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Systemic thromboembolism in children. Data from the 1-800-NO-CLOTS Consultation Service.

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Introduction

Historically, thromboembolic events (TE), including deep vein thrombosis (DVT), and pulmonary embolism (PE) were considered exclusively as adult disorders. Only recently, TE have been recognized as secondary complications in children being treated for critical underlying diseases (2, 18). In addition, it is becoming clear that TE in children result in significant mortality and long term morbidity (4, 5, 7, 11, 21). Therefore, determining the epidemiology of TE is an important first step in dealing with this relatively new disorder in children. To date, available information has come from small registries lacking sufficient power to delineate all aspects of TE over all pediatric age groups (2, 14, 18, 20). Also, because of the relatively recent recognition of TE in children, there is a serious lack of available information in relation to appropriate diagnosis, prevention and clinical management. This lack of information in the setting of a quickly growing clinical entity, has left many clinicians with insufficient tools for providing the best clinical management. A need existed for distribution of therapeutic guidelines based on best available evidence. Therefore, the 1-800-NO-CLOTS consultation service was initiated in 1994 with the two-fold goal of i) dissemination of the best available information on management of pediatric TE and ii) collection of data on the epidemiology of TE in a large cohort of pediatric patients (1). Free consultations were provided by telephone and the information on children was collected and entered into a centralized database. This paper summarizes data from the 1776 consecutive children with systemic TE referred to the service.

Materials and Methods

Data collection

The 1-800-NO-CLOTS service was managed by two pediatric hematologists (Drs Andrew and Massicotte) trained in adult thromboembolism who were available 24-hours a day seven days a week. The service was free to callers. Consultations consisted of personal communication, provision of therapeutic protocols and/or pertinent scientific literature. Data on all calls were collected immediately using a standardized data form. Information collected were; caller identification, address and subspecialty; patient age at the time the TE was diagnosed; gender; underlying diseases; TE location; imaging techniques; anticoagulant therapeutic interventions; prothrombotic testing and family history for TE. The age of the patients were between 0-18 years. For the purposes of the study, a systemic TE was defined as any thrombosis located in the arterial or venous system excluding TE in the intracranial vessels. A lower system TE was defined as any TE in the inferior vena cava (IVC) or abdominal, pelvic, or leg veins, and distal. Upper system TE was

defined as any TE distal to the superior vena cava. All intracardiac TE were classified as arterial unless the TE was in the right atrium which was classified as venous. The definition of children with a recurrent TE in the manuscript refers to a telephone consult about a recurrent TE. All intracardiac TE were classified as arterial unless the TE was in the right atrium which was classified as venous. Testing for prothrombotic markers was performed in the callers' institutions and normal ranges generated by their labs were used as basis for diagnosis of a deficiency. Also, recommendations and protocols supplied to the caller were recorded. Data were entered into a computer database (SPSS 8.0, SPSS Inc,. Chicago, USA). The study was approved by the ethics board of the Hospital for Sick Children, Toronto, Ontario.

Statistical Analysis

Demographic parameters were summarized by mean (SD) and are reported for all patients and by age group (neonates vs non-neonates). A series of simple logistic regression models regressing single factors against location (arterial vs. venous) were tested using the SAS System (Cary, NC, USA). The variables entered into the regression model included age, gender, primary disorder, presence of a central catheter, family history and previous TE. All statistically significant associations were indications to include the factor as a covariate in the initial multiple ordinal logistic regression model. Backward stepwise regression was used to reduce the ml to the final form. The score test for the proportional odds assumption was performed to confirm or reject the assumption.

Results

Between September 1996 and August 2001, more than 5000 calls were received by the 1-800-NO-CLOTS service. Callers reported 1776 children presenting with systemic TE. Data on children with central nervous system TE will be reported in a seperate manuscript. The remainder of calls concerned issues considered beyond the objective of this paper (e.g. prophylactic treatment, patients over 18 years of age).

Demographic Data On Callers

Seventy-four percent (n=1315) of callers were pediatric hematologists/oncologists, 11% (n=193) neonatologists, 7% (n=119) pediatric intensive care specialists, and 8% (n=149) other specialists. Origins of calls were 86% (n=1518) USA, 11% (n=197) Canada, 2% (n=32) Europe, and 1% (n=19) Australia. Demographic data of children: Infants under one year of age 47% (n=841) including neonates 26% (n=464) represented the largest

distinct pediatric age group. Twenty-two percent (n=391) of children were preterm. Fifty-seven percent (n=221) of these children had their TE during the neonatal period, while the remaining 43% (n=170) had their clots beyond the first month of life. In 108 children, clots occurred in multiple locations (i.e. arterial and venous, or systemic and central nervous system). Data on children with thrombosis in both venous and arterial locations (n=108) are excluded from analysis. Data are reported by TE location and by age group (Table 1). For the purposes of the manuscript neonates are defined as children less than one month of age and non-neonates are children over one month of age. The diagnosis of thrombosis from the callers was assumed to be accurate as all thrombosis were diagnosed by objective tests. Therefore, no further tests were recommended for diagnosis unless specifically requested by the caller. In a small percentage of calls the caller was requesting specific information on radiographic diagnosis (Table 2).

Venous Thrombosis

Patient Demographics

Venous thrombosis occurred in 78% (n=1312) of children, 18% (n=230) of which were neonates (Table 1). Males represented 52% and 51% of children, respectively, in the neonatal and non-neonatal groups.

Affected Vessels

The most frequently affected vessels in neonates were the inferior vena cava (IVC) and the right atrium, while in non-neonates the upper and lower venous system were most frequently affected. Pulmonary embolism was reported in 3% of neonates and 9% of non-neonates (Table 3).

Diagnosis

In neonates, ultrasound (74%) and echocardiography (32%) were the most frequently performed imaging techniques. For non-neonates, ultrasound and echocardiography were used in 80% and 17% of children, respectively. Venography was performed in 1% of neonates and 7% of non-neonates.

Associated Conditions

Ninety-four percent of children had at least one associated condition, 68% had at least two associated conditions. In neonates, prematurity and infection/sepsis were most frequently present while in non-neonates, infection/sepsis, prematurity, acute lymphoblastic

leukemia (ALL), non-ALL malignancy, and cardiac disorders were equally frequent. A family history for thrombosis was positive in 7% of both neonates and non-neonates. Central venous lines (CVLs) were associated with TE in 65% of neonates and in 64% of non-neonates. Previous TE were reported in 6% of non-neonates.

Prothrombotic Testing

Results from prothrombotic testing were available in 8% (n=37) of neonates, 49% (n=18) were positive. Abnormalities included activated protein C resistance (APCR) / Factor V Leiden mutation (n=13), protein C deficiency (n=3), and antithrombin (AT) deficiency (n=2). Results from prothrombotic testing were available in 23% (n=299) non-neonates, 39% (n=183) were positive. Abnormalities included APCR (n=43), antiphospholipid antibodies (n=43), AT deficiency (n=34), protein S deficiency (n=32), and protein C deficiency (n=31).

Treatment

Antithrombotic therapy had been initiated in 49% (n=113) of neonates and in 65% (n=701) of non-neonates. In neonates, low molecular weight heparin (LMWH) (n=65) and unfractionated heparin (UFH) were used in 58% (n=65) and 38% (n=43), respectively. In non-neonates, UFH was used in 46% (n=322) and LMWH in 38% (n=269). Warfarin was used in one neonate and 25% (n=172) of non-neonates. Lysis was used in 20% (n=22) of neonates and 15% (n=102) of non-neonates.

Arterial Thrombosis

Patient Demographics

Arterial TE occurred in 20% (n=356) of children, 52% (n=186) were neonates (Table 1). There were 56% and 60% males, respectively, in the neonatal and non-neonatal groups.

Affected Vessels

In neonates the aorta was most frequently affected, while in non-neonates the femoral artery and the heart, were most frequently affected (Table3).

Diagnosis

In neonates, ultrasound (83%, n=154) and echocardiography (14%, n=26) were the most frequently performed imaging techniques. Ultrasound and echocardiography were used in 54% (n=92) and 32% (n=54) of non-neonates, respectively.

Associated Conditions

Eighty-seven percent of children had at least one associated condition, 51% had two or more associated conditions. In both neonates and non-neonates, prematurity and cardiac disorders were the most frequently associated conditions. A family history for thrombosis was positive in 8% of neonates and 4% of non-neonates. A central arterial catheter was associated with the TE in 28% of non-neonates and in 59% of neonates. Previous TE were reported in 7% non-neonates.

Prothrombotic Testing

Results from prothrombotic testing were available in 10% (n=24) of neonates, 21% (n=5) were abnormal. Abnormalities included APCR/Factor V Leiden mutation (n=3), protein C deficiency (n=1), and AT deficiency (n=1). Results from prothrombotic testing were available in 4% (n=43) of non-neonates, 35% (n=14) were abnormal. Protein C deficiency (n=7), APCR (n=4), protein S deficiency (n=2), and AT deficiency (n=1) were the most common abnormalities.

Treatment

Antithrombotic therapy had been initiated in 49% (n=92) of neonates and 70% (n=119) of non-neonates. The most common anticoagulant drug was UFH in 63% (n=58) of neonates and 60% (n=71) of non-neonates. LMWH was administered in 24% (n=22) of neonates and 18% (n=22) of non-neonates. Lysis was used in 34% (n=31) of neonates and 23% (n=27) of non-neonates.

Multiple Logistic Regression Of Risk Factors Versus Location of TE

Results of the multiple regression model are shown in Table 4. Of the risk factors included in the first simple logistic regression model, only presence of a central catheter, primary disorder, and age group remained significant in the final multiple logistic regression model. Compared to arterial TE, venous TE was more likely to occur beyond the neonatal period (OR 4.56, 95% CI 3.30-6.31), and to be associated with a central catheter (OR 3.10, 95% CI 2.26-4.25). Children with ALL were more likely to suffer from venous TE than arterial TE (OR 5.72, 95% CI 1.18-27.76), whereas children with cardiac disorders (OR 0.27, 95% CI 0.12-0.60) were more likely to suffer from arterial TE than venous TE. Although formal statistics were applied to the data, care must be taken in interpretation of the findings as these data are limited by the nature of the cohort and the lack of a control group.

Discussion

The current paper reports on 1776 pediatric patients with systemic TE referred to the 1-800-NO-CLOTS service. The large patient cohort allowed, for the first time, assessment of the relative prevalence, risk factors and locations of TE , associated conditions and underlying disorders over all ages.

The venous system was the most common location for TE in all ages. The incidences and numbers of risk factors for venous TE were similar over age groups with presence of a CVL being the single most common associated risk factor. In contrast to adults, where about 25% of all venous TE occur in otherwise healthy individuals (6), the vast majority (90%) of children with venous TE had at least one associated condition, with 2/3 of children having two or more risk factors for TE. These findings agree data from the Canadian and Dutch registries (2, 18, 20). These data suggest that children are at a relatively low risk for idiopathic venous TE and occur only when one or multiple risk factors are present. Children with ALL were 5.7 times more likely to have a venous TE than an arterial TE. The increased risk for venous TE is likely related to the acquired AT deficiency, as congenital AT deficiency is associated with venous disease, and placement of CVL(10). In contrast to adults, where less than 5% of TE are located in the upper venous system (15), almost 40% of venous TE in children occurred in the upper venous system. The presence of a CVL was associated with 91% of TE in the upper venous system and 46% of TE in the lower venous system. These findings agree with previously published data (2, 11, 18, 20).

Diagnosis of venous TE in children in the 1-800-NO-CLOTS registry were primarily made by ultrasound and venography was rarely used. Venography was seldom used in both the Dutch and German neonatal registry (14, 20). The reason for routine choice of ultrasound is undoubtedly the ease, lack of invasiveness, and the belief, based upon adult studies, that ultrasound is sensitive for detection of venous TE. However, recent studies have shown that sensitivity of ultrasound for detection of TE in the central upper venous system in children is only 37% (8), and only 21 to 43% for detection of TE in the right atrium and IVC in neonates (17). The routine use of ultrasound, as indicated from data from the current study, suggests that about 2/3 of TE in children go undetected. Therefore, reported prevalences of TE in children are underestimated.

A serious major complication of venous TE is PE. In children, PE is almost certainly under diagnosed because of overlap of symptoms with those of underlying disorders and a low index of suspicion. The 1-800-NO-CLOTS registry reports an overall prevalence

of PE of 8%. The Canadian and Dutch registries showed that confirmed PE occurred in 15% and 10% of children, respectively (11, 20). However, as only clinically symptomatic PE were included, these incidences are most likely underestimated. In neonates, clinical diagnosis and imaging of PE is even more difficult, as indicated by the very low number of reported PE in that age group. Determining how to safely prevent these events is an urgent goal for clinical research.

Seventy-four percent of children with arterial TE were neonates and infants. Similar to venous TE, arterial TE were primarily associated with underlying disorders and presence of central catheters. Neonates and children with cardiac disorders were more likely to have an arterial TE than a venous TE which is probably related to use of umbilical artery catheters, cardiac catheters, ECMO circuits and valves. Accordingly, arterial clots in neonates and non-neonates were mainly found in the aorta, femoral artery or intracardiac.

Twenty-six percent of children with TE were adolescents. The prevalence of TE maybe explained by fact that adolescents are exposed to more risk factors for TE than younger children. For example, risk factors in adolescents that were not risk factors in children under 11 years of age, were oral contraceptives, obesity and systemic lupus erythematosus, which are common in adults. Also, adolescents are more comparable to the adult population in the hemostatic system composition (3). The relative protection from TE reported in the younger child, such as increased levels of $\alpha_2$macroglobulin, decreases in adolescence (9). Also, the adolescent has a decreased fibrinolytic capacity (12). Therefore, adolescents lose the protective features of the hemostatic system seen in younger children. In support of this, idiopathic TE were far more common in adolescents (21%) compared to the younger children (5%). Therefore, TE are likely distinct in adolescents and maybe more comparable to TE in adults.

Results from the 1-800-NO-CLOTS database on prothrombotic testing are unlikely to reflect the true prevalence prothrombotic abnormalities in children with TE for the following reasons. First, it is important to recognize that physicians primarily called in the acute phase of the event. Therefore, it was difficult to determine whether a reported factor deficiency was truly hereditary, or was acquired due to the acute TE and/or the childs underlying disorder. Secondly, testing was performed in a small percentage of children in the cohort (26% in venous TE and 19% in arterial TE) Thirdly, children who had a prothrombotic testing were selected as, at the time of the study, routine testing for prothrombotic markers was rarely performed in North America. The concept that this cohort is selected is supported by the increased percentage of positive children (60% in venous TE and 28%

arterial TE) in the small number of patients tested. These data are not supported by other reports in the literature where prevalences of abnormalities ranged between 7-16% in non-selected populations, respectively (16, 20).

Various anticoagulant treatments had been initiated prior to the consultation call. In arterial TE, UFH was three times more frequent than with LMWH. The preferred use of UFH reflects the mainly intensive care unit based patient-population, in which the ability to immediately reverse anticoagulation is critical for patient management. In venous TE, use of UFH and LMWH was similar, reflecting a gradual switch over time to use of LMWH in pediatrics due to predictable pharmacokinetics and safety profiles based on adult studies (13). Warfarin was seldom used in neonates likely due to the difficulties in managing oral anticoagulant therapy in this age group (19). A majority of calls were to obtain suggestions on optimum anticoagulation. This fact along with the heterogeneity in initial treatments is an indication the lack of information on management of children with TE.

Given the nature of the 1-800 consultation service there is a potential selection bias in the patient population. As the patients were referred to experts in the area of pediatric thrombosis, it is conceivable that there may have been a potential referral bias to only the more complicated, severe and unusual cases. However, the service was started at a time when little was known about management of thrombosis in children and the information available, was not widely disseminated. The calls were in regard to fairly routine management of thrombosis, which is highlighted by the fact that 50% of callers had not begun treatment. So likely these data are generalizable. In support of this, results reported here in terms of location, diagnostic technique, incidence of PE and number of risk factors, are in agreement with published population-based national registries from Canada, the Netherlands, and Germany (7, 14, 18, 20).

In summary, age is a significant risk factor for TE with younger children being at the highest risk. The presence of a CVL was associated with a threefold increased the risk for TE. The current practice for diagnosis of TE in children means that many TE go undetected especially in case of PE. Optimal treatment of TE is hampered by a lack of firm data on the safety and efficacy of anticoagulants in children. There is an urgent need for clinical trials determining management of TE in children.

Tabellen

Table 1: Frequency of Location of Thromboembolic Events in All Age Groups.

	Systemic Arterial (n=356)	**Systemic Venous** (n=1312)	**Multiple** (n=108)	**Total** (n=1776)
Neonates	40% (n=186)	50% (n=230)	10% (n=48)	26% (n=464)
Non-Neonates	13% (n=170)	82% (n=1082)	5% (n=60)	74% (n=1312)
1 to 12 months	21% (n=78)	75% (n=282)	5% (n=17)	21% (n=377)
1 to 5 years	14% (n=37)	80% (n=210)	5% (n=14)	15% (n=261)
6 to 10 years	11% (n=23)	86% (n=182)	3% (n=7)	12% (n=212)
11 to 18 years	7% (n=32)	89% (n=408)	5% (n=22)	26% (n=462)

Table 2: Questions asked by the callers.

	Neonates	**Non-Neonates**
Arterial Thrombosis	(n=157)	(n=145)
Should they treat?	21 (13%)	9 (6%)
Should they treat with anticoagulants?	34 (22%)	2115%)
Should they treat with lytics?	48 (31%)	27(19%)
How to treat?	61 (39%)	62 (43%)
How to treat with anticoagulants?	6 (4%)	15 (10%)
How to treat with lytics?	19(12%)	14 (10%)
Length of treatment	14 (9%)	6 (4%)
Radiographic diagnosis	7 (5%)	6 (4%)
Work-up	4 (3%)	8 (6%)
Lab management	0	4 (3%)
Other	8 (5%)	18 (12%)
Venous Thrombosis	(n=183)	(n=926)
Should they treat?	34 (19%)	97 (11%)
Should they treat with anticoagulants?	22 (12%)	112 (12%)
Should they treat with lytics?	38 (21%)	148 (16%)
How to treat?	63 (34%)	404 (44%)
How to treat with anticoagulants?	24 (13%)	117 (13%)
How to treat with lytics?	10 (6%)	33 (4%)
Length of treatment	24 (13%)	148 (16%)
Radiographic diagnosis	6 (3%)	52 (6%)
Work-up	10 (6%)	49 (5%)
Lab management	6 (3%)	33 (4%)
Other	11 (6%)	70 (8%)

Table 3: Location of Thromboembolic Events By Age Group.

Systemic Arterial			
Location of TE	**Neonates**	**Non-Neonates**	**All Ages**
Upper Venous System	26% (n=60)	39% (n=426)	37% (n=486)
Lower Venous System	11% (n=26)	42% (n=457)	37% (n=483)
PE	3% (n=7)	9% (n=97)	8% (n=104)
IVC	36% (n=83)	13% (n=146)	18% (n=229)
Right Atrium	29% (n=66)	13% (n=135)	15% (n=201)
Renal Veins	28% (n=64)	2% (n=24)	7% (n=88)
Systemic Venous			
Location of TE	**Neonates**	**Non-Neonates**	**All Ages**
Aorta	60% (n=112)	12% (n=21)	37% (n=133)
Femoral Artery	22% (n=40)	25% (n=43)	24% (n=85)
Iliac Artery	18% (n=34)	8% (n=13)	13% (n=47)
Renal artery	13% (n=25)	12% (n=21)	13% (n=45)
Intracardiac	5% (n=9)	25% (n=43)	14% (n=51)
Coronary Arteries	1% (n=2)	10% (n=17)	5% (n=19)

Table 4: Odds ratio of having a primary disorder in children with venous vs. arterial thrombosis, adjusted for age < 1 month (vs. ≥ 1 month) in a multiple logistic regression model.

	OR	**(95% CI)**	**p-value**
Primary Disorder			
ALL	5.720	(1.179, 27.763)	0.0305
Cardiac Disorders	0.269	(0.122, 0.593)	0.0011
Healthy	1.432	(0.612, 3.352)	0.4080
Non-ALL Malignancy	2.322	(0.771, 6.989)	0.1341
Other disorder	0.897	(0.416, 1.932)	0.7804
Prematurity	0.761	(0.340, 1.703)	0.5059
Risk Factor			
Age $>$ 1 month	4.558	(3.295, 6.306)	$<$0.0001
Central Catheter	3.101	(2.264, 4.248)	$<$0.0001

Table 5: Suggested Treatment.

	Neonates	Non-Neonates
Systemic Arterial TE		
No treatment	1 (1%)	1 (1%)
Antithrombotic Therapy		
Initial UFH	64 (34%)	63 (37%)
Long-term UFH	7 (4%)	2 (1%)
Initial LMWH	72 (39%)	51 (30%)
Long-term LMWH	59 (32%)	52 (31%)
Warfarin	2 (1%)	19 (11%)
Fibrinolytic therapy		
TPA	47 (25%)	38 (22%)
UK	12 (7%)	6 (4%)
SK	0	0
Other		
Aspirin	3 (2%)	14 (8%)
FFP	22 (12%)	23 (14%)
Surgery	1 (1%)	9 (5%)
Systemic Venous TE		
No treatment	3 (1%)	9 (1%)
Antithrombotic therapy		
Initial UFH	46 (20%)	197 (18%)
Long-term UFH	3 (1%)	13 (1%)
Initial LMWH	109 (47%)	493 (46%)
Long-term LMWH	110 (48%)	604 (56%)
Warfarin	3 (1%)	166 (15%)
Fibrinolytic therapy		
TPA	31 (14%)	80 (7%)
UK	17 (7%)	34 (3%)
SK	1 (¡1%)	1 (¡1%)
Other		
FFP	20 (9%)	44 (4%)

Abbreviations: TE, thromboembolic event; UFH, unfractionated heparin; LMWH, low molecular weight heparin; TPA, tissue plasminogen activator; UK, urokinase; SK, streptokinase; FFP, fresh frozen plasma.

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Lebenslauf

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