Venous thromboembolic disease in childhood epidemiology, risk factors and outcome
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Chapter 8

Pediatric venous thromboembolic disease (II): Mortality, recurrence, and the postthrombotic syndrome

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Abstract

To evaluate the long-term outcome of pediatric venous thromboembolism (VTE), the incidence and features of death and recurrence were prospectively determined in a consecutive cohort of 100 children with VTE at a single center over a 12-year period. The cumulative survival after the first thrombotic episode was 84% after one year of follow-up, and 77% after 7 years. The cumulative recurrence-free survival was 92% after 1 year of follow-up, and 82% after 7 years. The presence of congenital or persistent acquired prothrombotic disorders increased the risk of recurrence (hazard ratio, 5.0; CI, 1.2 to 20.4). The incidence and severity of the postthrombotic syndrome was analyzed in a subgroup of 33 patients with VTE of the lower extremities. Twenty-three (70%) children developed PTS: moderate in 3 and mild in 20 children. In conclusion, the risk of long-term complications is high in children with VTE.
Introduction

Venous thromboembolism (VTE) is a serious disorder in adults, which may cause considerable mortality and morbidity. Recurrent thrombosis and the postthrombotic syndrome (PTS) are the most important long-term complications of deep-vein thrombosis which have been extensively studied in adults. In children, the long-term complications of venous thromboembolic disease have not been thoroughly investigated, probably due to the low incidence of pediatric thrombosis. However, knowledge of the long-term sequelae of pediatric VTE and its specific risk factors is important for the development of effective and safe prophylactic and therapeutic guidelines. Nowadays, most of these guidelines have been extrapolated from adult ones.

In adults, the cumulative all-cause mortality after a first episode of VTE is about 20-40% after 2 years of follow-up. In children with VTE, the all-cause mortality rate has been reported to be between 16% and 23% after 2 to 3 years of follow-up. In 2.2% to 4.2% of these children, death is the result of the thrombotic event.

The cumulative incidence of recurrent thrombosis in adult patients is 17.5% after 2 years and 30.3% after 8 years of follow-up. Patients with transient risk factors are at less risk. The Canadian outcome study of 405 children with extremity thrombosis revealed recurrence in 8.1% after a mean follow-up of 2.86 years. Recurrent VTE was predominantly seen in older children. In another study, 301 children were followed for a median period of 7 years after a first episode of spontaneous thrombosis, and recurrent VTE occurred in 21%. 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 of especially 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. PTS occurs in about 60% of adult patients with proximal deep-vein thrombosis after sufficient anticoagulant therapy. The use of graduated compression stockings reduces this rate by about 50%. Very few studies reported about PTS in children. In the Canadian study, PTS was diagnosed on the basis of clinical signs and symptoms, including pain, swelling and brawny discoloration of the limb involved. PTS developed in 12.4% of the 405 children and was most frequently diagnosed in adolescents and in children with VTE of the lower extremity.

In order to add to the available information about long-term outcome of pediatric VTE, the incidence and features of death and recurrence were prospectively determined in a consecutive cohort of pediatric patients with VTE at a single center over a 12-year period. The incidence and severity of PTS was analyzed in a subgroup of patients with thrombosis of the lower venous system. Furthermore, we tried to identify potential risk factors for recurrent VTE.
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Methods

Patients
From January 1st, 1989 to December 31st, 2000, consecutive children in the age of 0 to 18 years with objectively diagnosed first venous thrombotic events were included in this prospective study in one tertiary center, the Emma Children’s Hospital/ Academic Medical Center in Amsterdam, the Netherlands. Children with VTE diagnosed at autopsy were excluded.

Clinical data forms were completed for each patient, which included the following information: age at time of diagnosis, gender, site of thrombosis, risk factors (clinical and prothrombotic), treatment and complications related to the thrombotic event, such as mortality, recurrence and the occurrence of PTS. 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 January 31st, 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 caval vein. The lower venous system included the veins distal to the inferior caval vein, up to and including the popliteal vein. Children with venous thrombosis in the lower extremity and either extension of the thrombus into the inferior caval vein or pulmonary embolism were classified as having thrombosis of the lower venous system.

Evaluation of acquired and congenital prothrombotic disorders took place before start and/or after cessation of anticoagulant treatment. Coagulation studies included evaluation for factor V R506Q mutation, factor II G20210A mutation, protein C, protein S, antithrombin, and the lupus anticoagulant. All results were compared to normal values established for age. The diagnosis of congenital deficiency of protein C, protein S or antithrombin was made when plasma concentration of these inhibitors were outside the age-specific reference ranges and one of the parents had the same disorder.

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 (vol/vol). After centrifugation (12,000 g x 10 min), plasma was collected and stored at -70 °C in 0.5 ml aliquots.

Factor V R506Q and factor II G20210A mutations were determined by DNA analysis as previously described. Protein C activity was measured using a chromogenic assay (Chromogenix, Mölndal, Sweden) after activation by copperhead snake venom. Protein C antigen was measured by ELISA (Boehringer/STAGO, Asnieres-sur-Seine, France). Free protein S antigen and total protein S antigen were measured by ELISA (Dako, Glostrup, Denmark), the first after polyethylene glycol precipitation. Antithrombin activity was measured by chromogenic assay (Chromogenix, Mölndal, Sweden). Assays for lupus anticoagulant consisted of a diluted prothrombin time (Inovin, Dade, Suisse) and Russell’s Viper Venom test (Gradipur, Australia).
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Recurrent VTE
Recurrent VTE was defined as objectively diagnosed new VTE, occurring during or after discontinuation of anticoagulation therapy instituted for the first thrombotic event.

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, 1 to 5 years after their first thrombotic event.

In these patients, the right and left lower extremities were classified according to the clinical criteria as previously described. PTS was objectively scored as absent in the case of class 0 (no visible or palpable abnormalities), mild in the case of class 1 to 3 (telangiectases, reticular veins, malleolar flare, varicose veins, edema), moderate in case of class 4 (skin changes ascribed to longstanding venous disease, such as pigmentation, venous eczema, lipodermatosclerosis) and severe in case of class 5 or 6 (skin changes as described in class 4 with healed or active ulceration). Furthermore, each patient was asked about the presence of subjective symptoms e.g. lower extremity heaviness, pain, itching or daily impairment.

Statistical analysis
Overall survival of VTE and the risk for recurrence were determined with Kaplan-Meier curves. Potential predictors for recurrent VTE in children included age, gender, the presence of congenital or persistent prothrombotic disorders, the presence of the most common triggering factors (central venous catheter, infection, heart disease, surgery, hypovolemia), no antithrombotic treatment for at least 3 months and extension of the thrombus (> 1 segment versus 1 segment). The relation between recurrent VTE and these predictors 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 twelve-year study period, a total of 100 children was objectively diagnosed with a first episode of VTE. The baseline and clinical characteristics are shown in Table 1. The children were prospectively followed for a median duration of 4.0 years (range, 1 month to 12 years). In most children, anticoagulant therapy was given during a period of 3 months. Two children who had life-threatening VTE and were positive for the lupus anticoagulants, received indefinite anticoagulation after the initial VTE.

Prothrombotic disorders were tested in 88 children. In the 12 patients (6 neonates and 6 older children) who were not tested for the presence of prothrombotic disorders, anticoagulant treatment was started without taking blood for coagulation studies in advance. During anticoagulant treatment, nine of these patients died due to their underlying disease and three patients were transferred to other hospitals and were therefore lost to follow-up. Congenital prothrombotic disorders were present in 13 (15%) and acquired prothrombotic disorders in 19 (22%) of the 88 tested children.
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Table 1. Baseline and clinical characteristics of the 100 study patients with a median age of 1.0 year (range, 0.1-17)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total group n</th>
<th>Characteristic</th>
<th>Total group n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>49</td>
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<td>Location of VTE</td>
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<tr>
<td>Cerebral venous system</td>
<td>4</td>
<td>(Doppler/compression)</td>
<td>61</td>
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<tr>
<td>Upper venous system</td>
<td>52</td>
<td>Echocardiography</td>
<td>27</td>
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<td>Lower venous system</td>
<td>44</td>
<td>Ventilation-perfusion</td>
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<td>Clinical risk factors</td>
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<td></td>
<td></td>
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<tr>
<td>Central venous catheter</td>
<td>57</td>
<td>Lung scanning</td>
<td>12</td>
</tr>
<tr>
<td>Infection</td>
<td>45</td>
<td>Computed tomography</td>
<td>6</td>
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<tr>
<td>Heart disease</td>
<td>14</td>
<td>Venography</td>
<td>4</td>
</tr>
<tr>
<td>Surgery</td>
<td>12</td>
<td>Others</td>
<td>2</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>11</td>
<td>No anticoagulant therapy</td>
<td>10</td>
</tr>
<tr>
<td>Immobility</td>
<td>10</td>
<td>UFH or LMWH / OAC</td>
<td>72</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>10</td>
<td>UFH or LMWH alone</td>
<td>10</td>
</tr>
<tr>
<td>Estrogen*</td>
<td>8</td>
<td>Thrombolytic therapy /</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
<td>UFH / OAC</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>31</td>
<td>Others</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: VTE Venous thromboembolism. UFH Unfractionated heparin, OAC Oral anticoagulant therapy. LMWH Low molecular weight heparin

* including oral contraceptives and high dose estrogen for tall stature

Mortality
The overall mortality rate was 20% (n=20). One patient died of sudden pulmonary embolism eight years after undergoing a Fontan procedure. All other children died as a result of their underlying diseases. The causes of death included prematurity and associated problems (n=8), congenital heart disease (n=3), metabolic disease (n=2), malignancy (n=2), cardiomyopathy (n=1), respiratory insufficiency (n=1), liver failure (n=1) and colitis (n=1). The cumulative survival after the first episode of VTE was 86% after one month of follow-up, 84% after one year, 81% after 3 years and 77% after 7 years. (Figure 1)

Recurrent thrombosis
Eleven children (11%) had a total of 16 recurrences. The median age of patients with recurrent VTE was 13 years (range, 3-16 years). Eight recurrences occurred in the ipsilateral leg, one recurrence occurred in the contralateral superior caval vein and two recurrences were pulmonary emboli. One pulmonary embolus was fatal. In two patients
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Figure 1. The cumulative overall survival of 100 children with venous thromboembolism

with recurrences the initial VTE had not been treated with anticoagulant therapy. In nine children unfractionated heparin had been given for 1 week and oral anticoagulants for 3 months. One patient was still on oral anticoagulant therapy at the time of recurrence, but did not have a international normalized ratio (INR) within the therapeutic range. The median time from the initial thrombotic event to the first recurrence was 6 months (range, 1 month – 7 years). The cumulative recurrence-free survival after first VTE was 99% after 1 month of follow-up, 93% after 6 months, 92% after 1 year, 87% after 4 years and 82% after 7 years (Figure 2).

Figure 2. The cumulative recurrence-free survival of 100 children with venous thromboembolism
Congenital prothrombotic disorders were present in 3 children with recurrent VTE, i.e. factor V R506Q mutation, antithrombin deficiency and a combination of factor V R506Q mutation and protein S deficiency. These children had a recurrence without additional clinical risk factors. Persistent acquired prothrombotic disorders were found in 5 other children with recurrent VTE: lupus anticoagulant (n=3), protein C deficiency (n=1) and protein C in addition to protein S and antithrombin deficiency (n=1). In two of these children, recurrent VTE occurred without an additional clinical risk factor.

In the univariate analysis, recurrent VTE was significantly more likely in children with increasing age and congenital or persistent acquired prothrombotic defects. In addition, a congenital or persistent acquired prothrombotic defect was identified as predictor for recurrence in the multivariate analysis (Table 2).

Table 2. Results of the univariate and multivariate analyses

<table>
<thead>
<tr>
<th></th>
<th>Univariate Hazard ratio</th>
<th>95% CI</th>
<th>Multivariate Hazard ratio</th>
<th>95% CI</th>
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<tr>
<td>Age</td>
<td>1.1</td>
<td>1.0-1.2</td>
<td>1.1</td>
<td>0.98-1.2</td>
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<td>Male versus female</td>
<td>1.3</td>
<td>0.4-4.3</td>
<td></td>
<td></td>
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<tr>
<td>Congenital or persistent</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acquired prothrombotic disorders</td>
<td>7.4</td>
<td>1.9-28.4</td>
<td>5.0</td>
<td>1.2-20.4</td>
</tr>
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<td>Central venous catheter</td>
<td>0.6</td>
<td>0.2-1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>0.5</td>
<td>0.1-2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.6</td>
<td>0.4-7.6</td>
<td></td>
<td></td>
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<tr>
<td>Hypovolemia</td>
<td>0.04</td>
<td>0.0-80.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0.5</td>
<td>0.1-4.1</td>
<td></td>
<td></td>
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<tr>
<td>Extent VTE (&gt; 1 segment versus 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>segment)</td>
<td>1.5</td>
<td>0.4-5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anticoagulant treatment for at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>least 3 months</td>
<td>2.2</td>
<td>0.5-10.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

per year increase in age

Abbreviation: VTE Venous thromboembolism

Postthrombotic syndrome
Forty-four of the total group of 100 patients developed VTE in the lower venous system. Eight of these patients died shortly after diagnosis and 3 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). All children were treated with anticoagulant therapy at the first thrombotic event: heparin and oral anticoagulants (OAC) (n=30) or thrombolytic therapy followed by heparin and OAC (n=3). Nine children used compression stockings. Four children wore them daily for at least two years. The five
other children used them occasionally for a maximum of 6 months.

Twenty-three of 33 children (70%) developed clinical PTS: moderate in 3 and mild in 20 children. All children 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 while standing or walking. They all had their initial VTE at adolescent age.

The children with mild PTS presented with varicose veins (n=12) and/or increased calf circumferences (n=16). Seven children had subjective symptoms and complained of heaviness or pain in the affected leg while standing or walking. Mild PTS was present in 13 of the 20 children less than 10 years old (65%) and in 7 of the 13 children from 10 to 18 years old (54%).

All children who wear compression stockings daily and 4 of the 5 children, who wear compression stockings occasionally, developed PTS.

**Discussion**

Little is known about the long-term outcome after VTE during childhood. This one center study prospectively assessed the incidence and features of complications after a first thrombotic event in a consecutive cohort of 100 children. The results show that the risk of these complications, including death, recurrent thrombosis and PTS, is high.

Overall mortality was 19% after 3 years, which is similar to the all-cause mortality in previous studies. The high mortality rate is caused by the severe underlying diseases, which are present in the majority of children with VTE. Most children died during the first month after the development of thrombosis.

The cumulative incidence of a first VTE recurrence was 13% after 4 years and 18% after 7 years of follow-up. The recurrence rate seems to increase with increasing duration of follow-up, which is reported in adults, as well. 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 clinical risk factors.

In this study, children with persistent prothrombotic disorders had a fifth-fold increased risk of recurrent VTE. Until now, only one study reported about risk factors for recurrent pediatric VTE; in children 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. Hence, testing of prothrombotic disorders seems to be worthwhile in children with a first episode of VTE in order to get informed about the risk of recurrence. These children might be candidates for prolonged prophylactic treatment, taken into account that 5 of the 8 children with persistent prothrombotic defects had recurrent VTE without additional clinical risk factors. In these children intermittent antithrombotic prophylaxis in high-risk situations would not have protected against recurrent VTE. Whether the results of testing for prothrombotic disorders will have consequences for the duration of treatment of VTE and the institution of antithrombotic prophylaxis during high-risk situations, needs to be investigated in children.
PTSS appeared to be an important complication of pediatric VTE in the lower venous system, as it occurs in 70% of these patients. This is about the same incidence of PTSS as in adult patients without compression stockings. As opposed to adults, PTSS in children is usually mild with increased calf circumferences and varicose veins. Moderate PTSS with skin changes was found in 9% of the children. None of the children had venous ulceration. Longer follow-up is necessary to investigate whether venous ulceration will eventually develop in children with mild or moderate PTSS. The Canadian pediatric study reported a much lower incidence of PTSS (12.4%), which might be explained by other definition of PTSS, shorter follow-up, inclusion of children with both lower and upper extremity VTE, and underdiagnosis of PTSS in young infants.

In adults, patients with ipsilateral recurrent VTE appeared to be at risk for development of PTSS. In this study, the subgroup was too small to investigate potential risk factors for the development of PTSS, or the effects of compression stockings or therapy in reducing PTSS. In adults, the use of compression stockings significantly reduces the incidence rate of PTSS. The high incidence of PTSS in children warrants a large prospective randomized trial to investigate the benefits of compression stockings in children after VTE. The type of anticoagulant treatment might also influence the outcome of VTE complications. In one study, half of the 32 children with VTE showed substantial clot lysis and did not develop recurrence or PTSS after combined thrombolytic and anticoagulant therapy. Three and 4 of the patients with poor clot lysis developed recurrent VTE and PTSS, respectively. This report, however, did not include a comparison group with standard regimens. Furthermore, all children with recurrent VTE had congenital prothrombotic disorders or persistent antiphospholipid antibody syndromes.

In conclusion, venous thromboembolic disease is a serious disorder in children because of its high risk of long-term complications. The presence of congenital or persistent acquired prothrombotic defects in children with a first episode of VTE seems to be a predictor for recurrence.

References

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