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Venous thromboembolism in children with cystic fibrosis: Retrospective incidence and intrapopulation risk factors

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ABSTRACT

Introduction: Pediatric venous thromboembolism (VTE) is a rare but serious medical condition. Cystic fibrosis (CF) is a risk for recurrent pediatric VTE and has potential thrombophilic tendency. However, much remains unknown, including incidence and intrapopulation risk factors.

Methods: A retrospective cohort of pediatric CF patients followed at Children's Hospital Colorado from January 1st 2003 through May 20th 2016 was examined. Cases were identified by informatics and validated manually. Data on CF severity, co-morbidities and treatment, central venous catheter (CVC) use, and thrombophilia were obtained from an institutional CF database and chart review.

Results: Nineteen VTE occurred in 458 participants followed for 3595 person-years, yielding an incidence rate of 53 VTE per 10,000 children with CF. VTE cases had additional co-morbidities including CF-related diabetes ($p = 0.002$) and sinus disease ($p = 0.04$), more total admissions ($p < 0.001$), admit days ($p < 0.001$), positive respiratory cultures ($p < 0.001$), pseudomonas infections ($p < 0.001$), steroid courses ($p = 0.001$), and total CVC days (PICC $p = 0.03$, port $p = 0.007$). On univariate analysis, older age (RR 1.162, $p = 0.007$), sinus disease (RR 2.62, $p = 0.05$), longer hospital stay (RR 1.03, $p < 0.001$), higher ESR (RR 1.02, $p = 0.03$) and CRP (RR 1.07, $p = 0.007$), and an absence of systemic steroids (RR 0.19, $p = 0.004$) increased the risk of VTE.

Conclusions: In this cohort, children with CF had a higher incidence of VTE when compared to the previously reported incidence in the overall pediatric population at Children's Hospital Colorado. Overall, those with VTE had a greater disease burden and older age, sinus disease, longer hospitalization and increased inflammation were VTE risk factors.

1. Introduction

Pediatric venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a rare but serious medical condition resulting in significant morbidity, mortality and healthcare costs. Frequently cited incidence rates of VTE in the pediatric population are 0.7 total cases per 10,000 children and 58 cases per 10,000 hospital admissions [1,2]. This clinical problem is growing, with data from the Pediatric Health Information System showing a 70% increase in the annual rate of pediatric admissions for VTE between 2001 and 2007 [2]. Further, in regards to VTE complications, 25% of pediatric patients with VTE develop chronic venous insufficiency [3], 2% to 9% of those with PE die as a consequence of their VTE [4,5] and mean total expenditures for a single diagnosis of pediatric VTE are as high as $105,359 [6].

Risk-stratified VTE prevention in hospitalized adults is now standard of care whereas pediatric hospital-acquired VTE prevention strategies remain limited by a paucity of data, due in part to the relatively low incidence of pediatric VTE and the marked heterogeneity across study populations. Single institution, case-control studies have identified some general risk factors for pediatric VTE including systemic infection, length of stay, mechanical ventilation and use of a central venous catheter (CVC) [7–10]. Notably, a few unique, higher risk sub-populations have been identified, including neonates [11], trauma patients [12,13], and those with cardiovascular disease [14]. Identification of higher risk sub-populations reduces heterogeneity and the study of risk variation between and within these groups allows for more precise risk stratification and in turn, more judicial use of thromboprophylaxis in the pediatric population as a whole.

Cystic fibrosis (CF) is a genetic disorder resulting in recurrent

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sinopulmonary infections, pancreatic insufficiency, diabetes, and liver disease. Airway infection and inflammation are hallmarks of CF and recurrent pulmonary infections are often treated with extended intravenous (IV) antibiotic courses necessitating the use of implantable ports and peripherally inserted central catheters (PICC). There is evidence to support thrombophilia in this sub-population, with a higher frequency of protein C and protein S deficiency as well as anti-phospholipid antibodies [15–18]. CF has also been shown to be a risk factor for recurrent VTE in a single-institution pediatric cohort [19]. Further, there are 10 published studies specifically on VTE in CF patients with implantable ports reporting a frequency of VTE as high as 25% [16]. Of these 10 studies, however, only two were pediatric and both had small sample sizes, with the larger including only 44 patients [20,21]. Currently, there is no published VTE incidence in the pediatric CF population, nor any data on VTE frequency or incidence in CF patients with PICCs, and finally, limited analysis of risk, including the contribution of underlying disease.

To address these knowledge gaps, we examined a retrospective cohort of pediatric CF patients cared for at Children's Hospital Colorado from 2003 through 2016, combining validated diagnoses of VTE and superficial vein thrombosis with demographics, CF disease characteristics, co-morbidities and treatment, CVC use, and thrombophilia testing. In this pediatric CF cohort, we defined the incidence of VTE and identified factors capable of delineating those at highest risk for VTE within this sub-population, as a first step to improving risk stratification.

2. Methods

2.1. Study participants

All study participants received care at the CF Foundation (CFF) accredited University of Colorado CF Care Center at Children's Hospital Colorado. This center has the largest CF pediatric population in the United States including > 375 patients with full datasets reported in the 2016 CFF patient registry. Participants or their guardians provided informed consent in accordance with the Declaration of Helsinki prior to entry into the institutional CF database. The Colorado Multiple Institutional Review Board approved both the institutional CF database and this study (#15-1582). Clinical and research databases were queried for patients age 30 days to 21 years who received care from January 1st 2003 to May 20th 2016 and all 458 eligible participants were entered into the cohort. The cohort was then screened for potential VTE cases through informatics followed by manual diagnostic validation. Informatics triggers included relevant ICD-9 and ICD-10 diagnosis codes, documentation of thrombosis in a radiographic report, documentation of thrombosis in nursing flowsheets and/or administration of therapeutic doses of heparin (low-molecular weight or unfractionated). Seventy-nine potential cases were found on initial screen, and after manual validation, 31 total thrombi were confirmed in 25 participants. One arterial clot, one calcified DVT and one fibrin sheath with PE symptomatology but with negative imaging were excluded, yielding a total of 28 thrombi (19 in deep veins and 9 in superficial) in 22 participants over 27 admissions. Eighteen thrombi were diagnosed with ultrasound, 5 with CT scan and 5 by other imaging modalities.

2.2. Data collection

Baseline demographics and data from all admissions within the study timeframe were collected and managed using REDCap (Research Electronic Data Capture) hosted at the University of Colorado, Anschutz Medical Campus [22]. Data obtained from the CF database included gender, race, CF genotype, presence of CF co-morbidities and date of co-morbidity diagnosis, indication for admission, admission-specific forced expiratory volume (FEV_1) percent predicted values, body mass index (BMI) and respiratory culture results. Additional data including admission-specific laboratory results, medication administration, and CVC use was obtained via informatics and was merged into the final, longitudinal REDCap database. For all laboratory results, the first value obtained during each admission was recorded. Administration of oral or IV steroids (prednisone or methylprednisolone), estrogen containing contraception, and/or CFTR modulator therapies (ivacaftor or lumacaftor/ivacaftor) was recorded as present or absent for each admission. For all CVCs, line type, insertion date and removal date were recorded. For thrombosis cases, additional data were collected by manual chart review including date of thrombosis diagnosis and hospital day of diagnosis, type and location of the thrombosis, central-line association, personal and family history of thrombosis and thrombophilia testing. Beginning in October of 2012, Children's Hospital Colorado instituted an institutional HA-VTE prevention clinical care guideline in an effort to standardize VTE risk assessment and thromboprophylaxis strategies. Available data on chemical and mechanical thromboprophylaxis was recorded for all cases [23].

2.3. Definitions

CF mutations are classically categorized into five classes based on molecular mechanism. Class I, II or III mutations are associated with more severe disease and class IV or V are associated with milder disease [24]. For our analysis, a participant with a combination of two class I, II or III mutations was classified as having a “severe” genotype, while any other combination (i.e. two mild or one mild/one severe or one mild/one unknown) was classified as a “mild” genotype. If a participant had one unknown/one severe or two unknowns, the genotype was classified as “uncharacterized”. Per institutional practices, chronic pseudomonas infection was defined as ≥ 50% of respiratory cultures positive for pseudomonas over the course of the study.

Low protein C was defined as a functional protein C level < 45% if tested in 2013 and earlier and < 37% if tested from 2014 through 2016 (reference range: 45–94% through 2013, 37–154% through 2016; Stachrom Protein C, Diagnostica Stago Inc., Parsippany, NJ, USA), low protein S as a free protein S < 60% (reference range: 60–124%; STA — Liatest Free Protein S, Diagnostica Stago Inc., Parsippany, NJ, USA) and low antithrombin as activity < 90% (reference range: 90–131%; Stachrom ATIII, Diagnostica Stago Inc., Parsippany, NJ, USA) and a positive dilute Russel's viper venom time (DRVVT) of a ratio > 1.22 (Reference: LA1 screen < 1.21, LA1/LA2 normalized ratio < 1.22; STAClot DRVV Screen and Confirm, Diagnostica Stago Inc., Parsippany, NJ, USA). Additionally, the institutional range for ESR is 0–20 mm/h and for CRP, the lower limit of detection is 0.5 with a reference range from 0.5 to 1.0. Both ESR and CRP were treated as continuous variables in the analysis.

VTE incidence rate was calculated using person-years defined as consent date or study start date minus censor date or study completion date, as not all participants were followed for the full duration of the study. Per the Children's Hospitals' Solutions for Patients Safety (CHSPS) 2017 operational definition, hospital-acquired thrombosis was defined as a thrombosis occurring ≥ 48 h after admission, within 30 days of a prior hospitalization or associated with a newly placed CVC [25]. CVC-associated thrombosis was defined as a thrombosis occurring in the same vessel as a current CVC. Line days to thrombosis diagnosis was calculated by subtracting the line insertion date from the thrombosis diagnosis date. Similarly, time to hospital-acquired thrombosis was calculated by subtracting the admission date from the thrombosis diagnosis date.

2.4. Statistical analysis

For the incidence rate, person-years was used for the denominator and was calculated by subtracting censor date or study completion date from the CF registry entry date or study start date for each participant and then totaled. The relationship between possible risk factors and