

Laboratory Testing for Thrombophilia in Pediatric Patients

On Behalf of the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (ISTH)

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General Basic Comments

Thrombophilia, or the genetic predisposition to thrombosis, has been determined in pediatric patients with thrombosis, from the newborn period through adolescence. In addition, acquired abnormalities in coagulation tests have been demonstrated to increase the risk of thrombosis in affected individuals (1). The manifestation of clinical thrombotic disease in infants and children with thrombophilia is skewed toward those children with more severe deficiencies or the concurrence of multiple thrombophilic traits. This has been most evident in neonates presenting with purpura fulminans and/or spontaneous large vessel thrombosis. Therefore, a laboratory evaluation should be done on every child with thrombosis, not limiting screening to a single trait already identified in the family. Children with recurrent unexplained thrombosis are likely to have a constitutional cause, especially if the family history is positive. In these cases, further evaluation for very rare, or even previously unrecognized thrombotic disorders is warranted. The pediatric patient with thrombosis has an average of two and as many as four or more predisposing and triggering prothrombotic factors (2). Most pediatric patients with thrombosis have significant underlying medical diseases (indwelling vascular catheters, infection, trauma, surgery, vascular malformation or damage, malignancy, chemotherapy with L-asparaginase, cardiac disease, prosthetic cardiac valves, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, ulcerative colitis, primary antiphospholipid antibody syndrome, polycythemia, sickle cell anemia and other hemoglobinopathies, renal disease, diabetes mellitus, appendicitis). Catheters are present in approximately 25% of thrombosis cases (3). Even children with two or more thrombophilic traits usually present clinically in the setting of trauma or inflammatory medical conditions. Children are more likely than adults to have one or more significant genetic or acquired coagulation deficiencies that may

require specific therapy for management of the acute thrombosis. Examples include severe genetic deficiencies of protein C or protein S and acquired deficiencies for which rapid replacement therapy may be necessary in order to interrupt consumptive coagulopathy or achieve successful anticoagulation. It is often clinically useful to determine the level of coagulation regulatory proteins acutely. This may involve repeat testing for one or two proteins but will not substantially increase costs. In addition, antiphospholipid antibodies and their effects on coagulation proteins may be transient and may be missed if testing is delayed three to six months. Finally, genetic testing may be very important in managing future pregnancies. Evidence for the association of thrombophilic factors with thromboses in children is as follows:

Venous thrombosis: Genetic abnormalities of antithrombin, protein C, protein S, factor V G1691A, prothrombin G20210A, fasting homocysteine and elevated lipoprotein (Lp) (a) concentration have been reported in children with venous thrombosis. Antiphospholipid antibodies including the lupus anticoagulant and anticardiolipin antibody have been associated with venous and pulmonary thromboembolism in children.

Arterial thrombosis: Vascular injury, indwelling catheters, congenital malformations, cardiac disease or vasculitis are present in most children with arterial thromboses. However, thrombophilia should be excluded in affected children. High titer lupus anticoagulants are associated with arterial and venous thrombosis in children.

Neonatal thrombosis: Neonates presenting with arterial and venous thrombosis have an increased risk of thrombophilia, particularly in settings with no obvious triggering event. Multiple thrombophilic traits are often determined in term neonates with severe or multifocal thrombosis. The benefit of screening for thrombophilia in this population has not been established.

Recommendations for Laboratory Testing in Children with Thrombosis

Pediatric patients should be tested for a full panel of genetic and acquired prothrombotic traits. Detection of one thrombophilic factor does not exclude the existence of a second or third. The evaluation

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may be performed in stages. All tests in level I (complete blood count with hematocrit, white blood count and platelet count, antithrombin, protein C activity, free and total protein S antigen, factor V G1691A and/or functional activated protein C resistance assay, prothrombin G20210A, MTHFR T677T and/or fasting homocysteine level, lipoprotein (a), lupus anticoagulant, anticardiolipin antibodies; sickle cell: screen or hemoglobin electrophoresis) should be performed initially. Any abnormalities may be repeated in three to twelve months, off anticoagulation therapy. Age-dependent reference ranges have to be taken into account (4). If all tests in level I are negative and the affected child has a strong positive family history for thrombosis, recurrent thrombosis or life-threatening thrombosis, then level II tests (euglobulin clot lysis time, plasminogen; dysfibrinogenemia evaluation: fibrinogen activity, antigen, thrombin time, reptilase time, fibrin degradation products, consider crossed immunoelectrophoresis; plasminogen activator inhibitor, heparin cofactor II, paroxysmal nocturnal hemoglobinuria (sucrose hemolysis); erythrocyte sedimentation rate, C-reactive protein) should be performed to determine a marker thrombosis risk and help decide long-term therapy. Tests in level III (factor VIII, factor XII, factor XI, von Willebrand factor level and multimers, spontaneous platelet aggregation, platelet receptor polymorphisms, tissue plasminogen activator, tissue factor pathway inhibitor) are currently under investigation and have not yet been linked to thrombosis in children.

Recommendations for Future Studies

Future studies are required for definitive recommendations regarding laboratory testing of children with thrombosis. To date, most

studies of genetic risk factors for thrombosis have been conducted in individuals of northern European extraction, while thrombosis is known to affect children of all races and ethnicities. Studies are needed in diverse racial ethnic groups to determine genetic risk factors that can be applied to children of other race and ethnicity. Little data is currently available regarding the influence of maternal or fetal genes on thrombotic risk in the fetus and neonate. Cost and medical efficacy of testing preterm infants with catheter-related thromboses remains to be determined. Finally, the role of thrombophilia in recurrence of childhood thrombosis, including implications for long-term anticoagulant therapy and recommendations for contact sports should be addressed.

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