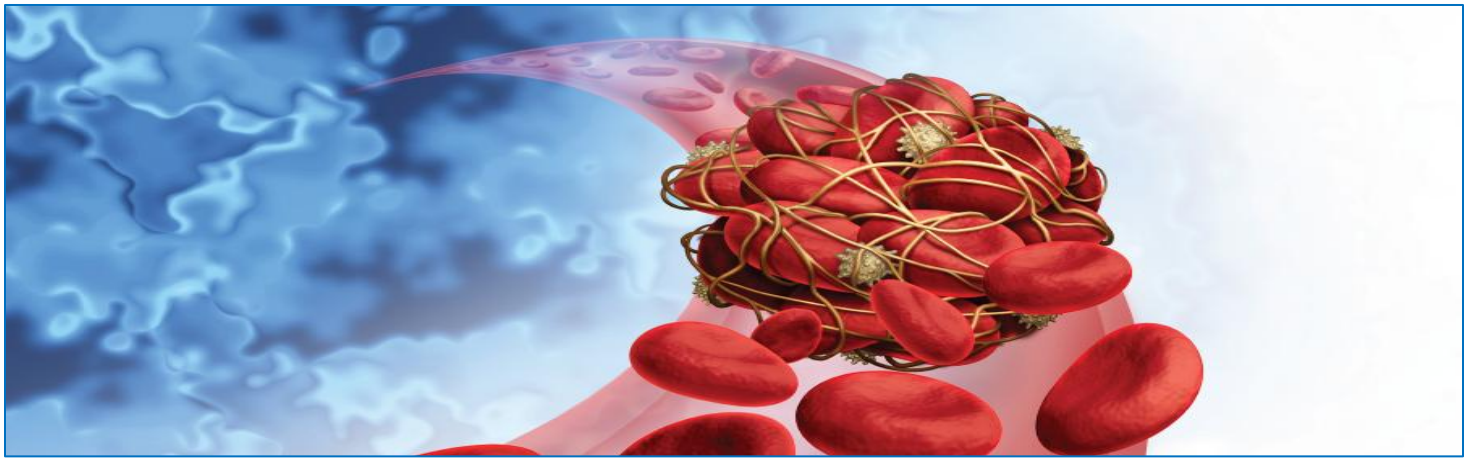
Pediatric Thrombophilia

A presentation of our clinical case.



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Tirana 2025

What is thrombophilia ?

Thrombophilia* is an abnormality of blood coagulation that increases the risk of *thrombosis .

Pediatric thrombosis and thrombophilia are increasingly recognized and studied.

Risk factors include :

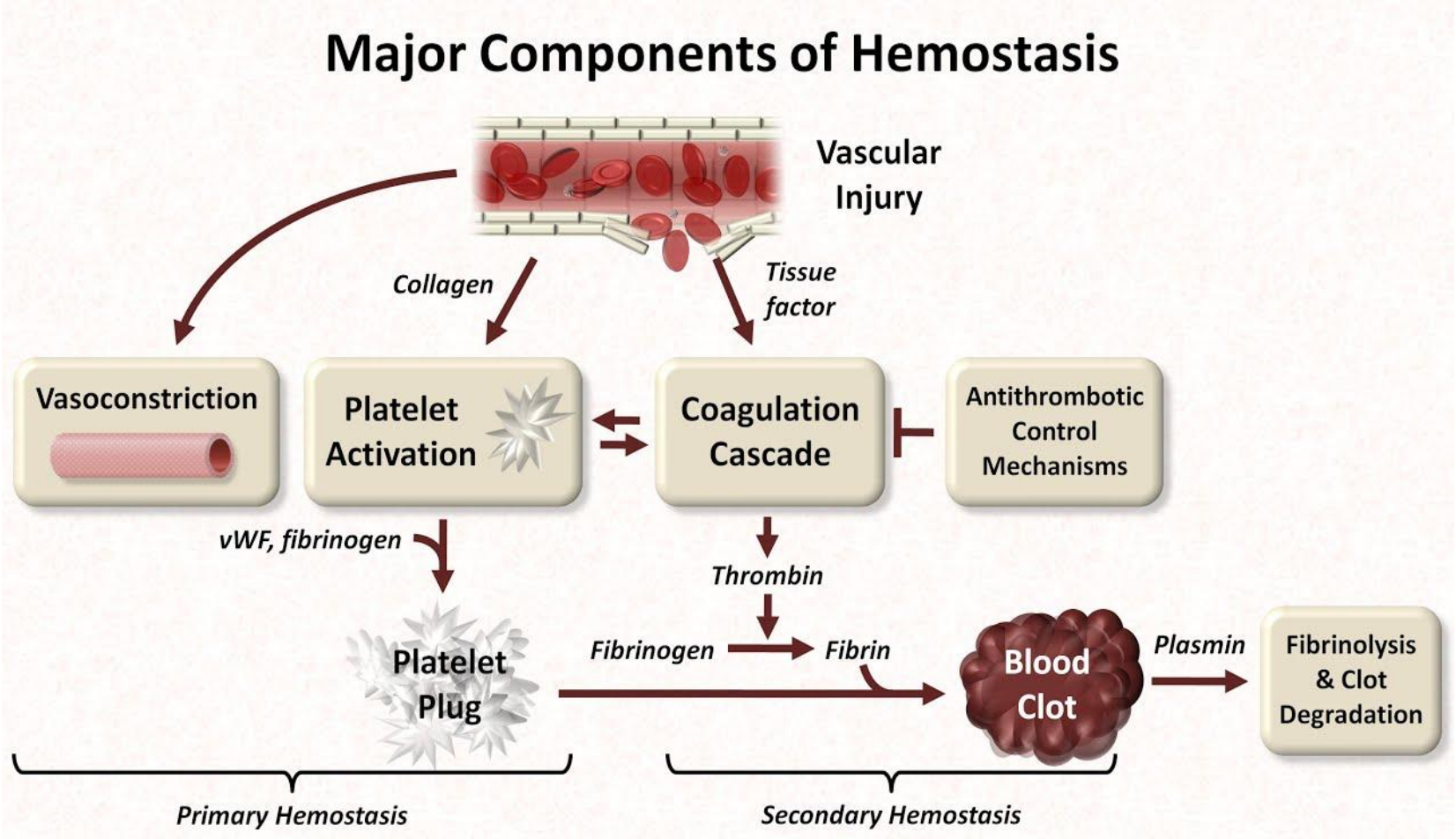
Acquired clinical risk factors
such as a central venous catheter and underlying disease.

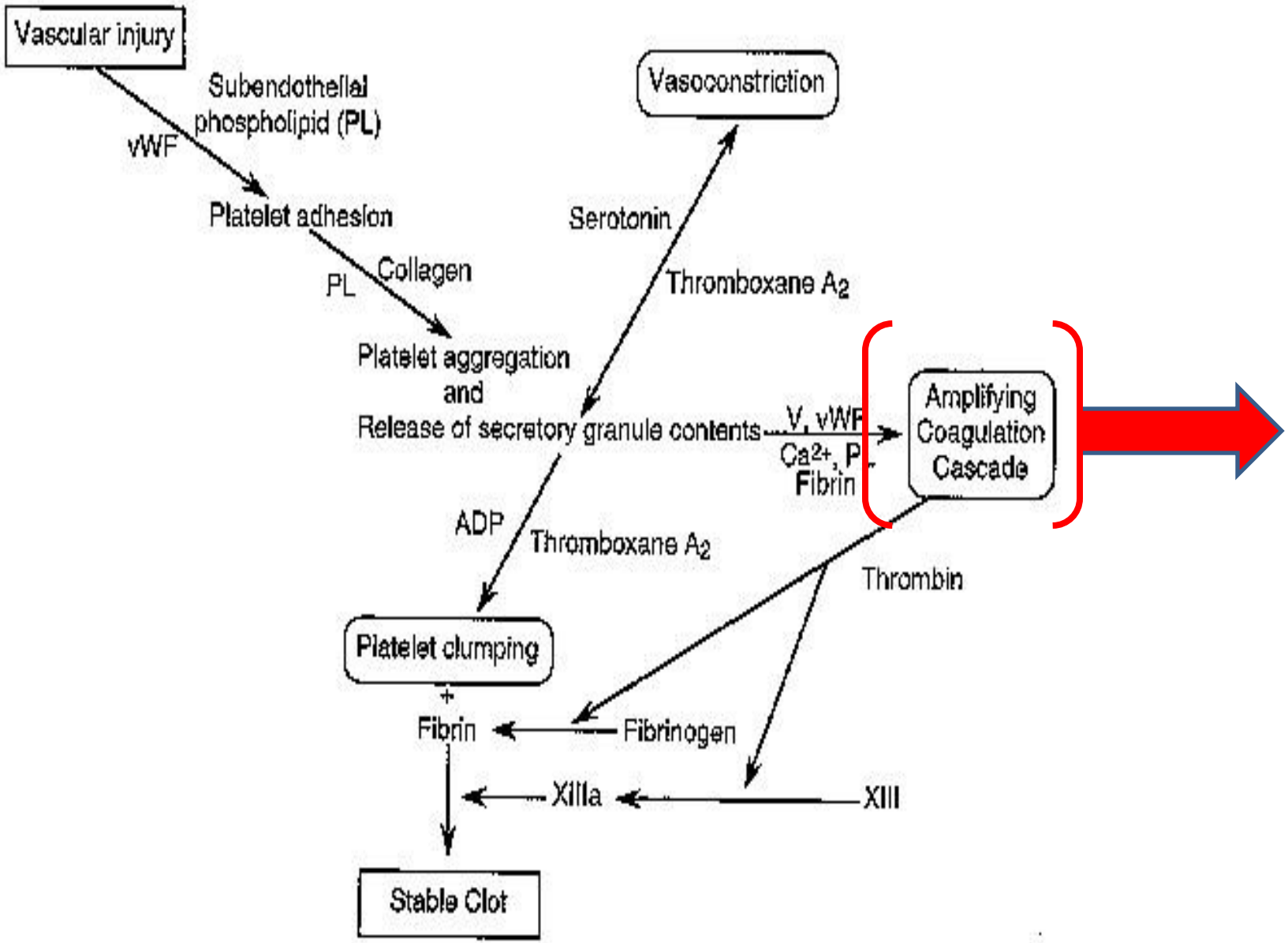
Inherited thrombophilia is defined as a genetically determined tendency to develop thrombosis.

An interaction between genetic and acquired factors.

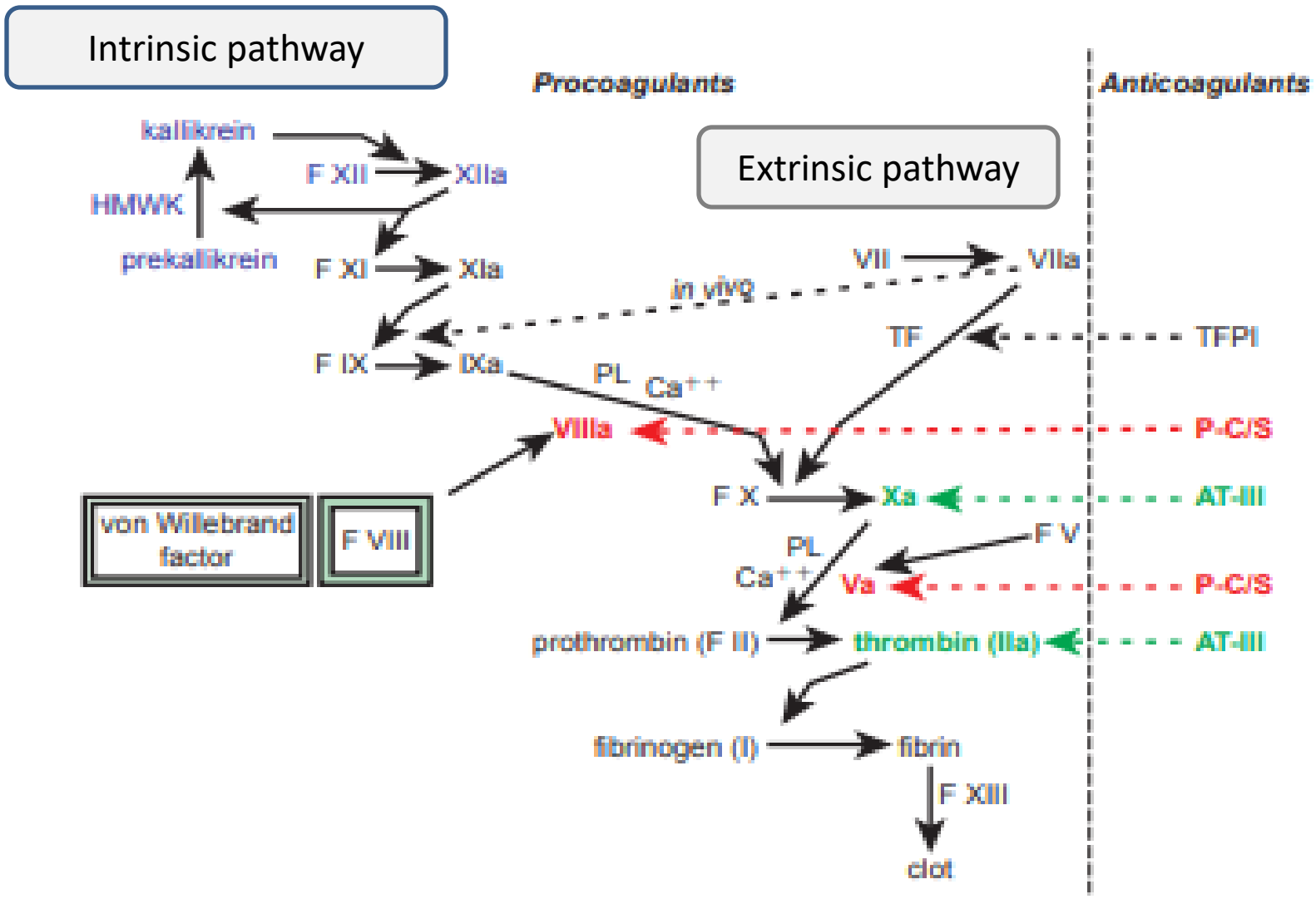
In contrast to adults, acquired clinical risk factors play a larger role than inherited thrombophilia in the development of thrombotic disease in children.

To understand this pathology, we must bring to attention some concepts of NORMAL HEMOSTASIS ….




Vascular injury
Subendothelial phospholipid (PL)
vWF
Platelet adhesion
PL
Collagen
Platelet aggregation and Release of secretory granule contents
Vasoconstriction
Serotonin
Thromboxane A2
V, vWF
Ca2+, P
Fibrin
Amplifying Coagulation Cascade
ADP
Thromboxane A2
Thrombin
Platelet clumping
+
Fibrin
Fibrinogen
XIIIa
XIII
Stable Clot

The clotting cascade,with sequential activation and amplification of clot formation .



HEMOSTATIC DISORDERS

Bleeding disorders associated with coagulation factor and fibrinolytic pathway factor deficiencies.

Isolated deficiencies of functional coagulation factors in the coagulation cascade congenital and acquired

Fibrinogen (Factor (1) deficiency
Prothrombin (Factor II) deficiency
Factor V deficiency
Factor VII deficiency
Hemophilia A (Factor VIII deficiency)
Factor VIII inhibitors (Factor VIII deficiency from antibody-mediated inhibition of Factor Vill activity)
Hemophilia B (Factor IX deficiency)
Factor X deficiency
Factor XI deficiency
Factor XIII deficiency
Deficiencies of Factor XII, prekallikrein, and high-molecular-weight kininogen (contact factors) are not associated with bleeding

Isolated factor deficiencies in the fibrinolytic pathway

Plasmin inhibitor deficiency

Disorders associated with deficiencies of multiple functional coagulation factors

Vitamin K deficiency
Disseminated intravascular coagulation (DIC)
Liver disease from multiple etiologies
Overdose of warfarin or heparin

Disorders associated with thrombosis

Bleeding disorders associated with altered platelet number (quantitative platelet disorders) or impaired platelet function (qualitative platelet disorders)

Quantitative platelet disorders: Thrombocytopenias

Thrombocytopenia due to increased platelet destruction-congenital and acquired

Immune

Immune thrombocytopenic purpura (ITP)
Drug-induced immune thrombocytopenia Posttransfusion purpura (PTP)
Neonatal alloimmune thrombocytopenia (NAIT)

Nonimmune

Disseminated intravascular coagulation (DIC) Thrombotic thrombocytopenic purpura (TTP) Hemolytic-uremic syndrome (HUS)
Hypersplenism

Thrombocytopenia due to decreased platelet production

Tumor infiltration of bone marrow
Drug-induced (nonimmune) thrombocytopenia by chemotherapeutic agents and other agents Aplastic anemia

Quantitative platelet disorders:

Thrombocytosis Essential thrombocythemia or other myeloproliferative disorder

Qualitative platelet disorders

Congenital and acquired

Defective platelet function resulting from a plasma factor deficiency
Von Willebrand disease ,Bernard-Soulier disease
Glanzmann thrombasthenia Storage pool disease ,Uremia-induced platelet dysfunction ,Drug-induced platelet dysfunction

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Disorders associated with thrombosis

THROMBOPHILIA

Relatively higher incidence

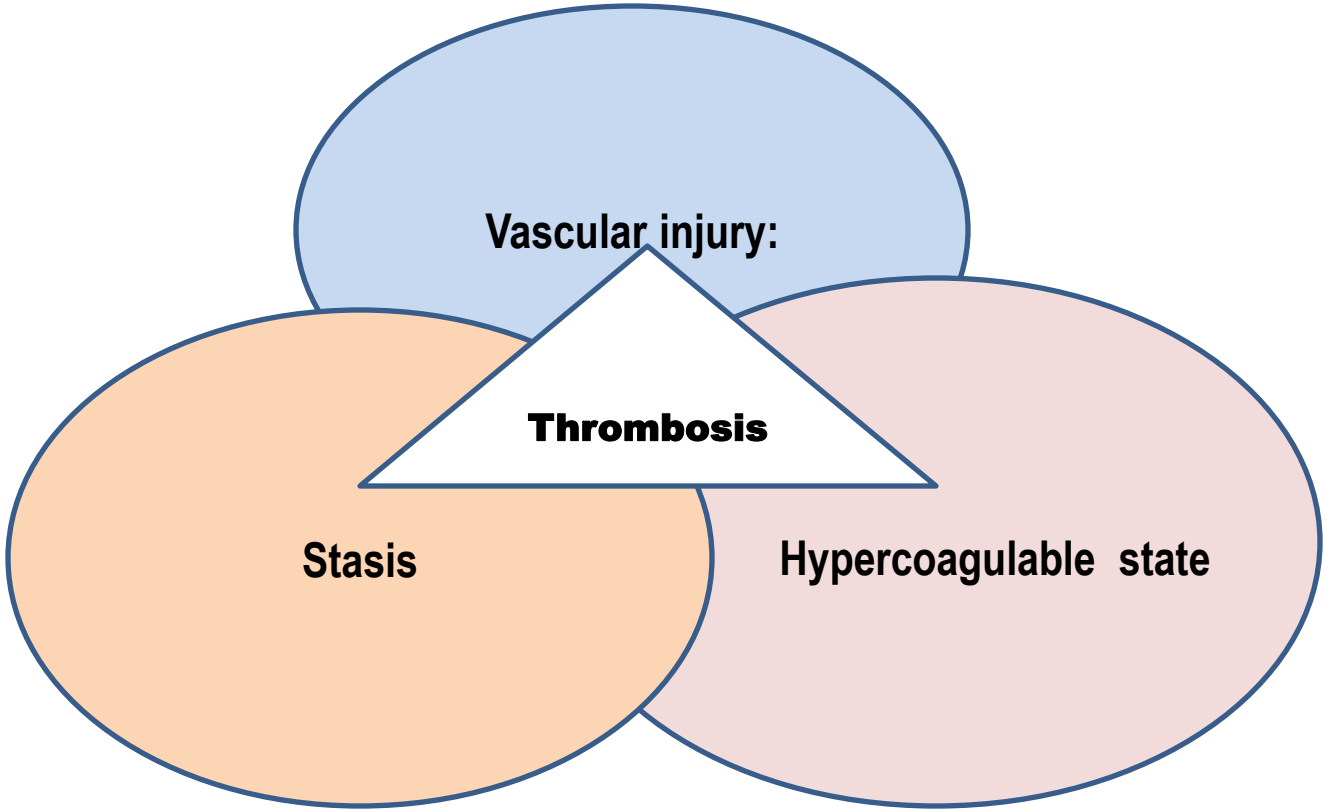
- Activated protein C resistance (the Factor V Leiden and related mutations)
- Prothrombin G20210A mutation
- Antiphospholipid antibody syndrome
- Heparin-induced thrombocytopenia

Relatively lower incidence

Protein C or S deficiency
Antithrombin deficiency
Plasminogen deficiency
Selected dysfibrinogenemias
Essential thrombocythemia
Thrombotic thrombo- cytopenic purpura (TTP)
Hemolytic-uremic syndrome (HUS)
Markedly elevated homocysteine

The Virchow's Triad has formed the basis for understanding the pathogenesis of thrombosis and is still widely used to assess VTE risk.

Since 1845, he postulated that three factors were important in the development of thrombosis:
(1) impairment of blood flow (stasis),
(2) vascular injury,
(3) alterations of the blood (hypercoagulability).



… Risks factors for Thrombosis in pediatric

General

- Indwelling catheter including PICC (peripherally inserted central venous catheter)
- Trauma
- Surgery
- Cancer
- Immobility
- Cardiac disease/prosthetic valve
- Systemic lupus
- Rheumatoid arthritis
- Inflammatory bowel disease
- Polycythemia/dehydration
- Nephrotic syndrome
- Diabetes
- Pregnancy
- Obesity
- Prematurity
- Paroxysmal nocturnal hemoglobinuria
- Antiphospholipid antibody syndrome
- Thrombotic thrombocytopenic purpura

Inherited thrombophilias

- Factor V Leiden mutation
- Prothrombin mutation
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Homocystinuria
- Elevated factor VIII
- Dysfibrinogenemia

Anatomic

- Thoracic outlet obstruction (PagetSchroetter syndrome)
- Iliac vein compression syndrome (May-Thurner syndrome)
- Absence of the inferior vena cava

Medications

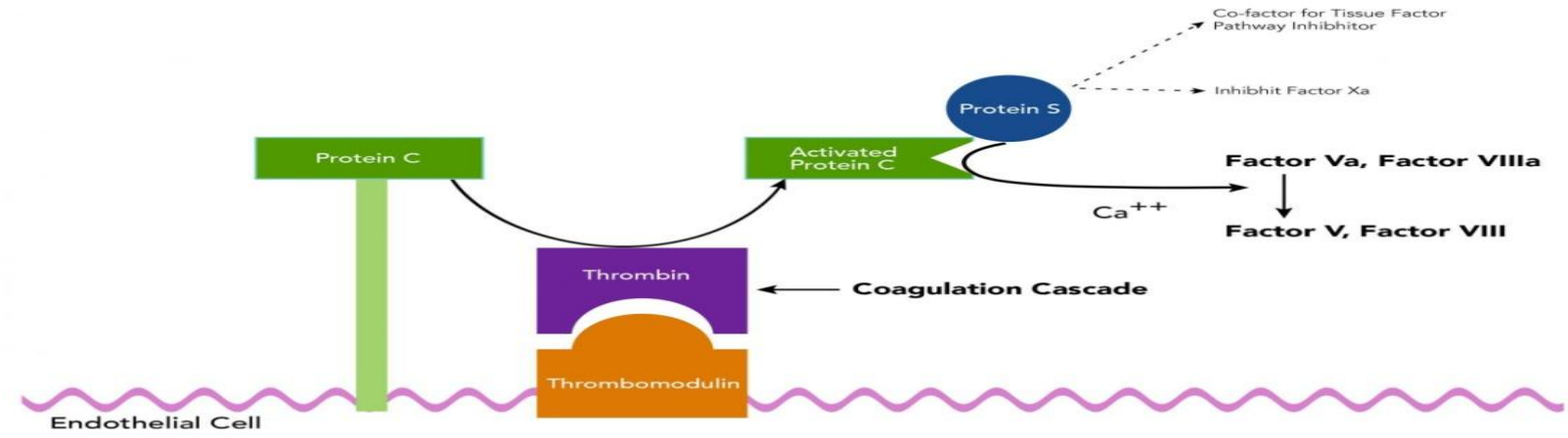
- Estrogen-containing contraceptives
- Asparaginase
- Heparin (heparin-induced thrombocytopenia)
- Corticosteroids

Review of inhereted thrombophilias conditions…

➢**Protein C** and **Protein S** are vitamin K dependent protein .

Protein C is activated by thrombin/thrombomodulin in APC .
Protein S is co- factor of APC.
Activated Protein C + Protein S = destroys factor Va and factor VIIIa =blocking coagulation.

<u>So protein C or protein S deficiency causes abnormal clotting blood.(especially VTE)</u>



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- In people with **factor V Leiden** thrombophilia (A particular mutation in the *F5* gene) factor V cannot be inactivated normally by APC .

As a result, the clotting process increasing the chance of developing abnormal blood clots

- **Antithrombin III** inhibits thrombin ,factor IXa , Xa ,XIa ,XIIa . Deficiency of antithrombin can be inherited or acquired and is associated with an increased risk of thromboembolism (lower extremities,mesenteric vein,pulmonary ,superior sagittal sinus)

- **Prothrombin 20210 Mutation,** When this mutation occurs, they make too much of the prothrombin protein, increases the tendency to form clots.

- **Other uncommon** Dysfibrinogenemias ,Hyperhomocisteinemia etc

Review of aquired thrombophilias conditions….

- The presence of **a central venous catheter** is the single most important risk factor.
  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 more preferable.
- **Antiphospholipid syndrome** (APS) is the most prevalent acquired thrombophilia.APS is an acquired autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss with characteristic laboratory abnormalities.
- **Congenital heart disease** can be a thromboembolic risk factor for children with mechanical or prosthetic valves and for those undergoing Blalock-Taussig shunt placement or a Fontan procedure.
- **Surgery, immobilization, and prolonged bedrest**. Compared with adults, children have a much lower risk of thrombosis after surgery. Prophylactic administration of LMWH is recommended for children with risk factors (eg, obesity, oral contraceptive use, cancer, central venous catheter).
- **Malignancy**-associated TE has been studied in acute lymphoblastic leukemia. The underlying mechanisms include the effect of leukemia itself and the use of chemotherapy, especially treatment with L-asparaginase.
- **Heparin-induced thrombocytopenia** is characterized by a decrease of more than 50% in the platelet count from the base line after a patient is given unfractionated heparin for 5 days or longer
- **Other condition** Use of estrogen-containing medications, Nephrotic syndrome, anatomical anomaly etc.

EPIDEMIOLOGY :

Studies have confirmed a significant increase in the diagnosis of venous thromboembolism (VTE) in pediatric tertiary hospitals .

The overall incidence of thrombosis in the general pediatric population is quite low 0.07/100,000 .

The rate of VTE in hospitalized children is 60/10,000 admissions.

•The most prominent peak is in early infancy accounting for up to 20% of pediatric VTE. (Thromboses tend to occur highest in neonates, particularly preterm neonates, more often in intensive care units)

•A second peak occurs during adolescence with about 50% of VTE events occurring in children 11–18 years old.

The presence of a central venous catheter (CVC and peripherally inserted central venous catheter) is the single most important risk factor for VTE in pediatric patients.

John A Sandoval, Michael P Sheehan, Charles E Stonerock, Shoaib Shafique, Frederick J Rescorla, Michael C Dalsing*Journal of Vascular Surgery* *2008 April*

The association between inherited thrombophilia and thromboses depends on this clinical scenario:
Adolescents who experience unprovoked thrombotic events have a very high prevalence of inherited defects (approximately 60%), while children who experience catheter-related thrombotic events have a controversial role in genetic thrombophilic defects.

- Factor V Leiden thrombophilia is the most common inherited form of thrombophilia. The prevalence in the general population of the US and Europe is 3-8% for one copy of the factor V Leiden mutation; about 1:5000 people have two copies of the mutation.

- Prothrombin-associated thrombophilia is the second most common genetic form of thrombophilia, occurring in approximately 1.7-3% of the general European and American population.

- Inherited antithrombin III deficiency has a prevalence of 1:500-5000 in the general population.

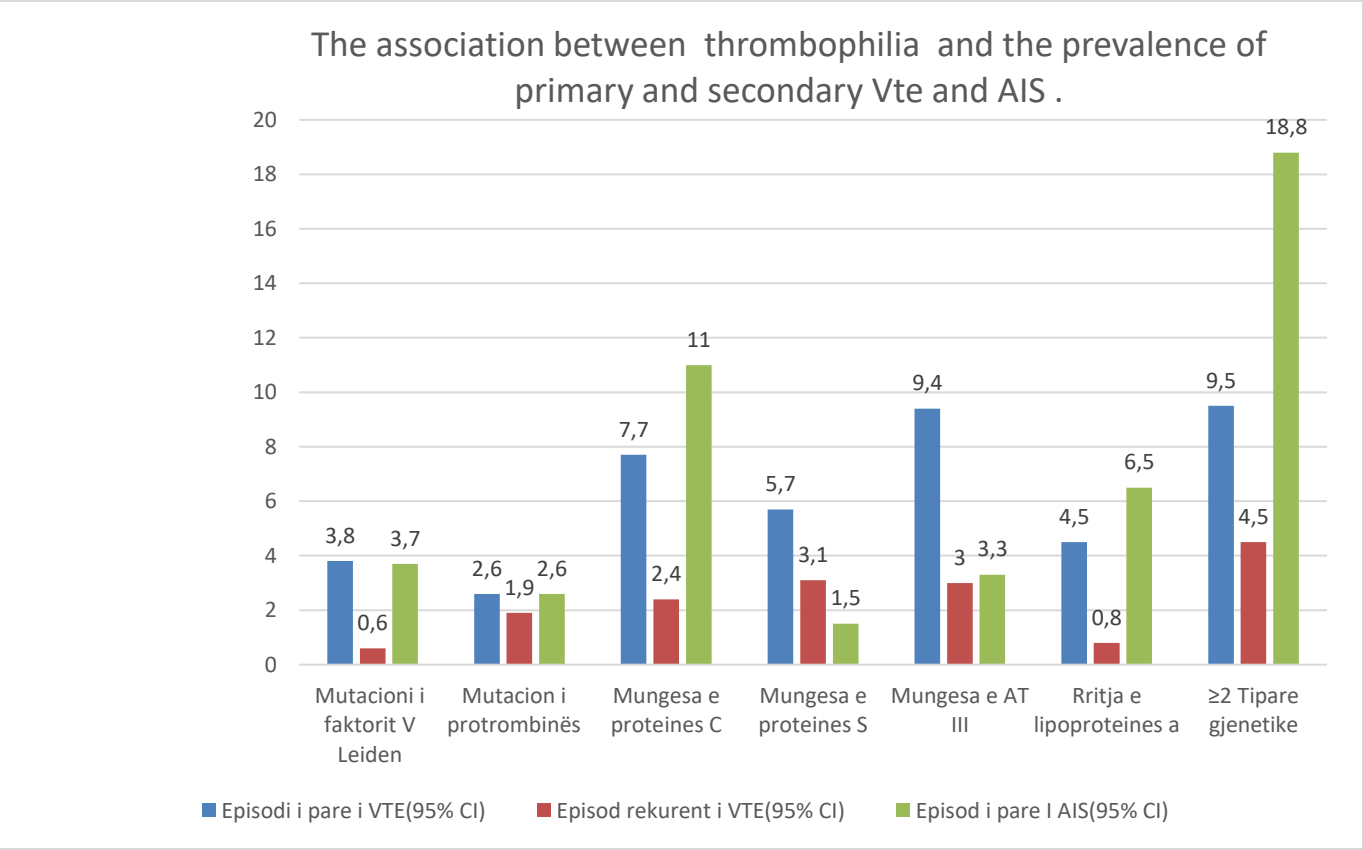
- Moderate protein S deficiency is estimated to affect 1:500 individuals. Severe deficiency is rare and its prevalence is unknown.

- Moderate deficiency of protein C affects about 1:500 individuals. Severe deficiency occurs in about 1:4000000 newborns.

RESEARCH ARTICLE | Originally Published 8 September 2008 |

Impact of Inherited Thrombophilia on Venous Thromboembolism in Children: A Systematic Review and Meta-Analysis of Observational Studies

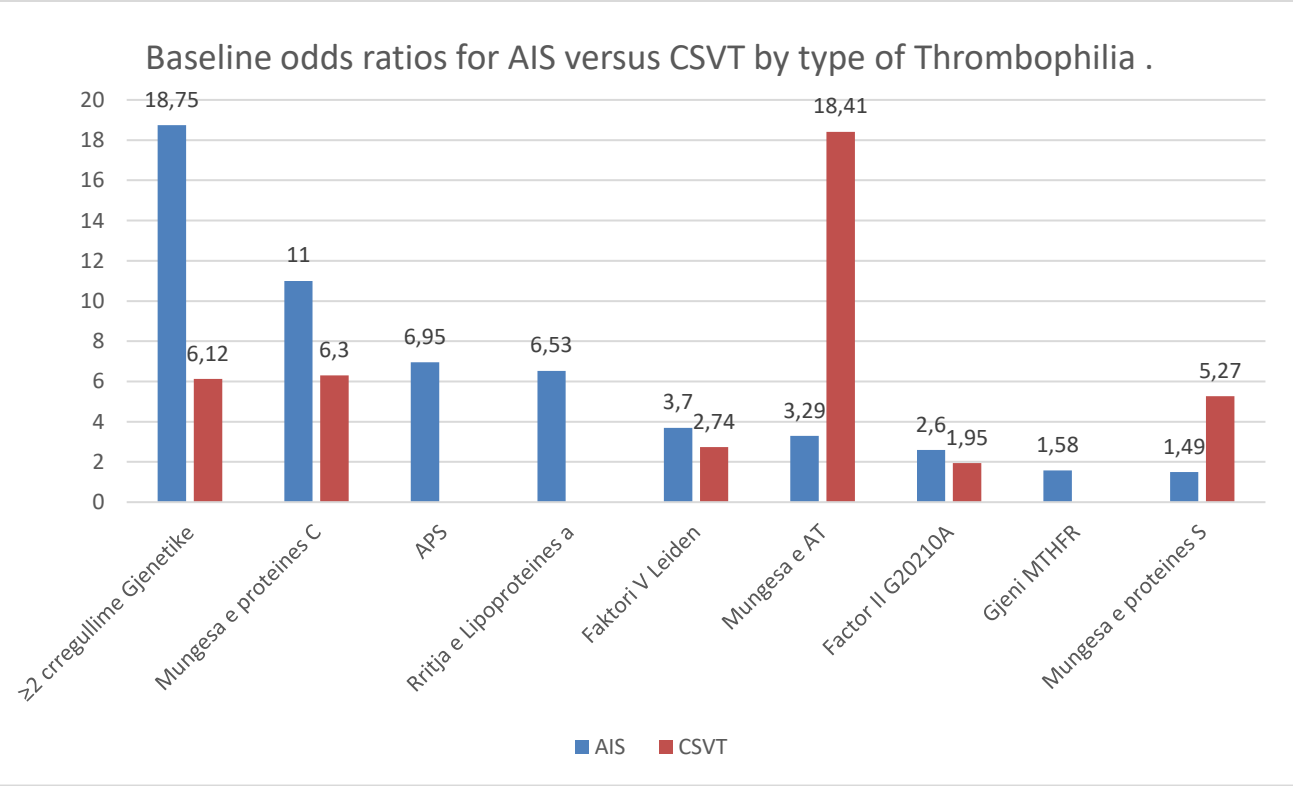
Guy Young, MD, Manuela Albisetti, MD, Mariana Bonduel, MD, Leonardo Brandao, MD, Anthony Chan, MD, Frauke Friedrichs, PhD, Neil A. Goldenberg, MD, ... SHOW ALL ..., and Ulrike Nowak-Göttl, MD | AUTHOR INFO & AFFILIATIONS



RESEARCH ARTICLE | Originally Published 12 April 2010 |

Impact of Thrombophilia on Risk of Arterial Ischemic Stroke or Cerebral Sinovenous Thrombosis in Neonates and Children: A Systematic Review and Meta-Analysis of Observational Studies

Gili Kenet, MD, Lisa K. Lütkhoff, Manuela Albisetti, MD, Timothy Bernard, MD, Mariana Bonduel, MD, Leonardo Brandao, MD, Stephane Chabrier, MD, ... SHOW ALL ..., and Ulrike Nowak-Göttl, MD | AUTHOR INFO & AFFILIATIONS



Clinical manifestations

- The clinical expression of a significant thrombophilia is mainly ***venous thrombosis***.
- When a blood clot breaks away and travels to another part of the body, it is called a TE.
- Symptoms depend on where the clot goes.

Site of thrombosis	Symptoms
Limb	Pain and swelling of the affected limb
Superior Vena cava	Headache, neck pain, neck and head edema
Inferior vena cava	Tenderness and edema in the lower limbs, abdominal pain
Splenic vein	Left upper quadrant abdominal pain, splenomegaly
Portal vein	Abdominal pain, splenomegaly
Renal vein	Flank pain and hematuria
Hepatic vein	Right upper quadrant pain, hepatomegaly
Mesenteric vein	Abdominal pain
Pulmonary embolism	Chest pain, cough, respiratory failure, dyspnea
CNS thrombosis	Headache, vomiting, focal neurologic signs, lethargy, asthenia

Molinari, A.C.; Saracco, P.; Cecinati, V.; Miano, M.; Parodi, E.; Grassi, M.; Banov, L.; De Mattia, D.; Giordano, P. Venous thrombosis in children: An emerging issue. Blood Coagul. Fibrinolysis 2011, 22, 351–361. [CrossRef]

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Some of the inherited thrombophilias also manifest with ***arterial thrombosis***.

Most arterial thromboembolism events in children are secondary to catheter use and often occur in neonates with umbilical arterial lines or in patients with cardiac defects undergoing cardiac catheterization.

Patients with an arterial thrombosis in an extremity have a cold, pale, or blue extremity with weak or absent pulses.

Ischemic stroke usually presents with hemiparesis, loss of consciousness, or convulsive seizures.

It may occur in the setting of a pathological process affecting the intracranial arteries (sickle cell disease, arteriopathy, traumatic arterial dissection) or be caused by venous thrombi embolizing into the arterial circulation.

Stepwise approach for diagnosis of thrombophilia .

A detailed anamnesis, a complete history, and physical examination are mandatory in the evaluation of individuals with a recent history of thrombosis.

General examination :

Complete blood count, A peripheral blood smear test, Full Biochemistry Profile,serological tests for autoimmune diseases.
X Ray, Ultrasound with Doppler flow , Spiral CT, CT and MR venography.

Coagulation tests :

Platelet count: Testing for HIT
PT ,aPTT,fibrinogen level
•A prolonged PT or aPTT and/or a low fibrinogen level may suggest disseminated intravascular coagulation;
• a prolonged aPTT at baseline may be due to the use of an inhibitor or lupus anticoagulant)
d dimer children often have other systemic disorders, such as sepsis or malignancy, which may elevate D-dimer concentrations,
a negative D-dimer value can be significant in ruling out a thromboembolism in these patients.

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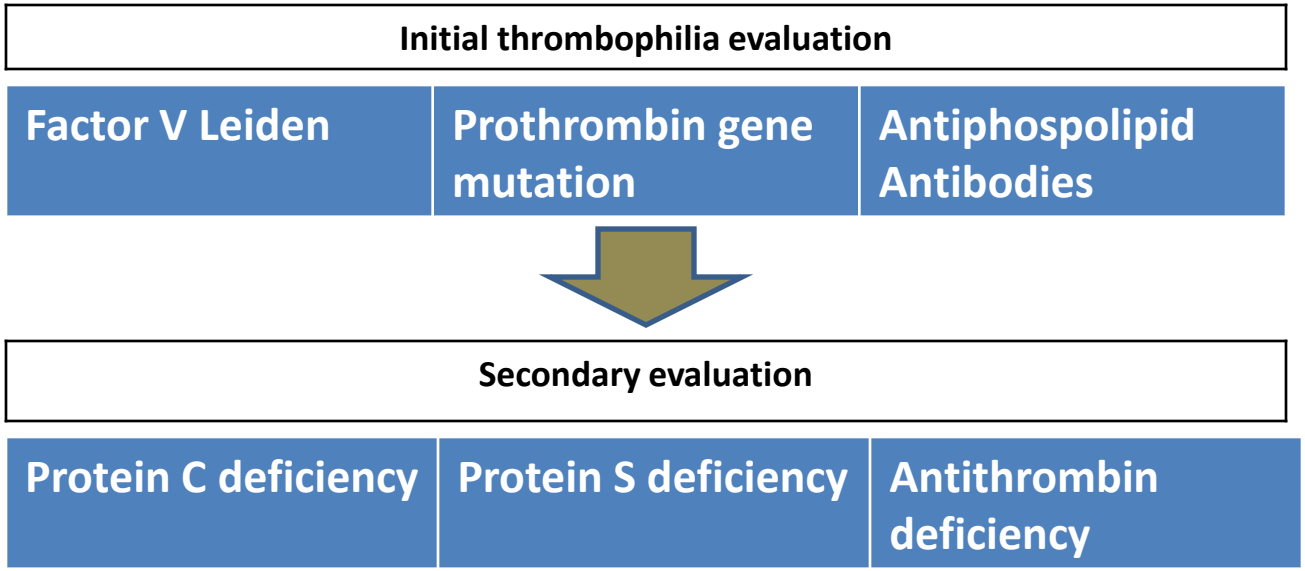
Natural anticoagulant system:



Additional selective testing :

Flow cytometry for PNH,

Analysis for JAK2 mutation (myeloproliferative syndrome), in cases of splanchnic or cerebral venous thrombosis,

Plasma ADAMTS13 activity (Thrombotic thrombocytopenic purpura),

Plasminogen activity.

Why and who

to test for inhereted thrombophilia in the pediatric population.

Why ?

There are three possible arguments to test for thrombophilia in children with a first venous thrombotic event:

First, if there is an association between inherited thrombophilia and the development of pediatric thrombosis, identification of a thrombophilic defect may help to learn why a young patient developed thrombosis, especially if the thrombotic event was unprovoked

Second, testing should be performed if a positive test result will change the patient's management, such as prolongation of anticoagulant prophylaxis of recurrent thrombotic events.

Finally, testing pediatric patient with VTE may help to identify asymptomatic relatives who may avoid thrombotic risk factors and benefit from thromboprophylaxis in high-risk situations.

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Who ?

Thrombophilia testing seems to be advisable in adolescents with unprovoked VTE and in children with a positive family history for VTE and less useful in neonates and children after a first episode of catheter-related VTE.

Thrombophilia testing according to "British Society for Haematology" guideline :

Thrombophilia testing: A British Society for Haematology guideline Deepa J. Arachchillage1,2 | Lucy Mackillop3 | Arvind Chandratheva4 | Jayashree Motawani5 | Peter MacCallum6,7 | Mike Laffan 2022

Stepwise approach for treatment of thrombophilia.

❖ **Treatment of acute venous thromboembolism event**

The management of infants and children with venous thromboembolism has become a daily activity of pediatric hematologists in tertiary care hospitals.

Studies suggest that where possible, pediatric hematologists with experience in thromboembolism (TE) manage pediatric patients with TE . When this is not possible, they suggest a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist.

Treatment options for VTE include observation, anticoagulation, and thrombectomy (pharmacological, pharmaco-mechanical, or surgical)

The American Society of Hematology published guidelines for the treatment of pediatric VTE.

Symptomatic DVT or PE	-Anticoagulation Provoked VTE: treat ≤3 mo (if provoking factor is resolved) Unprovoked VTE: treat 6-12 mo; consider longer duration based on patient's preferences - Avoid thrombolysis (unless life- or limb-threatening) -Avoid IVC filter (unless absolute contraindication to anticoagulation)	Observation may be necessary or reasonable for premature neonates or critically ill children at high risk of bleeding
Asymptomatic DVT or PE	• Anticoagulation or observation	Natural history is not well known; decision is likely to vary based on thrombus location and patient
Massive PE with hemodynamic compromise	• Thrombolysis followed by anticoagulation	
Submassive PE (no hemodynamic instability)	• Anticoagulation alone	
RVT	• Unilateral: anticoagulation alone • Bilateral: consider thrombolysis for bilateral RVT (life-threatening)	
Portal vein thrombosis	• Occlusive: anticoagulation • Nonocclusive: observation (close radiologic follow-up)	
Cerebral sinovenous thrombosis	• Anticoagulation	Decision in patients with intracranial hemorrhage needs to be individualized, but some patients may benefit from anticoagulation

Anticoagulation

The common anticoagulants used in pediatrics

•Dalteparin, a LMWH, was recently approved by the Food and Drug Administration (FDA) for use in pediatric patients >1 month of age, and is the first anticoagulant to receive FDA approval for pediatric VTE.
• Enoxaparin, also a LMWH, is the most frequently used anticoagulant in pediatrics.
•Warfarin remains the mainstay for oral anticoagulation in pediatric patients. Warfarin dosing studies in children have demonstrated that age is the greatest determining factor, and infants require the highest per kilogram dose.
•The 2018 ASH guidelines for pediatric VTE recommend that DOACs not be used in children until clinical trials are completed.

Thrombolysis

The drug used most in pediatrics is alteplase, a recombinant tissue plasminogen activator (rtPA)

Bleeding complications

Protamine is the only reversal agent for UFH and LMWH.
The antidote for warfarin is vitamin K.

❖CVAD-associated VTE.

• Studies suggests that all asymptomatic CVAD-associated thrombosis might not require specific treatment, particularly if the CVAD is removed.
• The ASH guidelines favor leaving the device in place if functional and clinically necessary over removal and placement of a new CVAD.
• If the line is nonfunctional or no longer needed clinically, then removal is recommended.

❖Replacement therapy with AT .

The ASH guideline panel suggests its use in pediatric patients who have failed to respond clinically to standard anticoagulation

❖Homozygous protein C deficiency management

During acute phase protein C concentrates and anticoagulant therapy should be administered rapidly.

The use of warfarin as initial therapy occasionally causes thrombotic cutaneous infarction as a result of decreased levels of vitamin K-dependent protein C.

FFP therapy can result in fluid overload leading to high levels of infant mortality.

Duration of therapy and Prophylaxis

❑ Pediatric guidelines according to the 2018 ASH recommend:

- Treatment of provoked VTE for a maximum duration of 3 months.
- Treatment of unprovoked VTE for a maximum duration of 6 to 12 months.
- Treatment of recurrent unprovoked VTE for an indefinite duration.

❑In asymptomatic individuals with known AT, PC and PS deficiencies, it would be beneficial to administer thrombosis prophylaxis during periods of risk (such as surgery, pregnancy, puerperium, use of OCs, immobility).

Effective treatment should be provided in conditions where fluid loss occurs intensively due to fever, diarrhea, vomiting, and hematocrit increases secondarily, predisposing to thrombosis.

AT replacement therapy will also be used as prophylaxis in high-risk situations in children already confirmed with AT deficiency.

❑The role of acetylsalicylic acid

Recommendations for use:

• Aspirin is a reasonable option for secondary prevention of AIS in children whose stroke is not due to SCD and in children who do not have a high risk of recurrent embolism or a severe hypercoagulable disorder.

• A dose of 3 to 5 mg/kg per day is a reasonable starting dose of aspirin for stroke prevention in children. If side effects related to this dose occur, a dose reduction to 1 to 3 mg/kg may be considered.

• In children taking aspirin for stroke prevention, it is reasonable to vaccinate them with the annual influenza vaccine to reduce the risk of Reye's syndrome. It is reasonable to stop using aspirin during influenza and varicella infections.

Presentation of our clinical case.

The Patient F.M., born on 12/09/2018 from Elbasan, was admitted to the Pediatric Intensive Care Unit, QSUNT on 29/01/2022 with these complaints :
Drowsiness, generalized tonic-clonic seizures, subfebrile temperature.

The history of the disease began three days ago, on 01/26/2022, where the child presented to the Pediatric Emergency Department of Elbasan with a condition of lipotimia. During his stay in the hospital, the child was drowsy, with a subfebrile temperature, and on 01/28/2022, the child had a generalized tonic-clonic convulsive seizure and then came with a follow-up epicrisis and then he was hospitalized in our hospital ,QSUNT.

Physical exam : Initial assessment revealed an illappearing. The degree of alertness: AVPU. Afebrile. Clean skin without pathological elements, with preserved turgor and elasticity, without bruises . Isochoric and photoreactive pupils. Neck with slight rigidity. Positive Brudzinski. Heart is with rhythmic tones. Full pulse. Calm respiration without dyspnea, without polypnea. A negative lung auscultation. Soft abdomen on palpation. Liver and spleen within normal limits. Limbs without edema. Deep Tendon reflexes present.

Medical history: He is the third child and has been vaccinated according to the vaccination schedule. He is under the care of the State Social Service "Bijat e Dashurise " – Mollas.

Family history: The child's mother died in October 2019. The child's grandfather reports that she often went to the hospital with epileptic seizures.

Laboratory values (29/01/2022)

Complete blood count:
RBC- $4.85x10^6$ /mm3, Hgb-12.5g/dl, Hct-38.6%, WBC-9.5K/uL, Neutrophils -5.2K/ul, Lymphocytes-3.4K/uL, PLT-204mije/mm3.
Basic metabolic panel: Glucose-67mg/dl , Urea-22.2mg/dl , Creatinine -0.52mg/dl, total bilirubin -0.26mg/dl, total protein -6.9 g/dl, Albumin- 4 g , ALT- 23U/L, AST- 32U/L, ALP – 112U/L , LDH-348 U/L, CK- 75U/L, PCR- 0.29 mg/dl, Na – 135mmol/l , K -4.4 mmol/l , Cl- 100 mmol/l .
Coagulation tests : PT – 83 %,INR -1.13 ,aPTT-22.7 sec, Fibrinogjen : 315 mg/dl
Lumbar puncture test : Number of cellls – 2 /mm3 ,Glucoz CSF -47 mg/dl ,protein CSF-240mg/dl Sterile culture.
Urinalysis : Eritrocite- 12 HPF,Leukocite -5 HPF.

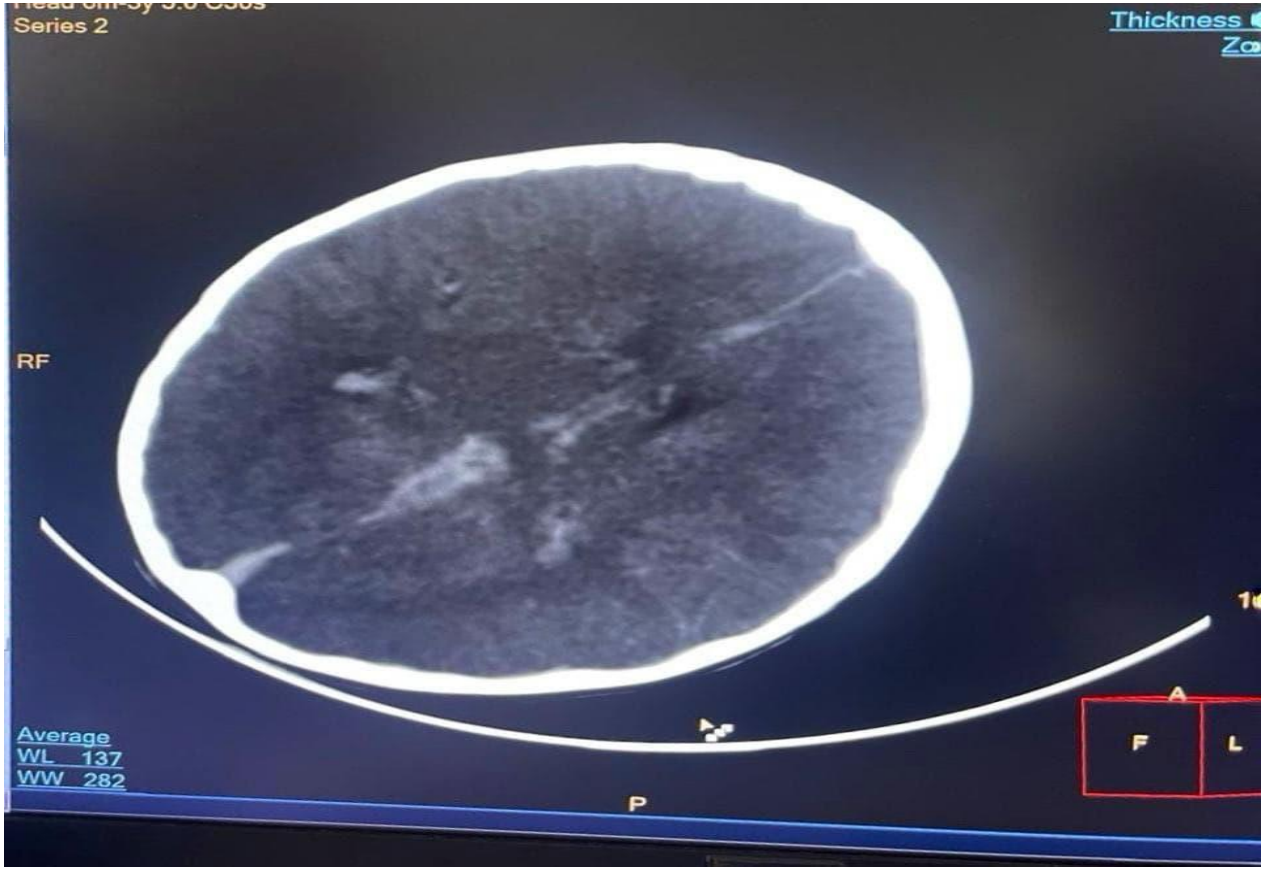
Imaging examination

A non-contrast Cranial CT scan (performed at Elbasan hospital)

CT shows hypodensity at the level of the rectus sinus , with an aspect in favor of a sinus thrombosis. No lesions of the cerebral and cerebellar tissue.

A contrast Cranial CT scan (performed at QSUNT) on 29/01/2022

CT shows a filling defect in the rectus sinus with an aspect in favor of a sinus thrombosis.



After hospitalization, the child was started on this intravenous treatment :

Ceftriaxon
Acyclovir
Omeprazole
Phenobarbital
Mannitol
Liquids with electrolytes
and **Enoxaparin SC 16 mg – 16000 UI 2 x SC**

The clinical condition gradually begins to improve and on 03/02/2022 he is transferred to the neuropediatric department.

Physical exam on 07/02/2025 The child had a better general condition, afebrile, active. In the neurological examination there was normal mental status, cranial nerves, coordination, and motor status.Heart with rhythmic tones. Respiration is calm, in vesicular auscultation. Soft abdomen, Liver and spleen within normal limits. Limbs without edema.

Laboratory value 07/02/2025

Complete blood count : RBC- 4.58x10^6 /mm3, Hgb-11.9g/dl, Hct-36.5%, WBC-8.8K/uL, Neutrophils -3.6K/ul, Lymphocites-4.4K/uL, PLT-572mije/mm3.

Basic metabolic panel Glucose-81mg/dl ,Urea-31.5mg/dl , Creatinine -0.47mg/dl, Total bilirubin -0.19mg/dl, total protein-7.2 g/dl, ALT- 25U/L, AST- 28 U/L, ALP – 128U/L , LDH-305U/L, PCR- 0.11mg/dl ,Na – 134mmol/l ,K -4.4 mmol/l , Cl- 102 mmol/l .

Coagulation tests : PT – 110%,INR – 0.94, aPTT – 23 sec ,Fibrinogjen -341 mg/dl

Treatment 07/02/2025

IV,Omeprazol IV,Acyclovir oral,**Aspirin 50 mg x1 ,**Depakin oral.

The child is discharged from the hospital on 08/02/2025

After being discharged from the hospital, the child was transported to the "Ospedale Bambino Gesu" in Rome.

The results of the analysis were as follows : (on 28/02/2022)

D dimer - 0.27ug/ml (<0.50)

Fibrinogjen- 233mg/dl (162-400)

$aPTT_{sec}$ - 27.6 (28.6-35.8)

$aPTT_{r}$ - 0.94 (0.91-1.13)

PT_{sec} - 15.1 (12.1/14.5)

$PT_{\%}$ - 80 (80-118)

INR - 1.15 (0.92-1.14)

Antitrombina III - 100 (101-131)

Proteina C - 36 (50-134)

Proteina S e lirë – 86 (63-120)

$APTT_{silice}$ - 0.85(0.80-1.20)

dRVVT Screen- 0.84 (<1.20)

APC Rezistence $_{sec}$-186.4 (>120 negative.<120 pozitive)

In this hospital was discovered the cause of the thrombosis that was **Protein C deficiency**. They recommended continuing aspirin treatment for 3 months and rechecking protein C levels.

The child continued treatment with Aspirin for three months
After a laboratory examination of the protein C level in June, it resulted normal and it was recommended to discontinue Aspirin, and to recheck the protein C level every three months.

The child was subsequently followed up in the Pediatric Onco-Hematology Service at QSUNT.

In consultation with the pediatric Onco-Hematologist, based on the history of the disease, clinical manifestations, and family history (the death of the mother at a young age and the neurological manifestations that she has manifested), a retrograde diagnosis of hereditary thrombophilia of protein C deficiency was suspected.

Screening testing was also recommended for the patient's brother and sister, who had not previously manifested thrombotic events.

Laboratory examination of protein C for the other two children in June 2022 respectively:
Child D.M., male, 8 years old: Protein C – 45% {70-160%}
Child V.M., female, 6 years old: Protein C- 50% {70-160%}

Starting Aspirin was recommended for the other two children, respectively ½ for the first child and 1/3 for the other child, for a duration of 3 months.

In the repeat protein C level after three months, on 09/09/2022 for all three children, the results were as follows:

Child F.M: Protein C – 126.7%
Child D.M: Protein C – 95.4%
Child V.M: Protein C – 97.5%

After these results, discontinuation of Aspirin was recommended for the other two children as well as follow-up every three months with the plasma level of Protein C for all three children..

Conclusions

- Thrombophilia is increasingly being diagnosed in pediatric patients, due to greater awareness of this disease, increased survival rates in patients with chronic diseases, and the more frequent use of catheters and interventional procedures.

- It is a multifactorial disease and Incidence is highest in the neonatal period and a second peak is observed in adolescence.

- Among acquired factors, central venous access devices are the most common risk factor.

- Among the congenital factors, the most common cause is Factor V Leiden deficiency, while prothrombin deficiency is the second. Protein C, protein S, and AT deficiencies are rarer, but are associated with a higher risk of thrombosis compared to FV or F II mutations.

- Thrombophilia testing is advisable in adolescents with unprovoked VTE and in children with a positive family history of VTE and less in neonates and children after an episode of catheter-related VTE.
- When testing specific anticoagulant levels, we must consider age-specific reference values on the one hand, as well as the impact of acute thrombosis and anticoagulant therapy on their values.

Recommendations

•We would recommend the pediatricians and family doctors to take a complete and detailed history of a child presenting with thrombotic phenomena, from the moment of birth , including the history of the disease, family history, and knowledge of the signs and symptoms of VTE in order to refer the child to a pediatric hematologist specialist in a timely manner.

• Testing is recommended to predict the risk of recurrence and the possibility of anticoagulant prophylaxis in high-risk situations, especially in patients with antithrombin deficiency where the prevalence of recurrence is higher.

• We should also draw attention to asymptomatic affected relatives who should avoid risk factors such as smoking and obesity, be informed about the thrombotic risks of contraception and pregnancy, and use thromboprophylaxis in other high-risk situations.

• Thrombophilia testing is expensive so it is recommended to perform appropriate testing according to the relevant Guidelines.