Venous thromboembolic disease in childhood epidemiology, risk factors and outcome
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Chapter 2

Venous thromboembolism in childhood:
a prospective two-year registry in The Netherlands

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Chapter 2

Abstract

Objective: To study the incidence, signs and symptoms, diagnostic tests, risk factors, therapy, and complications of pediatric venous thromboembolism (VTE) in The Netherlands.

Methods: A prospective 2-year registry of VTE in children aged ≤18 years.

Results: Ninety-nine patients were registered. The annual incidence of VTE was 0.14/10,000 children, 35% of whom were symptom free. Almost half of the patients were newborns. Neonatal VTE was almost exclusively catheter related, located in the upper venous system, and asymptomatic. In older children VTE was catheter related in approximately one third and more often located in the lower venous system. In 85% of all patients, thrombosis developed while the patient was in the hospital. Diagnosis was usually made by ultrasonography. In 98% of all patients, at least 1 risk factor was present. Congenital prothrombotic disorders were more often present in older children (21%) than in neonates (6%). A variety of treatment modalities were used. Morbidity consisted of bleeding (7%) and recurrent thrombosis (7%). Two children died as result of VTE.

Conclusion: VTE is mostly diagnosed in hospitalized children, especially sick newborns with central venous catheters and older children with a combination of risk factors. Primary prevention, optimal treatment, and long-term outcome of pediatric symptomatic and asymptomatic VTE need to be studied.
Introduction

Venous thrombosis is a rare disorder in children, with few studies reported in the literature. Until a decade ago, only case reports or small case series about pediatric venous thromboembolism (VTE) were available, and the incidence and associated morbidity and mortality rates were unknown. In 1994 the first prospective registry was published: this Canadian survey reported an annual incidence of symptomatic VTE in either the lower or upper extremity in children (aged 1 month to 18 years) of 0.07 per 10,000 children and 5.3 per 10,000 hospital admissions. Most children with VTE had serious underlying diseases, and approximately one third of all thrombotic events were associated with central venous catheters (CVCs). In the years that followed, 2 neonatal registries were published. The Canadian neonatal registry reported an incidence of symptomatic neonatal venous and arterial thromboembolism of 24 per 10,000 admissions to the neonatal intensive care unit. Almost all events were associated with CVCs, except in neonates with spontaneous renal vein thrombosis. The second neonatal survey in Germany estimated an incidence of symptomatic neonatal venous and arterial thromboembolism of 0.51 per 10,000 births. In adults, the incidence of VTE is much higher at 1 to 2 patients per 1000 inhabitants per year.

To assess the current incidence, signs and symptoms, diagnostic tests, risk factors, therapy, and complications of pediatric extremity and nonextremity VTE in The Netherlands, a prospective registry of VTE was made for children aged 0 to 18 years in cooperation with the Dutch Pediatric Surveillance Unit (DPSU) during 1997 and 1998.

Methods

In 1992, the DPSU developed a surveillance system for assessing the epidemiology of various childhood diseases in The Netherlands. Every month, notification cards are sent to all pediatricians in primary and secondary care centers and contact persons in tertiary care centers to register all children who meet the various case definitions. The pediatricians return this card to the DPSU after marking 'no children' or writing down the initials and date of birth of the patient. In 1997 and 1998, 91% of all monthly cards were returned to the DPSU. After notification of a patient was received, the notifying pediatrician was asked to answer a questionnaire or to return an anonymous discharge letter.

From January 1997 till January 1999, VTE was included in the registry. Pediatric patients from 0 to 18 years were eligible for entry if thromboembolism was objectively diagnosed in extremity and nonextremity venous systems, including cerebral veins and right atrium. Children with VTE diagnosed by autopsy, were excluded from the registry. Two groups were distinguished: neonates and children between the ages of 1 month and 18 years.

The questionnaire included questions about patient characteristics (birth weight and maturity of neonates, sex, and age at time of diagnosis), presenting signs and symptoms, site of thrombosis, type of test used to document thrombosis, risk factors (clinical risk factors and prothrombotic disorders), treatment given, complications of
treatment, and complications related to the thrombotic event.

VTE 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.

At the start of the study, there was no consensus about which prothrombotic disorders should be evaluated in pediatric patients with VTE in The Netherlands. Not every assay was therefore performed in every patient. Evaluation of prothrombotic disorders was performed before start of treatment and included factor V R506Q mutation, factor II G20210A mutation, antithrombin, protein C, protein S, homocysteine, and lupus anticoagulant. Factor V R506Q mutation and factor II G20210A mutation were determined by DNA analysis as previously described. Total and free protein S were measured by use of enzyme-linked immunosorbent assay, and protein C and antithrombin were measured by use of a chromogenic substrate assay. The diagnosis of a congenital deficiency of protein C, protein S, or antithrombin was made when plasma concentrations of these inhibitors were outside the age-specific reference ranges and one of the parents had the same disorder. Homocysteine was measured by high-performance liquid chromatography. Hyperhomocysteinemia was diagnosed when fasting concentrations of homocysteine were increased, by use of age-related normal values. Lupus anticoagulant was demonstrated by dilute prothrombin time and confirmed with dilute Russell’s viper venom time.

In this registry any exposure to a therapeutic agent was classified in a treatment group. Specific complications were recorded, including bleeding complications (the severity was not assessed), recurrence (objectively diagnosed new thrombotic event), and death.

The incidence of VTE was calculated by use of population age-distribution data from Statistics Netherlands in The Hague. In 1997 and 1998, the mean total population from 0 to 18 years was 3,626,343 children / year in The Netherlands. These children were divided into 6 age categories: 0 to 28 days (16,174 children), 29 to 365 days (177,911 children), 1 to 4 years (778,683 children), 5 to 9 years (985,961 children), 10 to 14 years (928,002 children) and 15 to 18 years (739,612 children).

Results

Case registration
A total of 115 children with VTE were reported. After the questionnaires were reviewed, 16 children were not enrolled because of arterial ischaemic stroke (n=4), left or right ventricle thrombosis (n=4), left atrium thrombosis (n=1), purpura fulminans (n=1), migraine (n=1), Wilms’ tumor (n=1), no objective radiologic confirmation of the diagnosis (n=2), postmortem diagnosis (n=1), and no response to the detailed questionnaire (n=1); 99 cases were therefore eligible for further evaluation. In The Netherlands, the annual incidence of VTE was calculated to be 0.14 per 10,000 children aged between 0 and 18.
years. The annual incidence of VTE per age category was 14.5 per 10,000 children from 0 to 28 days, 0.25 per 10,000 children from 29 to 265 days, 0.08 per 10,000 children from 1 to 4 years, 0.1 per 10,000 children from 5 to 9 years, 0.18 per 10,000 children from 10 to 14 years, and 0.05 per 10,000 children from 15 to 18 years.

Thirteen patients were reported by 8 of 84 primary care centers, 11 patients by 7 of 20 secondary care centers, and 75 patients by all 8 tertiary care centers. Two of the 8 tertiary care centers reported 46% of all the patients.

**Age and sex distribution**
Forty-seven children (47%) were neonates, of whom 26 had been born pre-term (Figure). The median gestational age of all neonates was 32 weeks (range, 25 to 42 weeks), with a median birth weight of 1589 g (range, 530 to 4580 g). The male-to-female ratio of the total group was 1:0.9.

**Figure.** Age distribution of the pediatric patients with venous thrombosis

![Age distribution of the pediatric patients with venous thrombosis](image)

**Site of thrombosis**
The veins most frequently involved in neonatal CVC-related VTE (n=44) were the inferior vena cava or right atrium (n=29) and portal vein (n=5) of the upper venous system and the femoral vein (n=4), iliac vein (n=1), or both (n=2) of the lower venous system. Non-CVC-related neonatal VTE (n=3) was located in the right atrium, portal vein, and renal vein.

In older children, CVC-related VTE (n=19) was mostly diagnosed in the superior vena cava (n=5) of the upper venous system and in the femoral vein (n=4) and iliac vein (n=3) of the lower venous system. Non-CVC-related VTE (n=33) was most frequently located in iliac and femoral vein (n=8), femoral vein (n=3), and popliteal vein (n=3) of the lower venous system and in the lung (n=4), and portal vein (n=3) of the upper venous system.
Pulmonary embolism (PE) was diagnosed in 1 neonate and 9 older children. Three PEs were in association with lower venous system VTE, and 2 with upper system VTE. Five patients had PEs only.

**Signs and symptoms**
In 32 of the 37 neonates with catheter-related thrombosis in the upper venous system, usually inferior vena cava or right atrium, no signs or symptoms were present. In these neonates, thrombosis was diagnosed by performance of echocardiography before removal of the CVC or was detected by performance of diagnostic procedures for other reasons, such as cardiac evaluation. In some neonates, thrombocytopenia raised a suspicion of VTE. Thrombosis was asymptomatic in only 3 of the 52 older children: 2 portal vein thromboses and 1 renal vein thrombosis associated with nephrotic syndrome.

Clinical manifestations of symptomatic thrombosis depended predominantly on the site of the thrombosis. Sinus thrombosis presented with headache, vomiting, and convulsions. Children with PE complained about thoracic pain, and they all had tachypnea. Patients with jugular vein, subclavian vein, and superior vena cava thrombosis were admitted with chylothorax, superior vena cava syndrome, or inability to aspirate blood from the Port-A-Cath. Renal vein thrombosis was diagnosed in patients with hematuria and kidney failure. All patients with thrombosis of the lower extremity had pain, swelling, and reddish or purple discoloration of the leg.

**Diagnostic tests**
Venous thrombosis was most frequently diagnosed by echocardiography (53%) and ultrasonography (43%) in neonates. In older children diagnosis was most frequently made by ultrasonography alone or in combination with other diagnostic modalities (69%). Venography had only been performed in 2 neonates and in 3 older children for the detection of thrombosis of the lower (n=2) and upper (n=3) venous system. Sinus thrombosis had been diagnosed by computed tomography scanning or magnetic resonance imaging. PE had been evaluated by ventilation perfusion lung scanning (n=8), echocardiography (n=1), and heart catheterization (n=1).

**Risk factors**
Eighty-four patients had development of venous thrombosis while in the hospital for other reasons. In 98% of all patients, at least 1 clinical risk factor or prothrombotic disorder was found. Two clinical risk factors or prothrombotic disorders were present in 74% of the neonates and in 81% of the older children. In neonates, 94% had a CVC, often in association with an infection. In the older children, clinical risk factors were more varied (Table 1).

Evaluation of the presence of prothrombotic disorders was performed in 18 of the 47 neonates and in 38 of the 52 children. Congenital disorders were found in 9 of the tested patients (16%), of which only 1 disorder was present in a neonate (factor V R506Q mutation). In the 8 older children, the following disorders were found: factor V R506Q mutation (3 of 29), protein S deficiency (3 of 36), protein C deficiency (1 of 35), factor II G20210A mutation (1 of 12), and hyperhomocysteinemia (1 of 16). One of the 8 children
had a "double hit", a combination of protein S deficiency and factor V R506Q mutation. At 8 years of age, he had development of venous thrombosis of the left leg during a pulmonary infection with *Mycoplasma pneumoniae*.

### Table 1. Clinical risk factors in neonates and older children with venous thrombosis

(Most patients had more than one risk factor)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Neonates (n=47)</th>
<th>Number (%)</th>
<th>Children (n=52)</th>
<th>Risk factor</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheter</td>
<td>n=44 (94%)</td>
<td>Infection</td>
<td>n=24 (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>n=28 (60%)</td>
<td>Central venous catheter</td>
<td>n=19 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asphyxia</td>
<td>n=6 (13%)</td>
<td>Heart disease</td>
<td>n=10 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>n=5 (11%)</td>
<td>Immobility</td>
<td>n=9 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>n=4 (9%)</td>
<td>Surgery</td>
<td>n=8 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>n=3 (6%)</td>
<td>Hypovolemia</td>
<td>n=5 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>n=1 (2%)</td>
<td>Trauma</td>
<td>n=4 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>n=1 (2%)</td>
<td>Malignancy</td>
<td>n=4 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
<td>n=3 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney disease</td>
<td>n=3 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraceptives</td>
<td>n=2 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previous thrombosis</td>
<td>n=2 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obesity</td>
<td>n=2 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-dose estrogens</td>
<td>n=1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asparaginase therapy</td>
<td>n=1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDG syndrome</td>
<td>n=1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sickle cell disease</td>
<td>n=1 (2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Carbohydrate-deficient glycoprotein

In 1 neonate and 12 older children, overt acquired prothrombotic disorders were present (23%). Nephrotic syndrome led to antithrombin deficiency in 1 neonate and 1 child. Protein S deficiency was present in a boy with sickle cell disease, and antithrombin deficiency was present in another boy treated with asparaginase. Two girls had an acquired protein S deficiency, one because of high-dose estrogen treatment for tall stature, another because of chickenpox. A combined protein S, protein C, and antithrombin deficiency was found in 1 boy with carbohydrate-deficient glycoprotein syndrome. A 2-year-old girl with congenital heart disease had acquired protein C deficiency after having undergone a Fontan procedure. A lupus anticoagulant was present in 5 of 21 older children who were tested. Except for 1 child, all others with congenital or acquired prothrombotic disorders had at least 1 additional clinical risk factor.
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Treatment
Seven neonates and 9 older children did not receive antithrombotic therapy. Supportive care was given in 2 neonates and 2 children with portal vein thrombosis and 5 neonates with catheter-related thrombosis of the inferior caval vein or right atrium. Two children with acute lymphatic leukemia and CVCs had their catheters removed. Another child died shortly after diagnosis. One child had iliac vein thrombosis that was diagnosed after he had development of postthrombotic symptoms, and 3 children had sinus thromboses.

The antithrombotic therapy given varied (Table II). The choice of treatment seemed to be determined by local preferences. For example, neonatal catheter-related thrombosis was treated with urokinase and vitamin K antagonists in 1 tertiary care center and with heparin and vitamin K antagonists by another tertiary care center. A third tertiary care center gave only supportive care. Deep venous thrombosis of the lower extremity was usually treated with heparin and vitamin K antagonists.

Table 2. Treatment of venous thrombosis in neonates (n=47) and older children (n=52)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Neonates</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Supportive care only</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>OAC only</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Heparin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin only</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Heparin and OAC</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>Heparin / LMWH</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Heparin / LMWH / OAC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH only</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>LMWH and OAC</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolyticum only</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Thrombolyticum and OAC</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Thrombolyticum / heparin / OAC</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Thrombolyticum / heparin / LMWH / OAC</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: OAC oral anticoagulant therapy, LMWH low-molecular-weight heparin

Complications
Thrombolytic therapy caused bleeding complications in about 25% of the patients (2 neonates and 3 older children) to whom it was given, whereas the rate was 2% each in those treated with vitamin K antagonists (1 neonate) and unfractionated heparin (1 child). Low-molecular-weight heparin was not associated with bleeding. The severity of the
A prospective two-year registry in the Netherlands

bleeding complications was not assessed.

After a follow-up period of 1 month to 1 year, recurrent VTE was reported in 1 neonate and 6 older children, 2 with the lupus anticoagulant syndrome and 1 with congenital protein S deficiency.

The overall mortality was 15% in the neonatal group and 17% in the pediatric group. All except 2 older children died as a result of their underlying disease. One child died of sudden PE, 8 years after undergoing the Fontan procedure. Another child with congenital heart disease and recurrent thrombosis died because there was no longer an intravenous route that was accessible for treatment.

Discussion

This study showed that the annual incidence of VTE in the general Dutch population of children aged 0 to 18 years is 0.14 per 10,000, of which 35% is asymptomatic. Excluding neonates and nonextremity VTE, the annual incidence is 0.05 per 10,000 children, which is similar to the incidence estimated in the Canadian registry. The incidence of both symptomatic and asymptomatic VTE in The Netherlands is expected to be higher than estimated on the basis of this registry. First, almost half of the patients with VTE were reported by 2 of the 8 tertiary care centers. One center is the main research center, where pediatricians have a special interest in VTE. In the other center, routine screening of the venous system before removal of the CVCs by echocardiography in neonates was performed, resulting in a large number of asymptomatic catheter-related VTEs. Prospective screening of CVCs was not performed in the other centers. Second, in this registry, 17- and 18-year-old patients with VTE were not reported. These children had probably been referred to nonpediatric departments. Finally, most thrombi were diagnosed in the upper venous system by echocardiography or ultrasonography, which has several limitations. Compression is not possible in the upper central veins because of the thoracic cage and because the presence of clavicles limits the view on distal subclavian veins.

Pediatric deep vein thrombosis mainly developed in hospitalized children. It was possible to identify 2 risk groups: sick neonates with CVCs and older children with a combination of risk factors. In the first group, most catheter-related thrombi were located in the upper venous system and were asymptomatic. In most of these neonates, deep vein thrombosis was found by cardiac evaluation or by screening the venous system before the CVC was removed. This finding suggests that prophylactic antithrombotic therapy and routine screening of all neonates with CVCs for asymptomatic VTE might be necessary. Before this conclusion can be drawn, it is important to know the precise incidence of asymptomatic VTE in neonates with CVCs. Furthermore, the acute and long-term consequences of treated and untreated VTE in neonates should be evaluated, because spontaneous recovery of neonatal VTE is possible. Only a few studies have been performed with prospective screening for deep vein thrombosis by echocardiography before the CVC is removed in neonates. Most of the detected thrombi were asymptomatic. The incidence of VTE varied from 2% to 14%. The above-mentioned tertiary care center in The Netherlands reported an incidence of 13%. These incidences might be
higher, because echocardiography may underestimate the real extent of catheter-related thrombosis.\textsuperscript{21} The long-term consequences have only been assessed in 1 study with neonatal jugular vein catheters. Ultrasonographic follow-up at a mean age of 3.7 years showed jugular vein thrombosis in 9 of 40 patients. Three patients had clinical symptoms, that is, soft tissue swelling of the neck and dilated collateral vessels. In only 1 patient, thrombosis had been clinically suspected during indwelling time, and the catheter had been withdrawn.\textsuperscript{22}

The second risk group consisted of children between 1 month and 18 years of age with a combination of risk factors. At least 2 risk factors were present in 81\% of these children. In this group, VTE was less frequently catheter associated (37\%) than in neonates, but various underlying disorders were present, such as infection, heart disease, immobility, and surgery. Infection was the most frequent underlying disorder (46\%). Recently, Gurgey et al\textsuperscript{23} also reported a high percentage of infection in children with non-catheter-related VTE (68\%). Some underlying diseases reported in this registry are known to be associated with acquired prothrombotic disorders, such as sickle cell disease, carbohydrate-deficient glycoprotein syndrome, and nephrotic syndrome.\textsuperscript{21,23} Congenital prothrombotic disorders were more often found in older children (21\%) than in neonates (6\%). However, children were more frequently tested than neonates because of both the lack of a standardized hypercoagulability protocol and the difficulties of obtaining blood for coagulation studies in sick neonates. On the other hand, in a prospective study, Salonvaara et al\textsuperscript{24} also reported a low incidence of prothrombotic disorders (10\%) in neonates with symptomatic catheter-related deep vein thrombosis.

Treatment of VTE in pediatric patients was rather varied, especially the treatment of nonextremity thrombosis such as thrombosis of the inferior vena cava and right atrium and sinus thrombosis. There appears to be a consensus about the treatment of thrombosis in the lower venous system. This treatment consists of unfractionated heparin and vitamin K antagonists in most centers. A variety of treatment modalities of this kind was also reported in other pediatric registries.\textsuperscript{16} It is probably caused by the lack of well-designed controlled trials relating to the optimum treatment of venous thrombosis in pediatric patients.

Seven children (7\%) had development of recurrent thrombosis, which is low compared with the rate reported in the Canadian registry (18.5\%).\textsuperscript{2} However, follow-up in the Dutch registry (1 month to 1 year) was shorter than in the Canadian registry (6 months to 3 years) and may be too short to draw a definitive conclusion about the recurrent rate. From adults it is known that the frequency of recurrences increases with longer duration of follow-up.\textsuperscript{25} Follow-up was too short to observe possible development of the postthrombotic syndrome in our patients. Thus far, only a few studies about the long-term consequences of VTE in children have been published.\textsuperscript{26,27} Knowledge of the extent of the late effects of VTE in pediatric patients is indispensable, because the incidence of pediatric VTE will probably rise as a result of the increase in patients with CVCs and chronic diseases. To a large extent, the morbidity of these patients will be determined by the long-term outcome of VTE. Studies to assess and prevent these late effects are needed.
References

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