Interpretation & Management of Hematologic Disorders Identified on Newborn Screening

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Objective

Hematologic conditions diagnosed by newborn screening
Diagnosis and management of

- Hemoglobinopathies
  - $\alpha$ and $\beta$ thalassemia
  - Sickling disorders
  - G6PD deficiency
Outline

Background:
• Hemoglobin: structure and development
• Hemoglobinopathy: nomenclature and Dx

Common hemoglobinopathies and management
• Thalassemia: Alpha and beta thalassemia
• Sickle cell disease

G6PD deficiency
Hemoglobin

Heme + Globin
Four globin chains:
- 2 α like globin chains
- 2 β like globin chains

Four heme group
- One per globin chain

Tetramer structure
# Hemoglobin: Names to know

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA</td>
<td>Adult Hb</td>
<td>$\alpha_2 \beta_2$</td>
</tr>
<tr>
<td>HbA2</td>
<td>Minor adult Hb</td>
<td>$\alpha_2 \delta_2$</td>
</tr>
<tr>
<td>HbF</td>
<td>Fetal Hb</td>
<td>$\alpha_2 \gamma_2$</td>
</tr>
<tr>
<td>Hb Barts</td>
<td>Abnormal Hb</td>
<td>$\gamma_4$</td>
</tr>
<tr>
<td>Hb H</td>
<td>Abnormal Hb</td>
<td>$\beta_4$</td>
</tr>
</tbody>
</table>

![Diagram of Hemoglobin Gene Cluster](image-url)
Hemoglobin switching: fetal to adult

- Hemoglobin F ($\alpha_2 \gamma_2$) is the predominant hemoglobin at birth
- Hemoglobin Barts ($\gamma_4$) disappears with increasing hemoglobin A ($\alpha_2 \beta_2$): A normal developmental phenomenon
Newborn screening
It is a law!

Every state in the U.S. has program to screen newborns for inherited disorders. Number of tests may vary by states but hemoglobinopathy screen is universal.
Thalassemia and other hemoglobinopathies: Global distribution

- Frequency of the mutant allele depends on the ancestry
- All newborns are screened regardless of race and ethnicity
Hematologic disorders on newborn screen

Thalassemia: Quantitative Disorders of Hb
- Alpha Thalassemia
- Beta thalassemia

Hemoglobinopathies: Qualitative Disorders of Hb:
- Sickle cell disease: SS, SC, Sickle beta thal
- Other Hemoglobinopathies: C, E
- Variant hemoglobins

Enzymopathy: G6PD deficiency
Quantitative Disorders (Thalassemias)
## Alpha Thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Pattern</th>
<th>Name</th>
<th>Features/ Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>αα/αα</td>
<td>FA</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>αα/α-</td>
<td>FA</td>
<td>Silent carrier</td>
<td>Genetic counseling</td>
</tr>
<tr>
<td></td>
<td>Barts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| αα/- -      | FA              | Alpha thal trait (minor) | Mild anemia/microcytosis  
Check for iron deficiency |
| α-/-α-      | Barts           |                       |                                                                                     |
| α -/- -     | FA with Barts   | Hemoglobin H disease (intermedia) | Moderate to severe anemia,  
hepatosplenomegaly  
Hb H inclusion  
May need PRBC transfusions |
|             | > 25%           |                       |                                                                                     |
| - -/- -     | ≈ 100% Hb Barts| Hydrops fetalis (major) | Fetal hydrops and demise  
Intrauterine PRBC transfusions  
HSC transplant |
# Beta Thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Name</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta/\beta)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>(\beta/\beta^0)</td>
<td>Beta thal trait (minor)</td>
<td>Normal count in neonate Elevated F and A(_2) Mild anemia, microcytosis</td>
</tr>
<tr>
<td>(\beta/\beta^+)</td>
<td>Beta thal Intermedia</td>
<td>Hypochromia and microcytosis Elevated F and A(_2) Variable hepatosplenomegaly Intermittent transfusion</td>
</tr>
<tr>
<td>(\beta^+/\beta^+)</td>
<td>Beta thal major</td>
<td>Normal counts in newborn F only pattern of electrophoresis Sever hypochromic microcytic anemia, hepatosplenomegaly Lifelong transfusion/ HSC transplant</td>
</tr>
<tr>
<td>(\beta^0/\beta^0)</td>
<td>Beta thal major</td>
<td></td>
</tr>
</tbody>
</table>
Clinical phenotype varies in thalassemia:

Number of genes affected or the type of mutation typically dictate the clinical phenotype.
Qualitative disorders (Hemoglobinopathies)
Hemoglobinopathy screen

All detected hemoglobin are reported
Reported in the order of amount present
FAS means HbF > HbA >HbS
FAS (sickle trait) ≠ FSA (sickle beta plus thal)
Variant hemoglobins
Newborn screen:
Common patterns

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Normal</td>
</tr>
<tr>
<td>FAS</td>
<td>Sickle cell trait</td>
</tr>
<tr>
<td>FS</td>
<td>Sickle cell anemia (SS) or sickle beta zero thal</td>
</tr>
<tr>
<td>FSA</td>
<td>Sickle beta plus thalassemia</td>
</tr>
<tr>
<td>FSC</td>
<td>Sickle-Hb C (SC) disease</td>
</tr>
<tr>
<td>FAV</td>
<td>Trait or heterozygous for Hb variant</td>
</tr>
</tbody>
</table>

α thal/ hemoglobin Bart can coexist with β globin mutations
Occasionally DNA analysis may be needed for diagnosis
Sickling disorders:

**Sickle cell disease**: group of diseases with presence of sickle gene: HbSS, HbSC, Sβ⁺thal, Sβ⁰thal, SD Punjab, SO Arab

Sickle shaped RBCs

Autosomal recessive

Sickle cell trait (AS): 1:10

Sickle cell disease 1:500 in US African Americans
Pathophysiology

A GAG to GTG substitution → replacement of glutamic acid residue by valine.

Upon deoxygenation HbS polymerization → sickling → vaso-occlusion.

Early manifestations: dactylitis and splenic sequestration

Steinberg MH, NEJM 1999
Dactylitis

- Often the first symptom of SCD (6 mo-2 y)
- Painful swelling of hand and feet. Infarction of bone marrow due to occlusion of blood supply.
- Rx: Hydration, pain management
Splenic sequestration

Signs and Symptoms
- Irritability
- Unusual sleepiness
- Looks pale
- Weakness
- Fast heart beat
- Big spleen
- Pain on the left side of the abdomen
After the newborn screening

Sickle cell trait (AS):
  • Genetic counseling

Sickle cell disease: SS, SC, Sβ^+thal, Sβ^0thal and other sickling disorders
  • Penicillin prophylaxis: at least up to age 5 years
    – 125 mg PO BID for < 3 years;
    – 250 mg PO BID ≥ 3 years
  • Hematology visit /confirmatory testing
  • Multidisciplinary infant sickle cell clinic
SCD Health Maintenance

• **Education and counseling:**
  – Pain and fever management
  – Spleen palpation
  – Penicillin prophylaxis
  – School and IEP
  – Physical activity

• **Immunizations:**
  – All recommended immunizations
  – 23 valent pneumovax at 2 and 5 years
  – MCV4 two doses (other meningococcal vaccines per ACIP)
  – Influenza vaccine
SCD Health Maintenance

Screening:
• Annual transcranial doppler to evaluate stroke risk (Hb SS and sickle β0 thalassemia) starting at 2 years of age
• Annual eye evaluation for retinopathy starting 10 years (Hb SC patients are at higher risk)
• Examination of hip for avascular necrosis
• Growth and development; neuropsych evaluation
• Mental health assessment

Disease modifying therapies as indicated:
• Hydroxyurea
• Chronic blood transfusion
• Hematopoietic stem cell transplant

Improved outcome for individuals living with SCD
G6PD deficiency
G6PD deficiency

Most common red cell enzyme disorder
X linked inheritance
↓ G6PD → ↓ NADPH production (free radical detoxification)
Hemolysis in response to oxidative stress: (ex. infections, drugs, fava beans) → anemia, jaundice
Heinz bodies and blister cells on peripheral smear

• **Clinical features ranges**: Asymptomatic/ neonatal jaundice/ hemolysis
### Classes of G6PD Enzyme Variants

<table>
<thead>
<tr>
<th>CLASS</th>
<th>LEVEL OF DEFICIENCY</th>
<th>ENZYME ACTIVITY</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Severe</td>
<td>Chronic nonspherocytic hemolytic anemia in the presence of normal erythrocyte function</td>
<td>Uncommon; occurs across populations</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
<td>Less than 10 percent of normal</td>
<td>Varies; more common in Asian and Mediterranean populations</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>10 to 60 percent of normal</td>
<td>10 percent of black males in the United States</td>
</tr>
<tr>
<td>IV</td>
<td>Mild to none</td>
<td>60 to 150 percent of normal</td>
<td>Rare</td>
</tr>
<tr>
<td>V</td>
<td>None</td>
<td>Greater than 150 percent of normal</td>
<td>Rare</td>
</tr>
</tbody>
</table>
G6PD deficiency

Denatured Hemoglobin
Heinz bodies
“Blister cells” on smear

Fava beans
G6PD deficiency

Education and counseling:
- Risk factors
- Drugs and other precipitating causes to avoid
- Sign and symptoms of acute hemolysis and anemia (change in urine color, pallor)

Management:
- Ranges from observation to red cell transfusion
Conclusion

Newborn screen is an important tool in identifying common inherited hematologic disorders.

Early diagnosis is crucial for appropriate management.

Collaboration between the primary physician and the hematologist is the key to improve the outcome of affected children.
Thank you

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