Bleeding and Thrombotic Disorders

Bleeding disorders
- von Willebrand disease
- Hemophilia A and B
- DIC
- TTP/HUS
- ITP

Thrombotic disorders
- Factor V Leiden
Platelet bleeding

- Superficial (skin)
- Petechiae
- Spontaneous

Factor bleeding

- Deep (joints)
- Big bleeds
- Trauma *

* Includes prolonged bleeding after dental work
Petechiae
Palatal petechiae
Palatal ecchymosis
Bleeding after buttock injection in patient with hemophilia
Bleeding and Thrombotic Disorders

Bleeding disorders
  • von Willebrand disease
Von Willebrand Disease

Things you must know

- Most common hereditary bleeding disorder
- Autosomal dominant
- vW factor decreased (or abnormal)
- Variable severity
What’s von Willebrand Factor?

- Huge multimeric protein
- Made by megbs and endothelial cells
- Glues platelets to endothelium
- Carries factor VIII
- Decreased or abnormal in vW disease
Extrinsic coagulation sequence

Exposure of membrane-bound tissue factor

Platelet adhesion: Held together by fibrinogen

vWF

Collagen
Intrinsic

IX

Extrinsic

TF VII

VIII

X

thrombin

V

fibrin

clot
Symptoms of Von Willebrand Disease

- Mucosal bleeding in most patients
- Deep joint bleeding in severe cases
Lab Tests in Von Willebrand Disease

- Bleeding time: prolonged
- PTT: prolonged ("corrects" with mixing study)
- PT: normal
Treatment of Von Willebrand Disease

- DDAVP (raises VIII and vWF levels)
- Cryoprecipitate (contains vWF and VIII)
- Factor VIII
Bleeding and Thrombotic Disorders

Bleeding disorders
  • von Willebrand disease
  • Hemophilia A and B
Hemophilia A

Things you must know

- Most common factor deficiency
- X-linked recessive in most cases (30% are spontaneous mutations)
- Factor VIII level decreased
- Variable amount of “factor” bleeding
BLEEDERS AND CARRIERS OF HEMOPHILIA DESCENDED FROM QUEEN VICTORIA

Only men have the disease.
Inheritance of Hemophilia

“Carrier” Mother and Father Without Hemophilia

Parents

Father (without hemophilia)  
XY

Mother (carrier for hemophilia gene)  
XX

Children

Son (without hemophilia)  
XY

Daughter (carrier for hemophilia gene)  
XX

Son (has hemophilia)  
XY

Daughter (does not carry hemophilia gene)  
XX
Inheritance of Hemophilia
Father With Hemophilia and Mother Who Is Not a Carrier

Parents

Father (with hemophilia) $XY$
Mother (not a carrier) $XX$

Children
Son (without hemophilia) $XY$
Daughter (carrier) $XX$
Son (without hemophilia) $XY$
Daughter (carrier) $XX$
Intrinsic

Extrinsic

VIII

IX

TF VII

X

thrombin

V

fibrin

clot
Deep joint bleeding in patient with hemophilia
Hemophilic arthropathy of knee

Normal knee

Knee of patient with hemophilia

Hemophilic arthropathy of knee
Joint Deformity in Hemophilia
Hemophilia A

Lab tests
• PTT prolonged
• Factor VIII level low
• DNA studies abnormal

Treatment
• DDAVP
• Factor VIII
Hemophilia B

Things you must know

• Factor IX level decreased
• Much less common than hemophilia A
• Same inheritance pattern
• Same clinical and laboratory findings
The diagram illustrates the coagulation cascade. The intrinsic pathway is represented by the yellow block labeled IX, which is activated by VIII. The intrinsic pathway leads to the formation of thrombin, which further activates fibrin to clot. The extrinsic pathway is represented by the gray block labeled TF VII, which is activated by TF. Both pathways converge at thrombin, forming fibrin and clot.
Bleeding and Thrombotic Disorders

**Bleeding disorders**
- von Willebrand disease
- Hemophilia A and B
- DIC
Thrombosis

Hemorrhage
Remember these for sure:

- Malignancy
- OB complications
- Sepsis
- Trauma
Bleeding and Thrombotic Disorders

Bleeding disorders
- von Willebrand disease
- Hemophilia A and B
- DIC
- TTP/HUS
Thrombotic Thrombocytopenic Purpura

Things you must know

• Pentad: MAHA, thrombocytopenia, fever, neurologic defects, renal failure

• Deficiency of ADAMTS13

• Big vWF multimers trap platelets

• Plasmapheresis or plasma infusions
Cleaved unusually large multimers of von Willebrand factor

ADAMTS 13

Endothelial cell

Secretion of multimers from Weibel–Palade body

Adhesion and aggregation of platelets

Uncleaved unusually large multimers of von Willebrand factor

ADAMTS 13

Endothelial cell

Secretion of multimers from Weibel–Palade body
Nasty creatures

Rodent of unusual size (ROUS)
- *The Princess Bride*, 1987

Von Willebrand multimer of unusual size (MOUS)
- *NEJM*, 1982
Thrombotic Thrombocytopenic Purpura

Clinical pentad

• Hematuria/jaundice (MAHA)
• Bleeding/bruising (thrombocytopenia)
• Fever
• Bizarre behavior (thrombi in CNS)
• Renal failure (thrombi in kidney)

Treatment

• Plasmapheresis (in acquired TTP)
• Plasma infusions (in hereditary TTP)
Hemolytic Uremic Syndrome

Things you must know

- MAHA and thrombocytopenia
- Most are related to E. coli infection
- Toxin damages endothelium
- Treat supportively
Bleeding and Thrombotic Disorders

Bleeding disorders

- von Willebrand disease
- Hemophilia A and B
- DIC
- TTP/HUS
- ITP
Idiopathic Thrombocytopenic Purpura

Things you must know

- Antiplatelet antibodies coat platelets
- Splenic macrophages eat platelets
- Diagnosis of exclusion
- Steroids or splenectomy
Bruising after minor trauma in ITP
Bleeding and Thrombotic Disorders

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Thrombotic disorders
• Factor V Leiden
Blood clot sequelae
Deep venous thrombosis
Deep venous thrombosis
Pulmonary embolus
Thrombosis Risk Factors

**Endothelial damage**
- Atherosclerosis

**Stasis**
- Immobilization
- Varicose veins
- Cardiac dysfunction

**Hypercoagulability**
- Surgery
- Carcinoma
- Estrogen/postpartum
- Thrombotic disorders
When should you worry about a hereditary disorder?

- no obvious cause
- family history
- weird location
- recurrent
- patient is young
- miscarriages
Factors V and VIII Leiden

Things you must know

• Most common cause of unexplained thromboses
• Inherited point mutation in factor V gene
• Factor V can’t be turned off
• High risk of thrombosis if homozygous
What is Factor V Leiden?

A mutated factor V gene
• Single point mutation
• Discovered in Leiden, Netherlands

Produces abnormal factor V
• Participates in the cascade
• Can’t be cleaved by protein C
Yeah, so?

You can turn it on...

...but you can’t turn it off!
Intrinsic

IX

VIII

V

Va

thrombin

fibrin

clot

Extrinsic

TF

VII
Intrinsic

VIII → VIIIa → IX

Extrinsic

TF VII → X

V → Va → X

thrombin

fibrin

clot

protein C
What is the risk of getting a clot?

- Heterozygotes: 7 times normal
- Homozygotes: 80 times normal
- Normal risk = 5 per 100,000 person-years!
Factor V Leiden

Diagnosis

• PTT and INR not helpful
• Need genetic testing

Treatment

• Don’t! Unless there is a thrombosis.
• Then give oral anticoagulants