Recurrent pediatric thrombosis: the effect of underlying and/or coexisting factors

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The objective of this study was to evaluate the underlying diseases, thrombus localization, and other risk factors in pediatric patients with recurrent thrombosis in order to obtain a sense of early awareness of the possible recurrences. We retrospectively evaluated both inherited and acquired thrombophilic risk factors in children with recurrent thrombosis that were diagnosed and treated at Hacettepe University, School of Medicine, Department of Pediatric Hematology, Ankara, Turkey. Both congenital and acquired risk factors associated with recurrent thrombosis, and treatment modalities were analyzed in detail. Among 569 children with thrombosis, 32 (5.6%) presented with recurrent thrombosis. Median age at first presentation in these 32 patients [11 women (34.4%) and 21 men (65.6%)] was 132 months. In all, 29 (90.6%) of the 32 patients had an underlying chronic disorder: the most common of which was congenital heart disease [*n* = 11 (34.4%)]. At presentation intracardiac localization, including the entrance of the inferior and superior vena cava, was observed in 10 of the patients (31.2%). Thrombosis recurred at the same location in 15 (47%) patients and at a different location in 17 (53%). Median time interval between the first and second episode of thrombosis was 6.5 months (range: 1–180 months). Considering both acquired and congenital thrombophilic factors, three (9.3%) patients, four (12.5%) patients, and 14 (43.8%) patients had five, four, and three risk factors, respectively. More than half of the patients had elevated plasma FVIII (>150 IU/dl) and D-dimer (>0.5 mg/ml) levels. Thrombectomy was performed in three patients with organized, chronic intracardiac thrombus. Tissue plasminogen activator (t-PA) was used more frequently to treat recurrence than the first event (15.6 vs. 28.1%) and consequently the complete resolution rate was higher (40 vs. 77.7%) at the second event. Thrombi partially resolved in 11 of the patients during the initial episode and in 10 patients during recurrence (34 vs. 32%). In all, 29 (87.5%) patients were using prophylaxis at the time of recurrence. [coumadin (*n* = 16), low molecular weight heparin (*n* = 12) and aspirin (n = 1)]. In total, four patients (12.5%) died because of their underlying disorders and six (18.7%) developed postthrombotic syndrome during the follow-up. Recurrent thrombosis should be expected, especially in cases with congenital heart disease, incomplete thrombus resolution, and elevated plasma FVIII/D-dimer levels. In the light of this knowledge we suggest aggressive treatment for pediatric patients with a high risk of recurrent thrombosis. *Blood Coagul Fibrinolysis* 23:434–439 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Although thrombosis is relatively rare in childhood, such risk factors as prematurity, congenital heart defects, infections, indwelling vascular access devices, and cancer may cause an increase its incidence. In addition, early awareness and improved imaging modalities might also cause an increase in its diagnosis. Adolescents and neonates have a high propensity for thrombosis [1]. On the contrary, there are distinct features that distinguish thrombosis in children from that in adults. Among them, the most striking is the high frequency of secondary events in children. Almost 90% of pediatric thromboses are multifactorial and related to underlying medical and surgical conditions [2–4]. By far, the most commonly reported risk factor is the presence of a central venous catheter (CVC) [5].

Despite advances in our knowledge of the pathogenesis and risk factors of pediatric thrombosis, clinical experience of recurrent venous thromboembolism (rVTE) in children remains limited. It is well known that following a first episode of thrombosis there is a lifelong risk of recurrence [6]. Some factors may be associated with the risk of rVTE, including multiple prothrombotic mutations, persistently elevated factor FVIII and/or D-dimer levels, and a family history of rVTE [7–10].

Due to the limited data available on pediatric rVTE, there are no definitive guidelines for decreasing and/or preventing recurrence. To the best of our knowledge the present study is the first on pediatric rVTE conducted in Turkey. The present study aimed to evaluate underlying risk factors both acquired and congenital and treatment

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modalities in pediatric patients with rVTE in order to obtain a sense of early awareness of the recurrence and to tailor our treatment strategies in these patients.

Materials and methods

Between January 1998 and September 2011, 569 pediatric VTE patients were diagnosed and treated at Hacettepe University, School of Medicine, Department of Pediatric Hematology Ankara, Turkey. The medical records of 32 of these patients (11 women) that had at least one recurrent episode of thrombosis were reviewed. Confirmation of a newly developed thrombosis based on classic imaging modality findings 7 days after the first episode was defined as recurrence [11].

Patient and family histories of thrombosis, such underlying risk factors as infections, cardiovascular diseases, surgery, trauma, cancer, the presence of a CVC, and location of the thrombosis during each episode were underlined in detail. Following clinical suspicion, the presence of a thrombosis was confirmed via Doppler ultrasonography, computed tomography (CT), MRI, and/or echocardiography.

Patients diagnosed as Moyamoya disease and/or cerebrovascular infarct at the time of the first and second thrombotic events were excluded from the study.

In terms of congenital thrombophilic risk factors, plasma protein C (PC), protein S, and antithrombin III (ATIII) levels were measured. PC (normal range: 70–130%) and ATIII activity (normal range: 80–120%) were analyzed in all patients using colorimetric substrates (STA Stachrom; Diagnostica Stago). Free protein S antigen was also measured using immuno-turbidimetric assay kits (normal range: 70–130%) (STA Liatest; Diagnostica Stago). FVIII (range: 55–170%) was measured in all patients via 1-stage clotting assay. Antiphospholipid antibodies were assayed using a standard enzyme-linked immunosorbent assay method.

DNA was isolated using a Magna Pure LC DNA Isolation Kit, and then factor V Leiden (FVG1691A) and prothrombin (PT) PT G20210A genotypes were determined using a LightCycler 1.2 instrument.

Generally, we treat with anticoagulation for at least 3 months in the presence of improvable risk factors and for 6 months in patients with idiopathic thrombosis. In the present study, maintenance was extended to 12 months in patients with residual thrombosis, and high FVIII and D-dimer levels [10].

The effectiveness of the treatment was assessed via anti-FXa (0.5–1 U/ml) for low molecular weight heparin (LMWH) and via partial thromboplastin time (PTT) (40–60 s) for unfractionated heparin. The therapeutic level of coumadin was achieved with the level of international normalized ratio (INR) between two and three.

Written informed consent was provided by the families of the patients included in the study. All abstracted information was saved and the confidentiality of the patients was ascertained. Simple descriptive analyses, including mean, median, and range, were used to summarize the results using SPSS v.10.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Among the 32 patients (11 women and 21 men), median age at the first presentation was 132 months (range: 1–312 months). In all, 13 (40.6%) of the patients were aged more than 12 years. None of the 32 patients had a family history of thrombotic events in first-degree relatives.

Underlying disorders

In total, 29 (90.6%) patients had an underlying chronic disorder and the most common was congenital heart disease ($n = 11$). Among the 11 patients with congenital heart disease, three (27.2%) had undergone shunt surgery: Blalock-Taussig anastomosis due to tetralogy of Fallot (TOF) ($n = 1$); the Fontan procedure due to tricuspid atresia ($n = 2$). Congenital heart disease was followed by rheumatological disease ($n = 5$), including Behcet's disease ($n = 2$), systemic lupus erythematosus ($n = 2$), and scleroderma ($n = 1$). One child had both Behcet's disease and TOF. Malignancy was noted in three patients: lymphoma ($n = 1$), melanoma ($n = 1$), and hepatocellular carcinoma ($n = 1$). The remaining underlying disorders were chronic diarrhea of unknown etiology ($n = 2$), metabolic disorders including homocysteinuria and oxalosis ($n = 2$), nephrotic syndrome ($n = 1$), chronic graft-versus-host disease ($n = 1$), chronic mastoiditis ($n = 1$), necrotizing enterocolitis ($n = 1$), staphylococcal infection at the time of recurrence ($n = 1$), and inflammatory bowel disease ($n = 1$) (Tables 1 and 2).

Thrombophilic risk factors

In terms of hereditary thrombophilia, FV G1691A and PT G20210A genotypes were heterozygous in nine (28.1%) patients and four (12.5%) patients, respectively, and two (6.25%) patients were heterozygous for both mutations. No patient was homozygous for MTHFR C677T, PT G20210A, or FV G1691A mutation. Homozygous PC deficiency was noted in only one patient (Tables 1 and 2).

Based on risk-stratification of both acquired and congenital thrombophilic factors, three (9.3%) patients had five risk factors, four (12.5%) patients had four risk factors, 14 (43.7%) had three risk factors, nine (28.1%) had two risk factors, and one patient had one risk factor. Thrombosis was idiopathic in only one patient (Tables 1 and 2).

FVIII and D-dimer levels

The plasma FVIII level (normal range: 80–150 IU/dl) was obtainable in 28 patients at the beginning; the level

Table 1 The features of the patients whose thrombosis recurred at the same location

Patient	Age and sex (months)	Underlying disease	First event	Treatment	Outcome	Interval (months)	Second event	Treatment	Outcome	FVL	Pro20210	Risk no
1	18/M	Behcet + TOF	R. atrium	Surgery[a]	CR	72	R. atrium	UFH + OAC	CR	–	–	5
2	2/M	TA + shunt	R. ventricle	LMWH	CR	144	R. ventricle	UFH + OAC	CR	–	–	4
3	36/M	VSD, arrythmia	L. atrium	UFH + LMWH	CR	4	L. atrium	LMWH	CR	–	–	2
4	72/F	CMP	L. ventricle	UFH + LMWH	CR	4	L. ventricle	UFH + OAC	CR	–	–	2
5	132/M	CMP	R. atrium	LMWH + OAC	CR	16	R.atrium	tPA + UFH	CR	–	–	3
6	204/F	CMP, arrythmia	R. atrium	LMWH	CR	24	R. atrium	UFH + OAC	CR	Hetero	–	3
7	30/M	R. heart failure	R. atrium	Surgery	CR	30	R. atrium	tPA + UFH	CR	–	–	2
8	216/M	TAPVR	Conduit	Surgery	CR	36	Conduit	tPA + UFH	CR	–	–	2
9	180/M	Hypoplastic RV	R. atrium	tPA + UFH	PR	6	R. atrium	tPA + UFH	CR	Hetero	–	2
10	312/M	CMP, arrythmia	R. subclavian v	tPA + UFH	PR	5	R. subclavian v	tPA + UFH	PR	–	–	3
11	120/M	IBD	L. femoral v	LMWH	PR	2	L. femoral v	tPA + LMWH	PR	–	Hetero	4
12	192/M	Mastoiditis	SVT	LMWH	CR	4	SVT	LMWH	PR	–	Hetero	3
13	180/F	Melanoma	R. femoral v	UFH + LMWH	PR	5	R. femoral v	UFH + OAC	CR	Hetero	–	3
14	72/M	BMT + GVHD	R. atrium + catheter	tPA + UFH	CR	3	R. atrium + catheter	LMWH	CR	–	–	4
15	120/M	FSGS	R. atrium + catheter	LMWH + removal	CR	12	R. atrium + catheter	LMWH	CR	–	–	2

BMT, bone marrow transplantation; CMP, cardiomyopathy; CR, complete resolution; FSGS, focal segmental glomerulosclerosis; GVHD, graft-versus-host disease; IBD, inflamatory bowel disease; LMWH, low molecular weight heparin; OAC, oral anticoagulant; PR, partial resolution; SVT, sinovenous thrombosis; TAPVR, total anomalies of pulmonary venous return; tPA, tissue plasminogen activator; UFH, unfractionated heparin; VSD, ventricular septal defect. [a]Thrombectomy.

Table 2 The features of the patients whose thrombosis recurred at a different location

Patient	Age and Gender (months)	Underlying disease	First event	Treatment	Outcome	Interva (months)	Second event	Treatment	Outcome	FVL	Pro20210	Risk no
1	192/M	Behcet	R. ventricle	tPA + UFH	PR	18	L. saphena magna	tPA + UFH	CR	Hetero	–	3
2	180/M	None	R. femoral v	UFH + LMWH	CR	4	L. femoral vein	UFH + OAC	CR	–	Hetero	3
3	132/M	None	PTE	tPA + UFH	CR	4	IVC	UFH + LMWH	CR	Hetero	–	3
4	132/F	Lupus	Cerebral infarct	Aspirin	CR	4	PTE	UFH + OAC	CR	Hetero	–	4
5	144/M	SCL	Cerebral infarct	Aspirin	CR	8	R. atrium	tPA + UFH	CR	–	–	3
6	1/F	None	Cerebral infarct	Aspirin	CR	180	L. popliteal vein	UFH+ OAC	PR	–	–	0
7	4/M	Diarrhea	L. jugular vein[a]	LMWH	CR	2	R. juguler vein[a]	LMWH	CR	Hetero	Hetero	5
8	18/M	Diarrhea	R. jugular vein[a]	LMWH	CR	8	L. jugular vein[a]	LMWH	CR	–	–	3
9	24/M	Lymphoma	R. jugular vein[a]	LMWH	CR	2	L. jugular vein[a]	LMWH	PR	–	–	3
10	2/F	NEC	L. jugular vein[a]	LMWH	CR	2	R. jugular vein[a]	LMWH	PR	–	–	2
11	24/F	CHD	R. jugular vein[a]	LMWH	CR	4	SVT	LMWH	CR	–	–	2
12	168/M	Oxalosis	IVC	UFH + OAC	PR	7	PTE	UFH + LMWH	CR	Hetero	Hetero	5
13	132/F	Lupus	L. femoral vein	LMWH	PR	22	R. popliteal vein	LMWH	PR	–	–	3
14	120/M	ProC	Purpura fulminans	R. femoral vein	LMWH+OAC	CR	24	L. femoral arteryLMWH + aspirin	PR	–	–	1
15	168/F	Infection	Portal+femoral v	UFH + OAC	PR	8	IVC	UFH + OAC	PR	Hetero	–	2
16	180/F	Hepatic CA	Portal v	LMWH	PR	1	R. atrium	LMWH	PR	–	–	3
17	168/F	Homocystinuria	SVT	LMWH	PR	6	R. atrium	tPA + UFH + OAC	CR	–	–	3

CHD, congenital heart disease; CR, complete resolution; F, female; IVC, inferior vena cava; LMWH, low molecular weight heparin; M, male; mo, months; NEC, necrotizing enterocolitis; OAC, oral anticoagulant; PR, partial resolution; PTE, pulmonary thromboembolism; SCL, scleroderma; SVT, sinovenous thrombosis; tPA, tissue plasminogen activator; UFH, unfractionated heparin. [a]catheter-related thrombosis.

in 15 (53.5%) of these patients was higher than 150 IU/dl and was more than 200 IU/dl in nine patients (32.1%). The median FVIII level was 153 IU/dl (range: 51–444 IU/dl). Patients with an elevated plasma FVIII level during the first thrombotic episode had FVIII levels higher than 150 IU/dl at recurrence.

Plasma D-dimer levels were obtained in 23 of the patients. In all, 20 (86.9%) had a D-dimer level more than 0.5 mg/ml (normal level: 0–0.48 mg/ml), vs. more than 1 mg/ml in 18 (78.2%) patients. The median D-dimer level was 2.3 mg/ml (range: 0.18–9.7 mg/ml).

Localization of initial thrombosis

Thrombosis localization at first presentation was intracardiac, including the inferior and superior vena cava entrance in 10 (31.2%) patients, followed by catheter-related thrombosis [$n = 7$ (21.8%)], deep vein thrombosis (DVT) of the lower extremities [$n = 6$ (18.7%)], cerebrovascular infarct [$n = 3$ (9.3%)], cerebral sinovenous thrombosis [$n = 2$ (6.2%)], inferior vena cava [$n = 1$ (3.1%)], portal venous system [$n = 1$ (3.1%)], subclavian vein [$n = 1$ (3.1%)], and pulmonary thromboemboli (PTE) [$n = 1$ (3.1%)]. Thrombosis recurred at the same location in 15 patients and at a different location in 17 patients (Tables 1 and 2).

Time interval between episodes

Thrombosis recurred three times in only one patient during the 12-year follow-up period, and in two patients thrombosis recurred twice following the first episode. Median time between the first and second episodes of thrombosis was 6.5 months (range: 1–180 months). Only one patient had recurrent thrombosis 1 month after the initial episode; this patient had catheter-related thrombosis, which recurred on the second catheter that replaced the first catheter. In total, 22 patients (68.7%) had recurrence within 1 year of the initial episode (Tables 1 and 2).

Treatment and outcome

Thrombectomy was performed in three patients with organized, chronic intracardiac thrombus, and all were given coumadin prophylaxis following the procedure.

Thrombolytic therapy (tissue plasminogen activator [t-PA]) (0.01–0.03 mg/kg per h) was given to five (15.6%) patients at the first thrombotic episode. Following the first t-PA treatment, although all patients were anticoagulated with heparin, followed by LMWH and/or coumadin for a long time, residual thrombosis was observed in three (60%) of the patients, which was confirmed via imaging techniques; thrombosis recurred at the same location in two of the three patients.

t-PA was administered to nine patients (28.1%) at the second thrombotic event and two (22.2%) had residual thrombosis after the treatment. t-PA was used more commonly for recurrent than first episode thrombosis (15.6 vs. 28.1%) and the complete resolution rate was higher in response to t-PA (40 vs. 77.7%).

In all, six patients – two with intracardiac thrombosis and four with DVT – were anticoagulated with heparin for first the 5–7 days post initial thrombotic event, followed by LMWH for 3–6 months, whereas, LMWH was initially used in 15 patients. The dose of LMWH increased from prophylactic to therapeutic in nine patients at recurrence.

Thrombus was partially resolved in 11 patients at initial episode and in 10 patients at recurrence (34 vs. 32%). The characteristics of recurrent thrombotic events are shown in Tables 1 and 2.

In total, 29 (87.5%) patients were administered prophylactic coumadin ($n = 16$), LMWH ($n = 12$) and aspirin ($n = 1$) at the time of recurrence.

Morbidity and mortality

In all, four patients died as of the time of this analysis due their underlying chronic disorder (lymphoma: $n = 1$; hepatocellular carcinoma: $n = 1$; congenital heart disease: $n = 2$). Postthrombotic syndrome (PTS), which is characterized by chronic skin changes, edema, and varicose veins, was observed in three of the six patients with DVT; all three had totally obstructed deep femoral veins with extension to the iliac veins and residual thrombosis after the first thrombotic event.

Discussion

The number of children diagnosed as VTE is increasing due to improvements in clinical awareness and diagnosis. Early recognition of VTE is important because it can limit morbidity and mortality. The long-term sequelae of pediatric thrombosis, such as residual thrombosis, recurrence, and PTS have been investigated [10,11]. The frequency of childhood rVTE is reported to be 4–18.5% [2,12,13]. In total, 32 of the present study's 569 patients (5.6%) had recurrence of thrombosis at the same or different anatomic location, which is similar to previous reports.

In the present study, thrombosis recurred at the same location in 50% of the patients (group 1) and a different location in the other 50% (group 2, Tables 1 and 2). The majority of patients in group 1 had underlying congenital heart disease, had undergone shunt surgery, and/or had cardiomyopathy. In nine of the 11 patients who had intracardiac thrombus (81.8%) resolution was complete, which may have been related to treatment with thrombectomy, close monitoring with echocardiography, and use of t-PA (Table 1). Patients in group 2 had a wide spectrum of underlying chronic disorders, including malignancy, and rheumatologic and metabolic disorders. In total, seven (41.1%) patients in group 2 had DVT, including portal vein (Table 2). Complete obliteration of the deep veins with thrombus, and the presence of

ongoing inflammatory processes and their effects on vascular endothelium are important risk factors associated with partial resolution of thrombosis and its recurrence [10].

In the present study, 32 (93.7%) patients had at least two risk factors for thrombosis. As shown in Table 1, three of nine patients (33%) with at least three risk factors had partial resolution, whereas all the patients with two or less predisposing factors had complete resolution. In the present study, incomplete thrombus resolution may have been because of the number of risk factors; however, because of the small study population this remains unclear.

The persistence of elevated plasma D-dimer and FVIII levels 3–6 months after the start of anticoagulation treatment is a significant risk factor for thrombotic recurrence [10]. A few pediatric studies reported that elevated FVIII and D-dimer levels are related to poor outcome in patients with thrombosis [14]. In the present study, the plasma FVIII level was higher than 150 IU/dl in 15 (53.5%) patients and more than 200 IU/dl in nine (32.1%). Interestingly, high plasma FVIII levels were noted in 33.3% of group 1, vs. 58.8% of group 2. This finding indicates that ongoing underlying inflammatory processes were related to high plasma FVIII levels and a high risk of thrombotic recurrence. The primary limitations of the present study are that plasma FVIII and D-dimer levels were not obtained in all patients during follow-up, particularly between thrombotic episodes, and a small study population that restricts generalization of the findings.

Nowak-Göttl *et al.* [9] reported that children with at least two prothrombotic risk factors have the highest risk for recurrence of thrombosis. Simioni *et al.* [15] reported that the recurrence rate is higher in carriers of the FV G1691A gene mutation than in normozygous patients. In the present study, heterozygous FV G1691A gene mutation was observed in nine (28.1%) patients, and two patients were heterozygous for both PT G20210A and FV G1691A; fortunately, their thromboses resolved completely at the second event. Natural anticoagulant deficiency was reported to be associated with an increase in the risk of thrombotic recurrence [16]. A recent study reported that the rate of first rVTE in patients with deficiency of a natural anticoagulant was 48%, with an incidence of 7.2/100 patient-years [16]. The patients with antithrombin III deficiency had a higher risk than those with PC or protein S deficiency [16]. Homozygote PC deficiency was observed in one patient whose first thrombosis was DVT of the right femoral vein, whereas the second event was femoral artery thrombosis that resolved partially.

Another important factor that affects the potential of recurrence and treatment success is the type of treatment modality, that is, conservative or aggressive. The limited use of thrombolytic therapy in the pediatric population due to the fear of bleeding might be related to incomplete resolution and recurrences in the present study. Successful results have been reported in a pediatric group using low-dose systemic t-PA (0.015–0.06 mg/kg per h for 12–96 h) pointing to the advantage of reducing hemorrhagic risk [17]. In the present study, t-PA was used in only five patients at the first thrombotic episode and in nine at thrombotic recurrence as an initial, emergent approach. Complete obstruction of the deep veins is known to increase the risk of incomplete resolution and PTS [10]. In the present study, use of t-PA in patients with a high risk of DVT, such as of the inferior vena cava and iliac veins, in addition to intracardiac thrombosis might have had decreased incomplete resolution consequently the further recurrences.

Generally, we treat with anticoagulation for at least 3 months in the presence of improvable risk factors and for 6 months in patients with idiopathic thrombosis. In the present study maintenance was increased to 12 months in patients with residual thrombosis, and high FVIII and D-dimer levels [10]. It was reported that the rate of recurrence was lower in patients that were anticoagulated for 30 months because of high plasma FVIII levels than in patients that were anticoagulated for only 6 months [18]. On the contrary, Estepp *et al.* [11] reported that the duration and/or effectiveness of LMWH therapy did not decrease the risk of recurrence in children after the first VTE episode. In the present study, 29 (90.6%) patients were receiving anticoagulant prophylaxis [coumadin ($n=16$), LMWH ($n=12$) and aspirin ($n=1$)] at the time of thrombotic recurrence. Anticoagulation prophylaxis did not appear to offer protection against recurrence. The low rate of compliance to parenteral LMWH and/or dietary recommendations in the patients who received coumadin therapy might have reduced the effectiveness of the therapy.

In conclusion, rVTE should be expected, especially in patients with congenital heart disease or ongoing inflammatory conditions, such as malignancy and collagen vascular disorders. On the contrary, residual thrombosis, and elevated plasma FVIII and D-dimer levels are well known risk factors for rVTE. As such, prophylactic anticoagulation should be given for a while, in addition to close monitoring of FVIII and D-dimer levels in patients with a high risk of rVTE.

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Conflicts of interest

This study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest to declare.

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