

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency **A Guide for the Referring Physician**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a group of hereditary disorders in which the activity of the erythrocyte enzyme G6PD is decreased. G6PD catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconate while reducing NADP to NADPH. The importance of G6PD in overall cell metabolism lies in its role in maintaining an adequate supply of NADPH, which is essential to keep several cellular systems in the reduced state. A deficiency of G6PD may result in hemolytic anemia.

G6PD deficiency is an X-linked recessive condition. The defect is usually expressed in affected males and is never transmitted from father to son but only from mother to son. Some females can be clinically affected as a result of homozygosity or the X inactivation process (Lyon hypothesis).

The prevalence of G6PD deficiency among the white population ranges from less than 1 in 1000 among northern Europeans to 50% of males among Kurdish Jews. G6PD deficiency of the type A- is very common in West Africa. In the United States the incidence among black males is approximately 11%.

MECHANISMS OF HEMOLYSIS:

The life span of G6PD deficient red cells is shortened under many circumstances. Reduction in enzyme activity may predispose to hemolysis because of the red cells' inability to tolerate oxidative stress, which usually results from a drug or infection. The production of H₂O₂ (and various free radicals) causes membrane damage and hemolysis.

There are some mutations in which the enzyme activity is so reduced that the life span of the red cells is shortened even in the absence of oxidative stress.

CLINICAL EFFECTS OF G6PD DEFICIENCY:

Although the G6PD gene defect is expressed in all tissues, the effect of a deficiency of the enzyme is more apparent in erythrocytes because of their long life span and absence of a nucleus to facilitate ongoing protein synthesis. Anemia is therefore the most frequent clinical manifestation of G6PD deficiency.

Variants not associated with enzyme deficiency

Some G6PD gene mutations are not associated with significantly reduced enzyme activity in erythrocytes. These variants have no clinical consequences. The most common variant, characterized by electrophoresis of the enzyme, is the G6PD type A, which is present in 20-40% of blacks. The normal or "wild type" enzyme is G6PD type B.

Mutations that cause anemia only in the presence of stress

In G6PD deficient subjects, hemolytic anemia may develop during the neonatal period, during infection, after ingestion of fava beans, or following exposure to certain chemicals (especially naphthalene mothballs) or drugs. The prototype of the most mild form of such deficiency is G6PD A- in which the red cell retains only approximately 10% of G6PD activity. This is encountered almost exclusively in African Americans. In G6PD A- deficiency hemolysis may be severe, but it is always self-limited since the young erythrocytes contain plenty of normal enzyme. G6PD Mediterranean is the

prototype of a more severe enzyme deficiency that produces anemia. Here the enzyme activity is approximately 1-2% of normal. Depending on the nature of the offending agent and the severity of the individual's enzyme deficiency, hemolysis affecting these individuals may be severe or even fatal.

The hemolytic episode in G6PD deficient subjects occurs within a few hours to several days after the insult. The episode is characterized by intravascular hemolysis: anemia with Heinz body formation, reticulocytosis, hemoglobinemia, hemoglobinuria, and jaundice. The peripheral blood smear characteristically reveals blister cells or eccentrocytes resulting from the removal of membrane and oxidized hemoglobin by macrophages.

Mutations that cause hereditary non-spherocytic hemolytic anemia

G6PD mutants that are associated with chronic non-spherocytic hemolytic anemia (CNHA) are rare. CNHA is usually first noted during infancy. In some instances neonatal jaundice is present. The severity of the hemolysis is variable with most patients have values between 8 and 9 gm/dl. Reticulocytosis is present. These patients often have splenomegaly but do not usually respond to splenectomy.

Special Situations

Favism: Favism is the acute and usually severe hemolysis that follows the ingestion of fava beans. This occurs exclusively in individuals with G6PD deficiency of the Mediterranean type. It is one of the gravest clinical consequences of G6PD deficiency. Favism can even occur in the breast-fed infant whose mother has ingested fava beans.

Neonatal Jaundice: Neonatal unconjugated hyperbilirubinemia may occur in some infants with G6PD deficiency even when the anemia is not severe. If it is untreated, kernicterus may occur. An increased incidence of icterus neonatorum has also been observed in Mediterranean or Asian infants with G6PD deficiency although not among full-term African American neonates with G6PD A- deficiency.

LABORATORY STUDIES

In the absence of hemolysis, the morphology of the red blood cells is usually normal. During hemolytic "crises", Heinz bodies (membrane-bound precipitates of denatured hemoglobin) develop initially. Depending upon the severity of the event, blister cells or "eccentrocytes", spherocytosis, and red cell fragmentation may be observed. Polychromasia and reticulocytosis are characteristic. Other abnormal findings are a high serum LDH, hyperbilirubinemia, and decreased serum haptoglobin. Diagnosis of G6PD deficiency depends on the demonstration of decreased enzyme activity by a screening test or enzyme assay. However, the G6PD value may be falsely normal in A- deficient individuals who have a high reticulocyte count at the time of a hemolytic episode.

TREATMENT

Most patients with G6PD deficiency are well and require no treatment during the steady state. Supplemental iron and folic acid are unnecessary. Blood counts need not be performed on a routine basis unless accelerated hemolysis is suspected. G6PD deficient patients should

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avoid drugs that might induce hemolytic episodes. Naphthalene mothballs should also be avoided because of their oxidant effects.

If there are any questions about information in this pamphlet, or about a patient with possible G6PD deficiency, please call a member of the pediatric hematology staff at the Center for Cancer and Blood Disorders.

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