Diagnosis of Inherited Thrombophilia in Pediatrics

Leslie Raffini, MD
Assistant Professor
Division of Hematology
The Children’s Hospital of Philadelphia
Philadelphia, Pennsylvania

What is thrombophilia?

LR Thrombophilia refers to the propensity to develop thrombosis. Inherited thrombophilias, which can usually be identified through laboratory testing, are listed in Table 1. Identification of these inherited defects has prompted an increase in thrombophilia testing over the last 2 decades.1

What is the prevalence of thrombophilia in children?

LR The prevalence of inherited thrombophilia in the general population varies depending on the test and the ethnicity of the patient. The factor V Leiden mutation is the most common inherited thrombophilia and is present in about 5% of U.S. Caucasians and is less frequent in other ethnic groups. The Prothrombin 20210 mutation is present in approximately 1–2% of Caucasians. Deficiencies of protein C, S, and antithrombin (AT) are more rare.

Epidemiologic studies show an increased risk of pediatric thrombosis in neonates and adolescents, and that the majority of children who develop thrombosis have multiple risk factors. There are acquired risk factors such as central venous catheters, cancer, and infection that play a major role in the pathophysiology of pediatric thrombosis; however, children who develop thrombosis—those with or without a positive family history—are frequently tested for inherited thrombophilia. The clinical utility of performing such tests remains controversial.

Which children should be tested for inherited thrombophilia?

LR There are 2 groups of children in whom thrombophilia testing may be considered: 1) children who have had a thrombotic event, and 2) children who have not had a thrombosis but have a family history. However, when and if these children should be tested is still a matter of debate and should be made on an individual basis, with an understanding of the potential benefits and limitations of testing.

What are the reasons to perform thrombophilia testing in a child with thrombosis?

LR Thrombophilia testing rarely influences the acute management of a child with a thrombotic event, with the exception of a neonate with a homozygous or double heterozygous deficiency of the anticoagulant proteins. These neonates may present with purpura fulminans, characterized by rapidly spreading skin lesions resulting from thromboses of the small dermal vessels followed by bleeding into the skin,2 a symptom that is associated with a high mortality rate if replacement therapy is not
initiated early. Neonates with purpuric skin lesions of unknown cause should receive empiric replacement with fresh frozen plasma, and laboratory studies for protein C, protein S, and AT should be performed immediately.

There are not enough data to determine whether the presence (or absence) of an inherited thrombophilia should influence the duration of therapy for a child with venous thromboembolism (VTE). The clinician must assess, on a case-by-case basis, whether the risk of recurrence is greater than the risk of bleeding to determine which patients may benefit from longer anticoagulation. Factors that may influence this decision include the specific thrombophilic defect, age, whether the thrombus was unprovoked or related to a central catheter, the presence or absence of other laboratory markers suggestive of poor outcome, and risk factors for bleeding including comorbid medical conditions and the use of antiplatelet agents.3

Identification of inherited thrombophilia may help provide insight as to why the child developed thrombosis, particularly if the event was unprovoked (ie, no other risk factors). Another potential benefit is that the identified individual may be more likely to receive thromboprophylaxis during future high-risk situations. Appropriate use of anticoagulant prophylaxis is grossly underutilized in hospitalized patients, and a prior knowledge of an inherited thrombophilia may improve adherence with guidelines.4 Lastly, discovery of an inherited defect will allow other family members to be counseled on their potential risk, allowing them to make an informed decision on whether or not to be tested.

**H&O** What are the reasons to perform thrombophilia testing in a child who has not had a thrombosis?

**LR** Thrombophilia testing in children who have a family member with a positive history of thrombophilia or VTE has become increasingly common, with little evidence to support this approach. Before testing children for inherited thrombophilia, clinicians should first consider whether the results can improve clinical outcomes, as medical benefit should be the primary justification for genetic testing in children and adolescents. The World Health Organization’s Review of Ethical Issues in Medical Genetics recommends that testing in children or adolescents should be carried out only if there are potential medical benefits or if an adolescent requests it for purposes of reproductive decision-making.5 The American Academy of Pediatrics and the American College of Medical Genetics recommend against predictive genetic testing for late-onset disorders unless there are specific interventions during childhood that will reduce morbidity or mortality.6,7

The rationale for testing asymptomatic children may be to: identify children who are at increased risk for VTE, allow an opportunity for education about signs and symptoms of VTE, guide thromboprophylaxis in high-risk situations, promote lifestyle modification including avoidance of behavioral prothrombotic risk factors such as sedentary lifestyle, overweight/obesity, and smoking, and inform discussion about contraception and family planning. At the moment, there is very little opportunity for thrombophilia testing to benefit a young child. The incidence of venous thrombosis in healthy children is extremely low (0.07/100,000), so it is unwarranted to consider long-term anticoagulation in an asymptomatic child.

Situations in which the presence of an inherited defect may influence medical decision-making mainly apply to older children. Knowledge of a thrombophilia in an adolescent female who may be considering oral contraceptive pills (OCPs) will allow her and her physician to discuss the increased risk of thrombosis associated with estrogen-containing contraception. This discussion should include the baseline annual incidence of VTE, which is approximately 1 per 12,500 in women of reproductive age and which increases to 1 per 3,500 for those on OCPs, and how this risk is influenced by the presence of an inherited thrombophilia. For subjects who are heterozygous for the factor V Leiden mutation and on OCPs, this baseline risk is increased 20–30-fold (relative risk) to approximately 1 per 500 women.8

**H&O** What can affect the results of tests that look for genetic predispositions in pediatric thrombophilia?

**LR** As some acquired conditions may affect assay results, familiarizing oneself to the potential influence of these conditions is important in making an accurate interpretation.

For example, one must be aware that concentrations of protein C, S and AT are lower in neonates and that they increase rapidly over the first 6 months after a baby is born; protein C concentrations remain below adult levels throughout much of childhood.9 Additionally, patients with single ventricle congenital heart disease and hepatic dysfunction may have decreased concentrations of these natural anticoagulants;10 vitamin K deficiency and warfarin use also cause a reduction of the vitamin-K dependent factors, protein C and S. AT concentrations may be disproportionately decreased by nephrotic syndrome, severe burns, and asparaginase; protein S may be decreased during pregnancy and in the presence of antiphospholipid antibodies.11-13 Therefore, many factors may influence protein-based prothrom-
Hematology

736  Clinical Advances in Hematology & Oncology  Volume 7, Issue 11  November 2009

often do not result in elevated homocysteine and are not
MTHFR is not indicated because these polymorphisms
with an increased risk of thrombosis.17 Factor VIII is
factors and those greater than 150 iu/dL are associated
increase transiently during periods of inflammation.18
also considered to be an acute phase reactant and may
plasma concentrations
VIII levels, the molecular mechanisms responsible are
before diagnosing hereditary thrombophilia.16
in a second sample (3–6 months later) is recommended
defect in a first-degree relative or confirming test results
botic defects, and checking for the presence of a similar
defect in a first-degree relative or confirming test results
in a second sample (3–6 months later) is recommended
before diagnosing hereditary thrombophilia.16

While heritability is said to contribute to factor
VIII levels, the molecular mechanisms responsible are
not thoroughly understood16; plasma concentrations
may be influenced by both genetic and environmental
factors and those greater than 150 iu/dL are associated
with an increased risk of thrombosis.17 Factor VIII is
also considered to be an acute phase reactant and may
increase transiently during periods of inflammation.18

Elevated levels of lipoprotein(a) are a risk factor for
atherosclerosis and myocardial infarction in adults19,20;
over the last decade, levels of lipoprotein(a) greater
than 72 nmol/L (30 mg/dL) have become increasingly
accepted as an inherited thrombophilia for venous throm-ophilia is low. Current adult guidelines suggest throm-
phylaxis in hospitalized patients based on major
target group rather than on individualized strategies.

In order to identify children who may benefit from
thromboprophylaxis, physicians may want to evaluate
those with acquired prothrombotic risk factors for
additional inherited risk factors. Unfortunately, there
are very little data to guide this therapy.

Last year, Jackson and Morgan developed an unvali-
dated scoring system for VTE risk—guidelines for peri-
operative thromboprophylaxis in children undergoing
surgery—using the following variables: age, congenital
heart disease, pre-existing medical problems including
prior thrombosis, current medical problems, medication
including oral contraceptives, and central venous cath-
eters.29 Similar to adult thromboprophylaxis guidelines,
the presence of an inherited thrombophilia was not
included. Unfortunately, there is currently a lack of evi-
dence to determine the utility of prophylaxis in children,
and how much inherited risk factors weigh compared to
acquired risks when making such decisions.

H&O What do you think future research should
address?

LR I think it is important to definitively address the
role of inherited thrombophilia in specific subsets of
patients (eg, neonates with catheter-related thrombosis,
children with leukemia, adolescents with unprovoked
thrombosis).30,31 Prior studies have been limited by the
small numbers of patients, but recent international col-
laborations permit analysis of large numbers of children
with thrombosis. In the future, prospective longitudi-
unal thrombosis cohorts are needed to monitor children for
long-term outcomes such as post-thrombotic syndrome
and recurrence. We can also expect multicenter clinical
trials that use clinical and laboratory data (including
inherited defects) to study treatment duration in chil-
dren with VTE and evaluate the use of thromboprophyl-
axis in high-risk children with leukemia.32,33 As new data
become available, our use of thrombophilia
testing will most likely change, and it will target indi-
viduals who are most likely to benefit from this testing.
Because of the lack of conclusive evidence to support
the clinical benefits of inherited thrombophilia testing,
studies may focus on new strategies to identify and clas-
sify hypercoagulable patients. Global coagulation assays
or molecular assays such as gene expression profiling or
single nucleotide polymorphisms would give the advan-
tage of assessing the interaction between inherited and
acquired factors and could perhaps lead to individual-
ized profiling of thrombotic risk, but the utilization of
these approaches remains to be determined.34,35
References


33. Goldenberg NA. Thrombophilia States and markers of coagulation activation in the prediction of pediatric venous thromboembolic outcomes: a comparative analysis with respect to adult evidence. Hematology/The Education Program of the American Society of Hematology. 2008;236–244.
