Pediatric Thrombophilia and Thrombosis: An Historical Perspective

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Thrombosis has historically been considered a disorder of older adults with predominant risk factors of cardiovascular disease, cancer and immobility. The identification of familial thrombosis in a Norwegian family with antithrombin deficiency by Olav Egeberg in 1965 initiated research in genetic thrombophilia presenting in otherwise healthy young adults. Almost 10 years after this discovery, Ewa Marciniak and colleagues in Kentucky described deep venous thrombosis and pulmonary embolism following femur fracture in a 15-year-old boy with antithrombin deficiency, and Björn Bjorke and colleagues reported fatal aortic thrombosis in two newborn infants of antithrombin-deficient mothers who may have been similarly affected. Over the ensuing 30 years, genetic mutations have been determined that cause quantitative or qualitative deficiencies of coagulation regulatory and fibrinolytic proteins, increases in procoagulant proteins and substances that mediate endothelial cell damage. Symptomatic pediatric patients have been found with each thrombophilic trait. However, it was not until Branson and others described the dramatic presentation of relapsing purpura fulminans in a newborn infant with severe genetic protein C deficiency that children with homozygous, compound and multiple trait thrombophilia were found to constitute a novel patient group that is important both scientifically as well as medically. Along with basic scientific advances, development of safe, effective plasma-derived and recombinant replacement proteins has allowed treatments that support healthy growth and development in children with previously fatal thrombotic disorders. Funding since 2001 from the Centers for Disease Control and Prevention (CDC) supports a pilot network of specialized centers that collects data systematically on demographics, evaluation and management of thrombosis patients, including children, to inform future clinical approaches. Currently, active debate centers on who to test, the timing of testing and which tests to order for children at risk for thrombophilia. Dr. Leslie Raffini will address controversies in thrombophilia testing in pediatrics.

Treatment of thrombosis has been extrapolated from adult data, often with disappointing results. Barriers to the conduct of rigorous pharmacodynamic, safety and efficacy studies include the low number of subjects available for research trials, infrequent funding of such trials by public and commercial entities, and practical limitations to the number and volume of blood samples needed for research. Consequently, until recently, there were no U.S. Food and Drug Administration (FDA)–approved indications for antithrombotic therapy in children and all therapy was, by default, off label. Dr. Guy Young will review the history of anticoagulant use in children and will discuss more recent pharmacodynamic studies of low-molecular-weight heparins and direct thrombin inhibitors in newborn infants, children and adolescents.

Finally, the choice of antithrombotic therapy, including agent, intensity and duration, has been hampered by lack of pediatric outcome data. Dr. Neil Goldenberg was one of the first investigators to collect pediatric prospective data systematically and analyze outcomes of thrombus progression, recurrence and post-thrombotic syndrome in children relative to plasma biomarkers and initial therapy. These biomarkers and outcomes constitute important measures for the design of future interventional trials in children with thrombosis.

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