrombin, all approaching adult levels in late childhood.10 Defining age-appropriate normal ranges for these proteins has difficulties. Current laboratory testing methods for levels of proteins C and S and antithrombin use a clot-based or colorimetric assay.10 Studies have demonstrated that age-appropriate pediatric ranges in healthy children for levels of proteins C and S and antithrombin may vary according to reagents, type of laboratory test system, and, potentially, ethnicity.10 Consequently, definitively diagnosing inherited thrombophilia, proteins C and S and antithrombin deficiency, in childhood may not be possible. In addition, ethical considerations exist because a child is unable to give informed consent to be tested, which if positive, may result in lifelong emotional, financial, and life-style changes.

The medical community continues to search for efficient methods to ascertain populations at risk for VTE and when identified, to provide safe and effective prevention. Holzhauer and colleagues have developed a unique method of identifying a known high-risk population without mass screening. However, due to the rarity of proteins C and S and antithrombin deficiency,1 the homogeneity of the study population and the challenges of using pediatric index cases, further studies are needed. Importantly, this study also demonstrated that patients with FV G1691A and FII G20210A abnormalities did not have a significantly increased VTE risk compared with patients without these abnormalities,1 yet in the general population these are the two most common inherited thrombophilic abnormalities tested for today. As a result of this new information, screening for these inherited abnormalities should be re-examined because the utility of testing may be in question. Identifying which individuals to test for thrombophilia still needs to be fully clarified; however, Holzhauer et al have increased our understanding of thrombophilia and the associated consequences and have generated new ideas for further studies.

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REFERENCES


