Etiopathogenesis of pediatric thrombosis

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Introduction

Thrombosis is a relatively rare event during childhood, affecting 0.7/100000 children, with the highest frequency found in newborn infants and adolescents [1,2]. The etiology of thrombosis is influenced by age, neonate versus non-neonate, as well as site, arterial versus venous. Thrombosis during childhood is almost always multifactorial, with both genetic and environmental factors important in the onset and progression of thrombosis [3,4]. This paper will review the etiology and pathogenesis of thrombosis in pediatric patients.

Infants and children beyond the neonatal period

The majority of infants and children present with thrombosis while hospitalized for a significant underlying medical condition. Idiopathic thrombosis is very rare in childhood; most symptomatic children manifest two or more risk factors, as displayed on Table I.

Venous thrombosis beyond the neonatal period

Venous thrombosis is more common in children than arterial occlusions. Inflammation related to infection, surgery, trauma, malignancy or connective tissue disorders is present in most children with venous thrombosis [3,4]. Blood disorders contributing to endothelial damage and stasis including sickle cell anemia, polycythemia and leukemia are rare but important risk factors for thrombosis.

Indwelling catheters are involved in approximately 30 to 60% of cases of venous thrombosis [3,5]. Catheter-related thrombi develop in children who require long-term support with venous access devices for chronic disorders such as cystic fibrosis, hemophilia, sickle cell anemia or short gut syndrome. However, in the setting of intense inflammation, such as sepsis or trauma, short-term femoral catheters placed for resuscitation often result in venous occlusion.

The term thrombophilia denotes a category of blood conditions that are associated with an increased propensity to develop thrombi. Thrombophilia may be genetic or acquired and both types are commonly determined in children with thrombosis [6,7]. Antithrombin deficiency is associated with a number of disorders including nephrotic syndrome, protein losing enteropathy and chemotherapy with L-asparaginase. Protein C deficiency is acquired by consumption during severe bacterial infections such as meningococcal sepsis and meningitis. Auto-immune protein S deficiency has been described following viral infections such as varicella [8,9].

Antiphospholipid antibodies (APA) include the lupus anticoagulant (LA), anticardiolipin antibody and anti-β2GPI antibodies. In young children APA usually occur following infection and are transient. APA in adolescents more commonly are persistent. By definition, detection of APA six weeks or more following initial determination constitutes the APA Syndrome (APAS). However following infections with organisms such as varicella or streptococcus, APA have been determined to resolve over several months, without apparent long-term risk of thrombus recurrence [9]. APAS may be secondary to systemic lupus erythematosus or other collagen vascular disease. However APAS in pediatric patients is usually primary, or idiopathic. Patients with APAS are at high risk for recurrent thrombosis following discontinuation of anticoagulation and most must be treated with warfarin for an indefinite time [10].
Table I. Underlying conditions predisposing to thrombosis in infants, children and adolescents

**Inflammatory States:** Infections, Surgery, Malignancy, Massive Trauma

**Inflammatory Disorders:** Systemic Lupus Erythematosus, Rheumatoid Arthritis, Inflammatory Bowel Disease, Diabetes Mellitus

**Antiphospholipid Antibodies:** Lupus Anticoagulant, Anticardiolipin Antibody, Anti-B2GPI antibody

**Acquired Deficiencies of Coagulation Regulatory Proteins:**
- Lupus Anticoagulant, Anticardiolipin Antibody, Anti-B2GPI antibody
- Elevated Lipoprotein (a), Homocysteine, Factor VIII, Sickle Cell Anemia

**Primary Hematologic Disorders:**
- Polycythemia/Hyperviscosity, Essential Thrombocythemia, Leukemia with a high white blood cell count, Sickle Cell Anemia, Immune Hemolytic Anemia

**Drugs:**
- Estrogens, Corticosteroids, L-Asparaginase

**Inflammatory Disorders**
- Trauma
- Nephrotic Syndrome, Protein Losing Enteropathy, Sepsis, Respiratory Distress Syndrome (Preterm Infants), Specific Factor Autoantibodies

The LA can be detected in approximately 25% of children at the time of thrombosis diagnosis [11]. Children with acute thrombosis who manifest the LA are at increased risk for pulmonary embolism [10]. The LA promotes thrombosis by mediating increased expression of tissue factor and increased activation of factor X.

A list of genetic thrombophilia traits is shown on Table II. Genetic thrombophilic risk factors include conserved point mutations like factor V Leiden and prothrombin 20210. Factor V Leiden is resistant to physiologic down-regulation by activated protein C following activation of factor V by thrombin, while the prothrombin 20210 mutation results in a 15 to 30% increase in plasma concentration of the procoagulant protein prothrombin. Other conserved polymorphisms are associated with increased plasma concentrations of PAI-1 and homocysteine, or increased platelet interactions through membrane glycoproteins.

Certain genetic mutations promote hypercoagulability through decreases in concentration or function of various coagulation proteins including antithrombin, protein C, protein S, plasminogen or fibrinogen. Hundreds of mutations have been described in genes encoding coagulation proteins and these non-conserved mutations tend to convey more severe thrombotic morbidity. Other genetic thrombophilic risk factors such as hyperhomocysteinemia are modified by environmental influences from diet, exercise level and smoking. The Perinatal and Pediatric Subcommittee of the International Society of Thrombosis and Hemostasis has recommended that children with thrombosis be evaluated for thrombophilia [12].

The inheritance of single thrombophilic genes increases the risk of symptomatic thrombosis during childhood, but does not appear to alter thrombus outcome or recurrence [13]. The concurrent inheritance of multiple prothrombotic traits increases the risk of both primary and recurrent thrombosis [14]. Thrombosis in children with genetic thrombophilia may be prevented by use of prophylactic anticoagulation around high risk procedures, such as surgery or immobilization.

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Small vessel thrombosis occurs in the syndromes of purpura fulminans (PF) as well as thrombotic thrombocytopenia purpura (TTP)/hemolytic uremic syndrome (HUS). Recurrent episodes of TTP/HUS beginning with onset during infancy have been described in children with genetic deficiencies of the metalloproteinase, ADAMST-13, the complement protein, H Factor, or the H Factor membrane cofactor, CD46. Similar chronic clinical syndromes with later age of onset have been associated with autoimmune decreases in these same proteins. The disorders are characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal, liver and central nervous system dysfunction.

**Special issues of venous thrombosis in adolescents**

Therapies such as estrogens alter concentrations and functions of several coagulation proteins and shift the balance of coagulation toward thrombosis.

Factor V Leiden, protein S deficiency and antithrombin deficiency are examples of hormonally responsive coagulopathies. Affected females often present with deep venous thrombosis (DVT) within a few weeks to months after beginning oral contraceptives or hormone replacement therapy, or during pregnancy. In addition to the direct effects of estrogens, physiologic changes associated with puberty promote thrombogenesis through increased red cell mass and viscosity. The presentation of severe genetic thrombophilia has been delayed until puberty in some affected children [16].

A vascular anatomic variant named the May-Thurner anomaly often presents with lower extremity DVT in adolescents. In this condition, the right iliac artery constricts the left iliac vein. Treatment with thrombolysis or mechanical thrombectomy and left iliac vein stenting has been employed in addition to anticoagulation.
Sequellae of venous thrombosis in pediatric patients

The syndrome of limb pain sufficient to limit activity in association with limb swelling, visible collateral formation and/or skin changes characterizes the post thrombotic syndrome (PTS). PTS has been reported in 10 to 60% of children following an episode of DVT [17–19]. Occlusive clot, elevated factor VIII and D-dimer both at DVT presentation as well as three to six months following the acute event, adolescent age and excessive body mass index (BMI) have been associated with the development of PTS [15,20,21]. Early restoration of venous blood flow, use of compressive stockings and reduction of inflammation may reduce the incidence or severity of PTS.

Arterial thrombi in non-neonates

Arterial thrombosis is usually caused by endothelial trauma. Most arterial thrombosis occurring beyond the neonatal period is related to the use of arterial catheters, chiefly cardiac catheterization. The rare syndrome called the Catastrophic APAS is characterized by unprovoked arterial and venous thrombosis and should be suspected in all children with peripheral arterial thrombi that are not catheter-related.

Stroke affects 8/100,000 children per year [22]. Eighty percent of strokes affect infants and children beyond the neonatal period and seventy-five percent of pediatric strokes are arterial. Arterial ischemic stroke (AIS) in the region of the brain perfused by the middle cerebral artery is the most common site of unprovoked arterial thrombo/embolism in children. Up to a third of children manifest a positive anticardiolipin antibody at the time of presentation with AIS [23]. A history of preceding upper respiratory infection is also common in children presenting with stroke. A patent foramen ovale may be responsible for recurrent embolic AIS. Valvular vegetations from APAS may also cause embolic stroke. Contrast (or bubble) echocardiography can exclude both of these possibilities. Genetic thrombophilia may present with arterial stroke, especially in infants [23]. A complete blood count should be performed on all children with stroke to exclude hematologic abnormalities including sickle cell anemia, thrombocytosis, polycythemia and leukemia.

Neonatal thrombosis

Overall, the rate of thrombosis in the neonatal period is much higher than that later in infancy [6]. Studies performed forty years ago demonstrated that neonatal clotting is accelerated in rate and degree as reflected on whole blood tests such as the thromboelastogram while plasma clot formation is delayed accounting for physiologic prolongations determined on the prothrombin time (PT) and activated partial thromboplastin time (PTT) [24]. Recent research has determined that increased thrombin generation in neonatal plasma is caused by decreased levels of tissue factor pathway inhibitor and antithrombin, while circulating soluble tissue factor is increased in preterm plasma [25,26]. In addition, physiologically increased hematocrit appears to predispose the newborn infant to thrombosis. Maternal diabetes is associated with an increased risk of neonatal thrombosis, and this risk may be mediated through further decreases in physiologically low levels of regulatory proteins, protein C and antithrombin. Both the plasma concentration and the multimeric size of the von Willebrand factor are increased in neonatal plasma. Adhesion of neonatal platelets, mediated by platelet GPIb and von Willebrand factor, is brisk and both the template bleeding time, as well as the closure time of the platelet function analyzer (PFA-100), are shorter in the neonate than in healthy children or adults, and contribute to the propensity for arterial thrombosis.

Neonatal venous thrombi

Indwelling venous catheters are present in a large proportion of cases, especially in thrombosis associated with bacteremia or clinical sepsis syndrome. The most common sites of unprovoked venous thrombosis in the neonate are renal vein thrombosis (RVT) and central nervous system sinus venous thrombosis (CSVT) [27]. Severe genetic thrombophilia usually presents in the neonatal period. Homozygous or compound heterozygous deficiencies of protein C or protein S present with disseminated intravascular coagulation, purpura fulminans or large vessel thrombosis.

Neonatal arterial thrombi

Arterial thrombi are usually associated with indwelling catheters, especially umbilical artery catheters and cardiac catheterization. Perinatal stroke appears to have a unique etiopathogenesis. In utero, the foramen ovale is patent. Thrombi originating from the placenta may enter the right heart through the umbilical vein and pass through the patent foramen ovale. The most direct vascular path from the ascending aorta is through the left carotid artery into the middle cerebral artery. Approximately seventy percent of neonatal strokes affect the left middle cerebral artery, causing right hemiparesis.

Special issues in neonatal thrombosis

Despite the large number of known genetic and acquired risk factors for thrombosis, a cause cannot be determined for approximately half of the newborn infants affected by stroke or venous thrombosis. The
risk for progression or recurrence of idiopathic perinatal thrombosis appears to be low.

**Summary**

Although uncommon, thrombosis is an important clinical problem in pediatric patients. True idiopathic thrombosis is extremely rare in children. Therefore, an underlying cause should always be sought. Thrombosis in children is almost always multifactorial, involving genetic and acquired thrombophilia, vascular damage and underlying inflammation. Genetic thrombophilia is frequently found in neonates as well as older children and adolescents with thrombosis. A laboratory evaluation for thrombophilia is almost always warranted in symptomatic children to determine the contributors to thrombogenesis, to prevent recurrent episodes and to allow genetic counseling for family members. Newborn infants and adolescents have unique age-related factors in the etiology and pathogenesis of thrombosis that should be considered. Children appear to suffer rates of PTS at least as high as that found in adults. Further research is needed regarding etiology and pathogenesis of thrombosis in children for prevention of primary and recurrent thrombotic events, optimal therapy for thrombosis in neonates and children, and prevention or limitation of PTS in affected patients.

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**References**


