Congenital Hemolytic Anemia

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KEYWORDS

• Hemolysis • Jaundice • Aplastic crisis • Splenectomy

KEY POINTS

- Congenital hemolytic anemia typically presents in childhood, but more milder forms can result in a delayed presentation until adulthood.
- The congenital hemolytic anemias can be broadly classified as red blood cell (RBC) membrane disorders, RBC enzyme disorders, or hemoglobinopathies.
- Congenital hemolytic anemias cause a baseline level of anemia, which can be exacerbated by episodes of hyperhemolysis or aplasia and result in symptomatic transfusion dependent anemia.
- Complications of congenital hemolytic anemia, such as gallstones, are common in adolescents and young adults.
- Splenectomy is an effective treatment for some congenital hemolytic anemias but is not necessary in all of the congenital hemolytic anemias.

INTRODUCTION

Red blood cells (RBCs) are biconcave discs with a diameter of 7.5 μm.[1] RBCs are efficient vehicles for oxygen exchange, and their function depends upon healthy hemoglobin and an easily deformed shape. RBCs depend upon anaerobic metabolism in order to maintain their shape, prevent oxidative damage, and maintain hemoglobin in its functional form. The average lifespan of an RBC is 100 to 120 days.[2] Premature destruction of red blood cells due to acquired or congenital abnormalities in hemoglobin, RBC membrane proteins, or in enzymes critical for RBC metabolism results in hemolytic anemia.[2] While there are several different types of hemolytic anemias, they are all characterized by similar features. RBCs have a shortened lifespan, and there is typically a compensatory increase in erythrocytosis. Patients are variably symptomatic from the anemia, and the anemia may worsen depending upon the clinical scenario.

Conflict of Interest: The author has served on advisory boards for Baxalta and CSL Behring on topics unrelated to hemolytic anemia.

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Hemolytic anemias are broadly classified into 2 groups: immune and nonimmune. In this article, the focus will be on congenital nonimmune hemolytic anemias.

The congenital hemolytic anemias are further divided into 3 categories: (1) disorders of the RBC membrane, (2) disorders of RBC enzymes, and (3) abnormal hemoglobin structures (Table 1). The most common of these disorders are hereditary spherocytosis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and alpha and beta hemoglobinopathies, respectively.[3] Although each of these anemias mediates hemolysis through different mechanisms, their clinical presentations and laboratory features are similar.

CLINICAL PRESENTATION

The congenital hemolytic anemias typically present in infancy or in early childhood. There may be a family history of hemolytic anemia that draws attention to the condition, or the infant may have significant hyperbilirubinemia out of proportion to what is expected in the newborn period. Alternatively, the patient may present at times of increased hemolysis with anemia, hyperbilirubinemia, and reticulocytosis. At baseline, the symptoms may be so limited that they go undetected. Patients may not present until adulthood in mild forms of congenital hemolytic anemia, but severe forms present in childhood. In an adult with a direct antiglobulin test-negative hemolytic anemia, a congenital hemolytic anemia should be considered.[4] The patients, regardless of age, present with pallor, anemia, jaundice, indirect hyperbilirubinemia, splenomegaly (not universally), and reticulocytosis.

Baseline

At baseline, the congenital hemolytic anemias often result in a mild-to-moderate chronic level of hemolysis that is well compensated by an increased reticulocytosis, and only mild-to-moderate anemia results. In each of the congenital hemolytic anemias presented, more severe forms can be present but are rare. In those instances, the chronic hemolysis occurs at a faster rate, and more significant anemia can develop.

Hemolytic Event

Although each of the congenital hemolytic anemias result in a baseline steady state that is largely asymptomatic, stresses such as infection, drugs, or toxins can result in increased rates of hemolysis and subsequent severe, transfusion-dependent anemias. In RBC membrane defects, increased hemolysis can occur, with illness likely due to increased splenomegaly and thus increased RBC destruction. The RBC enzyme disorders result in increased hemolysis with drug exposure, illness, or with certain foods as a result of increased oxidative stress.

Table 1
Types of congenital hemolytic anemia

Membrane and Cytoskeleton Defects	Enzyme Defects	Hemoglobin Defects
1. Hereditary spherocytosis (HS)	1. Glucose 6 phosphate dehydrogenase (G-6-PD) deficiency	1. Sickle cell disease
2. Hereditary elliptocytosis (HE)	2. Pyruvate kinase (PK) deficiency	2. Alpha thalassemia
3. Hereditary pyropoikilocytosis (HPP)		3. Beta thalassemia
		4. Unstable hemoglobin