Anemia (4)


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Congenital Hemolytic Anemias: Subtypes

1- Membrane defects: HS
2- Enzymopathies: G6PD Deficiency, PK Def
3- Hemoglobinopathies: B-Thal, SS
Anemia (4): Congenital Hemolytic Anemias

Case 4

18 yr old male presented to ER with headaches, dizziness, red urine and severe loin pain few hours after he ate fresh “fool” beans.

He looked jaundiced and sweaty.

His BP 90/60, Pulse rate 120.

He had no splenomegaly.

Hb 9 g/dl, WBC 16K, Plt 280K. Retics 9%. LDH 3000, Bilirubin 5; mostly indirect.
Diagnosis of case 4: G6PD deficiency: hemolytic anemia induced by fava(broad) beans (Favism)
Pentose Phosphate Pathway
Prevalence of G6PD: > 400 mill people/ Malaria belt
Clinical Features:

• Disease from completely asymptomatic to severe intravascular hemolysis upon exposure to oxidant stress.

• Common precipitating factors:
  – Drugs: Primaquine – Nalidixic acid – sulpha drugs –
  – Infections
  – Diabetic ketoacidosis
  – Favism: hemolysis after exposure to Fava beans, occurs in Gd$^{\text{Med}}$ variant
Clinical Syndromes: G6PD Deficiency

1- **Neonatal Jaundice**: severe/ Kernicterus /, 1-3 day after birth.

2- **Favism**: acute intravascular Hemolysis due exposure broad bean (Vicia fava), the offending agent is divicine, it produces free Oxygen radicals and autoxidation.

3- **Infection** which promote the formation of H₂O₂ following oxygen burst in neutrophils and macrophage may result in hemolysis

4- **Drug induced hemolysis**
Genetics

• 1989 - more than 400 variants of G6PD
• Variants divided 5 classes according to the residual enzyme activity based (WHO).
• Mediterranean and African (A-) variants - by far the most clinically significant.
• Enzyme activity scarcely detectable in the Mediterranean type
Genetics

• Majority of the variants - from a single point-mutation resulting in amino acid substitution in gene encoding for G6PD located at the Xq28 region on the tip of the long arm of the X-chromosome

• G6PD Mediterranean is frequently caused by mutation \(563 \text{ C} \rightarrow \text{T}\)
Therapy

• Avoid precipitating factors.
• Blood transfusion in severe hemolysis.
• Maintenance of good urine output during hemolytic episodes
• Folic acid.
• Exchange transfusion in newborn
Case 4 B

36 yr old lady presented with “anemia syndrome” and splenomegaly. She was mildly jaundiced. Hb 8g/dl, retics 10%, WBC, Plt were normal. LDH 1160, Bilirubin 3mg/dl d 1.DAT –ve.

Bld film: spherocytosis/splnc conditioning

Osmotic fragility test

Abd. US
Hereditary Spherocytosis

• Prevalence and inheritance
  • Common in Northern Europeans
  • Clinical severity is highly variable, but uniform within a given family
  • Typically the autosomal dominant homozygous is very severe or lethal
  • some recessively inherited
  • Supportive therapy
  • No consensus for splenectomy indications
Hereditary Spherocytosis

• Molecular pathology
  • Partial deficiency of spectrin
  • Combined deficiency of spectrin and ankyrin
  • Molecular Defects:
    • mutations of ankyrin: most common
    • mutations of band 3 protein
    • mutations of protein 4.2 (common in Japanese)
    • Others: β & α spectrin, protein 4.9 are rare
Case 4 C

18 yr old male complains of acute pain in his back, Dizziness, Fatigue, Shortness of breath and Headaches for the last 6 hours. He has had similar attacks in the past. P/E

Xray spine
Sickle Cell Disease

- Inherited as autosomal recessive
- Point mutation in beta globin gene ($\beta_6$ Glu $\rightarrow$ Val)
- Gene occurs in 8% of African-Americans
Sickle Cell Anemia Clinical Effects

- Chronic hemolytic anemia
  - Gallstones (bilirubin)
  - Risk of red cell aplasia (Parvovirus)
  - Decreased vascular tone
- Susceptible to infection
  - Functional asplenia
  - Infarcted tissue
  - Numerous manipulations
- Vaso-occlusion
- Autosplenectomy
Vascular beds susceptible to injury

- Brain
- Lung
- Ankle
- Erectile vasculature of the penis
Infectious complications of Sickle cell anemia

1- Related to absent spleen
   – Pneumococcus infections
   – Hemophilus infections
   – Dramatically improved with the use of prophylactic penicillin in childhood

2- Others: staphylococcal, Ostemyelilits
Sickle Cell Anemia Vaso-occlusion: Unique pathophysiologic feature

• Causes acute and chronic organ damage

• Acute complications
  – Sickle cell vaso-occlusive pain crisis
  – Hepatic crisis
  – Splenic crisis
  – Priapism

• Chronic organ damage
  – Stroke
  – Chronic lung disease with pulmonary hypertension
  – Renal failure
  – Avascular necrosis of bone
Sickle cell: avascular necrosis of the hip
Sickle Cell Anemia Vaso-occlusive Events (Pain Crisis)

• Precipitating factors
  – Hypoxia
  – Acidosis
  – Fever
  – Infection
  – Dehydration
  – Exposure to cold

• Perceived factors
  – Exposure to cold 34%
  – Emotional stress 10%
  – Physical exertion 7%
  – Pregnancy 5%
  – Alcohol consumption 4%
  – Not identified 40%

Sickle cell vaso-occlusive crisis

• Serious complication of sickle cell anemia
• Risk of acute event (<48 hours)
  – Acute chest syndrome
  – Splenic sequestration
  – Massive hemolysis
  – Risk of sudden death
Sickle Cell Anemia Painful Events: Management Principles

• Correct fluid/electrolyte abnormalities; use hypotonic fluid and limit volume to avoid overhydration

• Treat any underlying illness

• Opioid analgesics (meperidine is not recommended)

• Blood transfusion is not indicated for an uncomplicated pain episode

• Incentive spirometry should be used during waking hours
Prevention of Painful Episodes

• Hydroxyurea increases Hgb F
  – Reduces the frequency of painful episodes, acute chest syndrome, RBC transfusions and hospitalizations

• Non-pharmacologic approaches have not been fully evaluated

• Prophylactic transfusions showed a decreased incidence of painful crisis in pregnancy
Addiction and pseudo-addiction

• Addiction (abuse)
  – Overwhelming involvement with obtaining and using mind-altering drug

• Pseudo-addiction
  – Relief seeking behavior misidentified as addictive behavior
The “difficult” patient with sickle cell disease

- Approximately 5% of patients account for 25-50% of hospitalizations
- High use group has >10 hospitalizations/year
- Hospital stay is longer (10 days vs. 6 days)
- Young, poor, unemployed, male
- Difficult interpersonal interactions
- May be associated substance abuse
- Higher death rate
Acute Chest Syndrome: Clinical Findings

• Etiology - multifactorial
  – Rib infarct causing splinting/atelectasis
  – Pulmonary fat embolism
  – Infection (mycoplasma, chlamydia, viral)

• Indistinguishable from pneumonia
  – Pleuritic chest pain, fever, cough, tachypnea, hypoxia

• Laboratory diagnosis
  – Worsening anemia
  – Infiltrate on chest radiograph
## Acute Chest Syndrome: Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete recovery</td>
<td>91%</td>
</tr>
<tr>
<td>- Weaned of supplemental O₂</td>
<td>3.1±1.9 days</td>
</tr>
<tr>
<td>- Hospital discharge</td>
<td>5.4±2.3 days</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>3%</td>
</tr>
<tr>
<td>Death</td>
<td>6%</td>
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</table>
Acute Chest Syndrome: Prevention and Treatment

• Incentive spirometry
• Treat possible underlying infection
• Bronchodilators and supplemental oxygen
• RBC transfusion therapy
  – Simple transfusion
  – Exchange transfusion for:
    • Multiple lobes involved
    • Rapidly progressing
    • Worsening hypoxia
Deferasirox: Oral Iron Chelator in chronic blood transfusion

- Tridentate* iron chelator
  - An oral, dispersible tablet
  - Administered once daily
  - Highly specific for iron
- Chelated iron excreted mainly in feces (< 10% in urine)
Sickle Cell Trait

- Protection against malaria
- Genitourinary complications
  - Hyposthenuria/papillary sloughing
  - Painless hematuria
  - UTI during pregnancy
- Vaso-occlusive complications
  - Splenic infarction with hypoxia
  - Sudden death
  - Rhabdomyolysis

Sickle cell trait areas shown in orange stripes
Case 4 D

13 yr old male complains of skin pigmentation, abdominal swelling and pallor. He has been receiving blood transfusions since the age of 9 months. Stunted growth. Hb 6, MCV 55, retcs16%, s. Ferritin 5000.

P/E

Xray
## Beta Thalassemia

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Genotype</th>
<th>Hgb (g/dl)</th>
<th>Hgb Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor (Trait)</td>
<td>$\beta^+/\beta^+$ or $\beta/\beta^-$</td>
<td>10-13</td>
<td>$\uparrow$ Hgb A2, $\uparrow$ Hgb F</td>
</tr>
<tr>
<td>Intermedia</td>
<td>$\beta^+/\beta^+$</td>
<td>7-10</td>
<td>$\uparrow$ Hgb A2, $\uparrow\uparrow$ Hgb F</td>
</tr>
<tr>
<td>Major (Cooleys)</td>
<td>$\beta^+/\beta^-$ or $\beta^-/\beta^-$</td>
<td>&lt; 7</td>
<td>$\uparrow$ Hgb A2, $\uparrow\uparrow\uparrow$ Hgb F</td>
</tr>
</tbody>
</table>
Most commonly reported mutations in the B-globin gens in Jordanians

- Eight mutations constituted about 86% of the Jordanian thalassemic mutations
- These mutations were IVS1-110 (G>A) (25%), IVS2-1 (G>A) (15%),
- IVS2-745 (C>G) (14.2%), IVS1-1 (G>A) (10%), IVS1-6 (T>C) (8.3%), codon 37 (G>A) (6.3%),
- codon 39 (C>T) (4.6%), and codon 5 (-C) (3.8%)
Beta Thalassemia: Clinical Manifestations/complication

Osteoporosis

Extramedullary erythropoiesis/ tumor effect

Iron overload: skin, heart, liver, endocrine organs

Dilated cardiomyopathy secondary to severe anemia

Growth and development delayed

Large splenomegaly
Treatment/ Prevention of B thal major

- Blood Transfusion
- Iron chelation: deferroxamine (parenteral)
- Splenectomy
- Allo-BMT
- Supportive
- Prevention

Oral deferasirox