Red Blood Cell Enzyme Disorders

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KEYWORDS

• Glucose-6-phosphate dehydrogenase deficiency • Pyruvate kinase deficiency
• Other red cell enzyme disorders • Anemia • Splenectomy • Cholecystectomy

KEY POINTS

- Red blood cell enzyme disorders are important to recognize and diagnose for proper supportive care, monitoring, and treatment.
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder most commonly characterized by episodic hemolysis in the setting of oxidative triggers, such as fava beans, infections, and certain medications.
- Enzymopathies, such as pyruvate kinase deficiency, should be suspected in patients of all ages with a chronic hemolytic anemia in the absence of immune-mediated hemolysis, a hemoglobinopathy, or evidence of a red cell membrane disorder.
- Splenectomy partially ameliorates the anemia in most patients with pyruvate kinase deficiency and other red blood cell enzyme disorders.
- Glycolytic red cell disorders cause congenital hemolytic anemia with wide clinical heterogeneity and frequent complications, including neonatal jaundice, gallstones, and both transfusion-related and transfusion-independent iron loading.

INTRODUCTION

Mature red blood cells (RBC) are anucleate and devoid of ribosomes and mitochondria. Despite these limitations, RBCs survive 100 to 120 days in the circulation and effectively deliver oxygen to peripheral tissues. Glucose is the main metabolic substrate of RBCs, and it is metabolized by 2 major pathways: the glycolytic or "energy-producing" pathway and the hexose monophosphate (HMP) shunt or "protective" pathway (**Fig. 1**). The major products of glycolysis are ATP (a source of energy for numerous RBC membrane and metabolic reactions), nicotinamide adenine

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dinucleotide (a necessary cofactor for methemoglobin reduction by cytochrome b5 reductase), and 2,3-diphosphoglycerate (2,3-DPG; an important intermediate that modulates hemoglobin-oxygen affinity).

The consequence of red cell enzymopathies is hemolysis, and although these diagnoses are clinically diverse, the general laboratory findings, symptoms, and complications are similar. In these disorders, RBCs have a shortened life span, and clinical features vary from absent or mild anemia with episodic hemolysis to severe, chronic anemia requiring transfusions. Patients have a compensatory erythropoiesis, often with reticulocytosis, and, because of ongoing hemolysis, typically have scleral icterus or jaundice from elevation of the unconjugated bilirubin.

A hemolytic disorder should be suspected in the setting of a low hemoglobin, normal to elevated mean cell volume, elevated reticulocyte count, elevated indirect bilirubin level, and/or elevated lactate dehydrogenase (LDH). Testing for a RBC enzyme disorder should be pursued in patients with chronic hemolysis who have a negative direct Coombs test, no evidence of red cell consumption or a membranopathy, and a normal hemoglobin electrophoresis (Fig. 2). Suspicion for these

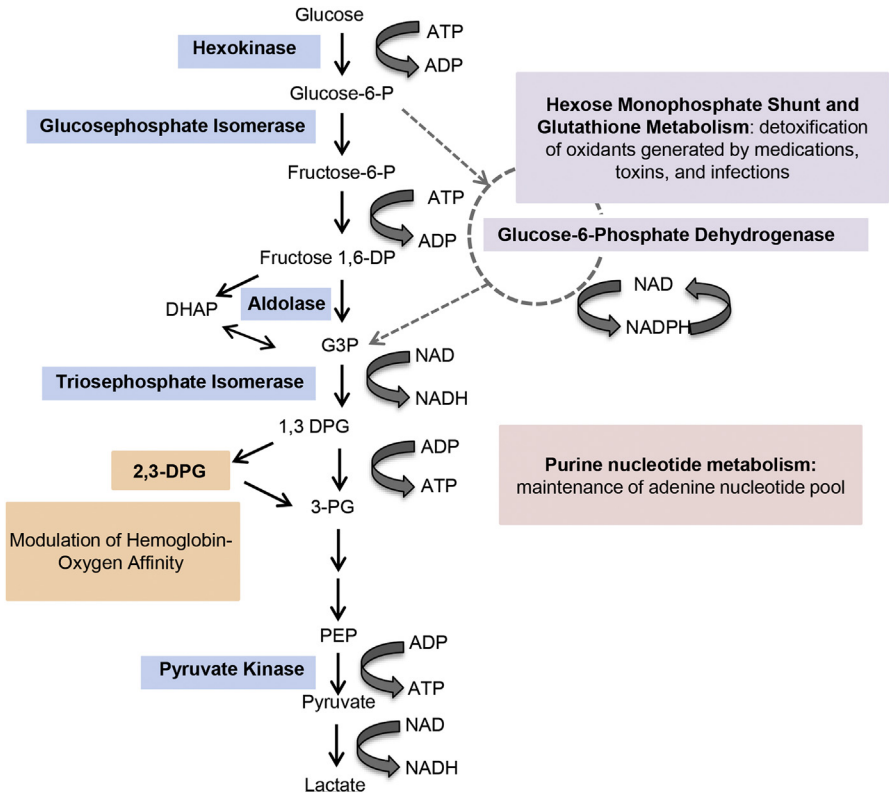

Fig. 1. Summary of overall glycolysis, hexose monophosphate shunt, glutathione metabolism, and red blood cell nucleotide metabolism. Blue boxes contain enzymes in glycolytic pathway that correlate with the more common glycolytic enzymopathies. 1,3-DPG, 1,3-diphosphoglycerate; 2,3-DPG, 2,3-diphosphoglycerate; 3-PG, 3-phosphoglycerate; DHAP, dihydroxyacetone phosphate; Fructose 1,6-DP, fructose 1,6-diphosphate; Fructose-6-P, fructose-6-phophate; G3P, glyceraldehyde-3-phosphate; Glucose-6-P, glucose-6-phosphate; PEP, phosphoenolpyruvate. *Dotted arrows* show the hexose monosphosphate shunt and glutathione metabolism pathway.