

Pediatric Thrombosis

Chularatana Mahasandana

Thrombosis is the formation of a blood clot or thrombus within the vascular system. This is the life-saving process when it occurs during hemorrhage. But it is a life-threatening event when it occurs at any other time because the clot can occlude a vessel and stop the blood supply to an organ or a part of the body. The thrombus, if detached, becomes an embolus and occludes a vessel at a distance from the original site, i.e. a clot in the leg may break off and cause a pulmonary embolus.

Normally, the clotting process is self-limiting; if not, abnormal clotting is the result. The limiting process of the clot occurs through several mechanisms. The most important are (1) removal of activated clotting factors by blood flow past the clot, (2) inactivation of clotting factors by cir-

culating inhibitors (i.e. antithrombin III [AT III], Protein C [PC], Protein S [PS]), (3) consumption of platelets and clotting factors by the clotting process, and (4) degradation of the clot by the fibrinolytic enzyme, plasmin.⁽¹⁾

Thrombosis is a rare disorder in the young and will occur when a sufficient number of risk factors are present simultaneously. In children, three or four risk factors are required before thrombosis occurs. With increasing age, vessel wall changes, different composition of the blood, and altered mobility may add to the risk profile, and fewer risk factors (two or more) are required for thrombosis to occur. This may explain why the incidence of thrombosis rises with age.⁽²⁾

CLINICAL MANIFESTATIONS OF PEDIATRIC THROMBOSIS⁽³⁻¹¹⁾

1. Venous Thromboembolism

- renal vein thrombosis (newborn)
- purpura fulminans (newborn)
- deep vein thrombosis
- pulmonary embolism
- digital ischemia
- chronic leg ulcer
- ? plasminogen deficiency
- ? nephrotic syndrome
- ? malignancy
- ? surgery, trauma

Risk factors

- ? indwelling venous catheter
- ? deficiency of ATIII, PC, PS
- ? FV Leiden, FII variant
- ? high fibrinogen, high FVIII
- ? lupus anticoagulant, anticardiolipin antibody

2. Arterial Thrombosis (digital ischemia, coronary artery thrombosis, carotid artery thrombosis, heart valve & chamber thrombi, etc.)

Underlying diseases

- Kawasaki disease
- Takayasu disease
- organ transplantation
- atherosclerosis
- hyperhomocystinemia
- autoimmune disease
- myeloproliferative disorders

Risk factors

- ? umbilical artery catheterization
- ? cardiac catheterization
- ? peripheral artery catheters
- ? lupus anticoagulant, anticardiolipin antibody (vasculitis, SLE)
- ? deficiency of ATIII, PC, PS
- ? FV Leiden, FII variant
- ? 2° thrombocytosis

3. Pediatric stroke (hemiplegia, with or without seizure)

Underlying diseases

- Moyamoya disease
- Kawasaki disease
- Takayasu disease
- thalassemia
- cyanotic congenital heart disease
- bacterial meningitis
- familial hyperlipidemia
- homocystinemia
- malignancy

Risk factors

- * all hypercoagulable states
- ? deficiency of ATIII, PC, PS
- ? FV Liden, FII variant
- ? lupus anticoagulant
- ? L-Asparaginase therapy
- ? major surgery
- ? dehydration

Laboratory Approach to Thrombotic Disorders in Pediatric Patients^(1,3,12)

1. complete blood count (CBC)
2. observation of blood clot: i.e. small clot & irregular shape in hyperfibrinolysis, dysfibrinogenemia; no clot in severe DIC
3. Activated partial thromboplastin time (APTT), Prothrombin-Time (PT), Fibrinogen
4. Lupus anticoagulant, anticardiolipin antibody
5. Measurement of PC, PS, AT III, FV Leiden, FII variant (Prothrombin G20210A mutation)
6. Measurement of plasminogen, plasmin, tissue plasminogen activator, D-Dimer

TREATMENT^(13,14)

A. Venous thromboembolism (VTE) in children

1. Heparinization (children > 2 months of age)

<u>Heparin</u> (5-10 d)	<u>Monitor</u>
standard heparin	APTT/anti-FXa (0.3-0.7 U/mL)
Low molecular wt heparin (LMWH)	anti-FXa (0.5-1.0 U/mL 4-6 hr after injection)
2. Oral anticoagulant (continue)

	<u>Monitor PT/INR</u>
• at least 3 months (single episode VTE)	INR 2-3
• indefinite (recurrent VTE)	INR 2-3
3. Children with congenital prothrombotic disorders should receive short-term prophylactic anticoagulation in high-risk situations, i.e. immobility, significant surgery, trauma.

B. Venous thromboembolism in newborns

1. Anticoagulation
standard heparin, short course (10-14 d) monitor anti-FXa (0.3-0.7 U/mL)
or LMWH (anti-FXa 0.5-1.0 U/mL)
If thrombus recurr or extends during observation, extend LMWH therapy or consider oral anticoagulation therapy.
3. Thrombolytic therapy (highly individualized)
4. Supplementation with plasminogen by administering either FFP or cryoprecipitate may be helpful

C. Purpura fulminans (Homozygous PC, PS deficient patients)

- initially replacement therapy (FFP, PC conc.) until the skin lesions have healed.
- oral anticoagulation—target INR values 3-4.5 (introduced under cover of replacement therapy)
- recurrent skin lesions—replacement therapy
- for patients with measurable plasma PC, PS; LMWH is a therapeutic option.

D. Arterial thrombosis

- antiplatelet drugs
- heparin
- oral anticoagulant

PROPHYLAXIS

- Heparin or LMWH

NEW ADVANCES

- whole blood monitors for use in anticoagulation clinics and at home
- subcutaneous catheters
- vena cava filters
- Thrombophilia programs (diagnosis, prevention and treatment of thromboembolic events)

Cases demonstration

1. Infant with purpura fulminans due to PS deficiency
2. A child with arterial thrombosis secondary to infection.
3. Digital ischemia secondary to autoimmune vasculitis.
4. Hemorrhagic brain infarction in severe β -thalassemia/Hemoglobin E disease.
5. Cerebral thrombosis in patient with acute lymphoblastic leukemia (following L-asparaginase therapy)

References

- 1) Normal control of the clotting process⁽⁴⁾ and fibrinolysis. In: Evatt B, Gibbs WN, Lewis SM, Mc Arthur JR, eds. Fundamental diagnostic hematology. The bleeding and clotting disorders. 2nd ed. U.S. Department of Health and Human services, Atlanta, Georgia and World Health Organization. Geneva, Switzerland. 1992.
- 2) Rosendaal FR. Thrombosis in the young: Epidemiology and risk factors. A focus on venous thrombosis. *Thromb Haemost* 1997; 78: 1: 1-6.
- 3) Hathaway WE, Goodnight Jr. SH. The infant and child with thrombosis. Disorders of hemostasis and thrombosis : a clinical guide. 1993; 307-314.
- 4) Streif W, Andrew ME. Venous thromboembolic events in pediatric patients. *Hematol/Oncol Clin North Amer* 1998; 12: 6: 1283-1312.
- 5) Manco-Johnson MJ. Disorders of hemostasis in childhood: Risk factors for venous thromboembolism. *Thromb Haemost* 1997; 78: 1: 710-714.
- 6) Nuss R, Hays T, Manco – Johnson MJ. Childhood thrombosis. *Pediatr* 1995; 96: 2: 291-294.
- 7) Kulthanan K, Krudum T, Pintadit P, Khokkaseam R, Kullavanijaya P. Chronic leg ulcers associated with hereditary protein S deficiency. *International J Dermatol* 1997; 36: 198-212.
- 8) Andrew M, David M, de Veber G, Brooker LA. Arterial thromboembolic complications in Paediatric Patients. *Thromb Haemost* 1997; 78: 1: 715-725.
- 9) von Scheven E, Athreya BH, Rose CD, Goldsmith DP, Morton L. Clinical characteristics of antiphospholipid antibody syndrome in children. *J Pediatr Sept* 1996; 339-345.
- 10) Mahasandana C, Suvatte V, Chuansumrit A, Malar RA, Manco-Johnson MJ, Jacobson LJ, Hathaway WE. Homozygous protein S deficiency in an infant with purpura fulminans. *The Journal of Pediatrics* 1990; 117: 5: 750-753.
- 11) Pung-amritt P, Poort SR, Vos HL, Bertina RM, Mahasandana C, Tanphaichitr VS, Veerakul G, Kankirawatana S, Suvatte V. Compound heterozygosity for one novel and one recurrent mutation in a Thai patient with severe protein S deficiency. *Thromb Haemost* 1999; 81: 189-192.
- 12) Van Cott EM, Laposata M. Laboratory evaluation of hypercoagulable states. *Hematol/Oncol Clin North Amer* 1998; 12: 6: 1141- 1166.
- 13) Andrew M, Michelson AD, Bovill E, Leaker M, Massicotte MP. Guidelines for antithrombotic therapy in pediatric patients. *J Pediatr April* 1998; 575-588.
- 14) Bovill E, Monagle P, Andrew M. Antithrombotic therapy in children. *Chest Suppl.* 1998; 114: 5: 748 S-767 S.