Platelet Storage Pool Disease

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10/28/2012
Clinical History

- **Patient:** 23-year-old female
- **Clinical course:** status-post cholecystectomy, complicated by retained common bile duct stones. Following three ERCP procedures to remove stone fragments, she developed hematobilia.
- She also required transfusion of RBC’s due to anemia.
Medical History

- No prior history of blood transfusions or anemia
- Lifelong “easy bruising”
- Nosebleed treated by cautery, age 10
- Irregular menses sometimes lasting a month, with clots
- Family history: Noncontributory
- Drug history: None
Physical Examination

- Grossly bloody stool
- No petechiae or ecchymosis
- No hepatosplenomegaly
Screening Coagulation Laboratory Results

- PT = 10 sec (Normal 8-14.6)
- aPTT = 35 sec (Normal 24-36.5)
- Plt = 254,000 /μL (Normal 150,000-350,000)
- Bleeding time =15min (Normal < 9 min)
Differential Diagnosis

- Asprin and other NSAID, Plavix
- vonWillebrand disease
- Dysfunctional platelets: storage pool disease, Glanzmann thrombasthenia, Bernard Soulier syndrome, uremia
Further Findings

- Medication history: No aspirin and other NSAID, Plavix
- von Willebrand disease: normal vWF and F VIII levels
- Dysfunctional platelets: abnormal platelet aggregation study
Platelet Granule Deficiency: Blood Smear
Platelet Aggregation Study

Ruled out:
- vWD
- Bernard Soulier Syndrome
- Glanzmann Thrombasthenia
- Plavix

Could not rule out:
- NSAIDs
- Platelet storage pool disease
Deficiency of Alpha Granules and Delta Granules: EM
Diagnosis

- Alpha-Delta Platelet Storage Pool Disease
Review of Platelet Functional Anatomy

- **Glycocalyx**: outer surface, rich in glycoproteins
- **Microtubules**: sub-membranous band, protein tubulin, provide structural support
- **Contractile microfilaments**: actin, myosin
- **Open canalicular system**: direct communication with extracellular environment
- **Dense tubular system**: derived from smooth endoplasmic reticulum, site for arachidonic acid metabolism
Ultrastructure Of Platelets Indicating Storage Granules

3 Types Of Platelet Granules

- **α-granules**: >300 proteins synthesized in megakaryocytes or endocytosed from plasma, involved in platelet adhesion:
  - VWF, P-selectin, fibronectin, fibrinogen, coagulation factors (factors V and XIII), growth factors (PDGF, TGF-β), and platelet factor-4.
- **δ-granules (dense bodies)**: primarily small molecules:
  - calcium, ATP, ADP, serotonin, histamine, and epinephrine.
- **Lysosomes**: mostly enzymes:
  - proteases, glycosidases
Platelet Membrane Glycoprotein

- Identified by
  - radio-active labeling of surface glycoproteins
  - solubilization of the membranes
  - electrophoresis on polyacrylamide gels
- Clinically important: GP Ib, V, IX, IIb, IIIa
Platelet Plug Formation

A. Injury

B. Initiation

C. Extension

D. Stabilization
Mechanisms of platelet activation and site of action of platelet inhibitors. Numerous platelet surface receptors initiate platelet activation leading to platelet aggregation, release of alpha and dense granule contents, and conversion of the platelet surface membrane to a catalytic surface for thrombin generation (‘platelet procoagulant activity’).
Screening Tests of Platelet Function

- Platelet count & morphology
- Bleeding Time
- PFA-100 analysis
  - An automated screening test available 24/7, replacing Bleeding Time test.
Platelet Function Testing

- Platelet count:
  - 130,000-350,000 x10⁹ /L

- Bleeding time:
  - a crude test of hemostasis
  - normal range: < 9 min.
  - poor reproducibility
  - no longer a recommended test
Platelet Function Testing

- **PFA-100**
  - screen to detect problems with primary haemostasis
  - replace the bleeding time
  - citrated whole blood is aspirated at high shear rates through disposable cartridges containing an aperture within a membrane coated with either collagen and epinephrine (CEPI) or collagen and ADP (CADP).
  - these agonists induce platelet adhesion, activation and aggregation leading to rapid occlusion of the aperture and cessation of blood flow termed the closure time (CT).
Platelet Aggregation Study

- **Principle:**
  - Aggregation in response to an added chemical stimulus can be monitored by change in transmittance

- **Stimulating agent:**
  - Arachidonic acid, ADP, collagen, epinephrine, and ristocetin
  - Platelet functional disorders have typical aggregation patterns
OPTICAL PLATELET AGGREGOMETRY: BORN PRINCIPLE

- Light in
- Light out
- PPP blank, no magnet
- PRP with magnet
- PRP with magnet
- PRP with magnet
- PRP with magnet

http://www.practical-haemostasis.com/Platelets/platelet_function_testing_lta.html
### Platelet Aggregation Patterns

#### Diagram:

- **NORMAL**
  - ADP: Normal aggregation pattern.
  - Epinephrine: Normal aggregation pattern.
  - Collagen: Normal aggregation pattern.
  - Arachidonic acid: Normal aggregation pattern.
  - Ristocetin: Normal aggregation pattern.

#### Table:

<table>
<thead>
<tr>
<th>Condition</th>
<th>ADP</th>
<th>EPI</th>
<th>COLL</th>
<th>ARACH</th>
<th>RISTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Willebrand disease</td>
<td>NORMAL</td>
<td></td>
<td></td>
<td></td>
<td>ABNORMAL</td>
</tr>
<tr>
<td>Storage pool disease</td>
<td>ABNORMAL</td>
<td>NORMAL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glanzmann thrombasthenia</td>
<td>ABNORMAL</td>
<td></td>
<td></td>
<td>NORMAL</td>
<td></td>
</tr>
<tr>
<td>Bernard-Soulier syndrome</td>
<td>NORMAL</td>
<td>+/-</td>
<td></td>
<td>NORMAL</td>
<td>ABNORMAL</td>
</tr>
</tbody>
</table>
Inherited Disorders of Platelet Function: Surface Membrane Defects

• Glanzmann thrombasthenia: autosomal recessive, defective GP IIb/IIIa
• Bernard Soulier syndrome: autosomal recessive, thrombocytopenia, large platelets, defective GP Ib,V,IX
• Collagen receptor defect: defective thrombospondin
• Platelet-type vWD: autosomal dominant, high affinity for vWF, borderline thrombocytopenia, addition of cryo-> aggregation
Platelet Storage Pool Disease

- The clinical syndrome is called $\alpha$-SPD, $\delta$-SPD, or combined $\alpha\delta$-SPD.
- These disorders, affecting the extension phase of clot formation
  - a/w impaired platelet function as indicated by decreased aggregation responses.
Platelet Storage Pool Defects

- a/w a variety of other inherited diseases
  - Hermansky-Pudlak syndrome
  - Chediak-Higashi syndrome
  - Wiskott-Aldrich syndrome
  - Thrombocytopenia-absent radius (TAR) syndrome
Acquired Platelet Storage Pool Defects

- a/w Systemic lupus erythematosus (SLE)
- cardiovascular bypass
- hairy-cell leukemia
- other disorders with chronic platelet activation.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
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</thead>
<tbody>
<tr>
<td>Dense body deficiency</td>
<td>Decreased dense bodies with decreased secretion of ADP and serotonin</td>
</tr>
<tr>
<td>Gray platelet syndrome</td>
<td>Decreased α-granules and contents</td>
</tr>
<tr>
<td>Factor V Quebec</td>
<td>Severe multimerin deficiency, protease degradation of α-granules</td>
</tr>
<tr>
<td>Mixed α-granule/dense body deficiency</td>
<td>Decreased α-granules and dense bodies</td>
</tr>
</tbody>
</table>
Platelet Storage Pool Deficiency

- Platelet aggregation due to deficiencies in either dense granules/alpha granule contents or both.
- Normal morphology, no granules in EM
- Platelet aggregation studies:
  - NO 2nd wave-ADP, epinephrine
  - ↓collagen +AA, normal ristocetin
  - ↑ATP:ADP ratio
Platelet Storage Pool Deficiency
Storage Pool Deficiencies

- **Gray platelet syndrome**
  No α granules,
  Large gray plt, no granules
  From cardio pulmonary bypass
  Plt agg blunted with all agents except ADP/epi

- **Quebec plt disorder**
  No α granules

- **Wiscott Aldrich syndrome**
  x-linked
  No δ granules EM
  Small granulated plt, like FeDa
  Thrombocytopenia, infection, eczema
  ↑ malignancy

- **Chediak Higashi**
  No δ granules EM

- **Hermansky-Pudlak Syndrome**
  No δ granules EM
  ↑ pigment reticuloendothelial cell
  • Swiss cheese platelets
  • ↑ AK, nevi, tumors, pulmonary fibrosis
  • Puerto Rican/Swiss, ↑vW

- **Thrombocytopenia w absent radii**
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Bleeding symptoms</th>
<th>Platelet count (\times 10^9/l)</th>
<th>Platelet ultrastructure</th>
<th>Inheritance (gene)</th>
<th>Platelet function abnormality</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Storage pool disease (α-SPD)</strong></td>
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<tr>
<td>GPS</td>
<td>mild to moderate</td>
<td>30–100</td>
<td>↓ / empty α-granules, ↑ platelet size</td>
<td>autosomal recessive (most) or dominant (gene(s) unknown)</td>
<td>normal or ↓ aggregation with thrombin, collagen ↓ aggregation with epinephrine</td>
<td>myelofibrosis</td>
</tr>
<tr>
<td>OPD</td>
<td>mild to moderate</td>
<td>normal or ↓</td>
<td>↓ α-granule content</td>
<td>autosomal dominant (PLAU)</td>
<td>↓ aggregation with ADP, arachidonate</td>
<td></td>
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<tr>
<td>ARC syndrome</td>
<td>mild</td>
<td>normal</td>
<td>lack of α-granules, ↑ platelet size</td>
<td>autosomal recessive (VPS33B, VIPAR)</td>
<td></td>
<td>arthrogryposis multiplex congenita, renal dysfunction, cholestasis, ichthyosis, recurrent infections</td>
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<tr>
<td><strong>δ-Storage pool disease (δ-SPD)</strong></td>
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<tr>
<td>HPS (subtype 1–8)</td>
<td>moderate to severe</td>
<td>normal</td>
<td>↓ dense granules</td>
<td>autosomal recessive (HPS1–HPS8)</td>
<td>↓ second wave of aggregation</td>
<td>oculocutaneous albinism, ceroidlipofuscinosis, nyctagmus, ↓ visual acuity, (HPS2: immunodeficiency, HLH; HPS1,4: granulomatous colitis, pulmonary fibrosis) partial albinism, immunodeficiency, HLH, neurological defects, hepatosplenomegaly partial albinism, silver hair, (GS1: neurological defects; GS2: immunodeficiency)</td>
</tr>
<tr>
<td>CHS</td>
<td>moderate to severe</td>
<td>normal</td>
<td>↓ dense granules, giant inclusion bodies</td>
<td>autosomal recessive (LYST)</td>
<td>↓ second wave of aggregation, ↑ ATP/ADP ratio</td>
<td></td>
</tr>
<tr>
<td>GS (subtype 1–3)</td>
<td>mild to absent</td>
<td>normal or ↓</td>
<td>n.d.</td>
<td>autosomal recessive (MYOSA, RAB27A, MLPH)</td>
<td>n.d.</td>
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<tr>
<td><strong>αδ-Storage pool disease (αδ-SPD)</strong></td>
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<tr>
<td>X-linked dyserthropoietic anemia with</td>
<td>moderate</td>
<td>mostly ↓</td>
<td>↓ dense granules, variable α-granules, ↑ platelet size</td>
<td>X-linked dominant, (GATA1)</td>
<td>↓ aggregation</td>
<td>β-thalassemia, congenital erythropoietic porphyria</td>
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<tr>
<td>thrombocytopenia/ X-linked macrothrombocytopenia</td>
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<tr>
<td>WAS</td>
<td>moderate to severe</td>
<td>10–100</td>
<td>↓ granules, ↓ platelet size</td>
<td>X-linked recessive (WAS)</td>
<td>↓ aggregation</td>
<td>eczema, immunodeficiency, risk for autoimmune disorders</td>
</tr>
</tbody>
</table>

n.d. = Not detected.