Glucose-6-Phosphate Dehydrogenase Deficiency and the Need for a Novel Treatment to Prevent Kernicterus

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KEYWORDS

• Hyperbilirubinemia • Bilirubin • Kernicterus • G6PD deficiency • Jaundice • Neurotoxicity • Activator • Chaperone

KEY POINTS

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency increases the risk of kernicterus in jaundiced newborns.
- G6PD is a major source of protection against bilirubin-induced oxidative stress in the developing brain.
- There is need in both developed and developing nations for a novel treatment for kernicterus, especially in regions with a high rate of G6PD deficiency.
- The authors propose a small-molecule activator or pharmacologic chaperone for G6PD as a therapy for kernicterus in both G6PD-deficient and -normal infants with hyperbilirubinemia.

INTRODUCTION

Approximately 80% of newborns worldwide have some degree of hyperbilirubinemia and visible jaundice.[1] Severe cases of hyperbilirubinemia can progress to kernicterus and lead to permanent developmental disorders. Several risk factors contribute to hyperbilirubinemia and kernicterus, including glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is one of the most common human enzymopathies. In the developing world, lack of access to common treatments for hyperbilirubinemia, along with a high rate of G6PD deficiency, leads to a high incidence of kernicterus. In this article, the authors highlight the need for a novel therapy to prevent kernicterus and discuss the pharmacologic activation of G6PD as a promising therapeutic strategy.

Disclosure Statement: The authors have nothing to disclose.
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Clin Perinatol 43 (2016) 341–354
http://dx.doi.org/10.1016/j.clp.2016.01.010 perinatology.theclinics.com
0095-5108/16/$ – see front matter

HYPERBILIRUBINEMIA AND KERNICTERUS

Hyperbilirubinemia results from increased bilirubin production coupled with inefficient bilirubin excretion. Hemolysis and subsequent heme breakdown produce bilirubin, which is conjugated and excreted in the liver. However, an immature liver-conjugating ability in newborns leads to reduced bilirubin removal and increased levels of bilirubin in circulation.

Low to moderate levels of total serum/plasma bilirubin (TB) levels (<20 mg/dL) are nontoxic and can be reduced by noninvasive treatments such as phototherapy, which uses light in a narrow wavelength band with a peak around 460 to 490 nm to photodegrade bilirubin into excretable byproducts. In cases of severe hyperbilirubinemia, exchange transfusion is used. Other therapies, less commonly used, include intravenous immunoglobulin (mechanism of action unknown) and pharmacologic therapies to reduce bilirubin production or increase bilirubin conjugation.[2]

If severe hyperbilirubinemia is left untreated, bilirubin can cross the blood-brain barrier, leading to acute bilirubin encephalopathy, which is reversible if identified and treated early. If chronic, kernicterus can result, which is characterized by lethargy, decreased feeding, high-pitched cry, fever, seizures, and even death. Up to 84% of infants with kernicterus will develop chronic bilirubin encephalopathy, characterized by permanent movement disorders, mental retardation, and hearing loss.[3]

It is difficult to estimate the incidence of kernicterus because of delayed diagnosis, an error in the ICD coding, underreporting, or lack of reporting in third-world countries.[4] The incidence of severe hyperbilirubinemia is estimated to be 2 to 45 per 100,000 births, and of kernicterus to be 0.4 to 2.7 per 100,000 births in developed countries.[5] The incidence of kernicterus in developing countries is higher due to a variety of factors, such as poor infrastructure, lack of resources, genetic differences, prematurity, low birth weight, home birthing, underfeeding, and sepsis.[5–7]

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

G6PD deficiency is one of the most common human enzymopathies and is estimated to affect 400 million people worldwide, with 11 million G6PD-deficient infants born each year.[8,9] The deficiency is caused by single-nucleotide polymorphisms (SNPs) leading to single amino acid changes in the protein. More than 400 SNPs, responsible for 160 different amino acid changes, have been observed in G6PD deficiency.[10,11] These mutations can cause deficiencies of varying severities and are classified into 4 clinical categories (**Table 1**). Most of the G6PD deficiencies can be accounted for by a few common and relatively mild (class II or III) mutations,

Table 1
Clinical classification of glucose-6-phosphate dehydrogenase mutations

Classification of G6PD Mutations		Clinical Outcome
Class I	<10% activity	Severe; CNSHA
Class II	<10% activity	Severe episodes of hemolytic anemia
Class III	10%–60% activity	Mild episodes of hemolytic anemia
Class IV	60%–150% activity	Asymptomatic

Adapted from Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet 2008;371:64–74.