JNP

Understanding and Managing Glucose-6-Phosphate Dehydrogenase Deficiency

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ABSTRACT

Glucose-6-phosphate dehydrogenase deficiency (G-6-PDD) is a genetic defect that leaves erythrocytes vulnerable to hemolysis upon certain exposures. The resulting anemia, although generally self-limiting, may be severe enough to necessitate exchange transfusion. In addition, neonates are at risk from an unusually abrupt rise in bilirubin that is strongly associated with kernicterus. Although the condition is often benign, the potential for significant morbidity makes ignorance of the defect a threat to patients and quality of care. In this article we review the history, pathophysiology, clinical manifestations, differential diagnosis, diagnostic screening, and the role of the nurse practitioner in caring for patients with this disorder.

Keywords: anemia, G-6PD deficiency, hemolytic anemia, neonatal hyperbilirubinemia, Red blood cell enzyme deficiency

CJ, a high school basketball player, woke up one morning with a fever and, reluctant to miss practice, took antibiotics prescribed for his sister. A day later, pale and complaining of severe back pain, he was sent from school to his primary care provider. A careful record review revealed to the nurse practitioner (NP) caring for him that CJ had glucose-6-phosphate dehydrogenase deficiency (G-6-PDD). His previous experience with hemolysis was as a newborn. After 15 years of excellent health, CJ's parents remained only vaguely aware of his diagnosis, highlighting how far from awareness the defect is even among those directly impacted. Because both quality of life and longevity remain unaltered for the majority of those susceptible to G-6-PDD, the disorder remains unfamiliar despite significant prevalence and the potential for serious morbidity.[1] The purpose of this article is to foster broader awareness and prompt recognition of G-6-PDD to prevent hemolysis and its sequelae. The pathophysiology, clinical presentation, differential diagnosis, diagnostic screening, and the role of the NP in caring for patients with G-6-PDD are reviewed.

OVERVIEW

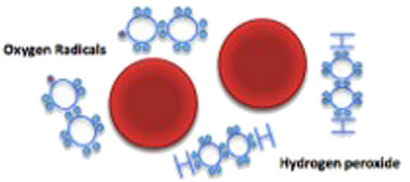
G-6-PDD is a genetic disorder responsible for hemolysis and anemia, but, unlike sickle-cell disease, is caused by an erythrocyte enzyme deficiency. Insufficient stores of glucose-6-phosphate dehydrogenase prevent red bloods cells from defending themselves against oxidative damage. Most often, afflicted persons are merely predisposed to the possibility of cell destruction in the presence of certain triggers that they must learn to avoid. Hemolytic attacks may require hospital resources, but are generally self-limiting; however, deficiency can sometimes take the form of a chronic debilitating hemolytic disease,[2] or generate an exponential increase in neonatal bilirubin that is more likely to cause kernicterus because of its extremely sudden onset. Thirty percent of infants with kernicterus in the United States are G-6-PDD cases,[3] although Nock et al.[4] asserted that G-6-PDD is rarely considered a cause for neonatal hyperbilirubinemia. Due to the risks of hemolysis and the role G-6-PDD plays in the prevention of malaria worldwide, this is a disorder that deserves better recognition.[5]

PREVALENCE

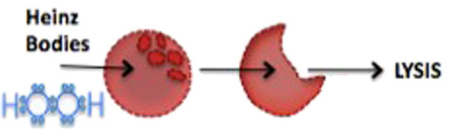
G-6-PDD is the most common enzyme defect, thought to affect about 470 million people—an almost 5% global prevalence. Estimates are highest in sub-Saharan Africa, the Middle East, and

Box 1: The Role of Glutathione in the Prevention of Hemolysis

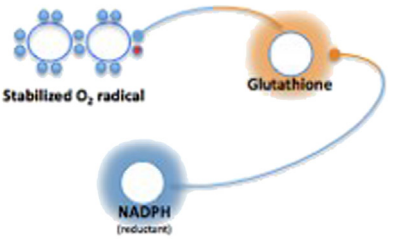
As oxygen carriers, red blood cells are highly vulnerable to oxygen radicals which are easily converted to reactive oxygen species like hydrogen peroxide (H_2O_2).



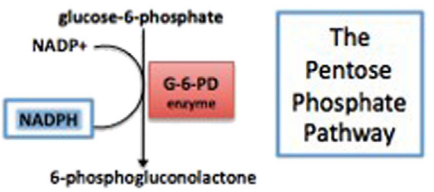
H_2O_2 causes the hemoglobin within red cells to precipitate into Heinz bodies. The spleen detects and pinches off the Heinz bodies and ultimately removes the affected cells from the bloodstream (hemolysis).



Glutathione, an anti-oxidant, prevents H_2O_2 formation by donating the electron that oxygen radicals are missing. These extra electrons are created by a metabolic process called the Pentose Phosphate Pathway (PPP), in which G-6-PD plays an essential role.



Deficiency of G-6-PD limits the rate at which the PPP can create NADPH to fuel glutathione with the extra electrons it needs to inactivate reactive oxygen species.



Adapted from Luzzato & Poggi, 2008 (10), Cappellini & Fiorelli, 2008 (1) and Fibach & Rachmilewitz, 2008 (9).

Southeast Asia,[6] but emigration patterns are increasing encounters in industrialized nations.[1,3,7] Between 11% and 13% of African Americans are affected.[4]

HISTORY AND PATHOPHYSIOLOGY

During World War II, Dr. Ernest Beutler of the US Army's Malaria Research Project resolved the long-observed problem that a small subset of individuals consistently developed hemolytic anemia when treated for malaria with the drug primaquine.[8] All were African American, indicating a genetic instigator. Beutler demonstrated that hemolysis occurred as a result of inherent defect in the soldiers' red blood cells, where the oldest of the red blood cells had remarkably low levels of glutathione, a substance that protects the cell form oxidative stress. Oxidative stress is a condition where reactive oxygen species (consisting of radicals like the superoxide ion and nonradicals like hydrogen peroxide) overwhelm the capacity of antioxidants, like glutathione, to oppose them.[9] The oldest red cells were missing a key element in glutathione assembly, the reduced coenzyme nicotinamide adenine dinucleotide phosphate (NADPH). The oldest red cells were missing the reduced coenzyme nicotinamide adenine dinucleotide phosphate (NADPH), a key element in glutathione assembly. NADPH is produced by mitochondria, but without such organelle erythrocytes get their NADPH from the pentose phosphate pathway, a metabolic process that breaks down a small amount of glycolytic glucose. G-6-PD is an essential enzyme in this process.[10] Box 1 shows how glutathione prevents hemolysis. As red cells age, their stores of G-6-PD diminish, but, in Beutler's sick servicemen, the G-6-PD enzyme was entirely missing except in their very youngest red blood cells. Once G-6-PD is used up in a cell, NADPH