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Acute Prognostic Factors for Post-Thrombotic Syndrome in Children with Limb DVT: A Bi-Institutional Cohort Study

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ABSTRACT

Background: Early identification of children with deep venous thrombosis (DVT) of the limb who are at heightened risk for post-thrombotic syndrome (PTS) is important in order to evaluate therapeutic interventions aimed at decreasing the risk and severity of PTS.
Objective: We sought to evaluate acute prognostic factors for PTS in children following DVT of the limbs.
Materials and Methods: In this bi-institutional mixed cohort study with prospective ascertainment of PTS using a validated pediatric instrument, we collected data on patient/thrombus characteristics, thrombophilia testing results, and outcomes in children (<21 years at event) diagnosed with acute limb DVT at Rady Children's Hospital of San Diego and Children's Hospital Colorado.
Results: Median age at presentation was 13 years (range, 0–18 years). Cumulative incidence (i.e. risk) of PTS was 23%, at a median follow-up duration of 33 months (range, 13.2-65 months). The presence of a lupus anticoagulant by dilute Russell Viper venom time (dRVVT) testing within two weeks of DVT diagnosis was associated with markedly increased odds of developing clinically-significant PTS (OR: 16.8, 95%CI 1.60-176.2; $P=0.02$). The presence of an infectious or inflammatory condition at DVT presentation was neither associated with PTS risk nor dRVVT positivity. CONCLUSION: An acutely positive dRVVT following diagnosis of limb DVT appears to be a significant prognostic factor for development of clinically significant PTS in children. Larger collaborative cohort studies are required to substantiate these findings, evaluate other prognostic factors, and determine whether the present association is modulated by persistent dRVVT positivity or beta-2-glycoprotein-I dependence.

Introduction

While venous thromboembolism (VTE) in children is a seemingly rare condition, the incidence is increasing dramatically and is associated with significant long-term morbidity. The estimated annual incidence of VTE in children is 0.07-0.14/10,000; however, among hospitalized patients this is estimated at 58/10,000 admissions and is continuing to rise, likely as a result of improvements in intensive interventions for critically ill children [1–3]. Nearly 10% of children experience a recurrent event within one year and approximately 25% with deep venous thrombosis (DVT) affecting the limbs develop post-thrombotic syndrome (PTS), a manifestation of chronic venous insufficiency characterized by pain, swelling, ulceration, and/or functional impairment [4,5].

Although an elevated D-dimer and factor VIII level at diagnosis have been associated with a poor outcome (lack of thrombus resolution, recurrent thrombosis, or PTS) following VTE in children, better delineation of prognostic factors specifically for PTS in children has been limited [4]. Kuhle and colleagues reported that children with lack of resolution of DVT were nearly four times more likely to develop PTS than children with complete thrombus resolution [6]. However, this important study did not employ a validated pediatric PTS outcome measure. More recently, in a small prospective cohort employing a validated pediatric PTS outcome measure, Goldenberg et al. demonstrated a high risk of PTS in children with completely veno-occlusive DVT in whom factor VIII and D-dimer were both elevated [7].

Abbreviations: ACA, anticardiolipin antibodies; BMI, body mass index; CDC, Centers for Disease Control; CTV, computed tomogram with venography; CHCO, Children's Hospital Colorado; dRVVT, dilute Russell viper venom test; DVT, deep venous thrombosis; ELISA, enzyme-linked immunosorbant assay; IVC, inferior vena cava; MRV, magnetic resonance venogram; PTS, post-thrombotic syndrome; RCHSD, Rady Children's Hospital San Diego; SVC, superior vena cava; VTE, venous thromboembolism; WHO, World Health Organization.

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Early identification of children with DVT who are at greatest risk for PTS is important in order to evaluate therapeutic interventions aimed at decreasing the risk and severity of PTS. Accordingly, in this bi-institutional mixed cohort study with prospective ascertainment of PTS, we sought to evaluate acute prognostic factors for PTS in children following DVT of the limbs. We hypothesized that acute hypercoagulable states frequently mediated by inflammation (e.g., antiphospholipid antibodies and elevated factor VIII) would be prognostic of pediatric PTS.

Materials and Methods

Subjects

With institutional review board approvals, we conducted a mixed cohort study of children presenting with acute limb DVT at Rady Children's Hospital San Diego (RCHSD) and Children's Hospital Colorado (CHCO). Patients presenting between January 2005 and March 2010 at RCHSD were identified retrospectively from the hematology database, enrolled after informed consent discussion and signature, and followed prospectively through September 2011. At CHCO study subjects were enrolled with written informed consent in a prospective cohort study between March 2006 and December 2010; data for patients diagnosed with acute VTE prior to March 2006 were collected retrospectively prior to that date and prospectively (including PTS) thereafter. Inclusion criteria for the present sub-cohort across the two institutions consisted of age <21 years at diagnosis, acute limb DVT (all deep venous extremity veins and isolated superior vena cava (SVC), inferior vena cava (IVC), and azygous veins) confirmed by radiological imaging (compression ultrasound with Doppler, computed tomogram with venography [CTV], and/or magnetic resonance venogram [MRV]). Exclusion criteria included the following: initial treatment with thrombolysis or thrombectomy and lack of PTS evaluation 12 or more months following DVT diagnosis.

Data Collection

The following clinical data were collected: age, body mass index (BMI), thrombus location, presence of a central venous catheter at the affected site (or within the preceding 30 days in the same vessel as VTE), co-morbid conditions, therapeutic intervention, recurrent thrombotic events, length of medical follow-up, laboratory analysis of inherited and acquired thrombotic risk factors, and occlusion status of vessel. We determined BMI percentiles using Centers for Disease Control (CDC) growth charts for children ≥2 years of age and World Health Organization (WHO) growth charts for children less than 2 years of age. A BMI was not calculated for preterm infants less than 1 year of age at the time of diagnosis.

Results of thrombophilia assessment were collected for analysis as putative prognostic factors if obtained within two weeks of presentation, not including genetic testing (which could be obtained at any time point). Thrombophilia testing performed in the local and referral clinical laboratories consisted of the following: protein C and antithrombin activities by chromogenic assay; free protein S antigen by enzyme-linked immunosorbant assay (ELISA); factor V Leiden and prothrombin G20210A polymorphisms by polymerase chain reaction; lupus anticoagulant testing by dilute Russell viper venom test (dRVVT); factor VIII activity by one-stage clotting assay; and D-dimer by either quantitative or semi-quantitative immunoturbidimetric assay or fluorescence immunoassay. Anticardiolipin antibodies, ß2-gylcoprotein-I antibodies, and homocysteine were infrequently tested at RCHSD. Severe protein C deficiency was defined in children greater than three months of age with a level <20% and a mild deficiency if the level was <40%. A severe protein S deficiency was defined if the level was <20% and a mild deficiency if the level was <40%, irrespective of age. We characterized a severe antithrombin deficiency in children greater than three months of age with a level <30% and a mild deficiency if the level was <60%. The dRVVT was positive if the screen:confirm ratio was >1.20 at RCHSD or >1.22 at CHCO.

In concordance with present guidelines for pediatric PTS outcome reporting we evaluated the principal outcome, clinically-significant PTS, using a standardized outcome assessment tool; in this case, the Manco-Johnson instrument was employed [7,8]. This outcome assessment tool combines a scoring system for the presence of physical examination abnormalities including edema, superficial collateral veins, venous stasis dermatitis, and venous stasis ulcers with a scoring system for a history of functional limitations of activities of daily living or chronic lower extremity pain either with physical activity or at rest. Clinically-significant PTS was defined as a score of at least 1 in both categories. Evaluation for PTS was undertaken at ≥1 year. For serial measurements beyond one year, the latest measurement was used for analysis.

Statistical Analysis

Fisher's exact testing or Mann Whitney U testing was employed to compare differences in frequencies or distributions (respectively) of variables of interest between subjects with and without PTS. Univariate logistic regression was performed to evaluate risk factors for PTS. Variables included age, BMI, infectious or inflammatory condition at diagnosis, and thrombophilia findings. Thrombophilia results were evaluated categorically, with the exception of factor VIII levels, which were analyzed as a continuous variable. We determined *a priori* that antiphospholipid antibody as a category would be highly collinear with dRVVT as a specific test for the lupus anticoagulant; therefore, only one of the two variables would be included in a multivariate model. We further determined *a priori* that variables for which $P<0.1$

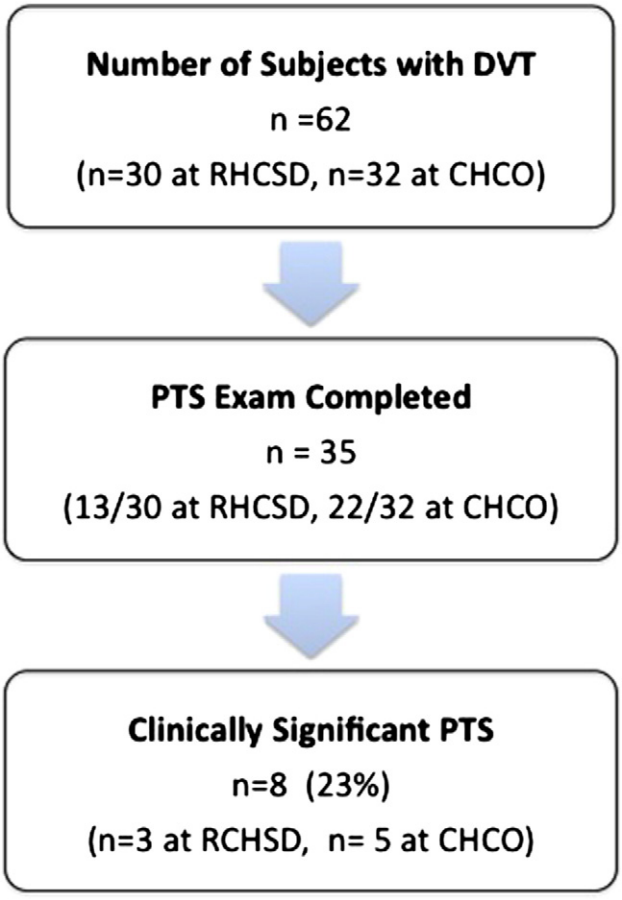

Fig. 1. Flow diagram of disposition of events in the study population. RCHSD: Rady Children's Hospital San Diego, CHCO: Children's Hospital Colorado.