Bleeding and Thrombotic Disorders
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Bleeding and Thrombotic Disorders

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

Thrombotic disorders
  • Factor V Leiden
<table>
<thead>
<tr>
<th>Platelet bleeding</th>
<th>Factor bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Superficial (skin)</td>
<td>• Deep (joints)</td>
</tr>
<tr>
<td>• Petechiae</td>
<td>• Big bleeds</td>
</tr>
<tr>
<td>• Spontaneous</td>
<td>• Trauma *</td>
</tr>
</tbody>
</table>

* Includes prolonged bleeding after dental work
Petechiae
Palatal petechiae
Palatal ecchymosis
Purpura
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 megas and endothelial cells
- Glues platelets to endothelium
- Carries factor VIII
- Decreased or abnormal in vW disease
Platelet adhesion: Held together by fibrinogen
Intrinsic

Extrinsic

thrombin

fibrin

clot

VIII
IX

V

X

TF
VII
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)  Mother (not a carrier)
XY                      XX

Children

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

IX

VIII

Extrinsic

TF VII

V

thrombin

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
Intrinsic

IX

VIII

V

Extrinsic

TF

VII

thrombin

fibrin

clot
Bleeding and Thrombotic Disorders

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• Hemophilia A and B
• DIC
Widespread activation of coagulation

Endothelial damage

Generalized platelet aggregation

Microthrombi in the circulation

CLOTTING FACTORS

PLATELETS

FDPs
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
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
Factor V 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
You can turn it on…

…but you can’t turn it off!
Intrinsic

IX

VIII

V

Va

thrombin

Extrinsic

TF

VII

X

fibrin

clot
The diagram illustrates the process of blood clotting, which can occur through Intrinsic or Extrinsic pathways.

**Intrinsic Pathway**
- **VIII** → **VIIIa**
- **IX**
- **V** → **Va**
- **X**
- Thrombin
- Fibrin
- Clot

**Extrinsic Pathway**
- **TF**
- **VII**
- **X**
- Thrombin
- Fibrin
- Clot

The Intrinsic pathway involves the activation of factor VIII (VIIIa), which leads to the activation of factor IX (IX). The Extrinsic pathway involves tissue factor (TF) and factor VII (VII), which activate factor X (X) to form thrombin. Thrombin then converts fibrinogen to fibrin, leading to clot formation.
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