Venous Thromboembolism in Children
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Case 1: A 4-year-old boy with acute lymphoblastic leukemia (ALL) and disseminated candidiasis was found to have a right atrial thrombus on a routine imaging study. He had a central venous catheter (CVC) and was receiving chemotherapy that contained asparaginase. Thrombophilia workup was negative.

Case 2: A 17-year-old girl presented to the emergency department with a 3-week history of left-sided chest pain and shortness of breath. She had been taking high-dose estrogen therapy for congenital tall stature. D-dimer was positive. Chest CT revealed multiple small pulmonary emboli and infarcts. Lower-extremity venous ultrasound was negative for deep vein thrombosis, and echocardiography showed normal right ventricular function. Thrombophilia workup was negative.

Epidemiology
Decreased capacity to generate thrombin, increased capacity of α2-macroglobulin to inhibit thrombin, and enhanced antithrombotic potential by the vessel wall appear to contribute to the low incidence of venous thromboembolism (VTE) during childhood. Nevertheless, VTE is being diagnosed more frequently in children. The annual incidence is 0.07 to 0.14 per 10 000 children, or 5.3 per 10 000 hospital admissions of children, and 24 per 10 000 admissions to neonatal intensive care units.1–3 The highest incidence is during the neonatal period, followed by another peak in adolescence. Patients in neonatal and pediatric intensive care units and oncology patients are particularly at high risk. Teenage girls have twice the rate of VTE as do teenage boys. This appears to be due to the use of oral contraceptives and pregnancy.4

Risk Factors
Idiopathic VTE in the pediatric population is relatively infrequent and is almost always associated with an underlying disease or risk factor. Both congenital and acquired conditions contribute to the development of thrombosis. More than 90% of children with VTE will have ≥2 predisposing factors (Figure).

Acquired Conditions
The presence of a CVC is the most important acquired trigger for development of VTE in children, contributing to >90% of all neonatal venous thrombosis and to >50% of all cases in other age groups.1–3,5 Other acquired conditions associated with neonatal thrombosis include perinatal asphyxia, infection, congenital heart disease, and hypovolemia. In the pediatric population, other risk factors include malignancy, trauma, surgery, hormonal therapy, and lupus. The risk of VTE is significantly increased with a CVC in the femoral and subclavian veins, suggesting that placement in the brachial or jugular veins may be preferable.6 External catheters and large-bore lines appear to be associated with a higher risk of VTE, particularly in oncology patients.7

ALL is the most common cancer associated with thrombosis in children. The reported rate of VTE in childhood ALL varies from 1.1% to 36.7%, with an overall average of 3.2%.8 VTE seems to be an uncommon event in children with brain tumors (reported rates of 0.64% and 2.8%), even though it is the second most common malignancy in this age group.9,10 CVC dysfunction contributes to the development of thrombosis in children with brain tumors and appears to reduce overall survival.10 Children with non-ALL malignancies and VTE tend to be older (>9 years), are more likely to develop VTE at sites distant from CVC, and are less likely to have inherited prothrombotic mutations.11,12

The acquired clinical conditions may be transient or persistent over time. Transient clinical conditions include the use of high-dose estrogen, varicella, and the nephrotic syndrome.13–15 Persistent
clinical conditions associated with acquired prothrombotic disorders are the carbohydrate-deficient glycoprotein syndrome and Fontan procedures. The common denominator is an imbalance between procoagulant and anticoagulant proteins, leading to a prothrombotic state.

Congenital Conditions

Congenital prothrombotic conditions in pediatric patients include factor V Leiden mutation, prothrombin gene mutation, and deficiencies of antithrombin III, protein C, and protein S, with the homozygous variants being more prothrombotic. The incidence of factor V Leiden is between 0% and 5% in the general population, with the highest prevalence among whites. Both heterozygous and homozygous forms of factor V Leiden can cause VTE in children, usually in the presence of an acquired risk factor. The prothrombin gene mutation is the second most common inherited defect linked to VTE. Its prevalence is ≈2% in the white population and 4% to 5% in the Mediterranean population. Two small cohort studies describe the incidence of antithrombin III deficiency as 1% to 3%. The role of other potentially thrombophilic conditions, such as hyperhomocysteinemia and high levels of factors VII, VIII, IX, XI, and lipoprotein(a), has not been established in the pediatric population.

Long-term Outcomes

The all-cause mortality rate in pediatric patients ranges from 14% to 23%, with the VTE-related mortality being 1% to 2%, reflecting the severity of the underlying clinical conditions in this population. After 3 years of follow-up, the cumulative incidence of a first VTE recurrence is ≈9%, with 1 study reporting a rate as high as 21%. Risk of recurrent VTE after a spontaneous first thrombotic event appears to be significantly higher in patients with lupus anticoagulant or in those who carry a single or combined congenital prothrombotic risk factor. Elevated levels of plasma factor VIII, D-dimer, or both at diagnosis and a persistent elevation of at least 1 of these factors after standard-duration anticoagulant therapy predict a poor outcome in children with thrombosis.

Postthrombotic syndrome (PTS) that consists of pain, swelling, skin pigmentation, and sometimes ulceration of the leg is an important complication of pediatric VTE. At least one third of patients develop PTS, and the incidence can be as high as 60%. However, PTS in pediatric patients is usually mild, with increased limb circumferences, swelling, varicose veins, pain, and pigmentation. Few patients develop venous ulceration. Risk factors for the development of PTS are unclear. Combined fibrinolytic and anticoagulation treatment for VTE might reduce the incidence of PTS.

Diagnosis

The clinical presentation of VTE depends on the location of the thrombi. Most pediatric venous thrombi are catheter related and therefore are located in the upper venous system. Many are asymptomatic. When symptoms occur, they may include swelling, pain, and discoloration of the upper extremity, superior vena cava syndrome, chylothorax, and chylopericardium. VTE in the lower extremity usually causes abdominal, inguinal, or leg pain, swelling of the abdomen or leg, and reddish or blue-purple discoloration of the lower extremity. Sepsis and repeated loss of patency of the catheter raise suspicion of catheter-related thrombosis. Chronic catheter-related thrombosis often presents with collateral circulation. In some neonates, thrombocytopenia appears to be the only sign of VTE due to consumption of platelets. Homozygous protein C and S deficiency may present as neonatal purpura fulminans, which is characterized by rapidly progressive purpura and ecchymosis, often developing into large areas of skin necrosis with bulla formation.

Compression together with Doppler venous ultrasonography is the most commonly used modality for the diagnosis of VTE in children. This noninvasive modality is sensitive and specific for diagnosing proximal-vein thrombosis of the lower extremity and the extrathoracic portion of the upper extremity in children. CT with intravenous contrast is used to evaluate the upper venous system and the abdominal and pelvic venous systems.
Ventilation-perfusion lung scanning and chest CT with contrast are used to diagnose pulmonary embolism, whereas MRI and catheter-based angiography are used to evaluate the intracranial venous system, superior vena cava, and proximal subclavian veins. Echocardiography can detect cardiac and proximal superior vena cava thrombi and assess right ventricular function. Catheter-based venography is rarely used because of challenging technical difficulties. D-dimer and factor VIII levels may be useful in monitoring therapy and determining duration of treatment.

**Treatment**

Anticoagulation is the mainstay of therapy for VTE in children. Unfractionated heparin is the most frequently used anticoagulant for the initial treatment of VTE in children because of its short half-life (Figure 2). Low-molecular-weight heparin (LMWH) is now being increasingly used because its pharmacokinetics are more predictable than unfractionated heparin, thereby minimizing the frequency of monitoring (Figure 3). LMWH can be administered subcutaneously, thereby eliminating the need for continuous venous access. The risk of heparin-induced thrombocytopenia and osteoporosis is also decreased compared with unfractionated heparin. LMWH does not interfere with diet or drugs, a recurrent problem with oral anticoagulants. Infants need higher doses of LMWH and may require plasma infusion because they have physiologically low levels of antithrombin III.

In children, the initial treatment of VTE is heparin or LMWH followed by LMWH or bridging to oral anticoagulants (Figure 3). However, monitoring oral anticoagulant therapy in children is difficult. Breast-fed infants are very sensitive to oral anticoagulants because they ingest low concentrations of vitamin K in breast milk. In children, oral anticoagulants are affected by other medications, impaired absorption, total parenteral nutrition, or nutrient formulas that contain high concentrations of vitamin K. Monitoring can be especially difficult in neonates because of poor venous access. Because they use blood obtained by capillary punctures instead of venipunctures, whole-blood point-of-care prothrombin time/international normalized ratio devices may be a solution. Furthermore, these monitors may be used at
home and appear to be acceptable and reliable in the outpatient laboratory and home settings.\textsuperscript{31}

Fibrinolytic agents such as tissue plasminogen activator can be used locally and systemically. No studies assessing their efficacy and safety in children are available. These agents have been used in children who develop a large new pulmonary embolism, particularly if the pulmonary embolism is hemodynamically compromising, or if there is an extensive thrombus that threatens an extremity.\textsuperscript{32}

Temporary filters are usually placed in children with large vena cava thrombi who have unstable cardiovascular function. Surgical thrombectomy is used very rarely.

Major bleeding from anticoagulation therapy is rare. Minor bleeding complications occur but can be managed with optimal supportive care. Heparin-induced thrombocytopenia has been reported in \textasciitilde 1\% of patients treated with heparin.\textsuperscript{33,34} Therapy with argatroban and lepirudin has been used on the basis of adult data.

Pediatric patients with uncomplicated venous thrombosis are usually treated for 3 to 6 months. There is increasing evidence that patients who have clot progression while on therapy, patients with completely occlusive clots on presentation, and patients with persistently high levels of inflammatory markers are at risk for treatment failure and may benefit from a longer duration of anticoagulation. Long-term anticoagulation prophylaxis may be considered for some patients such as those who carry combined heterozygous prothrombotic risk factors with spontaneous thrombosis, symptomatic patients with antiphospholipid syndrome or homozygous protein S or protein C deficiency, and patients with recurrent life-threatening VTE.

Prevention

Routine prophylactic anticoagulation for VTE in children with CVCs is not yet recommended because the clinical relevance of these primarily asymptomatic thrombi is unknown and needs further evaluation. Prophylactic anticoagulation is useful for children with congenital thrombophilia who are in high-risk situations such as after trauma or surgery or during identified time-limited risk periods such as severe infection or presence of a CVC. Use of fitted compression stockings and addressing comorbid conditions such as obesity will prevent sequelae such as PTS.

Cases 1 and 2

Case 1 highlights the silent nature of CVC-associated thrombosis in a patient with several risk factors. The best intervention is to remove the catheter as soon as possible. Anticoagulation is considered if the catheter must remain in place or if the underlying disease is a risk factor for thrombosis. In this case, the line was removed, and the patient received anticoagulation through the period that he was treated with t-PA.

Case 2 demonstrates a frequent clinical scenario in the adolescent population. Hormonal therapy was a trigger and was discontinued. The patient was treated with enoxaparin monotherapy without warfarin for 6 months.\textsuperscript{35}

References


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