Thrombosis Research 141 (2016) 178–182

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Risk factors and co-morbidities in adolescent thromboembolism are different than those in younger children

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ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form 10 March 2016
Accepted 16 March 2016
Available online 18 March 2016

Keywords:
Adolescent
Deep vein thrombosis
Pediatrics
Risk factors
Thromboembolism

ABSTRACT

Introduction: In adolescent thromboembolism (TE), multiple risk factors (RFs) and co-morbidities (CMs) are reported, though overall prevalence has not been evaluated. We hypothesized that the spectrum of RFs/CMs in adolescent TE differs from children overall and sought to review Texas Children's Hospital's experience.
Patients/methods: Medical records of adolescents aged 12–21 years, diagnosed with arterial or venous TE (AT/DVT) from 2004 to 2014, were retrospectively reviewed and analyzed with IRB approval.
Results: Sixty-four adolescents (median age 16, range 12–20 years) met study criteria. Fifty-seven (89%) had DVT and six (9%) had AT. Associated RFs/CMs included obesity (47%), CVC (27%), infection (27%), surgery (27%), autoimmune disease (19%), immobility (22%), anatomical abnormality (20%), cancer (8%), estrogen therapy (6%), tobacco use (6%), trauma (3%), inherited thrombophilia (19%), and other medical conditions (11%). Fifty-two (81%) had ≥2 RFs/CMs. Therapy included anticoagulants, antiplatelet agents, and interventional therapy. Of those with follow-up imaging, 49 had complete or partial resolution, 5 had no change and 4 had progression. Fourteen (22%) had recurrent TE. The majority with recurrent TE (79%) had ≥2 RFs at initial diagnosis. Mean time to recurrence was 4.80 years; time to recurrence was shorter for occlusive TE ($p = 0.026$).
Conclusion: Adolescent TE is often multi-factorial with the majority having ≥2 RFs at diagnosis, suggesting the need for detailed evaluation for RFs in this population, which may enable optimal management including thromboprophylaxis, and institution of RF-modifying strategies to prevent occurrence/recurrence.

1. Introduction

Thromboembolism (TE) in the pediatric population has become a growing concern with increased incidence noted during the past two decades [1]. This rise is thought to be related, at least in part, to technological advances in diagnostic modalities and improved survival of critically ill patients [2,3]. Pediatric TE, unlike in adults, is infrequently spontaneous or idiopathic (5–10% in children versus 40% in adults), likely due to a more robust, less injured vasculature in children [2–4]. Therefore, children are more likely to have an underlying risk factor for the development of TE. The presence of central venous catheter (CVC) is reportedly the most common cause for TE in neonates and children overall [5].

Pediatric studies report a bimodal distribution of TE events, with the majority occurring in neonates and adolescents [6,7]. The increased prevalence of adolescent TE in comparison to children of other ages is well-documented [3,6,8,9]. This higher incidence in adolescents is in part due to the transition to a more adult-like coagulation profile [4]. In contrast to neonates and children, a variety of risk factors (RFs) and co-morbidities (CMs) for TE including cancer, obesity, trauma, and use of oral contraceptives have been described in the adolescent population [2,10]. However, there are no articles published addressing the overall prevalence of these RFs and CMs in an exclusively adolescent population. Recognition of RFs and CMs is clinically important as this may lead to measures to prevent occurrence or recurrence of adolescent TE.

We sought to review our experience with adolescent TE, including the prevalence of RFs and CMs, presenting features, management and outcome at our institution. We hypothesized that the spectrum of RFs and CMs in adolescent TE is varied, different from the predominance of CVC-related TE reported in children overall.

2. Patients and methods

We retrospectively reviewed the medical records of adolescents at Texas Children's Hospital (TCH) with a diagnosis of TE from January 1, 2004 to January 31, 2014, as approved by the Institutional Review Board. Adolescent age was defined as patient aged 12–21 years of age at the time of diagnosis of TE. Patients with thrombosis of an artery

Abbreviations: TE, thromboembolism; CVC, central venous catheter; RFs, risk factors; CMs, co-morbidities; TCH, Texas Children's Hospital; AT, arterial thrombosis; DVT, deep vein thrombosis; SVT, superficial vein thrombosis; PE, pulmonary embolism; CR, complete resolution; PR, partial resolution; IVC, inferior vena cava; tPA, tissue plasminogen activator.

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http://dx.doi.org/10.1016/j.thromres.2016.03.021
0049-3848/

(AT), deep vein (DVT), pulmonary embolism (PE), and/or ischemic stroke were eligible for this analysis. Adolescents with only superficial vein thromboses (SVTs) were excluded. The data collected included demographic data, body mass index, previous history of TE, family history of TE, tobacco use, current medications including estrogen therapy, comorbid diagnoses, trauma, recent surgical or invasive procedures, history of immobilization, presenting signs and symptoms, laboratory data, initial and follow-up imaging studies, management details and outcome. Specifically regarding TE, details about age at diagnosis, site of TE, occlusion status, embolic complications, specific medical and/or interventional therapy and outcomes (including recurrence) were gathered. Occlusion status was determined by imaging modalities; occlusive TE was defined as TE that completely occluded the vessel blocking blood flow, and non-occlusive TE was defined as TE that only partially occluded vessel. Outcomes were defined as complete or partial resolution (CR/PR), no change or progression based on follow-up imaging findings for all thrombi.

2.1. Statistical analysis

Patient characteristics, risk factors and treatment were summarized using mean and standard deviation, median and 25th and 75th percentiles, or frequency and percentage for all patients, by recurrence status and by resolution/progression status. Comparisons of characteristics and risk factors between resolution/progression status were analyzed using Fisher's exact test, ANOVA and Kruskal-Wallis test. Comparisons by recurrence status were analyzed using time to event methods, specifically the log-rank test. Kaplan-Meier plots were provided for the overall time to recurrence and any comparisons that were significant using the log-rank test.

3. Results

3.1. Patient characteristics

During the study period, 94 adolescents with TE were evaluated at TCH. Of these, 23 were excluded due to age < 12 years at diagnosis of TE. Two were excluded as they had only hemorrhagic stroke without an ischemic component. Two were excluded due to having only SVTs. Two were excluded due to TE diagnosed clinically and not confirmed on diagnostic imaging. One was excluded due to having cutaneous microthrombi only. Sixty-four patients met the inclusion criteria who comprised the study population.

The median age at diagnosis was 16 years (range 12–20 years). Thirty-two subjects (50%) were male. Table 1 depicts the characteristics of the TE events noted in our cohort. Presenting features of TE in 59 patients (92%) included pain, swelling, color change of extremity, paresthesia, oxygen requirement, chest pain, shortness of breath, dyspnea, headache, emesis, rash, catheter dysfunction and unresponsiveness; six (9%) TEs were detected incidentally. Thirteen (20%) had a family history of TE. Five (8%) had past history of TE prior to age 12 years; four of these had recurrence in different sites. Of the 57 with DVT, 65% (N = 37) had at least one occlusive area and 22% (N = 13) were non-occlusive. Eight imaging studies did not specify degree of occlusion.

3.2. Risk factors and co-morbidities

Table 1 and Fig. 1 depict the predisposing RFs and CMs identified in our population at time of TE diagnosis. These included obesity [body mass index >95th percentile for age and sex as per Centers for Disease Control and Prevention [11,12]], CVC, infection, surgery, autoimmune disease, immobility, anatomical abnormalities, cancer, estrogen therapy, tobacco use and trauma. Other medical conditions associated with TE risk (N = 7; 11%; Fig. 1) included hemoglobin SS (N = 1), diabetes mellitus (N = 3), iron deficiency anemia (N = 1), end stage renal disease with low protein C (N = 1) and nephrotic syndrome (N = 1).

Table 1
Patient Characteristics, Risk Factors and Outcome.

All Patients N(%)	Total	CR + PR	No Change	Progression	p-value*
	64 (100%)	49 (77%)	5 (8%)	4 (6%)	
Arterial Thrombosis[a]	6 (9%)	5 (10%)	0	1 (25%)	0.41
Head/Neck	3 (5%)				
Abdomen	1 (2%)				
Upper Extremities	1 (2%)				
Lower Extremities	2 (3%)				
DVT[a]	57 (89%)	45 (90%)	5 (100%)	3 (75%)	0.41
Head/Neck	11 (17%)				
Abdomen	5 (8%)				
Upper Extremities	17 (27%)				
Lower Extremities	32 (50%)				
PE	17 (27%)	14 (28%)	0	0	0.29
Occlusive	37 (58%)	29 (58%)	2 (40%)	3 (75%)	0.71
Risk Factors (RF):					
CVC	17 (27%)	11 (22%)	2 (40%)	1 (25%)	0.68
Obesity	30 (47%)	26 (52%)	0	1 (25%)	0.06
Infection	17 (27%)	13 (26%)	2 (40%)	0	0.40
Tobacco	4 (6%)	3 (6%)	0	0	1.0
Cancer	5 (8%)	3 (6%)	2 (40%)	0	0.08
Surgery	17 (27%)	13 (26%)	0	2 (50%)	0.20
Immobility	14 (22%)	8 (16%)	2 (40%)	2 (50%)	0.10
Autoimmune	13 (20%)	12 (24%)	1 (20%)	0	0.82
Estrogen	4 (6%)	4 (8%)	0	0	1.0
Anatomic RF	13 (20%)	10 (20%)	1 (20%)	2 (50%)	0.26
Trauma	2 (3%)	2 (4%)	0	0	1.0
Inherited RF	12 (19%)	8 (16%)	1 (20%)	2 (50%)	0.19
RF ≥2	52 (81%)	40 (80%)	4 (80%)	3 (75%)	1.0

DVT = deep vein thrombosis; PE = pulmonary embolism; CVC = central venous catheter; CR = complete resolution; PR = partial resolution.
* p-value compares those with follow up data for the outcome.
[a] Some patients had AT and/or DVT in >1 location

Inherited thrombophilic RFs were present in 12 out of 50 (24%) tested; seven subjects had heterozygous Factor V Leiden (FVL) mutation, 1 had homozygous FVL mutation, 1 had Prothrombin 20210 mutation, 1 had MTHFR mutation with elevated homocysteine, 2 had protein C deficiency and 1 had protein S deficiency.

3.3. Diagnosis, treatment and clinical outcome

The imaging modalities used to diagnose TE included Doppler ultrasound (US; N = 51), echocardiogram (echo; N = 4), computed tomography (CT; N = 15), CT with angiography (N = 7), magnetic resonance imaging (MRI; N = 2), MRI with angiography (MRA; N = 1), MRI with venography (MRV; N = 6), venography (N = 1) and angiography (N = 2). Twenty-four subjects (37%) had >1 modality used at diagnosis.

All subjects were treated with anticoagulation therapy including unfractionated heparin, low molecular weight heparin, argatroban, fondaparinux, or warfarin, with 52% treated with more than one anticoagulant. Four subjects (6%) received the antiplatelet agent, aspirin. Twenty patients (31%) had interventional therapy performed, including thrombectomy, endarterectomy, angioplasty, stenting and/or inferior vena cava (IVC) filter placement. Tissue plasminogen activator (tPA) was used in 16 subjects (25%). Of the 37 patients with occlusive DVT, 43% received interventional therapy.

Four subjects were lost to follow up and two had PE only with no follow-up imaging. Of the 58 subjects with follow-up imaging, 49 had CR or PR, 5 had no change and 4 had progression (Table 1). Of those who received interventional therapy, 85% had CR or PR. Twenty-two percent of the study population experienced TE recurrence and the majority of this subset (79%) had ≥2 RFs at the time of their initial diagnosis (Table 2). Thirteen of the thirty-seven (35%) with occlusive TE were noted to have recurrence (Table 2). The mean time to recurrence was 4.80 years (95% CI: 4.12, 5.48) and the 25% recurrence rate was 3.16 years (Fig. 2). When comparing time to recurrence by TE characteristics and RFs, the time to recurrence was shorter among those diagnosed with an occlusive thrombosis (p = 0.026; Fig. 2).