Hemolytic Disorders Causing Severe Neonatal Hyperbilirubinemia

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KEYWORDS

• Bilirubin • Hemoglobin • Anemia • Jaundice • Next-generation DNA sequencing • Kernicterus • BIND • End-tidal carbon monoxide

KEY POINTS

- A shortened erythrocyte life span, because of hemolytic disorders, is a common cause of extreme neonatal hyperbilirubinemia.
- Clinical and laboratory examinations can frequently identify the underlying cause of extreme neonatal hyperbilirubinemia.
- Newer diagnostic tests include end-tidal carbon monoxide to identify hemolytic jaundice, eosin-5-maleimide (EMA) flow cytometry to identify red blood cell (RBC) membrane defects such as hereditary spherocytosis (HS), and next-generation sequencing (NGS) of relevant genes to look for mutations and polymorphisms.

NEONATAL HEMOLYTIC DISORDERS

After RBCs are released from the marrow into the blood, they circulate for about 120 days before they are culled by the reticuloendothelial system and their constituents recycled.[1] It is widely accepted that the circulating life span of RBCs in neonates is significantly shorter than 120 days, perhaps approximating 80 days.[2–5] When a neonate's RBC life span is significantly shorter than 80 days, because of intrinsic or extrinsic factors, erythropoiesis increases in an attempt to compensate, as evidenced by a rise in reticulocyte count. However, when RBC production cannot increase sufficiently to keep pace with the increased loss of RBCs because of their short life

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span, the hematocrit and amount of hemoglobin decrease, defining the condition as hemolytic anemia.

During the first days and weeks after birth, the major adverse consequence of a short RBC life span is hyperbilirubinemia,[6,7] which is because each molecule of heme liberated from RBC by hemolysis is metabolized to 1 molecule of bilirubin.[6–10] High levels of bilirubin in the serum can lead to transient or permanent neurologic impairment.[11–13]

A week or so after birth, the bilirubin-metabolizing system has generally matured sufficiently to conjugate and excrete the bilirubin load imposed by a moderately foreshortened RBC life span. Thus, in neonates with a shortened RBC life span, jaundice is the primary problem during the first days, and then anemia becomes the more significant issue in the weeks that follow. In some instances, a relatively slow insidious drop in hemoglobin culminates in a clinical deterioration, with pallor, poor feeding, tachypnea, and tachycardia, a clinical picture that somewhat resembles that of an infectious process. Such neonates may present to emergency departments with significant unanticipated anemia requiring emergent transfusion.[13]

The most common causes of neonatal hemolytic jaundice and anemia are listed in Table 1. The laboratory tests required to confirm hemolysis are listed in Table 2; these tests are divided into 2 categories, the first being those that indicate accelerated hemoglobin metabolism and the second being those that confirm accelerated erythropoiesis to compensate for hemolysis. At the onset of a hemolytic episode, the tests indicating hemolysis usually yield positive result, whereas those indicating accelerated erythropoiesis in response to the hemolysis may require several days before they give positive result.

HEMOLYTIC DISORDERS ARE FREQUENTLY RESPONSIBLE FOR EXTREME NEONATAL HYPERBILIRUBINEMIA

Intermountain Healthcare is a not-for-profit health care system in the western United States that owns and manages 18 hospitals with labor and delivery services. A review of 10 years of data from the Intermountain Healthcare system revealed

Table 1
Causes of neonatal hemolytic jaundice

Varieties	Examples
Alloimmune	ABO hemolytic disease Rh hemolytic disease Hemolytic disease involving RBC antigens (Kell, Kidd, Duffy)
Mutations in RBC structural proteins	HS Hereditary elliptocytosis Pyropokilocytosis
Mutations in RBC enzymes	G6PD deficiency Pyruvate kinase deficiency Others
Unstable hemoglobins	F Poole Hasharon Others
Microangiopathic hemolytic disorders	DIC Infection without DIC T-activation Infantile pyknocytosis

Abbreviations: DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase.