Venous thromboembolic disease in childhood epidemiology, risk factors and outcome
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Chapter 10

Summary, general discussion and perspectives
Pediatric venous thromboembolism (VTE) is a rare disease and as a consequence information is lacking in the literature. In this thesis, several aspects of pediatric VTE are investigated in order to give answers to the following questions: What is the incidence of pediatric VTE in The Netherlands and which children are at risk? What is the clinical presentation of VTE in childhood? What is the role of prothrombotic risk factors in the etiology of pediatric VTE and which subgroups of children with VTE have an increased risk of a positive test for congenital prothrombotic disorders? What is the possible underlying mechanism, leading to VTE in girls using estrogen for tall stature? What is the clinical outcome of pediatric VTE, including death, recurrence and the postthrombotic syndrome (PTS)? And finally, what is the risk of the PTS in children with congenital heart disease (CHD)?

Incidence of venous thromboembolic disease in childhood
To study the incidence of VTE in The Netherlands, a prospective 2-year registry of VTE in children aged ≤18 years was established in co-operation with the Dutch Pediatric Surveillance Unit (Chapter 2). Ninety-nine patients were registered. The annual incidence of VTE was 0.14 per 10,000 children. Almost half of the patients were newborns. Neonatal VTE was almost exclusively catheter related and located in the upper venous system. In older children, VTE was catheter related in approximately one third, and more often located in the lower venous system. Many older children had underlying diseases, such as sickle cell disease, associated with acquired prothrombotic risk factors. In 85% of all patients, thrombosis developed while the patient was in the hospital. Congenital and acquired prothrombotic disorders were present in 16% and 23% of the tested children, respectively. In most children, at least one additional clinical risk factor was present. A variety of treatment modalities were used. So, pediatric VTE is a rare disease and mostly develops in hospitalized children, especially neonates with central venous catheters (CVCs) and older children with a combination of risk factors.

Clinical presentation of venous thromboembolic disease in childhood
Chapter 3 shows that the diagnosis of pulmonary embolism (PE) can easily be missed because of the subtlety of symptoms of PE. Tachypnea may be the only symptom of PE and pediatricians rarely consider PE as a cause of tachypnea. This chapter describes three children of various ages with persistent tachypnea are described: a girl after orthopedic surgery for kyphoscoliosis, a boy with nephrotic syndrome, and a neonate with Hirschsprung disease. Other causes of tachypnea were diagnosed and treated before PE was considered.

Chapter 4 and 5 describe two children with VTE and underlying diseases known to be associated with acquired prothrombotic disorders. One boy developed deep vein thrombosis of the lower extremity after a period of immobilisation because of a stroke-like episode (Chapter 4). He had cerebellar hypoplasia and borderline cognitive impairment. Coagulation studies revealed decreased plasma levels of the coagulation factors V, factor VII, factor XI, factor XII, and of the inhibitors antithrombin, protein C, and free protein S. The clinical and coagulation abnormalities suggested the diagnosis of carbohydrate deficient glycoprotein (CDG) syndrome, which was confirmed by decreased
phosphomannomutase activity in leucocytes and fibroblasts. This syndrome is usually accompanied by severe psychomotor retardation and external dysmorphism, such as abnormal subcutaneous fat distribution and inverted nipples. This study showed that even in the absence of these two features, CDG syndrome should be ruled out in children with cerebellar hypoplasia and/or multiple coagulation abnormalities.

Chapter 5 discusses one girl with post-varicella purpura fulminans as a result of severe acquired protein S deficiency caused by anti-protein S antibodies. In the patient and in her sister with varicella without purpura fulminans, the concentrations of anti-protein S antibodies were determined and followed. Furthermore, the epitope of the anti-protein S antibodies was studied using mini-protein S, a recombinant variant of protein S consisting of the first 242 amino acids of protein S, and lacking the sex hormone binding globulin (SHBG)-like domain. In the patient plasma concentrations of free protein S antigen and total protein S antigen reached normal levels in four months and five weeks, respectively. The concentrations of the anti-protein S antibodies decreased to 25% of the initial level in the course of five months. In the patient’s sister, anti-protein S antibodies were present as well, but the concentrations were lower than those in the patient. In the first months after onset of varicella, 62% of the anti-protein S antibodies were directed against the first 242 amino acids of protein S and 38% against the SHBG-like domain. Five months after the onset of varicella, when plasma levels of free protein S and total protein S had reached normal adult levels, 86% of the antibodies were directed against the first 242 amino acids of protein S. In conclusion, after varicella, a heterozygous auto-antibody response may develop, possibly resulting in severe acquired protein S deficiency and purpura fulminans. Epitopes of these anti-protein S antibodies are situated on both the first 242 amino acids of protein S and the SHBG-like domain.

Risk factors of venous thromboembolic disease in childhood
Chapter 6 discusses the role of clinical and prothrombotic risk factors in the etiology of pediatric thromboembolic disease, as prospectively evaluated in a consecutive cohort of 100 children with VTE at the Emma Children’s Hospital / AMC over a 12-year period. The most important clinical risk factors were central venous catheter and infection. Congenital and acquired prothrombotic disorders were found in 15% and 22% of the tested children, respectively. In most of these children, at least one additional clinical risk factor was present. Children with an acquired or congenital prothrombotic disorder may therefore develop thrombosis, but it seems to occur only when additional clinical risk factors are present. After multivariate analysis, congenital prothrombotic disorders were significantly more frequently present in children with a positive family history and in children who developed the initial symptoms of thrombosis at home.

One of the clinical risk factors of pediatric venous thrombosis is the use of high dose of estrogen for tall stature. Chapter 7 describes the evaluation of the changes in coagulation and fibrinolytic system during and after estrogen treatment (200 and 300 mg estradiol) in 25 healthy girls with expected final height exceeding 185 cm, as calculated by the method of Bayley and Pinneau. No difference in the effects on hemostasis was found between the 2 treatment groups. All 25 patients developed protein S deficiency during estrogen treatment. In most girls, this persisted for 4 weeks after cessation of estrogen
administration. Protein S deficiency was accompanied by significantly increased prothrombin fragment 1+2 and fibrinopeptide A, indications of a prothrombotic state. Despite these abnormalities, only 4 cases of venous thrombosis have been described in the literature. Compensatory mechanism for the thrombotic tendency might be an increase in protein C activity and elevated levels of plasminogen and plasmin-α2 antiplasmin and decreased levels of histidine-rich glycoprotein, indicating increased fibrinolytic activity.

**Complications of venous thromboembolic disease in childhood**

Chapter 8 showed that the incidence of complications of pediatric VTE is high. The incidences and features of death and recurrence were prospectively determined in a consecutive cohort of 100 pediatric patients with VTE at the Emma Children’s Hospital / AMC over a 12-year period. Cumulative survival after the first thrombotic episode was 84% after one year of follow-up, and 77% after 7 years. 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 PTS was analysed in a subgroup of 33 patients with VTE of the lower extremities. Twenty-three (70%) children developed PTS: this was moderate in 3 children and mild in 20.

Asymptomatic venous thrombosis seems to cause PTS, as well (Chapter 9). The majority of children with CHD will undergo cardiac catheterisation and/or surgery, requiring the insertion of central venous catheters, usually into the femoral veins. One of the acute complications is (a)symptomatic venous thrombosis, which may lead to PTS in the long-term. The incidence and severity of the PTS was investigated in 28 unselected children with CHD five to ten years after their first cardiac catheterisation. Mild PTS was present in half of the patients. Partial or complete occlusion of the investigated vein was found in four patients (17%). In all patients studied, the venous valves of the deep system were competent. This high incidence of mild PTS in children with CHD warrants a prospective trial to investigate the incidence and risk factors of asymptomatic VTE and subsequently the efficacy and safety of antithrombotic prophylaxis in children with CHD in periods of femoral catheterisation.

**Study bias**

Bias might have occurred in all observational studies presented in this thesis. The incidence of VTE in The Netherlands is probably higher than estimated on the basis of the prospective registry in chapter 2. First, despite regular contact with most of the contact persons of the centers, some patients with VTE will not have been registered. Second, only one tertiary care center performed routine screening of the central venous catheters, resulting in a large number of asymptomatic VTEs. Third, children above 16 years were not reported. They had probably been referred to nonpediatric departments. Furthermore, management differences might have caused diagnostic suspicion bias, especially in neonates with central venous catheter-related VTE. Finally, most thrombi were diagnosed by non-invasive radiographic tests, although venography is the gold standard diagnostic test. A registry study is not the best way to study the frequencies of prothrombotic disorders in children with VTE. A high prevalence of children were not tested for the
Summary, general discussion and perspectives

presence of prothrombotic disorders. Testing might have been performed in a selected group of children, such as children with a positive family history of VTE, leading to a high percentage of prothrombotic disorders in children with VTE.

Less bias probably occurred while investigating the frequency of prothrombotic disorders in a prospective cohort of 100 children with VTE in one center (Chapter 6). Selection bias because of referral of patients with VTE to a tertiary care center seems unlikely, as coagulation studies were performed after referral. So, the results of the tests did not play a role in the decision for referral.

The complications of pediatric VTE, including mortality and recurrence, were investigated in the same cohort of 100 patients (Chapter 8). Evaluation of PTS took place in a subgroup of patients with VTE of the lower extremity. About 10% of these patients were lost to follow up after discharge of the hospital. If these patients would have participated in the study and would not have developed the PTS, the total percentage of the PTS would still be high. Observer bias might have occurred, especially because the investigator was not blinded to the location of the previous VTE in the patients. However, several investigators independently scored identical post-thrombotic signs and symptoms in many patients.

In the estrogen study, each patient acted as his own control (Chapter 7). Therefore, bias caused by differences in two participating centers or low plasma protein S concentration before start of study, is unlikely.

In children with CHD, PTS was investigated retrospectively which had several disadvantages (Chapter 9). Causes of PTS other than venous thrombosis could not be ruled out. Furthermore, it was impossible to detect the precise moment and the risk factors for venous thrombosis and subsequent PTS. Again, observer bias might have occurred. Despite these disadvantages, the high percentage of PTS warrants a prospective study, investigating the incidence and risk factors of asymptomatic venous thrombosis and PTS in children with CHD.

Central venous catheters

Central venous catheters have become an important component in the treatment of neonates and children on the intensive care units and in children with primary diseases such as cancer, malabsorption and cardiac diseases. CVCs are thrombogenic because their surfaces are foreign, they damage vessel walls, blood flow is disrupted, and some substances infused are damaging to vessels. Both the national registry and the cohort study show that the presence of a CVC is the most important clinical risk factor for development of venous thrombosis (Chapter 2 and 6). It is important to note that in the national registry approximately one third of the neonatal catheter-related thrombi were asymptomatic. These thrombi were found by cardiac evaluation or by screening the venous system before removal of the catheter. As routine screening was performed in one neonatal intensive care unit in The Netherlands, the estimated incidence of pediatric venous thromboembolic disease might only be the tip of the iceberg.

Will it be necessary to screen all CVCs before removal of the catheter to look for asymptomatic thrombi? Moreover, as a CVC appeared to be the most important risk factor in children with VTE, should we consider using prophylactic anticoagulation in children
with a CVC? Before answering these questions, it is important to know the precise incidence of symptomatic and asymptomatic thrombi in children with CVCs. In neonates, only a few studies have been performed with prospective screening for deep vein thrombosis by ultrasonography before removal of the catheter. Most of the detected thrombi were asymptomatic. The incidences of VTE varied from 2% to 14%. 14 In children on the pediatric intensive care unit, prospective studies evaluating the presence of venous thrombi in the lower extremities by ultrasonography showed incidences of predominantly asymptomatic thrombi from 10% to 44%. 15,16 Recently, 24 children with cancer and implantable CVCs were evaluated by contrast venography of the upper venous system after removal of the port, either electively after completion of chemotherapy or because of catheter-related complications. Twelve children (50%) had abnormal venography results. Three of these children had dilated superficial chest veins; the others had no symptoms.

Children on long-term Total Parenteral Nutrition (TPN) form a special high risk group. A total of 34 children and adolescents with gut failure, who all received long-term TPN (duration 2 months to 9 years) were studied by means of ventilation perfusion lung scanning and echocardiography. Major thrombotic events were identified in 12 patients (35%) and 4 died as a consequence. 3 In another study, the frequency of catheter related VTE assessed by venography in 12 children on TPN was 67%. 17 In different patient groups with CVCs, the incidence of catheter related VTE therefore seems to be high, although most thrombi appear to be asymptomatic.

May these asymptomatic thrombi considered benign? There are some reasons why asymptomatic catheter related thrombi seem to be of clinical importance. First, catheter related VTE is associated with PE, which may be fatal. 14 The risk of PE in the presence of an asymptomatic catheter related thrombus is unknown. However, as shown in Chapter 3, the diagnosis of PE may easily be missed because of the subtlety of the symptoms. Second, many children with CVCs have right-to-left intracardiac shunts that increase the risk of stroke in case of catheter related VTE. Third, PTS levels in children with asymptomatic catheter related thrombi might be considerable. Chapter 9 showed that mild PTS developed in half of the children with CHD after asymptomatic VTE because of femoral catheterisation. Finally, catheter related VTE seems to be associated with catheter related sepsis. 18 To test the arguments listed above, prospective trials are needed to investigate the acute and long-term complications of the asymptomatic catheter related thrombi. If asymptomatic catheter-related thrombi appear to be of clinical importance, prophylactic treatment will be indicated. As yet, the best prophylaxis for catheter related thrombi is to consider whether a patient really needs a CVC, before inserting that catheter into a vein of the patient.

The national registry showed a variety of treatment modalities particularly for the asymptomatic catheter related thrombi. This is probably the result of a lack of well designed controlled treatment trials in children. The low incidence of pediatric VTE means that it is difficult to perform these trials in one center. Centralised registration of children with VTE may be a way of extending the expertise and creating the conditions for large trials to investigate the long-term complications of asymptomatic and symptomatic VTE and the safety and efficacy of antithrombotic prophylaxis and treatment.
Venous thromboembolic disease in specific disorders

In addition to children with CVCs, VTE frequently occurs in children with specific disorders, such as heart disease (after Fontan procedure), renal disease, acute lymphoblastic leukaemia (asparaginase treatment), and sickle cell disease (Chapter 2 and 6). For example, the incidences of VTE following Fontan procedures range from 3 to 20%. The mortality rate of these thrombotic events is high. Little is known, however, about the safety and efficacy of antithrombotic prophylactic treatment in these specific patient groups. Recently, a large multicenter, prospective trial of prophylactic anticoagulation therapy following Fontan procedures started, comparing aspirin to initial heparin therapy followed by warfarin. For other patient groups with a high risk of VTE, prospective trials investigating the efficacy of antithrombotic prophylaxis would be worthwhile, as well.

The role of prothrombotic risk factors

In children, venous thrombosis is a multifactorial disease caused by clinical and prothrombotic risk factors. In adults, the established congenital prothrombotic risk factors are protein S, protein C and antithrombin deficiencies, and factor V and factor II mutations. In both the national registry (Chapter 2) and the cohort study (Chapter 6), congenital and acquired prothrombotic disorders (including the presence of the lupus anticoagulants) were present in about 15% and 22% of the children with VTE, respectively. In the majority of the children of both studies, the congenital and acquired prothrombotic defects were unmasked by the presence of an additional clinical risk factor. Children with a prothrombotic disorder therefore seem to develop thrombosis only in the presence of an additional clinical risk factor.

Is routine testing of prothrombotic disorders warranted in children with VTE? Disadvantages of screening include the psychological burden of being a carrier of a congenital prothrombotic defect, the prescription of prophylaxis in relatively low risk situations with risk of bleeding complications, and the problems that might develop with insurance companies.

In view of the frequencies of prothrombotic defects in children with VTE, testing seems to be worthwhile, especially in children with a positive family history of VTE and children who developed the first symptoms of VTE at home (Chapter 6). One of the potential benefits of testing is the understanding of the pathogenesis of pediatric VTE when a prothrombotic defect is identified. Furthermore, the presence of a prothrombotic disorder might have consequences for the duration of treatment of the initial VTE. The follow-up study showed that children with congenital or persistent acquired prothrombotic risk factors had a fivefold increase in risk of recurrence (Chapter 8). These children might be candidates for long-term antithrombotic prophylaxis. However, the safety and efficacy of long-term prophylaxis have never been investigated in children. In adults, long-term anticoagulation reduces the risk of recurrence, although one study in adults with idiopathic VTE showed that prolongation of anticoagulant therapy delays recurrence until anticoagulant therapy is stopped, rather than reducing the risk of recurrence. There seems to be agreement that children with known congenital prothrombotic disorders should receive prophylactic anticoagulation in high risk situations, although no studies have been
performed to assess the safety and efficacy of this measures. In the outcome study, most recurrent VTE were idiopathic in children with congenital or persistent acquired prothrombotic disorders (Chapter 8). This suggests that continuous anticoagulant therapy might be more effective than intermittent prophylaxis. Continuous anticoagulant therapy might become safer by reducing the doses of oral anticoagulant therapy at an international normalized ratio of 1.5 to 2. The efficacy and safety of these measures are currently being studied in adult patients. Finally, the discovery of a prothrombotic defect may benefit the patient’s family in terms of identifying other affected relatives. The benefits and disadvantages of screening the patient’s family should be clearly discussed with them before screening.

Conclusion
Venous thrombosis is an uncommon disorder in childhood with an estimated incidence of 0.14 per 10,000 children in The Netherlands. It is mostly diagnosed in hospitalized children, especially sick newborns with CVCs and older children with a combination of risk factors or underlying diseases known to be associated with acquired prothrombotic disorders. Both clinical and prothrombotic risk factors contribute to the etiology of pediatric VTE. Children with a positive family history of VTE and children who developed the first symptoms of VTE at home have an increased risk of positive congenital prothrombotic testing. The incidence of pediatric VTE will probably rise because of the increased use of CVCs and the increased survival of children with chronic diseases associated with a prothrombotic state. The prevention of venous thrombosis will become an important issue in the future because of the high frequency of complications of this disease in children.

References


