Diagnosis and Treatment of Inherited Platelet Disorders

Presented to Atlanta ISTH Advanced Training Course
Tuesday, November 1, 2016
Disclosures for Michele P. Lambert, MD, MTR

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>AstraZeneca, Inc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Consultant</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Major Stockholder</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Speakers Bureau</td>
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<td>GSK</td>
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</table>

Presentation includes discussion of the following off-label use of a drug or medical device:  
<N/A>
What do you do?

- 16 year old with platelet count of 60K and mucocutaneous bleeding referred for “ITP”

- 12 year old with “chronic ITP” since 1 year of age with platelet counts of 80-90K and no bleeding

- 3 month old with mucocutaneous bleeding and petechiae with platelet count of 375K

- 9 year old with congenital heart disease, mild developmental delays and some facial dysmorphism with previously near normal platelet counts and now a platelet count of 3K and bleeding.
Overview

- When to suspect a platelet disorder
- Diagnostic testing and limitations
- Platelet disorder classics
- General principals in the treatment of the inherited platelet disorders
Types of inherited platelet disorders

- With or without thrombocytopenia
- With or without platelet dysfunction
- With or without bone marrow failure
- With or without dysmegakaryopoiesis
When to suspect and inherited platelet disorder

- Bleeding out of proportion to platelet count
- Family history of thrombocytopenia, bone marrow failure or leukemia
- Family history of undefined bleeding disorder
- Mucocutaneous bleeding (with or without a change in platelet count)
- "Familial" ITP or syndromic thrombocytopenia
- Whenever you are thinking about vWD as cause of bleeding
Why care about platelet disorders

- Each individual disorder is “rare”
- In aggregate not that uncommon
- Mild platelet function defects may be as common as von Willebrand disease in some populations
Diagnosis of IPD: Guidance from ISTH

**DIAGNOSTIC ALGORITHM**

**Flowchart**

**PROBAND**

**Clinical evaluation:**
- Personal and family history and bleeding score: bleeding manifestations typical of IPFD
- Physical examination: bleeding manifestations typical of IPFD
- Syndromic forms: hearing loss; immunodeficiency; renal function; cardiac function; mental retardation; facial dysmorphism; eyes; bone; skin

**Preliminary laboratory investigation**

**Potential platelet function disorder**

- **NORMAL/LOW**
- **NORMAL**

**Platelet count**

**Routine coagulation tests**

**VWF screening**

**Low**

**Thrombocytopenia**

**ABNORMAL**

**VWD**

Blood clotting defect

Afibrinogenemia

**PLATELET FUNCTION STUDIES**

**NEXT GENERATION SEQUENCING**
Diagnosis of suspected IPD

- First and most important part of diagnosis is to get family and personal history
- Includes some type of bleeding score to help quantitate bleeding
- Obtain history of any associated medical diagnoses or findings in family or patient
Typical bleeding in platelet disorders

- Mucocutaneous bleeding
  - GI, GU, oral bleeding
  - Epistaxis
  - Petechiae, purpura and bruising

- Surgical or traumatic bleeding

- Rarely see joint bleeding or non-traumatic musculoskeletal bleeding

- Rarely intracranial bleeding
Diagnosis of suspected IPD

- Laboratory testing only with clinical suspicion (or to f/u incidental finding of thrombocytopenia)
  
- Complete Blood Count (CBC) with evaluation of peripheral smear
  - Size of platelets
  - Confirm platelet number
  - Platelet morphology (granularity)
  - Associated changes in red cells or white blood cells
Diagnosis of suspected IPD

- Evaluation of platelet function
- Routine coagulation testing including vWD testing
- ? Molecular testing
Peripheral smear and IPD
Peripheral smear and IPD
Peripheral smear and IPD
Key platelet functions

- Binding to cell surface receptors
- Shape change
- Membrane changes
- Granule secretion
Platelet aggregation testing

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Use</th>
</tr>
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<tbody>
<tr>
<td>Arachidonic acid (not always done) and U46619</td>
<td>Test thromboxane pathway (aspirin)</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Reacts with multiple receptors to test full aggregation independent of prostaglandin and ADP pathways</td>
</tr>
<tr>
<td>ADP</td>
<td>Binds to specific receptor (weak agonist)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Binds to specific receptor to cause release of ADP</td>
</tr>
<tr>
<td>Collagen</td>
<td>Depends on intact membrane receptors, thromboxane pathway and membrane phospholipase pathway (Platelet Factor 3)</td>
</tr>
<tr>
<td>Ristocetin</td>
<td>Requires functional vWF receptor (GP1b/V/IX complex)</td>
</tr>
</tbody>
</table>
## Classic aggregation patterns

<table>
<thead>
<tr>
<th>Disorder</th>
<th>ADP</th>
<th>Epinephrine</th>
<th>Collagen</th>
<th>Ristocetin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage Pool Def.</td>
<td>0</td>
<td>Absent 2nd wave</td>
<td>0 to +</td>
<td>++++</td>
</tr>
<tr>
<td>Glanzmann’s</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++++</td>
</tr>
<tr>
<td>Bernard-Soulier</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>
Platelet aggregation testing

- Reasons for an abnormal test
  - “Tired platelets” (partially activated platelets)
  - Medications: aspirin, NSAIDs, theophyllin, caffeine, antibiotics (penicillins, sulfonamides), anti-seizure meds, psychiatric drugs, antihistamines
  - Long delay between drawing blood and running test

- Platelet disorder
Key platelet functions

- Binding to cell surface receptors
- Shape change
- Membrane changes
- Granule secretion
Platelet function testing

- Light transmission aggregometry (LTA) only tests:
  - Receptor binding and signaling
  - Some information on granule release (epi)

- To really know about granules, need to measure granule content/release
  - Lumiaggregometry
  - Seratonin release (depends on uptake)
  - Flow cytometry (more alpha granules)
Evaluation of suspected IPD

- Family or patient history suggestive of bleeding disorder
- Incidentally found thrombocytopenia

CBC with review of smear

- Normal platelet count
- Thrombocytopenia
  - large platelets
  - normal platelets
  - small platelets

Platelet aggregation

- vWD studies
  - normal
  - vWD type 2B
  - platelet-type vWD

- Abnormal vWD type 2B
- Platelet aggregation

- Nonspecific pattern
- Specific pattern

- MGSD
- PT/J

- Bone marrow

- MYH9-related disorders
  - 22qDS
  - PT/J

- Flow cytometry
  - BSS
  - GT
  - P2Y12R
  - GPVI
  - TXA2R

- Immune function
- WAS
- XLT
<table>
<thead>
<tr>
<th>Platelet Function Disorders with Thrombocytopenia</th>
<th>Platelet count reduction</th>
<th>Platelet size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard–Soulier syndrome</td>
<td>Moderate to severe</td>
<td>Giant</td>
</tr>
<tr>
<td>Filaminopathy-related macrothrombocytopenia</td>
<td>Mild to moderate</td>
<td>Large</td>
</tr>
<tr>
<td>Familial platelet disorder associated with acute myeloid leukemia</td>
<td>Mild to moderate</td>
<td>Normal</td>
</tr>
<tr>
<td>GATA1-related disease</td>
<td>Severe</td>
<td>Large</td>
</tr>
<tr>
<td>Gray platelet syndrome</td>
<td>Mild</td>
<td>Large</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia variant</td>
<td>Mild to moderate</td>
<td>Large</td>
</tr>
<tr>
<td>Medich platelet syndrome</td>
<td>Mild</td>
<td>Large</td>
</tr>
<tr>
<td>Paris–Trousseau syndrome</td>
<td>Moderate to severe</td>
<td>Normal or slightly increased</td>
</tr>
<tr>
<td>Platelet type von Willebrand disease</td>
<td>Mild</td>
<td>Normal or slightly increased</td>
</tr>
<tr>
<td>Stormorken syndrome</td>
<td>Mild to moderate</td>
<td>Normal</td>
</tr>
<tr>
<td>Velocardiofacial syndrome</td>
<td>Mild</td>
<td>Large</td>
</tr>
<tr>
<td>Wiskott–Aldrich</td>
<td>Severe</td>
<td>Small</td>
</tr>
<tr>
<td>White platelet syndrome</td>
<td>Mild</td>
<td>Large</td>
</tr>
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</table>
# Syndromic Platelet Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Structural Defect</th>
<th>Platelet Defect</th>
<th>Associated abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrogryposis renal dysfunction and cholestasis syndrome</td>
<td>VPS33B; VIPAS39</td>
<td>Abnormal alpha granules</td>
<td>Arthrogryposis, renal dysfunction, cholestasis, cerebral malformations, dysmorphic features</td>
</tr>
<tr>
<td>Filaminopathies</td>
<td>Filamin A</td>
<td>Abnormal aggregation, secretion and adhesion</td>
<td>Skeletal dysplasia, MR, cardiac valvular dystrophy, congenital intestinal pseudo-obstruction, terminal osseous dysplasia</td>
</tr>
<tr>
<td>Gsα platelet defect</td>
<td>Increased Gsα expression and function Gsα deficiency</td>
<td>Abnormal aggregation inhibition test Decreased cAMP formation on Gas activation</td>
<td>Short stature, MR, brachydactyly, pseudohypoparathyroidism</td>
</tr>
<tr>
<td>HPS, Chediak-Higashi</td>
<td>Vesicle trafficking</td>
<td>Reduced aggregation and secretion</td>
<td>Skin, ocular and hair hypopigmentation, nystagmus</td>
</tr>
<tr>
<td>LAD III</td>
<td>Kindlin 3</td>
<td>GT defect</td>
<td>Leukocytosis, recurrent infection</td>
</tr>
<tr>
<td>Stormorken syndrome</td>
<td>Ca release activated Ca channel</td>
<td>Pro-coagulant activity</td>
<td>Miosis, muscle weakness, dyslexia, ichthyosis, asplenia</td>
</tr>
<tr>
<td>22q11.2 DS</td>
<td>GPIb-Beta</td>
<td>Abnormal adhesion</td>
<td>VCFS, DiGeorge</td>
</tr>
<tr>
<td>Wiskott-Aldrich</td>
<td>WASP, WISP</td>
<td>Abnormal granule release</td>
<td>Eczema, immunodeficiency</td>
</tr>
</tbody>
</table>
Molecular diagnosis

- Avoids extra or inappropriate treatment
- Provides information about required follow up and monitoring
- May give information about familial risks
- Has resulted in significant advances in our understanding of platelets/IPD in the last 10 years
General points about treatment

- If bleeding:
  - Control bleeding early and use multimodal therapies if needed
  - DDAVP has been shown to be effective in storage pool, mild platelet function defects and maybe Bernard Soulier Syndrome
  - rFVIIa has been approved by FDA for use in patients with Glanzmann Thrombasthenia who are platelet refractory
  - Antifibrinolytic therapies are important adjuvant
  - Platelet transfusions in the setting of severe/life threatening bleeding
General points about treatment

- Prevention is the best protection
  - Good oral care
  - Avoid head trauma (although no clear place for significant activity restriction in mild disorders)
- Early presentation for any bleeding episodes
- Avoid repeated nasal cautery if possible
General points about treatment

- Eltrombopag has been used to raise platelet counts in severely thrombocytopenic patients with MYH9 related disorders.

- May be a role for TPO-RA in thrombocytopenias especially short term (to raise for procedure).
Take home points

- Platelet disorders are individually rare, but in aggregate are probably more common than is generally appreciated
- Mucocutaneous bleeding
- Think platelet disorder if you think of vWD and the workup is negative or in refractory "chronic ITP"
- Treatments are mainly supportive and rely on early diagnosis of bleeding
Thank you