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Regular Article

Prevalence and risk factors for post thrombotic syndrome after deep vein thrombosis in children: A cohort study

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ABSTRACT

Background: While post thrombotic syndrome (PTS) is increasingly recognized as a frequent and potentially serious complication of deep vein thrombosis (DVT) in children, limited information is available regarding predictors of PTS.
Methods: Using the Mayo Clinic Master Diagnostic Index, all pediatric patients (age 0 to 18 years) with a potential DVT based on ICD-8 codes over the 15-year period, 1995 to 2009 were identified. A validated PTS survey instrument was mailed to eligible patients followed by a second mailing and three reminder phone calls for non-responders. Baseline clinical and radiographic characteristics were abstracted from patient medical records and tested as potential predictors of PTS using logistic regression. Associations were summarized by calculating odds ratios (OR) and corresponding 95% confidence intervals.
Results: Ninety patients agreed to participate. The mean age (±SD) at DVT diagnosis and survey completion were 12.8 (±6.1) and 19.3 (±7.7) years, respectively. Fifty three respondents (59%) reported mild PTS whereas 12 (13%) reported moderate-to-severe PTS. Pain (34%) and dilated blood vessels (40%) were the most frequent PTS symptom and sign, respectively. On multivariate analysis, predictors of PTS included duration between incident DVT and survey completion (OR 1.75; 95% CI: 1.08 – 2.84) and number of thrombosed vein segments (OR 1.40; 95% CI: 1.05 – 1.86).
Conclusion: Over 70% of children with DVT report subsequent symptoms or signs of PTS, though only 13% report clinically significant, moderate-to-severe PTS. Number of thrombosed vein segments at diagnosis and time duration between incident DVT and survey completion were independent predictors of PTS.

Introduction

Historically, deep vein thrombosis (DVT) was thought to be rare in children. Epidemiological studies from Canada and the Netherlands estimated the incidence of DVT in children to be 0.07 and 0.14 cases per 10,000 children (and neonates), respectively [1,2]. More recently, however, a retrospective cohort study from 40 tertiary care pediatric centers in the Unites States noted a 70% increase in the annual rate of venous thromboembolism during the time period of 2001 to 2007 [3]. As deep vein thrombosis is increasingly recognized in children, it becomes important to study its late complications in this population. Post thrombotic syndrome (PTS) is a syndrome complex of pain, swelling, dilated blood vessels, varicosities and eventually stasis ulceration that might develop after one or recurrent episodes of DVT [4]. While the exact pathophysiology of PTS is unknown, it is thought to be a clinical manifestation of venous hypertension resulting from residual venous outflow obstruction or venous valvular incompetence secondary to valve damage following a DVT [4,5]. Extravasation of red blood cells, fibrin and inflammatory mediators occur as a result of the venous hypertension resulting in symptoms of swelling, pain, skin discoloration and venous ulceration [6].

Emerging data from pediatric studies suggests that PTS is common in children though there is a wide variation in its reported prevalence, with estimates ranging from 0 to 70% [7]. This variation might in part be explained by the fact that several older studies did not evaluate PTS as a primary objective, nor did they report on the use of standardized criteria for diagnosis of PTS [1,8–10]. A recent systematic review of

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literature has reported a 26% incidence of PTS in children after incident DVT [11]. Previous work from our group has shown that patients with moderate-to-severe PTS report significantly lower quality-of-life scores as compared to patients with no PTS and mild PTS [12].

Since children can be expected to live for decades following a DVT, and the physical and psycho-social ramifications of a potentially debilitating condition such as PTS in this population is significant [12], it becomes incumbent upon us to have a critical understanding of risk factors that predispose children to PTS, particularly clinically significant moderate-to-severe PTS. Identification of such risk factors would help develop evidence-based treatment protocols for management of DVT. The objective of this study was to estimate the prevalence of PTS in children with a history of DVT using a previously validated survey instrument that incorporated standardized diagnostic criteria and to determine the predictors of PTS by retrospectively reviewing the medical records of all responders.

Patients and Methods

Study Design, Population and Setting

The Mayo Clinic Master Diagnostic Index was used to identify all unique cases of DVT in children using modified ICD-8 codes, diagnosed or treated at the Mayo Clinic over the 15 year period, 1995 to 2009. Eligible patients were defined as children between the ages of 0 – 18 years at the time of incident DVT diagnosis. Arm DVT included the superior vena cava (SVC), jugular, innominate, subclavian, and axillary veins either alone or in combination. Leg DVT included the inferior vena cava, iliac, femoral and popliteal veins alone or in combination. A "text code" search was also conducted to ensure complete enumeration. The Mayo Clinic medical records of these patients were then reviewed to identify all eligible patients for the study. The study was approved by the Mayo Clinic Institutional Review Board.

Measurements

A survey instrument we previously developed and validated was used to assess the presence and severity of PTS in children and young adults [13]. The majority of the survey instrument was composed of the elements of the Kuhle Scoring system, revised for self-administration [5]. Questions on "paresthesia" and "pruritus" were incorporated from the original Villalta instrument [14]. A question on "night cramps" which has been previously reported as a symptom of PTS in both adult and pediatric studies was incorporated in our survey as well [15,16]. Two separate versions of the survey instrument were used for the purposes of this study: 1) a parent-proxy version for children < 18 years of age, and 2) a self-reported version for young adults ≥ 18 years.

The instrument assessed current signs (5 items) and symptoms (5 items) of PTS using a dichotomous scale for measuring response [yes (score = 1) and no (score = 0)], with the exception of venous ulceration (score = 9). A final summated PTS score was calculated and categorized as mild (score 1-3), moderate (score 4-8) and severe (score ≥9). The Mayo Clinic Survey Research Center mailed the survey to all eligible patients, sent a second mailing to initial non-respondents, and completed an additional three reminder phone calls for all non-responders to the initial mailings. Accurint® - a commercially available database containing information from a variety of data sources - was used to obtain contact information for patients lost to follow up.

The Mayo Clinic medical records of all survey respondents were reviewed for demographic and baseline clinical and radiographic characteristics using a data collection instrument designed for this study. Radiographic data was included only for patients with pre-treatment images available for review. All available images were re-interpreted by a single pediatric radiologist blinded to the survey results. Radiographic data was also excluded if findings consistent with chronic venous thrombosis were present at the time of diagnosis. Thrombosed vein segments were graded on the degree of thrombotic venous occlusion (complete versus partial), number of involved vein segments at diagnosis and response to treatment (complete resolution, partial resolution with chronic vessel wall changes and no resolution). Baseline clinical characteristics included:

1. *Body composition at diagnosis of DVT:* Patients were classified as overweight if their BMI percentile for age and sex was between the 85th and 95th percentiles for patients between 2 and 20 years of age, or a weight-for-length percentile at or above the 95th percentile for children under 2 years of age [17]; and as obese if the BMI percentiles for age and sex were greater than the 95th percentile for patients between 2 and 20 years of age.
2. *Thrombophilia:* Standard thrombophilia testing included antiphospholipid antibodies (i.e, lupus anticoagulant; IgG and IgM isotype anti-cardiolipin antibodies), activated protein C-resistance (APC-R) ratio with reflex genotyping for Factor V Leiden mutation if APC-R ratio is abnormal, prothrombin G20210A mutation, antithrombin activity and antigen, protein C activity and antigen level, total and free protein S antigen, protein S activity, fibrinogen level, plasma fibrin D-dimer and homocysteine level.
3. *Type of therapy:* Acute DVT therapy was classified as catheter directed thrombolysis, systemic thrombolysis, pharmaco-mechanical thrombectomy, unfractionated heparin/low molecular weight heparin therapy and vitamin K antagonism with warfarin. These therapies were provided alone or in combination.
4. *Recurrence:* Ipsilateral DVT recurrence was defined as a second thrombus that was identified after completion of anticoagulation of the incident thrombus.

Statistical Analyses

Standard statistical methods were used to summarize the parameters: frequency and percent for categorical parameters and mean (SD), median, and range for ordinal or continuous scaled parameters. Since our previous work clearly identified that only moderate-to-severe PTS impacts health related quality of life [12], we decided to analyze our outcome (PTS score) in two ways: (a) absence vs. presence of PTS, and (b) no-mild PTS vs. moderate-severe PTS. Baseline characteristics were tested univariately for an association with PTS using the Kruskal-Wallis test for ordinal or continuous factors and the chi-square or Fisher's exact test for categorical factors. Multivariable logistic regression models were fit using stepwise and backward variable selection methods to identify factors associated with PTS, after adjusting for years between incident DVT and survey completion. Associations were summarized by calculating odds ratios (OR) and corresponding 95% confidence intervals. Analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc., Cary, NC). All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant.

Results

Study Cohort

Two hundred and thirty four patients were eligible for the study. Twenty-one patients had participated in the pilot validation of the PTS instrument. Sixteen patients (7%) had died since the incident DVT. No patient died as a direct complication of the DVT. Progressive malignancy (n = 7) and underlying cardiac pathology (n = 5) were the most common causes of death. Seventy-three (37%) of the 197 eligible patients responded to the survey. Because no changes were made in the survey instrument since its validation, the 21 participants of the survey validation cohort were included in this study. Four patients not meeting