CYSTIC FIBROSIS AS A RISK FACTOR FOR RECURRENT VENOUS THROMBOSIS AT A PEDIATRIC TERTIARY CARE HOSPITAL

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Objective To evaluate risk factors for recurrent thrombosis in pediatric patients.

Study design This prospective observational cohort study enrolled 120 patients with acute venous thromboembolism from January 2003 to April 2005. Data collection included medical and family history, radiologic and laboratory studies, therapy, and follow-up.

Results The overall prevalence of recurrent thrombosis in our cohort was 19/120 (15.8%). Patients with recurrence were older, with a median age of 14.8 years (range 2 weeks-23.6 years), compared with 10.1 years (range newborn 23.4 years) in patients without recurrence ($P = .03$). Six of the 19 patients with recurrent thrombosis had cystic fibrosis (CF), compared with 0/101 without recurrence ($P < .001$). Five of these 6 patients were colonized with *Burkholderia cepacia* in their sputum. Central venous catheters were associated with most, but not all, of the thromboses in patients with CF.

Conclusions In this study, patients with CF had a high risk of recurrent venous thrombosis, as well as a high prevalence of colonization with *B cepacia*. The cause of this risk has not been defined. This observation may have important implications for thromboprophylaxis, particularly in the setting of central venous catheters. *(J Pediatr 2006;148:659-64)*

Venous thromboembolic events (VTE) are a significant cause of morbidity at pediatric tertiary care hospitals. VTE are frequently a complication of treatment and supportive care for acute and chronic childhood illnesses. Currently, most therapeutic decisions regarding anticoagulation in children are extrapolated from adult studies, and therefore the optimal duration of anticoagulation, and indications for thromboprophylaxis are not well established.[1] Although the risk of recurrent thrombosis in adults has been well documented, there are limited data in children. The Canadian Childhood Thrombophilia Registry reported that 33/405 (8.1%) of children had a recurrent VTE with a mean follow-up of 2.9 years.[2] Nowak-Gottl et al[3] reported 21.3% of pediatric patients with spontaneous deep venous thrombosis (DVT) had recurrent events with a median time of 3.5 years after withdrawal of anticoagulation, with recurrence more likely in older children. These data compare with a 17.5% recurrence rate over 2 years in adults with a first DVT.[2,4]

Children with development of VTE are an extremely heterogeneous group, ranging in age from premature infants to adolescents. Although the presence of a central venous catheter (CVC) is the most prevalent risk factor for VTE, most children with VTE have more than one risk factor, and such risk factors may be inherited or acquired.[2] Given the heterogeneity of this population, the risk of recurrence is likely to vary, and it is therefore unlikely that a single therapeutic strategy is optimal or desirable.

To better understand the risk factors associated with recurrent VTE in children, we prospectively established a cohort of pediatric patients with VTE. We aimed to identify risk factors for complications of VTE, including recurrent thrombosis and post-phlebitic syndrome. Interestingly, one of the early findings of this cohort is the high risk of recurrent VTE in patients with cystic fibrosis (CF), especially those who have respiratory colonization with *Burkholderia cepacia*. This association is not previously well documented and may have important implications regarding treatment strategies for these patients.

METHODS

The Institutional Review Board at the Children's Hospital of Philadelphia approved these studies.

CF	Cystic fibrosis	LMWH	Low-molecular-weight heparin
CVC	Central venous catheter	VTE	Venous thromboembolic event
DVT	Deep venous thrombosis		

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Table I. Characteristics of patients with and without recurrent thrombosis

Patient characteristics	Patients without recurrence (n = 101) n, (%)	Patients with recurrence (n = 19)	*P* value
Male	53 (52)	11 (58)	N.S.*
Ethnicity			N.S.†
Caucasian	69 (68)	12 (63)	
African-American	27 (27)	6 (32)	
Hispanic	3 (3)	1 (5)	
Other	1 (1)	0 (0)	
Median age and range (yrs)	10.1 (0–23.4)	14.8 (.002–23.6)	$P = .03$‡
Cystic fibrosis	0	6	$P < .001$*
CVC	41	14	NS
Infection	36	9	NS
Surgery	17	0	NS
Malignancy	14	3	NS
OCP	7	0	NS
Cardiac	4	0	NS
IBD	3	1	NS
Sickle cell disease	2	2	NS
SLE	1	0	NS
Other	25	6	NS
Thrombophilia (# tested)			
Factor V Leiden mutation (109)	11	0	
Prothrombin gene mutation (106)	1	0	
Lipoprotein(a) > 30 (95)	17	2	
Antithrombin Deficiency (93)	4	3	
Protein S Deficiency (89)	3	1	
Protein C Deficiency (93)	0	0	
APLS (104)	2	0	

OCP, Oral contraceptive; *IBD,* inflammatory bowel disease; *SLE,* systemic lupus erythematosis; *APLS,* antiphospholipid antibody syndrome.
*Fisher's exact test.
†Chi-square test for trend.
‡Wilcoxon rank-sum test.

Patients

Subjects who presented clinically and had a documented VTE were consecutively recruited between January 2003 and April 2005. Informed consent was obtained from either the patient (if 18 years of age or greater) or the parent (if the patient was less than 18 years of age). Assent for study participation was obtained from children older than 7 years when possible.

Data Collection

Information regarding the location and extent of thrombosis, underlying medical disease, presence of a central line and other known or potential risk factors, history of thrombosis, family history of thrombosis, thrombophilic laboratory evaluation, radiology studies, and therapy were collected by chart review at presentation. In addition, patients were followed up as outpatients in the hematology clinic.

Laboratory Studies

The standard laboratory evaluation for thrombophilia in patients with VTE at Children's Hospital of Philadelphia includes complete blood count, prothrombin time, partial thromboplastin time, factor V Leiden mutation analysis, prothrombin 20210 gene mutation analysis, protein C activity, protein S level (free and total antigen), antithrombin activity, lipoprotein (a) level, plasma homocysteine concentration (non-fasting), anticardiolipin antibody titer (immunoglobulin M and G), anti-β2glycoprotein antibody titer (immunoglobulin M and G), and dilute Russell Viper Venom time.

Statistical Analysis

Statistical analysis was performed with STATA 7.0 software (College Station, Texas). Because these data were not normally distributed, medians and intraquartile ranges were used to describe patient characteristics. Statistical assessment was carried out with nonparametric tests, including Fisher's exact test, Wilcoxon rank-sum test, and the χ^2 test for trend. All statistical tests were 2-sided, with $P < .05$ considered to be statistically significant.

RESULTS

Between January 2003 to April 2005, 120 pediatric patients with 133 episodes of acute venous thrombosis were enrolled in this study. Patient characteristics are described in Table I, and the distribution of thrombosis location is listed in Table II.