**Review of Bleeding Disorders**

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No Disclosures

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**Case 1**

- A 20 year college student is home on spring break and needs two impacted wisdom teeth removed
- Her mother has a “bleeding disorder” characterized by heavy menses, bleeding after delivery and wants her evaluated preop
- The patient has no personal history of any bleeding and has normal menses

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**Case 1**

- She has had no previous surgery and is on no medications except oral contraceptives
- Physical Exam is completely normal
- Screening labs show:
  - normal CBC
  - PT 11” (INR 1.1)
  - PTT 36” (normal up to 35”)

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**Did you make the correct decision?**
**What if anything should be done?**

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**Case 2**

- A 55 yo woman comes in complaining of “easy bruising”
- She states that she had black and blue marks on her arms, legs
- She has no other bleeding, had two uneventful pregnancies
- Has had longstanding arthritis in hands, feet and takes Aleve, Advil
- Recently started taking 81 mg ASA tablets to protect her heart.

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**Case 2**

- Physical exam shows multiple ecchymoses on arms, legs, back of hands
- Heberden’s nodes and other osteoarthritic changes in hands
- Screening lab tests:
  - Hb 12.5, Hct 36%, platelet count 450,000
  - WBC 9500 65% PMNs, 30% lymphs
- You decide to order platelet aggregation tests
Case 2 – Platelet aggregation

Red – patient
Blue—control

Case 2

• What is the likely diagnosis?
• What are the next steps you should take?
• What advice would you give your patient if she needs future surgery?
• How can she get rid of the annoying black and blues?

Brief Review of Hemostasis

• Primary hemostasis
  • Vessel wall injury
  • Platelet adhesion: vWF, collagen, GpIIb
  • Activation, secretion
  • Aggregation: GpIIb/IIIa, fibrinogen

• Secondary hemostasis
  • TF/VIIa key regulator
  • Thrombin generation/fibrin formation major events
  • "All the rest is details"

Mucocutaneous vs. delayed bleeding

Primary Hemostasis -- platelets, vasculature, mucocutaneous bleeding
  a. Easy bruising
  b. Epistaxis
  c. Early bleeding after tooth extraction
  d. Intra- or post-op bleeding
  e. Menorrhagia
  f. Specific medications (ASA, NSAIDS)

Secondary Hemostasis -- delayed bleeding, lack of fibrin formation/stabilization
  g. Late bleeding after tooth extraction or surgery

Platelet Activation

Discoid Platelet → Activated Platelet → Granule Secretion

Adhesion to collagen
Signaling
Shape change
Granule movement
GpIIb/IIIa binding
to vWF

PLATELETS
Platelet GpIIb/IIIa
vWF

ADHESION
ADP
TXA2

RELEASE
Platelet GpIIb/IIIa
Fibrinogen

AGGREGATION
GpIb/IX/V
Receptor for vWF
Bernard-Soulier syndrome
Autosomal recessive
Presents early in life
Muco-cutaneous bleeding
Giant platelets, thrombocytopenia

GpIIb/IIIa
Receptor for fibrinogen
Glanzmann’s thrombasthenia
Autosomal recessive
Presents early in life
Muco-cutaneous bleeding
Normal platelet count

Platelet Granules
Dense Granules
– Contain ADP, ATP, calcium and serotonin
– Release recruits additional platelets to plug
  • Deficiency in δ-SPD → a mild bleeding disorder
  • Platelet function studies may show absent secondary wave with epinephrine, low dose ADP →
Alpha Granules
– Contain vWF, PDGF, PF-4, VEGF among other proteins
– Release promotes clot maturation, angiogenesis and wound healing
  • Deficiency in α-SPD → a mild bleeding disorder
  • Variable aggregation defects

Major Platelet Defects
• Membrane disorders-- Bernard-Soulier, Thrombasthenia
• ADP receptor
• Collagen receptor
• Granules -- storage pool disease
• Signaling disorders
• Platelet coagulant function

Some Drugs Affecting Platelets
• Aspirin, NSAIDs
• Antithrombotics --- Integrilin, Abciximab, Clopidogrel
• Penicillins (high doses), misc. other drugs
• Alcohol
• Heparin

The Bleeding History
• Personal History
  – location of bleeding
  – surgical procedures
  – menstruation/childbirth
  – transfusion requirement
• Family History
• Medication History

Platelet Aggregation Studies
Platelet-rich plasma from patient
Epinephrine
ADP
Collagen
Arachidonate
Ristocetin (RIPA)
Aggregation to Epinephrine/ADP

Light transmission

Primary Aggregation Wave

Secondary Aggregation Wave

Time

Platelet Function Studies

<table>
<thead>
<tr>
<th>Epineph</th>
<th>Collagen</th>
<th>ADP</th>
<th>Arach</th>
<th>Histo</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Absent</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>GpIia def</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
<td>vWD</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Normal</td>
<td>Glukaragakis's (Gplb/vIia def)</td>
</tr>
<tr>
<td>Second wave absent</td>
<td>Normal or decreased</td>
<td>Second wave absent</td>
<td>Absent</td>
<td>Normal</td>
<td>Aspirin, Storage pool deficiency</td>
</tr>
</tbody>
</table>

Secondary Hemostasis: Coagulation

Fibrin stabilizes platelet plug

Coagulation Cascade Screening Tests

aPTT PT TT

Mixing Studies: Diffentiate factor deficiency vs. inhibitor

Mix at 1:1 (Normal:Patient)

Incubate 2 h at 37°C

Normal Plasma Patient Plasma

Correction: factor deficiency Does not correct: inhibitor
Inhibitors

- Lupus Anticoagulants
- Specific Factor Inhibitors
  - Associated with congenital hemophilia
  - Acquired inhibitors -- rare, elderly

Thrombocytopenia

Evaluation for ITP

- All Patients
  - CBC with review of smear
  - ANA
  - HIV testing
- For Patients with Atypical Features
  - bone marrow biopsy

Differential Diagnosis

- Immune Thrombocytopenia Purpura
- Thrombotic Thrombocytopenia Purpura
- DIC
- Drug Effect
- Primary Bone Marrow Disorder
- Pseudo-thrombocytopenia

Heparin-induced Thrombocytopenia (HIT)

- > 50% fall in platelet count
- Usually 4 days after start of heparin
- Venous thromboembolism
- Re-exposure can occur after 1 day of heparin
- 90% of suspected cases are something else

Pathogenesis of HIT

- Heparin-PF-4 antibody complex
- Only complexes with IgG are pathogenic
- Bind to platelet Fc gamma IIa receptor and cause platelet activation
- Immunogenicity UFH >> Low Mr heparin >> fondaparinux
- 15% --- <1% --- ? (several cases)
The 4 “T”s

<table>
<thead>
<tr>
<th>Test</th>
<th>True Positive</th>
<th>True Negative</th>
<th>False Positive</th>
<th>False Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count &lt;50% or platelet count &lt;20</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Timing of platelet fall</td>
<td>Close to the event time or &gt;4 weeks</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
| Diagnosis of HIT

- Check Pre-test probability with “4 Ts”
- If < 3 no testing is needed
- Heparin-PF-4 ELISA has high NPV
- If test is negative patient does not have HIT
- If OD is <1.0 in ELISA most likely antibodies are not platelet-activating
- If OD is >1 antibodies are likely to be platelet activating

The Hemophilias

- Factor VIII Deficiency (Hemophilia A)
- Factor IX Deficiency (Hemophilia B)
- Factor XI Deficiency
- Other Factor Hereditary and Acquired Factor Deficiencies

Factor VIII Deficiency

- Frequency 1:5000 live male births (X-linked)
- About one-quarter of mutations are spontaneous
- Currently about 15,000 cases in U.S.
- Definitions (% of normal factor level):
  - Mild 5 to 30%
  - Moderate 1 to 5%
  - Severe ≤ 1%

Factor IX Deficiency

- About 1:25,000 live male births (X-linked)
- Similar breakdown into mild, moderate, and severe as for Hemophilia A
- Inhibitors develop less frequently

Hemophilia Management

- In an emergency (i.e. after head trauma or with significant bleeding) give factor first and ask questions later
  - Relevant questions are type of hemophilia and whether there is a known inhibitor
  - Patients tend to know when they need treatment --- listen to them
**Factor XI Deficiency**

- Autosomal Transmission
- Higher prevalence in Ashkenazi population which may approach 1:1000
- Levels do not necessarily correlate with bleeding (patients may bleed with levels above 30%)
- Patients may present late in life with no prior bleeding history

**Factor VIII Inhibitors**

- Congenital Hemophilia
  - develop in about 5 to 10% of children early in the course of treatment
  - low titer versus high titer responders
- Acquired Hemophilia
  - idiopathic, associated with malignancy, rheumatologic disease and pregnancy
  - soft tissue bleeding predominates

**von Willebrand Factor**

- Large multimeric plasma protein
- Also present in endothelial cells, platelets and subendothelium
- Intravascular carrier for AHF- Factor VIII
- Links platelets to vascular wall subendothelium

**von Willebrand Factor Levels**

- ABO blood linkage: levels in AB > A, B > O
- von Willebrand Factor and Factor VIII are acute phase reactants & levels vary over time
  - cannot assess in the setting of stress
  - strenuous exercise can elevate levels
  - von Willebrand Factor levels increase throughout pregnancy, decline rapidly postpartum

**vWD Subtypes**

- Type 1 is difficult to diagnose because it is mild. Persons with Type O blood have lower VWF levels.
- Type 2 VWD are functional disorders and one particular type, 2N, can behave like hemophilia A.
- Type 3 VWD is very severe and clinically presents like a combination of hemophilia A and vWD

**Therapy for vWD**

- Desmopressin (ddAVP)
  - synthetic analogue of vasopressin
  - transiently increases vWF and Factor VIII in plasma
- ε-aminocaproic acid (Amicar)
  - antifibrinolytic amino acid (lysine analogue)
- Intermediate-purity factor concentrates
  - Humate-P
When to Use What

- Desmopressin (ddAVP)
  - Mild Type I disease for most procedures
  - Moderate Type I disease for minor procedures
  - Mild Type IIA disease for minor procedures
- Intermediate purity factor concentrates
  - Moderate/severe Type I disease for major procedures
  - All other procedures in Type IIA patients
  - All significant procedures in Type IIB patients

Which of the following make it unlikely that a patient has heparin-induced thrombocytopenia?

a) Clinical 4T score <3
b) Negative Heparin-PF-4 ELISA
c) Treatment with fondaparinux
d) All of the above

Answer to question #1
d). All of the above

Which of the following statements is true?

a) Patients with Type I von Willebrand’s Disease have occasional hemarthroses (joint bleeding)
b) Factor IX deficiency (Hemophilia B) is an autosomal recessive disorder
c) Patients with Factor XI deficiency are often diagnosed after a post-operative hemorrhage
d) Treatment with DDAVP is effective in patients with Type III von Willebrand’s Disease

Answer to question #2

a) False
b) False
c) True
d) False