Putting some hematology into Pediatric Hematology/Oncology: a review of Hemophilia and Sickle Cell Disease in the Pediatric Patient

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Objectives:

- Review Hemostasis and Hemoglobin production
- Discuss the pathophysiology of hemophilia and sickle cell anemia
- Describe the common reasons bringing these patients to medical attention
- Discuss treatment options for hemophilia and sickle cell disease
- Describe Future directions in the care of these patients
Hemophilia: a deficient hemostatic system
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Intrinsic pathway

Kallikrein → Pre-kallikrein

Factor XII → Factor XIIa

Factor XI → Factor XIa

Factor IX

Factor IXa. Factor VIIIa

Factor VIII

Factor X → Factor Xa. Factor Va

Factor V

Extrinsic pathway

Factor VII

Tissue factor. Factor VIIa

Factor II (prothrombin) → Factor IIa (thrombin)

Fibrinogen → Fibrin
Hemophilia: the diagnosis

- Hemophilia A - factor VIII deficiency
  - 80% of those affected
- Hemophilia B - factor IX deficiency
  - 20% of those affected
- Amount of factor determines symptoms
  - Mild: 5-30%
  - Moderate: 1-5%
  - Severe: <1%
Hemophilia: genetics

- Life-long bleeding disorder
- X-linked inheritance
- New mutation in 30%
Family tree with carrier mother
Family tree with affected father

- Normal Mother (XX)
- Father with Hemophilia (XY)
- Carrier Daughters (XX, H)
- Normal Sons (XY, XY)
Family tree with carrier mother and affected father
Hemophilia clinical problems

• Bleeding characterized by joint and soft tissue hemorrhages
• Can also have mucosal, GI, CNS bleeds
• Symptoms of bleeding: swelling, redness, pain
• Recurrent bleeding can result in target joints
Hemophilia treatment in general

- Replace what’s missing
- Recombinant factor products
  - Factor VIII 1U/kg of factor raises levels by 2%
  - Factor IX 1U/kg of factor raises levels by 1%
- Prophylaxis has become the mainstay of treatment for people with severe hemophilia or moderate hemophilia with frequent bleeding
Prophylaxis

- Initiated at ~1 year of age, when child begins to walk
- Requires venous access device
- Designed to keep trough factor levels >2%
- Goal is to prevent joint damage and deterioration
- Schedule
  - Hemophilia A → 3 times/wk
    - 50% on Mon and Wed
    - 100% on Fri
  - Hemophilia B → 2 times/wk
    - 50% on Tues
    - 100% on Fri
Hemophilia- in the hospital

• Scheduled surgeries: port placement
  – Pre-op infusion of factor
  – Scheduled factor post-op
• Breakthrough/traumatic bleeding
  – Infuse first, then image
  – Continue infusions until symptoms resolve
  – Risk for compartment syndrome
Compartment syndrome

Definition: tissue pressure within a closed muscle compartment exceeds the perfusion pressure and results in muscle and nerve ischemia.

Pain out of proportion to the injury

Surgical emergency: emergent fasciotomy and factor infusion.
Complications/comorbidities

- Target joints
- ADHD
- Port infections
- Infections associated with factor
- Osteoporosis
- Development of inhibitors
Factor inhibitors

• Inhibitors are antibodies that block the function of coagulation proteins
• Develop in 25-30% of children with Hemophilia A
• Develop in 1-3% of children with Hemophilia B
• Complicates treatment
Treatment in the face of inhibitors

- Overcome the inhibitor
  - Increase the dose of factor replacement
- Bypassing agents
  - FEIBA
  - Novo 7
- Plasmapheresis
- Immune tolerance
Future directions

• Open studies at OHSU:
  – Gait study
  – Use of ankle braces for pain control
  – ADHD and risk of injury
  – New factor replacements
  – Universal data collection

• Gene therapy??
Summary- hemophilia

- Hemophilia is secondary to a genetic defect resulting in decreased levels of factor VIII or XI
- Treatment is factor replacement- prophylaxis and on demand
- Can be complicated by inhibitor development
- Bleeding can lead to development of compartment syndrome- a medical emergency
Questions?
Red cells and normal hemoglobin

- Each red cell contains ~640 million hemoglobin molecules
- Hemoglobin is responsible for oxygen delivery
- The red cell has to be deformable to get into close contact with tissues
  - The red cell is 8 micrometers and has to pass through 3.5 micrometer sized vessels
Normal hemoglobin production

- Hemoglobin molecules are made up of 4 subunits.
- The combination of subunits determines the type of hemoglobin.
- Fetuses produce a specific type of hemoglobin.
- Switch to mostly adult hemoglobin by 3–6 months of age.
- Adult hemoglobin is denoted by subunits ζ, δ, γ, and β.
Sickle cell disease - qualitative hemoglobin problem

- Single change in the DNA coding for the β-globin results in the sickle β-globin
- Hemoglobin S (α₂β₂⁰⁺) is insoluble and forms crystals when exposed to low oxygen
- The sickle hemoglobin polymerizes into long fibers which results in the red cell sickling
Sickled Cells - don’t deform
Sickle Cell pathophysiology

- Impaired blood flow - hypoxia
- ↓ NO → vasoconstriction
- Coagulation triggered
  - Sticks to endothelium
  - Vascular injury
  - Increased red cell breakdown
- Membrane damage
- Acidic environment
Sickle cell clinical problems

- Vaso-occlusive events: acute, painful episodes caused by intravascular sickling and tissue infarction
- Varied manifestations
  - Pain
  - Acute Chest Syndrome
  - Stroke
Painful events

• Acute onset of deep, gnawing, throbbing pain
• Secondary to bone marrow ischemia → infarction
• Common sites:
  – Lumbar spine
  – Knee
  – Shoulder
  – Elbow
  – Femur
Painful events

• Moderate-Severe events- managed in the hospital
  – Tailor treatment to patient and pain
  – Should be treated as medical emergency
  – Hydrate judiciously
  – Get pain under control quickly
  – Reassess frequently
  – NSAIDs help
  – No Oxygen needed
  – Transfusions don’t help
Acute Chest Syndrome

- Acute illness with lung injury – chest pain, fever, respiratory symptoms + new infiltrate on CXR
- May develop when in the hospital for pain
- High morbidity and mortality
- Treatment
  - Oxygen
  - Antibiotics
  - Bronchodilators
  - Pain meds
  - Transfusion
  - Judicious fluids
Stroke

- Ischemia and infarct secondary to damaged vessels
- Can also have hemorrhagic stroke
- Can be isolated or develop in the setting of acute chest, aplastic crisis, viral illness, painful event, dehydration
- Treat with exchange transfusion
Fever and infection

- Most common cause of death in sickle cell patients
- Splenic dysfunction increases risk of bacteremia
- Treat as emergency- fever in immunocompromised host
- Penicillin prophylaxis has decreased infections significantly
- Vaccinations are critical in these patients
If that wasn’t enough...

- Sickle Cell patients are at risk for
  - Aplastic crisis
  - Splenic sequestration
  - Gallstones
  - Priapism
  - Renal dysfunction
  - Pulmonary hypertension
  - Leg ulcers
Current therapies & Future directions

- Increase the percentage of Hgb F-Hydroxyurea
- Folic acid
- Penicillin
- Chronic transfusions
- Bone marrow transplants
Summary-Sickle Cell

- Genetic disease characterized by abnormal hemoglobin
- The change in hemoglobin results in increased red cell breakdown, vascular injury, and ischemia
- Patients are at risk for several life-threatening complications including infection, acute chest syndrome, and stroke
- Painful events should be managed promptly and with frequent reassessments
Questions?
Thank You!