PEDIATRICS   **Hematology**

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THALASSEMIA

- It is the most *common genetic disorder* on worldwide basis.
- Children with thalassemia have *shorter RBC life, more HbF, & the RBC^S are more sensitive to the oxidative stress.*

Epidemiology

- There are *> 200 mutations* for β-thalassemia (most of them are rare, about 20 mutations represent 80% of the total).
- About 3% of the world's population carry genes for β-thalassemia.
- About 5-10% of the population of south-east Asia carry genes for α-thalassemia.
- Normally, there are 2 β-globin genes & 4 α-globin genes, which → tetrameric globin protein which combines with heme → hemoglobin (Hb).

Pathophysiology

- Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Abnormalities in these proteins are referred to as hemoglobinopathies. There are approximately 800 variant hemoglobins.
- After 8 wk of fetal life, the embryonic hemoglobins are formed: Gower-1 (ζ2ε2), Gower-2 (α2ε2), and Portland (ζ2γ2). At 9 wk of fetal life, the major hemoglobin (Hb) is Hb F (α2γ2). At approximately 1 mo of fetal life, Hb A (α2β2) appears, but does not become the dominant hemoglobin until after birth, when Hb F levels start to decline. A minor hemoglobin, Hb A2(α2δ2) appears shortly before birth and remains at a low level after birth. The final hemoglobin distribution pattern that occurs in childhood is not achieved until at least 6 mo of age, and sometimes later. The normal hemoglobin pattern is >95% Hb A, ≤3.5 Hb A2, and <2.5% Hb F.

- *In β-thalassemia*, there is an excess of the α-globin chains relative to the β-globin chains & γ-globin chains, which → α-globin tetrameric inclusions (α4) which interact with RBC membrane & ↓ RBC survival → anemia & ↑ erythroid production. There are normal levels of γ-globin & δ-globin chains production, which → ↑ HbF (α2γ2) & ↑ HbA2 (α2δ2) respectively.
- *In α-thalassemia*, there is an excess of the β-globin & γ-globin chains relative to α-globin chains, which → Bart's Hb (γ4) in fetal life & HbH (β4) after birth, which → extravascular hemolysis.
- In bone marrow, the thalassemic mutations disrupt the maturation of the RBC^S, which → *"ineffective erythropoiesis"* i.e. the marrow is hyperactive but there are relatively few reticulocytes associated with severe anemia.

HOMOZYGOUS β-THALASSEMIA (THALASSEMIA MAJOR OR COOLEY'S ANEMIA)

Clinical presentations

- Patients usually become symptomatic during the 2nd 6 months of life (if untreated) due to progressive hemolytic anemia with profound weakness & cardiac decompensation (Hb is about 1-6 g/dl).
- Blood transfusion depends on the ability of the child to compensate for the degree of anemia (usually from 2 months-2 years of life).
- Severe anemia may → fatigue, poor appetite, & lethargy.
- The classic presentation of the sever thalassemic facies (frontal bossing, mandibular malocclusion, & prominent malar eminence due to extra-medullary hematopoiesis), pathologic fractures, marked hepatosplenomegaly, & catchexia is still seen in some developing countries. The spleen may become so enlarged, which → mechanical discomfort & 2ry hypersplenisim.
- Pallor, hemosiderosis, & jaundice may → the greenish-brownish complexion of the patients color.
- Transfusion therapy → ↓ severity of these features & ↑ "transfusional hemosiderosis" due to iron overload especially in developed countries.

Iron overload may → • Liver fibrosis & cirrhosis, Diabetes mellitus (pancreas), Growth retardation & hypogonadic hyoogonadism (pituitary glands, testes, & ovaries), Hypocalcemia & osteoporosis (parathyroid gland), Arrythmias, myocarditis, & intractable heart failure (heart)

Laboratory findings

- Hb-electrophoresis → absence or ↓ HbA relative to HbF.
- Infants usually born only with HbF.
- With time, there will be severe anemia, few reticulocytes, numerous nucleated RBC^s, & microcytosis (with almost no normal appearing RBC on the smear).
- The unconjugated serum bilirubin is usually ↑.
- Even if without transfusion, there will be iron accumulation (↑ serum ferritin & ↑ transferrin saturation).
- Bone marrow hyperplasia can be seen on radiographs.

Treatment

- *Regular blood transfusion* (a post-transfusion Hb level of 9.5 g/dl is the goal).
- Excessive iron store from transfusion cause many of the complications of *β-thalassemia major.* Accurate assessment of excessive iron stores is essential to optimal therapy. The serum ferritin is useful in assessing iron balance trends but does not accurately predict quantitative iron stores. Quantitative iron by "liver biopsy" is the standard method for accurately determining iron stores for patients. T2*MRI software is now being used to estimate iron stores in the liver & heart among patients with *β-thalassemia major.*

- Excessive iron stores can be prevented by use of deferoxamine (desferal) or deferasirox (Exjade). *Chelation therapy* by desferoximine is given subcutaneously over 10-12 hrs/day, 5-6 day/week. S/E of desferoxamine → ototoxicity, retinal changes, bone dysplasia with truncal shortening. The oral iron chelator deferasirox (Exjade) is commonly available in USA. For many patients & families, deferasirox has replaced deferoxamine. Althoug the optimal dose of deferasirox is well defined, some patients have a less than-expected response to the maximum approved dose (30 mg/kg/day).
- *Splenoctomy* may be indicated for patient with :
  • thalassemia intermedia & falling steady state of Hb.
  • ↑ transfusion requirement.
  S/E of splenoctomy → there may be serious infections, so, all patients should be fully immunized against encapsulated bacteria before splenoctomy & they should be on long-term penicillin prophylaxis after that.
- *Bone marrow transplantation* may be successful for some patients (most patients <15 yrs of age, without iron overload, without hepatomegaly, & who have HLA-matched siblings).

OTHER β- THALASSEMIA TYPES

◙ **THALASSEMIA INTERMEDIA** → microcytic anemia (Hb>7 g/dl), growth failure, hepatosplenomegaly, hyprbilirubinemia, thalasemic facies which usually develop at 2-5 yrs of age.

◙ **THALASSEMIA MINIMA & MINOR** → more severe than thalassemia trait but less severe
than thalassemia intermedia.

◙ **THALASSEMIA TRAIT** → minimal or no anemia (Hb is about 9-12 mg/dl), microcytosis, & ↑ RBC count. Hb-electrophoresiss may reveal ↑ HbF & ↑ HbA2.

α-THALASSEMIA

- It is most commonly found in south-east Asia.
- Infants are identified in the newborn period by ↑ production of Bart's Hb (γ4) during the fetal life & its presence at birth.
- There are 4 α-globin genes & 4 deletional thalassemia phenotypes as follows :
  1. Deletion of 1 α-globin gene → *silent carrier* with normal appearance.
  2. Deletion of 2 α-globin genes → *α-thalassemia trait* with mild microcytic anemia.
  3. Deletion of 3 α-globin genes → *HbH disease* with moderate microcytic anemia, splenomegaly, & jaundice.
  4. Deletion of 4 α-globin genes → *α-thalassemia major* with hydrops fetalis.
- Diagnosis → by : • exclusion (↓ MCV without identifiable cause).
  • number of missing α-genes by molecular technique & PCR.

GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY (G6PDD)

- It is an *X-linked* disease where hemolysis is mainly confined to males.
- is responsible for 2 clinical syndromes, **episodic hemolytic anemia**, and **chronic nonspherocytic hemolytic anemia.**
- This X-linked deficiency affects more than **400 million people** worldwide, representing an overall **4.9%** global prevalence.
- G6PD catalyzes the conversion of glucose 6-phosphate to 6-phosphogluconic acid. This reaction produces NADPH, which maintains glutathione in the reduced, functional state. Reduced glutathione provides protection against oxidant threats from certain drugs and infections that would otherwise cause precipitation of hemoglobin (Heinz bodies) or damage the RBC membrane.
- Most heterozygous females do not have evident clinical hemolysis after exposure to oxidant drugs. Rarely, the majority of RBCs is G6PD deficient in heterozygous females because the inactivation of the normal X chromosome is random and sometimes exaggerated **(Lyon-Beutler hypothesis).**
- **Variants:** The **normal** enzyme found in most populations is designated **G6PD B+**. A normal variant, designated **G6PD A+**, is common in Americans of African descent.
- Approximately **13% of male Americans of African** descent have a mutant enzyme (**G6PD A−)** that results in a deficiency of RBC G6PD activity (5-15% of normal).
- **Italians, Greeks, and other Mediterranean, Middle Eastern, African, and Asian** ethnic groups also have a high incidence, ranging from **5% to 40%,** of a variant designated **G6PD B−** (**G6PD Mediterranean**).
- A third mutant enzyme with markedly reduced activity (**G6PD Canton**) occurs in approximately **5%** of the **Chinese** population.
- **Clinical presentations:** The most common manifestations of this disorder are neonatal jaundice and episodic acute hemolytic anemia, which is induced by **infections** (as hepatitis & sepsis), certain **drugs**, and **fava beans**.
- **Most individuals with G6PD deficiency are asymptomatic**, with no clinical manifestations of illness unless triggered by infection, drugs, or ingestion of fava beans.
- Typically, hemolysis ensues in about **24-48 hr** after a patient has ingested a substance with oxidant properties. In severe cases, hemoglobinuria and jaundice result, and the hemoglobin concentration may fall precipitously.
- G6PD deficiency can produce **hemolysis in the neonatal period**. In G6PD A−, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. In newborns with the G6PD B− and G6PD Canton varieties, hyperbilirubinemia and even kernicterus may occur. When a **pregnant** woman ingests oxidant drugs, they may be transmitted to her G6PD-deficient fetus, and hemolytic anemia and jaundice may be apparent at birth.

- **Chronic nonspherocytic hemolytic anemia** has been associated with **profound deficiency of G6PD** caused by enzyme variants, particularly those defective in quantity, activity, or stability. Persons with **G6PD B−** enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant drugs. Splenectomy is of little value in these types of chronic hemolysis.

- **Drugs** that elicit hemolysis in these individuals include aspirin, sulfonamides, Nalidixic acid, Chloramphenicol, Nitrofurantoin, Vitamin K analogs, Methylene blue, and antimalarials, such as primaquine. The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency.

- In some individuals, ingestion of **fava beans** also produces an acute, severe hemolytic syndrome, known as *favism*. Fava beans contain **divicine, isouramil, and convicine**, which ultimately lead to production of **hydrogen peroxide** and other reactive oxygen products. Favism is thought to be more frequently associated with the **G6PD B−** variant (as in Iraq).

- **Investigations:** The onset of acute hemolysis usually results in a precipitous fall in hemoglobin and hematocrit. If the episode is severe, the hemoglobin binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine.

- Unstained or **supravital preparations of RBCs** reveal precipitated hemoglobin, known as **Heinz bodies**. The RBC inclusions are not visible on the Wright-stained blood film. Cells that contain these inclusions are seen only within the **first 3-4 days** of illness because they are rapidly cleared from the blood. Also, the blood film may contain red cells with what appears to be a **bite** taken from their periphery and **polychromasia** (evidence of bluish, larger RBCs), representing reticulocytosis.

- The diagnosis depends on direct or indirect demonstration of **reduced G6PD activity** in RBCs. By direct measurement, enzyme activity in affected persons is **≤10% of normal**.

- Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells in the A− variety. Testing may therefore have to be **deferred for a few weeks** before a diagnostically low level of enzyme can be shown. The diagnosis can be suspected when G6PD activity is within the low-normal range in the presence of a high reticulocyte count. G6PD variants also can be detected by **electrophoretic and molecular analysis.**

- **Treatment:** If severe hemolysis has occurred, **supportive therapy** may require **blood transfusions**, although recovery is the rule when the oxidant agent is discontinued.

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