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ORIGINAL ARTICLE

Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome

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Summary. To learn more about the frequencies of congenital prothrombotic disorders in pediatric venous thromboembolism (VTE) and the outcome of this disease, we evaluated consecutive patients from 0 to 18 years with objectively diagnosed VTE at a single tertiary center over a 12-year period. We included 100 patients, with a median age at diagnosis of 1.0 year (range 2 days to 17 years). At least one underlying clinical condition was present in 96% of the patients. Factor (F)V G1691A mutation was present in 13%, FII G20210A mutation in 3%, antithrombin deficiency in 1%, protein C deficiency in 1% and protein S deficiency in 1% of the tested patients. Combined defects were present in 2.6% of the 77 patients with a complete work-up. Positive family history appeared to be the only predictor for positive testing for congenital disorders (OR 14.9, 95% CI 1.9–113). The overall mortality rate was 20%. The cumulative recurrence-free survival was 92% after 1 year of follow-up, and 82% after 7 years. The incidence and severity of the post-thrombotic syndrome was analyzed in a subgroup of 33 patients with VTE of the lower extremities. Twenty-three (70%) patients developed PTS: moderate in three and mild in 20 patients. In conclusion, congenital prothrombotic disorders seem to play a role in the development of pediatric VTE, and the risk of complications of this disease is high.

Keywords: mortality, pediatrics, post-thrombotic syndrome, recurrence, risk factors, venous thromboembolism.

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Introduction

Pediatric venous thromboembolism (VTE) is a multifactorial disorder with an annual incidence of 1 per 100 000 patients (aged 0–18 years) [1,2]. National registries show that VTE usually develops in acute and chronic sick children with a combination of underlying clinical conditions [1–4]. The presence of central venous catheters (CVCs) is a major trigger for development of venous thrombosis, especially in neonates [4]. To what extent congenital prothrombotic disorders play a role in the etiology of VTE in children is not completely elucidated. In adults, the prevalence of the five established congenital defects, including factor (F)V G1691A mutation, FII G20210A mutation, and deficiencies of antithrombin, protein C and protein S, is estimated to be about 30% in unselected patients with confirmed venous thrombosis [5,6]. In pediatric patients with VTE, published frequencies of single congenital prothrombotic disorders vary from 10 to 59% [7–14] and combined congenital prothrombotic disorders from 3 to 21% [7,8,11,12].

As result of the low incidence of pediatric VTE, only a few studies have reported on outcome, including mortality, recurrence and post-thrombotic syndrome (PTS). The all-cause mortality rate has been reported to be between 16% and 23% after 2–3 years of follow-up [15–17]. In 2.2–4.2% of these patients, death was the result of the thrombotic event. The Canadian outcome study of 405 pediatric patients with extremity thrombosis revealed recurrence in 8.1% after a mean follow-up of 2.86 years [17]. Recurrent VTE was predominantly seen in older patients. In another study, 301 patients were followed for a median period of 7 years after a first episode of spontaneous thrombosis, and recurrent VTE occured in 21% [12]. The presence of congenital prothrombotic defects appeared to be an independent risk factor for recurrence.

In adults, venous thrombosis mostly occurs in the lower extremities. As a consequence, PTS, especially of the lower extremities, has been well described in adults, and can be clinically classified into seven classes with increasing severity of the clinical objective signs of chronic venous disease [18]. PTS occurs in about 60% of adult patients with proximal deep-vein thrombosis (DVT) after sufficient anticoagulant therapy.

The use of graduated compression stockings reduces this rate by about 50% [19,20]. Very few studies have reported PTS in children [15–17,21]. In the Canadian study, PTS was diagnosed on the basis of clinical signs and symptoms, including pain, swelling and brownish discoloration of the limb involved. PTS developed in 12.4% of the 405 patients and was most frequently diagnosed in adolescents and in patients with VTE of the lower extremity [17].

The purpose of this study was to evaluate the role of congenital prothrombotic disorders in the etiology of pediatric VTE and to find predictors for the presence of these disorders in pediatric patients with VTE. In addition, we hoped to learn more about the clinical outcome of pediatric VTE, including mortality, recurrence and PTS.

Methods

Patients

From 1 January 1989 to 31 December 2000, consecutively admitted patients in the age range 0–18 years with first venous thrombotic events, were evaluated in one tertiary center, the Emma Children's Hospital/Academic Medical Center. All thrombotic events were objectively confirmed by standard imaging methods. Patients with VTE diagnosed at autopsy were excluded.

In the study center, ultrasonography was used to detect extremity and abdominal VTE. With compression ultrasonography, VTE was diagnosed when residual lumen of the vein was observed after gentle probe pressure. When compression could not be performed, a focal intraluminal filling defect or the absence or change of flow detected by color Doppler ultrasonography confirmed clinical suspicion of VTE. In cases of high clinical suspicion and negative ultrasonography results, venography was used to diagnose first VTE by the presence of an intraluminal-filling defect that was constant in all films and was seen in at least two different projections. CVC-related thrombi in the superior vena cava and/or right atrium were detected by echocardiography by direct imaging of the thrombus. Ventilation–perfusion lung scanning was performed for detection of pulmonary embolism (PE). The same criteria used for adults were used to interpret the scans [22]. Computed tomography, magnetic resonance imaging and angiography were used to detect sinovenous thrombosis. Signs of sinovenous thrombosis included an absence of flow-related signal and visualization of the thrombus.

At time of diagnosis, clinical data forms were completed for each patient including the following information: age at time of diagnosis, gender, race, signs and symptoms, site of thrombosis, type of objective imaging method used to document VTE, underlying clinical conditions, family history of venous thrombotic events in first- and/or second-degree relatives, treatment and complications related to the thrombotic event, such as mortality, recurrence and the occurrence of PTS. Spontaneous VTE was defined as VTE without the presence of underlying clinical conditions. Follow-up data were obtained at regular visits at the outpatient clinic. Cessation of follow-up occurred at the earliest of death, last outpatient contact, or 31 January 2001.

Venous thrombosis was classified as occurring in the cerebral, upper or lower venous system. The cerebral venous system included the veins cranial to the neck veins. The upper venous system included the veins of the neck, upper extremities, thorax and abdomen up to and including the inferior vena cava. The lower venous system included the veins distal to the inferior vena cava, up to and including the popliteal vein. Patients with venous thrombosis in the lower extremity, and either extension of the thrombus into the inferior vena cava, or pulmonary embolism, were classified as having thrombosis of the lower venous system.

Congenital prothrombotic disorders

Coagulation studies included evaluation for FV G1691A mutation, FII G20210A mutation, and deficiencies of antithrombin, protein C, and protein S. Blood samples were obtained before start and/or at least 3 months after cessation of anticoagulant treatment. When plasma values of protein C, protein S or antithrombin were below normal adult values, measurements were repeated and parents were also tested. The diagnosis of congenital deficiencies of antithrombin, protein C, or protein S was made when plasma concentrations of these inhibitors were twice outside the age-specific reference ranges and one of the parents had the same disorder [23–26].

Samples for blood coagulation and mutation analysis were obtained by venipuncture and collected in plastic tubes containing trisodium citrate 3.2% and EDTA, respectively. The ratio of anticoagulant to blood used was 0.1: 0.9 (v/v). After centrifugation ($12\,000 \times g$ for 10 min), plasma was collected and stored at $-70\,^{\circ}C$ in 0.5 mL aliquots.

FV G1691A and FII G20210A mutations were determined by DNA analysis as previously described [27,28]. Protein C activity was measured using a chromogenic assay (Chromogenix, Mölndal, Sweden) after activation by copperhead snake venom (normal adult value, 0.7–1.2 U mL^{-1}). Protein C antigen was measured by ELISA (Boehringer/STAGO, Asnieres-sur-Seine, France; normal adult value, 0.65–1.10 U mL^{-1}). Free protein S antigen and total protein S antigen were measured by ELISA (Dako, Glostrup, Denmark; normal adult values, 0.26–0.61 U mL^{-1} and 0.65–1.08 U mL^{-1}, respectively), the first after polyethylene glycol precipitation. Antithrombin activity was measured by chromogenic assay (Chromogenix, Mölndal, Sweden; normal adult value, 0.80–1.40 U mL^{-1}).

Recurrent VTE

Patients were objectively evaluated for recurrent VTE by standard imaging methods when they presented with new symptoms of VTE during or after discontinuation of anticoagulation treatment instituted for the first thrombotic event. Diagnosis of recurrence was made after radiological confirmation of new VTE.

Postthrombotic syndrome

The incidence and severity of PTS were determined in a subgroup of the total study population, i.e. patients with VTE of the lower venous system, 0.5–3 years after their first thrombotic event.

In these patients, the right and left lower extremities were classified by one investigator (C.H.v.O.) according to the clinical criteria as previously described [18]. PTS was objectively scored as: 0 = absent (no visible or palpable abnormalities), 1–3 = mild (telangiectases, reticular veins, malleolar flare, varicose veins, edema), 4 = moderate (skin changes ascribed to longstanding venous disease, such as pigmentation, venous eczema, lipodermatosclerosis), and 5–6 = severe (skin changes as described for a score of 4, with healed or active ulceration). Furthermore, each patient was asked about subjective symptoms such as lower extremity heaviness, pain, and itching or daily impairment.

Statistical analysis

Potential predictors for a positive test for congenital prothrombotic disorders in patients with venous thrombosis included age at event, gender, the absence of a CVC, location of venous thrombosis in the lower venous system, and the presence of a positive family history for venous thrombotic events in first- and/or second-degree relatives. In patients with a complete work-up for congenital prothrombotic disorders, the relationship between these potential predictors and the presence of a congenital prothrombotic defect was first explored univariately by means of logistic regression analysis. Predictors for a positive test were identified using multivariate logistic regression analysis.

Overall survival of VTE and the risk for recurrence were determined with Kaplan–Meier curves. Potential predictors for recurrent VTE in pediatric patients included age, gender, the presence of congenital prothrombotic disorders, the presence of the most common triggering factors (CVC, infection, heart disease, surgery, hypovolemia), no antithrombotic treatment for at least 3 months and extension of the thrombus (>1 segment vs. 1 segment). In patients with a complete work-up for congenital prothrombotic disorders, the relationship between these predictors and recurrent VTE was first explored univariately by means of Cox regression analysis. Predictors for recurrent VTE were identified using multivariate Cox regression analysis.

Results

Patient characteristics

During the 12-year study period, 100 consecutive pediatric patients were radiologically diagnosed with a first episode of VTE. The median age at diagnosis of VTE was 1.0 year (range 2 days to 17 years). The mean age was 4.9 years. The baseline and clinical characteristics are shown in Table 1.

At least one underlying clinical condition was present in 96% of the patients. Two or more were present in 77% of the patients. Presence of CVC was the most frequent underlying clinical condition, especially in neonates (88%) and infants (95%). The mean time interval between catheterization and diagnosis of VTE was 14 days (range 1–150 days). In about 50% of the 57 patients with a CVC, septicemia was also present. Non-catheter-related infections included gastroenteritis ($n = 5$), urosepticemia (3), urinary tract infection (2), pneumonia (2), osteomyelitis (2), and mastoiditis (1). Surgery had been performed in one neonate (cardiovascular surgery), one infant (cardiovascular surgery), five children (cardiovascular surgery 1, orthopedic surgery 2, kidney transplantation 2), and five adolescents (kidney transplantation 1, neurosurgery 1, orthopedic surgery 3).

In four patients (two children and two adolescents), no underlying clinical conditions were present. In these patients with spontaneous VTE, thrombi were located in the portal vein (2), iliac and femoral veins (1), and subclavian and axillary veins (1). Their family history was negative for VTE.

In most children, anticoagulant treatment after the first thrombotic event consisted of heparin [unfractionated (UF) or low molecular weight heparin (LMWH)] followed by acenocoumarol for a total period of 3–6 months. In three patients with life-threatening VTE, thrombolytic therapy was added in the acute phase. In four patients, including one adolescent with life-threatening PE and positive lupus anticoagulant, one adolescent with positive lupus anticoagulant and recurrent VTE, one adolescent with congenital antithrombin deficiency and one adolescent with sinus thrombosis and congenital protein C deficiency, the intention was to treat for the long term. They received anticoagulant treatment at least until 31 January 2001. UF or LMWH alone was given to 11 patients. Nine died before acenocoumarol could be started. Two had malignant disease and were treated by LMWH for 3 months, as easy interruption of antithrombotic treatment was necessary for lumbar punctures.

No anticoagulant treatment was given to 10 patients, including three neonates with catheter-related thrombosis in right atrium, one neonate with renal vein thrombosis, two children with portal vein thrombosis, and two adolescents with renal vein thrombosis after kidney transplantation. Two children with catheter-related thrombosis had their catheter removed.

All patients were followed for a median duration of 4.0 years (range 1 month to 12 years) to evaluate outcome.

Congenital prothrombotic disorders

In 88 patients, one or more congenital prothrombotic disorders were tested. A complete work-up was performed in 77 patients. The results of the coagulation studies are shown in Table 2.

Congenital prothrombotic disorders were present in 13 patients. FV G1691A mutation was present in 3/26 tested neonates (12%), 1/23 tested children (5%) and 4/20 tested adolescents (20%). In these patients, VTE was located in the deep veins of the leg (5), inferior vena cava (1), pulmonary artery (1) and renal vein (1). One infant with FII G20210A mutation developed VTE of the left leg. Antithrombin deficiency (antithrombin activity 0.54 U mL^{-1}) was present in one adolescent with

Table 1 Baseline and clinical characteristics of the 100 study patients with first VTE

	Total group ($n = 100$) [n (%)]	Patients without complete work-up ($n = 23$) [n (%)]
Male sex	49 (49)	12 (52)
Age at diagnosis of first VTE		
Neonates	33 (33)	10 (43)
Infants (1 month–2 years)	19 (19)	8 (35)
Children (2–12 years)	26 (26)	3 (13)
Adolescents (12–18 years)	22 (22)	2 (9)
Race		
Caucasian	80 (80)	19 (83)
African	20 (20)	4 (17)
Symptomatic VTE	71 (71)	10 (43)
Location of VTE		
Cerebral venous system	4 (4)	–
Upper venous system	52 (52)	15 (65)
Lower venous system	44 (44)	8 (35)
Diagnostic tests		
Ultrasonography (compression/Duplex)	64 (64)	11 (48)
Echocardiography	27 (27)	12 (52)
Ventilation–perfusion lung scanning	12 (12)	–
Computed tomography	6 (6)	–
Venography	4 (4)	–
Magnetic resonance imaging/angiography	4 (4)	–
Lineography	1 (1)	–
Underlying clinical condition		
Central venous catheter	57 (57)	20 (87)
Infection	45 (45)	13 (57)
Heart disease	14 (14)	7 (30)
Surgery (max. 1 week before diagnosis)	12 (12)	–
Hypovolemia	11 (11)	2 (9)
Immobility	10 (10)	2 (9)
Kidney disease	10 (10)	–
Estrogen*	8 (8)	–
Malignancy	7 (7)	2 (9)
Others	31 (31)	3 (13)
None	4 (4)	–
Positive family history	8 (8)	–
Treatment after first VTE		
No anticoagulant therapy	10 (10)	3 (13)
UFH or LMWH/OAC	72 (72)	13 (57)
UFH or LMWH alone	11 (11)	6 (26)
Thrombolytic therapy/UFH/OAC	3 (3)	1 (43)
Others	4 (4)	–

VTE, venous thromboembolism; UFH, unfractioned heparin; OAC, oral anticoagulant therapy (acenocourmarol); LMWH, low molecular weight heparin. *Including oral contraceptives and high dose estrogen for tall stature.

DVT of both legs and PE. Another adolescent, who suffered from sinus thrombosis, had protein C deficiency (protein C activity 0.43 U mL^{-1}, protein C antigen 0.39 U mL^{-1}). Two children (out of the 77 patients with a complete work-up; 2.6%) had a combination of congenital prothrombotic disorders, i.e. FV G1691A mutation/protein S deficiency (free protein S antigen, 0.08 U mL^{-1}; total protein S antigen, 0.62 U mL^{-1}) and FV G1691A mutation/FII G20210A mutation. They both developed DVT of one leg. All patients with congenital prothrombotic disorders had at least one additional underlying clinical condition.

Table 2 Congenital prothrombotic disorders in tested pediatric patients and in general Caucasian adult population

	Patients tested (n)	Disorder (n/%)	General population (%) [5,6]
Factor V G1691A mutation	80	10 (13)	5
Factor II G20210A mutation	79	2 (3)	2
Antithrombin deficiency	86	1 (1)	0.2
Protein C deficiency	84	1 (1)	0.2–0.5
Protein S deficiency	83	1 (1)	0.2–0.5

In the four children with spontaneous VTE, complete work-up for congenital prothrombotic disorders was performed and no disorder was present.

Mortality

The overall mortality rate was 20%. One patient died of sudden massive PE 8 years after undergoing a Fontan procedure. All

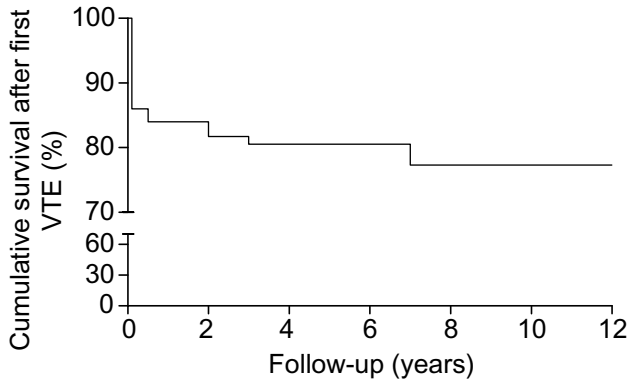

Fig. 1. The cumulative overall survival of 100 pediatric patients with venous thromboembolism.

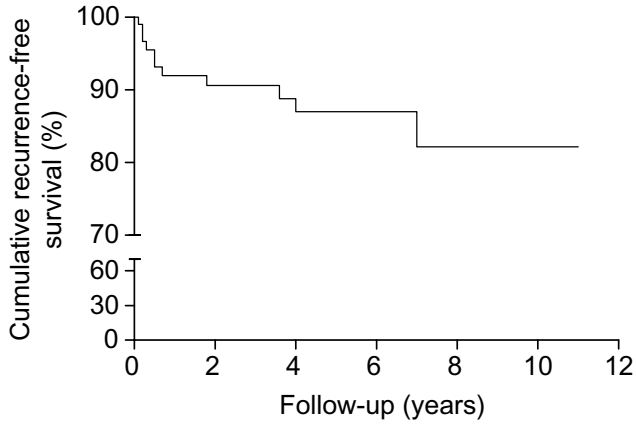

Fig. 2. The cumulative recurrence-free survival of 100 pediatric patients with venous thromboembolism.

other children died as a result of their underlying clinical conditions. The causes of death included prematurity and associated problems ($n = 8$), congenital heart disease (3), metabolic disease (2), malignancy (2), cardiomyopathy (1), respiratory insufficiency (1), liver failure (1) and colitis (1). The cumulative survival after the first episode of VTE was 86% after 1 month of follow-up, 84% after 1 year, 81% after 3 years and 77% after 7 years (Fig. 1).

Recurrent thrombosis

Eleven children (11%) had a total of 16 recurrences. The median age of these patients at time of initial VTE was 13 years (range 3–16 years). The median age at time of first recurrence was 14 years (range 5–20 years). In five patients, the first recurrent event occurred in the ipsilateral leg. Diagnosis was made by venography in two patients and by ultrasonography in three patients. Ultrasonography showed only new VTE, as the initial ultrasound had been normalized after anticoagulant treatment for the first thrombotic event. Two patients had recurrences in the ipsilateral leg and in the lung, diagnosed by ultrasonography and ventilation–perfusion lung scanning. Two recurrences were pulmonary emboli only, diagnosed by ventilation–perfusion lung scanning. Two patients had recurrences in the contralateral leg, diagnosed by venography ($n = 1$) or ultrasonography ($n = 1$).

Three of the 11 patients had congenital prothrombotic disorders (i.e. FV G1691A mutation, antithrombin deficiency and a combination of FV G1691A mutation and protein S deficiency). These patients developed five spontaneous recurrent thrombotic events. The remaining eight patients had recurrences in association with underlying clinical conditions, such as trauma, heart disease, kidney disease, central venous catheter and systemic lupus erythematosus. Of the four patients with spontaneous initial VTE, one had a recurrence after trauma.

Nine recurrences occured in seven patients after discontinuation of antithrombotic treatment, which was given for 3 months. The median time from cessation of treatment to the recurrent event was 3 months (range 1 month−4 years). Two patients with long-term antithrombotic treatment had five recurrences. One of them did not have an international normalized ratio within therapeutic range twice. Two patients had a recurrence after untreated initial VTE.

The cumulative recurrence-free survival after first VTE was 99% after 1 month of follow-up, 92% after 1 year, 91% after 3 years and 82% after 7 years (Fig. 2).

Postthrombotic syndrome

Of the 100 patients, 44 developed VTE in the lower venous system. Eight of these died shortly after diagnosis, and three were lost to follow-up after discharge from the hospital. The median age at time of first VTE of the remaining 33 patients was 7 years (range 0.1–17 years). The female : male ratio was 1 : 1.8. All patients were treated with antithrombotic treatment at the first thrombotic event: heparin and acenocoumarol ($n = 30$), or thrombolytic therapy followed by heparin and acenocoumarol ($n = 3$).

Of 33 patients, 23 (70%) developed clinical PTS, moderate in three and mild in 20 patients. All patients with moderate PTS had increased calf circumferences, telangiectases, malleolar flare, varicose veins and pigmentation of the skin, and complained of heaviness or pain in the affected leg when standing or walking. They all had their initial VTE at adolescent age.

The patients with mild PTS presented with newly formed varicose veins ($n = 12$) and/or increased calf circumferences ($n = 16$). Seven patients had subjective symptoms, and complained of heaviness or pain in the affected leg when standing or walking. Mild PTS was present in 13/20 patients (65%) $<$10 years old and in 7/13 children (54%) aged 10–18 years old.

Statistical analysis

In the univariate analysis, positive testing for congenital prothrombotic disorders was significantly more likely in patients with advancing age (OR 1.2, 95% CI 1.1–1.3), thrombosis in the lower extremity (OR 5.6, 95% CI 1.1–28.3), a positive family history of VTE (OR 21.3, 95% CI 3.9–116.3) and in patients without a CVC (OR 10.4, 95% CI 1.3–87). In the multivariate

analysis, a positive family history of VTE (OR 14.9, 95% CI 1.9–113) appeared to be the only predictor for positive testing for congenital prothrombotic disorders.

No predictors for recurrent VTE were identified using univariate Cox regression analysis.

Discussion

Congenital prothrombotic disorders seem to contribute to the development of VTE in pediatric patients, as in our study population the prevalence of each congenital prothrombotic disorder was higher than in the general caucasian adult population (Table 2).

A limitation of this study is the incomplete laboratory work-up of the patients. However, almost half of the patients without complete work-up were neonates with CVCs. Salonvaara *et al*. showed that 10% of neonates with CVCs had congenital prothrombotic disorders [13], so it is likely that testing of all patients would not have changed our results significantly. Selection bias because of referral of patients with VTE to a tertiary care center seems unlikely, as coagulation studies were performed after referral.

The observation that congenital prothrombotic disorders seem to play a role in development of pediatric VTE is consistent with previous reports [7–12,14]. In most of these reports, however, the prevalences both of one congenital defect and of combined defects in pediatric patients with VTE were much higher than those in this study. An important cause of this variation in reported frequencies might be the heterogeneity of the study populations. The current patient cohort contained 20% African patients, whereas most other study populations comprised Caucasian patients only [8–10,12,14]. It is known that in the Caucasian population the prevalence of FV G1691A mutation is higher than in the African population [29]. Furthermore, spontaneous VTE was rare in the current study. Only 4% of the patients had VTE without underlying clinical conditions, whereas this was 38% and 41% in the studies of Junker *et al*. and Ehrenforth *et al.*, respectively [8,9]. Surprisingly, none of our patients with spontaneous VTE appeared to have congenital defects, which can probably be explained by the low number of spontaneously affected patients. The low incidence of spontaneous VTE in our study might be caused by recruitment bias, as our center is a tertiary center with neonatal and pediatric intensive care units, and a large oncology and cardiology department. In addition, ambulatory adolescent patients with development of spontaneous VTE at home might have been referred to non-pediatric departments. However, a registry study in the Netherlands, participated by more than 90% of all pediatricians in primary, secondary and tertiary centers, also showed a low incidence of spontaneous VTE in pediatric patients [2]. Furthermore, in our center, all patients in the age of 0–18 years with VTE are treated by the pediatric hematology department, as agreed with the department of adult vascular medicine.

As the heterogeneity of the study populations might cause variation in reported frequencies of congenital prothrombotic disorders in pediatric patients with VTE, predictors for the presence of congenital defects were identified. A positive family history of VTE appeared to be the only predictor for positive testing. However, the relevance of this observation is uncertain because of the large 95% confidence interval. Therefore, the precise role of congenital prothrombotic disorders in the development of VTE in pediatric patients is still unclear and should be investigated in more homogeneous pediatric patient groups in large prospective multicenter trials.

Little is known about the long-term outcome of pediatric VTE. This study showed that after 3 years of follow-up overall mortality was 19% and the cumulative incidence of a first VTE recurrence was 9%, which are similar to the results of previous studies [15–17]. The recurrence rate seems to increase with increasing duration of follow-up, which has also been reported in adults [20,30]. In adults, the recurrence rate is almost twice as high as in pediatric patients. This increased recurrence rate may be caused by the presence of more persistent underlying clinical conditions.

It is important to identify pediatric patients with increased risk of recurrence, as these patients might be candidates for prolonged anticoagulant treatment or intermittent antithrombotic prophylaxis in high-risk situations. Until now, only one study had reported on risk factors for recurrent pediatric VTE; in patients with a spontaneous first thrombotic event, the risk of recurrent VTE appeared to be significantly higher in patients carrying a single (OR, 4.6; 95% CI, 2.3–9.0) or combined (OR, 24.0; 95% CI, 5.3–108.7) congenital prothrombotic risk factor [12]. The presence of one or more congenital defects was not a predictor for recurrence in the current study. This is probably the result of the low number of spontaneous VTE, causing a low prevalence of congenital defects.

PTS appeared to be an important complication of pediatric VTE in the lower venous system, as it occurred in 70% of these patients. This is about the same incidence of PTS as in adult patients without compression stockings [19]. As opposed to adults, PTS in pediatric patients is mild with increased calf circumferences and varicose veins. Moderate PTS with skin changes was found in only 9% of the patients. None of the patients had venous ulceration. Longer follow-up is necessary to investigate whether venous ulceration will eventually develop in pediatric patients with mild or moderate PTS. The Canadian pediatric study reported a much lower incidence of PTS (12.4%), which might be explained by different definitions of PTS, shorter follow-up, inclusion of patients with both lower and upper extremity VTE, and underdiagnosis of PTS in infants [17].

This follow-up study is limited by the small number of patients investigated for PTS. Selection bias might have occurred, as about 10% of the patients with lower extremity VTE were lost to follow-up after discharge from hospital. However, if these patients had participated in the study without developing PTS, the total percentage of patients with PTS would still be high. Furthermore, as the investigator was not blinded to the location of the initial VTE, observer bias might have occurred. However, PTS was scored with standardized

objective criteria, which probably decreased the influence of observer bias on the results.

In adults, patients with ipsilateral recurrent VTE appear to be at risk for development of PTS [20]. In this study, the subgroup was too small to investigate potential risk factors for the development of PTS, or the effects of compression stockings or therapy in reducing PTS. In adults, the use of compression stockings significantly reduces the incidence rate of PTS [19]. The high incidence of PTS in pediatric patients warrants a large prospective randomized trial to investigate the benefits of compression stockings in this patient group after VTE of the lower extremity.

References

1 Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, Bernstein M, Brisson L, Cairney B, DeSai D. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood* 1994; **83**: 1251–7.

2 van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HSA, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr* 2001; **139**: 676–81.

3 Nowak-Göttl U, von Kries R, Göbel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal Ed* 1997; **76**: F163–7.

4 Schmidt B, Andrew M. Neonatal thrombosis. report of a prospective Canadian and international registry. *Pediatrics* 1995; **96**: 939–43.

5 Lensing AWA, Prandoni P, Prins MH, Büller HR. Deep-vein thrombosis. *Lancet* 1999; **353**: 479–85.

6 Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999; **353**: 1167–73.

7 Bonduel M, Hepner M, Sciuccati G, Torres AF, Pieroni G, Frontroth JP. Prothrombotic abnormalities in children with venous thromboembolism. *J Pediatr Hematol Oncol* 2000; **22**: 66–72.

8 Ehrenforth S, Junker R, Koch HG, Kreuz W, Münchow N, Scharrer I, Nowak-Göttl U. Multicentre evaluation of combined prothrombotic defects associated with thrombophilia in childhood. Childhood Thrombophilia Study Group. *Eur J Pediatr* 1999; **158** (Suppl. 3): S97–104.

9 Junker R, Koch HG, Auberger K, Münchow N, Ehrenforth S, Nowak-Göttl U. Prothrombin G20210A gene mutation and further prothrombotic risk factors in childhood thrombophilia. *Arterioscler Thromb Vasc Biol* 1999; **19**: 2568–72.

10 Kosch A, Junker R, Kurnik K, Schobess R, Günther G, Koch H, Nowak-Göttl U. Prothrombotic risk factors in children with spontaneous venous thrombosis and their asymptomatic parents: a family study. *Thromb Res* 2000; **99**: 531–7.

11 Lawson SE, Butler D, Enayat MS, Williams MD. Congenital thrombophilia and thrombosis: a study in a single centre. *Arch Dis Child* 1999; **81**: 176–8.

12 Nowak-Göttl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, Schobess R, Ehrenforth S. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood* 2001; **97**: 858–62.

13 Salonvaara M, Riikonen P, Kekomäki R, Heinonen K. Clinically symptomatic central venous catheter-related deep venous thrombosis in newborns. *Acta Paediatr* 1999; **88**: 642–6.

14 Schobess R, Junker R, Auberger K, Münchow N, Burdach S, Nowak-Göttl U. Factor V G1691A and prothrombin G20210A in childhood spontaneous venous thrombosis – evidence of an age-dependent thrombotic onset in carriers of factor V G1691A and prothrombin G20210A mutation. *Eur J Pediatr* 1999; **158** (Suppl. 3): S105–8.

15 Gurgey A, Aslan D. Outcome of noncatheter-related thrombosis in children: influence of underlying or coexisting factors. *J Pediatr Hematol Oncol* 2001; **23**: 159–64.

16 Massicotte MP, Dix D, Monagle P, Adams M, Andrew M. Central venous catheter related thrombosis in children. analysis of the Canadian Registry of Venous Thromboembolic Complications. *J Pediatr* 1998; **133**: 770–6.

17 Monagle P, Adams M, Mahoney M, Ali K, Barnard D, Bernstein M, Brisson L, David M, Desai S, Scully MF, Halton J, Israels S, Jardine L, Leaker M, McCusker P, Silva M, Wu J, Anderson R, Andrew M, Massicotte MP. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. *Pediatr Res* 2000; **47**: 763–6.

18 Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J Vasc Surg* 1995; **21**: 635–45.

19 Brandjes DPM, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; **349**: 759–62.

20 Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; **125**: 1–7.

21 Häusler M, Hübner D, Delhaas T, Mühler EG. Long term complications of inferior vena cava thrombosis. *Arch Dis Child* 2001; **85**: 228–33.

22 The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective work-up of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990; **263**: 2753–9.

23 Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P. Development of the human coagulation system in the full-term infant. *Blood* 1987; **70**: 165–72.

24 Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Castle V, Powers P. Development of the human coagulation system in the healthy premature infant. *Blood* 1988; **72**: 1651–7.

25 Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. *Blood* 1992; **80**: 1998–2005.

26 van Teunenbroek A, Peters M, Sturk A, Borm JJJ, Breederveld C. Protein C activity and antigen levels in childhood. *Eur J Pediatr* 1990; **149**: 774–8.

27 Poort SR, Michiels JJ, Reitsma PH, Bertina RM. Homozygosity for a novel missense mutation in the prothrombin gene causing a severe bleeding disorder. *Thromb Haemost* 1994; **72**: 819–24.

28 Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med* 1995; **332**: 912–7.

29 Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. *JAMA* 1997; **277**: 1305–7.

30 Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000; **160**: 761–8.