



Inherited Bleeding Disorders

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Objectives

- ❁ **To understand the key components of a bleeding history**
- ❁ **To be able to state the inheritance pattern, clinical features, laboratory evaluation and treatment for the most common hereditary bleeding disorders.**
- ❁ **To identify critical factors influencing family coping skills with chronic illnesses**

Causes for Deficiencies of Clotting Factors

• Impaired production

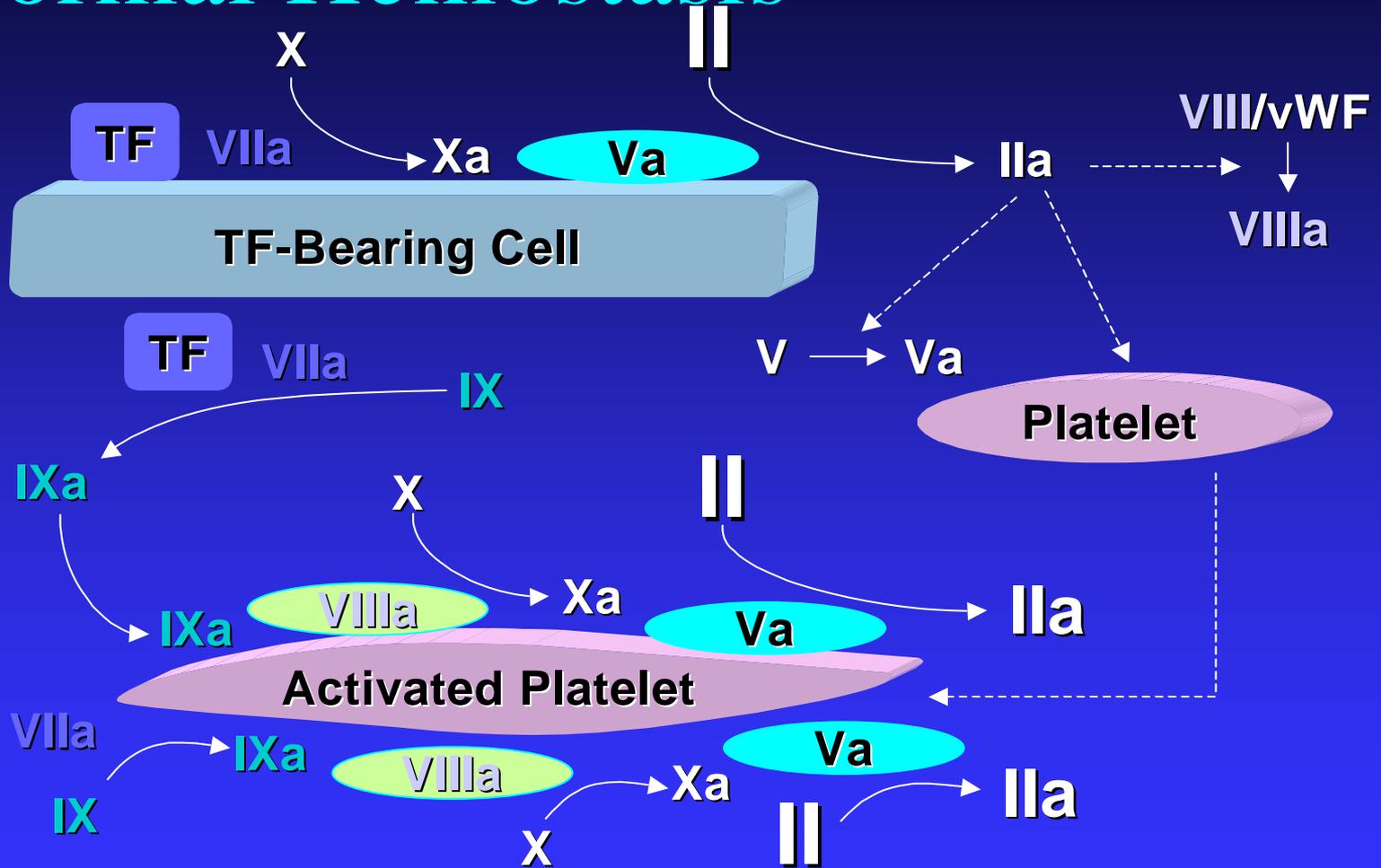
- Hereditary absence of protein or abnormal protein
- Vitamin K (deficiency or antagonism-- coumadin)
- Liver disease

• Increased use of clotting factors (ie. DIC)

• Inhibition of clotting factors

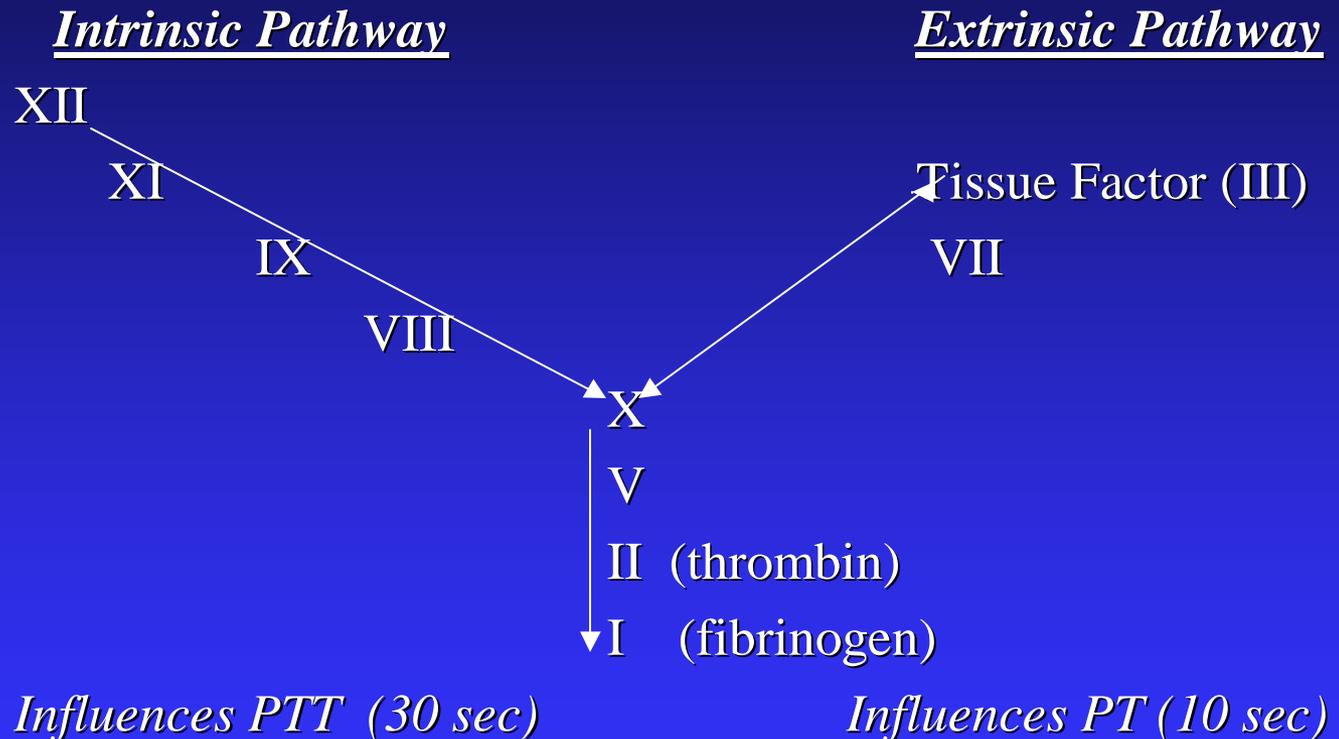
- Anticoagulants (heparin)
- Circulating inhibitor or anticoagulant

Normal Hemostasis



Hoffman et al. *Blood Coagul Fibrinolysis* 1998;9(suppl 1):S61.

Clotting for Dummies



* No IV (really Ca)

*No VI (really V)

Basic Laboratory Tests of Coagulation

• aPTT (activated partial thromboplastin)

- 25-30 sec
- Affected by V, VIII, IX, X, XI, XII
- used to monitor heparin therapy

• PT (prothrombin time)

- 11-13 sec
- Affected by II, V, VII, X
- used to monitor coumadin therapy

Lab testing (continued)

• Mixing studies (1:1 mix)

- Mix normal plasma with patient plasma; minimal factor concentrations should be 50%
- If corrects, factor deficiency.
- If does not correct, inhibitor present.

• Fibrinogen level

- 170-400 mg/dl
- low/abnormal with afibrinogenemia, DIC, liver disease



Hereditary Coagulopathies

a brief review

Von Willebrand Disease

- ⊗ **Inheritance:** usually autosomal dominant
- ⊗ **Incidence:** 1:100
- ⊗ **Sx:**
 - » mucosal bleeding
 - » epistaxis
 - » easy bruisability/hematomas
 - » menorrhagia

Von Willebrand (cont)

⊗ Dx:

- prolonged bleeding time
- prolonged PTT
- decreased platelet aggregation with ristocetin
- decreased FVIII, VWF antigen and activity
- abnormal multimers
- ****Mild disease may not be evidenced by abnormal labs

⊗ Tx; DDAVP, cryoprecipitate, factor

Hemophilia A: Factor VIII

- **Inheritance: x-linked**
- **incidence: 1:10,000 live males**
- **SX:**
 - **Joint bleeds (knee, elbow, ankle)**
 - **Muscle bleeds (forearm, calf, ileopsoas)**
 - **Any organ can be affected and therefore life-threatening**

Hemophilia A (cont)

☼ DX:

- prolonged aPTT
- decreased FVIII assay
- carrier testing available

☼ Tx:

- recombinant Factor VIII
- DDAVP in mild cases

Hemophilia B: Factor IX Deficiency

- **Inheritance:** x-linked
- **Incidence:** 1:100,000 live males
- **Sx:** as with Hemophilia A
- **Dx:**
 - prolonged aPTT
 - decreased FIX assay
 - carrier testing available
- **TX:** recombinant Factor IX concentrate

Severity of Hemophilia

- Severe: less than 1%
- Moderate: 2-5%
- Mild: greater than 5%

Relationship of Severity and Age to Symptoms

⊗ Severe:

- most diagnosed by age four
- spontaneous or with trauma

⊗ Moderate

- may have spontaneous bleeds, but usually with trauma

⊗ Mild “clinically silent”

- almost always with trauma/surgery
- often diagnosed after age 10 (oral surgery, T&A)

Relationship (cont)

⊗ Neonatal:

- circ/cord/blood draw
- cephalohematoma, CNS

⊗ Infancy:

- palpable subcutaneous ecchymoses over bony prominences
- frequent bruising as crawl/walk
- hematomas with IM immunizations
- oral mucosal bleeds--days or even weeks!

⊗ Toddler

- soft tissue
- periarticular



Relationship (cont)

- **Preschool**

- muscle/joint

- **Childhood/Adolescence**

- muscle/joint

Complications: Inhibitors

• Definition

- Immune system response to “foreign” factor
- Alloantibodies against Factor VIII or Factor IX, usually IgG immunoglobulins

• Prevalence

- 20-30% of patients with severe hemophilia A
- 1-4% of patients with severe hemophilia B

Terms related to inhibitors

• **Anamnestic response**: a rise in the inhibitor concentration following the infusion of factor concentrate

• **Titer**:

- **High**: ≥ 10 BU
- **Low**: < 10 BU

• **Responders**:

- **Low**: titers do not increase with infusions
- **High**: titers do increase with infusions

Who gets inhibitors?

- **Severity**—more exposure to factor
- **Age**---highest rate from ages 3-7 years
- **PUPS**---higher rate than Non-PUPS
- **Genetics**
 - African Americans
 - Sibling
- **Product use**

Immune Tolerance

Repetitive infusions of factor concentrate to modify the pathological immune response

• Protocols vary on dose and frequency

- 100 u/kg/12 h to 100/u/kg/weekly
- With or without IVIG, cytoxan, rituximab, plasmapheresis

Tentative conclusions re: IT

- Inhibitor levels at enrollment are a better predictor of outcome than type of response (max inhibitor level); success >65% if <10 BU
- Higher doses generally yield faster results
- Long-term maintenance for suppression generally recommended

Rare Hereditary Coagulopathies

- **Inheritance: Autosomal recessive**
- **Factor I: fibrinogen**
 - **two types: quantitative/qualitative**
 - **Sx: lifelong bleeding**
 - » bruising, difficulty with ovum implantation, may have thrombotic complications
 - **Dx: prolonged PT and aPTT, long BT**
 - **Tx: cryoprecipitate**

Rare Hereditary Coagulopathies

FII

- two types: quantitative/qualitative; severe post surgical and trauma bleeding
- DX: prolonged PT and aPTT, \downarrow FII
- TX: FFP

FV

- may or may not have bleeding sx
- prolonged PT and aPTT, \downarrow Fv
- treated with FFP if bleeding

Rare coagulopathies (cont)

• FVII

- heterozygotes usually asymptomatic
- Dx: prolonged PT \rightarrow FVII
- SX: menorrhagia, epistaxis, bruising
 - may be similar to hemophilia
- Tx: rFVIIa, PCCs, FFP

• FX: two types (qualitative, quantitative)

- Dx: prolonged PT and aPTT, \rightarrow FX
- SX: umbilical stump bleeding, similar to hemophilia
- Tx: PCCs, FFP

Rare coagulopathies (cont)

FXI

- Ashkenazi Jews
- SX: variable, unpredictable
- Dx: prolonged aPTT, decreased XI
- Tx: FFP/ concentrate in Europe

FXII

- no hemorrhagic diatheses, no tx

Rare coagulopathies (cont)

FXIII

- **SX:**
 - umbilical stump bleeding
 - poor wound healing, delayed bleeding, fertility problems
 - high incidence of CNS bleeds
- **Dx**
 - prolonged PT and aPTT; abnormal clot stability in 5M urea
- **Tx:**
 - FFP or cryoprecipitate; long half-life; prophylaxis

Components of Bleeding History

- **Demographics**
- **Medical background**
 - medications
 - chronic health conditions
- **Bleeding history**
 - **Bruising**
 - compare to other children
 - location
 - size
 - frequency

Components of Bleeding History

☼ Nosebleeds

- frequency
- severe (cause anemia?, soak pillow?)
- Unilateral or bilateral

☼ Cuts/scrapes

☼ Oral

- gum bleeding
- with brushing teeth
- more than once/mo; more than one hour
- tongue or mouth bleeding

Components of Bleeding History (continued)

• Joint bleeding

- swollen, warm, tender joints
- Which joints?
- Associated with trauma/surgery
- How often?

• Surgery

- Excess bleeding noted by surgeon?
- Transfusion required?

Components of Bleeding History (continued)

• Menses

- How many pads/tampons on heaviest/lightest days? How many days?
- Ever needed transfusion? Ever anemic?

• Neonatal history

- Bleeding from circ/cord?
- Bruises at birth? If so, where?

• Family history



Family/Patient Perspective

- Genetic nature
- Home infusion
- Blood borne pathogens
- Comprehensive care
- Financial constraints
- "Normalcy of life"--daycare, school, sports, discipline
- Future hopes



Psychosocial Issues

Hemophilia, like all chronic illness, affects patients and families at multiple levels beyond just the biological aspect of missing clotting factor.

Illness affects families emotionally, financially, socially, and physically. Role disruption and adaptation can be a constant. Families adjust from the image they had of their child, family, life to a reality that is likely different from the “way it’s supposed to be”.

Psychosocial Issues

Common issues in Hemophilia:

- ⊗ Emotional- Guilt, fears, ↑ stress in family.
- ⊗ Financial- Very expensive disorder, getting and keeping health insurance is a big issue. Parents ability to work may be affected.
- ⊗ Social/Developmental- Sports, school, etc.-balance protecting child and letting them be “normal”.
- ⊗ Family- Impacts on parents individually and as a couple, siblings and extended family members reactions.
- ⊗ Physical- Learning to manage disorder, infusing, etc.