Congenital Platelet Disorders

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## Disclosures for Mike Makris

<table>
<thead>
<tr>
<th>Role</th>
<th>Disclosures</th>
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</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Bayer, Biotest, BPL, CSL Behring, Grifols, Kedrion, LFB, NovoNordisk, Octapharma, Pfizer, SOBI</td>
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<td>Major Stockholder</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Scientific Advisory Board</td>
<td>NovoNordisk</td>
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Inherited platelet disorders

- True prevalence is underestimated
- Many lack a family history
- Many de novo mutations (e.g., 20-30% in MYH9)
- Variable bleeding tendency
- Not all present in childhood
Platelet Disorders

• Reduced function
  • Thrombocytopenia (term not used much)

• Reduced count
  – Thrombocytopenia
UK registered patients

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A</td>
<td>7,700</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>1,707</td>
</tr>
<tr>
<td>VWD</td>
<td>10,598</td>
</tr>
<tr>
<td>Glanzmann Thrombasthenia</td>
<td>125</td>
</tr>
<tr>
<td>Bernard Soulier syndrome</td>
<td>85</td>
</tr>
<tr>
<td>Other platelet disorders</td>
<td>2,222</td>
</tr>
</tbody>
</table>

UK population: 66 million
Disorders of platelet function
Disorders that mainly affect surface components of platelets

Glanzmann thrombasthenia: no aggregation with natural agonists

Reduced response to collagen

Scott syndrome: decreased prothrombin conversion

Altered response to stimuli: ADP (P2Y12), TXA2 (TPα), 5-HT, PAF, adrenaline...

Platelet-type VWD: spontaneous binding of VWF to GP Ibα

Bernard-Soulier syndrome: lack of adhesion to VWF and abnormal response to thrombin

Nurden P & Nurden AT. T&H 2008; 99:253-263
Disorders that mainly affect intracellular components of platelets

α-GRANULES:
- Gray platelet syndrome
- Quebec platelet syndrome, α,δ-SPD

METABOLISM:
- Glycogen synthetase
- Production of ATP

ENZYMES:
- Cyclooxygenase
- TXA₂ synthetase
- Lipoxygenase

DENSE GRANULES:
- Hermansky-Pudlak, Chediak-Higashi
- and Griscelli syndromes, δ-SPD

CYTOSKELETON:
- MYH9 disorders and giant platelet syndromes
- Wiskott-Aldrich syndrome

Nurden P & Nurden AT. T&H 2008; 99:253-263
Glanzmann Thrombasthenia

- Autosomal recessive
- Rare (1 in 1 million)
  - exc in countries with consanguinity
- Primary haemostatic defect
- Mostly severe
- Abnormality in platelet glycoprotein IIb/IIIa (αIIb/β3)
- Treat with platelet transfusion or recombinant VIIa
- Risk of alloantibodies against IIb/IIIa
Glanzmann Thrombasthenia platelet aggregation
## Classification of Glanzmann Thrombasthenia

<table>
<thead>
<tr>
<th>Type</th>
<th>Proportion</th>
<th>αIIb/β3</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>75</td>
<td>Absent or trace (&lt;5%)</td>
</tr>
<tr>
<td>II</td>
<td>15</td>
<td>Substantially reduced (5-20%)</td>
</tr>
<tr>
<td>Variant</td>
<td>10</td>
<td>Abnormal (&gt;20%)</td>
</tr>
</tbody>
</table>
Type of bleeding in Glanzmann Thrombasthenia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of patients reporting this symptom</th>
</tr>
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<tbody>
<tr>
<td>Menorrhagia</td>
<td>80-95 (of menstruating females!)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>80</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>60</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>20</td>
</tr>
<tr>
<td>Muscle haematoma</td>
<td>10</td>
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</tbody>
</table>
Pregnancy in Glanzmann Thrombasthenia

• Risk of bleeding at delivery
• Risk of affected baby
  • Will depend if there is consanguinity
• During pregnancy baby platelets (heterozygous) cross the placenta
• Mum can mount immune response
  • Develops anti-IIb/IIIa alloantibodies
• Mum with platelet alloantibodies
  • Will not respond to platelet transfusions
  • Antibodies cross the placenta – risk of bleeding in baby
Bernard Soulier syndrome

• Autosomal recessive
• Rare (1 in 1 million)
  • exc in countries with consanguinity
• Primary haemostatic defect
  • Prolonged bleeding time with variable thrombocytopenia
• Giant platelets
• Abnormality in platelet glycoprotein Ib/V/IX
• Treat with platelet transfusion or recombinant VIIa
Bernard Soulier Syndrome platelet aggregation
Giant platelets in Bernard Soulier syndrome
Platelet storage pool disease

Deficiency of:

• Dense granules (δ-SPD)

• Alpha granules (α-SPD)

• Both granules (αδ-SPD)
Platelet granule release

Agonists (FIIa, Collagen, ADP)

Signals

Activation

Shape change

Membrane fusion

Release of granule contents
Platelet storage organelles

α granules
- Adhesive proteins
- Clotting factors and their inhibitors
- Fibrinolytic factors and their inhibitors
- Proteases and antiproteases
- Growth and mitogenic factors
- Chemokines, cytokines
- Anti-microbial proteins
- Membrane glycoproteins

dense (δ) granules
- ADP/ATP
- Serotonin
- Histamine
- Inorganic polyphosphate

lysosomes
- Enzymes including cathepsins
- Acid hydrolases

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Types of platelet secretion defects

α-granule defects

δ-granule defects

Receptor, signalling or granule trafficking defects

Release of granule contents

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**Platelet storage pool disease**

- Mild bleeding disorder
- Can be isolated – often due to Fli-1 mutations
- Can be syndromic eg Hermansky Pudlak syndrome

**Treatment**
- Desmopressin
- Tranexamic acid
- Platelet transfusion
Platelet storage pool disease aggregation
Hermansky-Pudlak syndrome

• Autosomal recessive
• Worldwide 2 per million (but 1 in 1800 in Puerto Rico)
• Symptoms
  • Albinism
  • Platelet dense granule deficiency
  • Pulmonary fibrosis, granulomatous colitis, nystagmus
• 8 HPS genes
  • 90% of cases are due to HPS1 mutations
Grey platelet syndrome

- Autosomal recessive
- Mild to moderate bleeding
- Severe deficiency of α-granules
- Macrothrombocytopenia
- Myelofibrosis
- Due to \textit{NBEAL2} mutations
Other platelet function defect disorders

• Mild
• Not always well defined
• Precise definition only for a minority
• Often mildly abnormal platelet aggregation
• Usually no treatment required
• Treatment:
  • Desmopressin and tranexamic acid
  • If significant bleeding despite this – platelet transfusion
Disorders of platelet number
Inherited thrombocytopenia

• Commoner than generally believed
• Mostly mild bleeding tendency
• Variable platelet size
• Most disorders identified very recently
• Molecular genetic diagnosis
• Many are syndromic
The evolving view of inherited thrombocytopenias

Balduini CL Haematologica 2016;101:2-4
The molecular identification of inherited platelet disorders

Balduini CL. Haematologica 2017 (in press)
Pattern of inheritance

• X-linked
  • Wiskott-Aldrich syndrome
  • X-linked thrombocytopenia

• Autosomal dominant
  • MYH9 defects
  • FLI1 defects

• Autosomal recessive
  • Glanzmann Thrombasthenia
  • Bernard Soulier syndrome
Platelet size by diagnosis in inherited thrombocytopenia

Noris P et al. Blood 2014; 126:e4-10
May-Hegglin anomaly
Fechtner syndrome
Epstein syndrome

MYH9 related disorders
Peripheral blood in MYH9 thrombocytopenia

Neutrophil inclusion and
Large platelet

Normal immunofluorescence for non-muscle myosin heavy chain IIA

Speckled staining in patients with MYH9 defects
MYH9 related thrombocytopenia

• Macrothrombocytopenia
• Mild bleeding disorder
• Defect in non-muscle myosin chain IIA
• Neutrophil inclusions
• Autosomal dominant
• Associated with:
  • Renal defects
  • Sensorineural deafness
  • Cataracts at a young age
Inherited thrombocytopenia associated with haematological malignancy

- **RUNX1 (AML1)**
  - Familial platelet disorder with propensity to acute myeloid leukaemia (FPD-AML)
  - AML or MDS in 40%
- **ETV6**
  - ALL in 20%
- **ANKRD26**
  - AML in 8%
Treatment of inherited thrombocytopenias

- Often no treatment is required
  - Platelet count is relatively high
  - Macrothrombocytopenia leads to increased surface area
- Topical measures and pressure
- Tranexamic acid
- Eltrombopag
- Romiplostim
- For some disorders eg Wiskott-Alrich
  - Splenectomy, stem cell transplant, gene therapy
Eltrombopag for MYH9 thrombocytopenia

Eltrombopag use in inherited thrombocytopenia

• Useful for surgery or in those with frequent bleeding
• Start 3 weeks before surgery
• Most need 75mg once daily
• MYH9: Most respond
• ANKRD26: Most respond
• Wiskott Aldrich and XLT: some respond

• Only use short term in conditions associated with malignancy
Why avoid platelet transfusion if possible?

• Antibody development
  • HLA
  • Platelet specific

• Transfusion transmitted infection
  • Including bacterial infection

• Allergic reactions
Summary

- Severe platelet function defects
  - Rare but easy to diagnose
- Mild platelet function defects
  - Common but difficult to diagnose
  - Can be managed with tranexamic acid +/- DDAVP
- Inherited thrombocytopenias
  - Much commoner than thought
  - At least 30 different genetic causes
  - Bleeding is often not the concern, but syndromic features are
  - TPO agonists often help if needed pre-surgery