**Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)**

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### EPIDEMIOLOGY

G6PD deficiency is found with increased frequency in Africa, Asia, the Mediterranean, and the Middle-East. Those places are known as high-risk area of Malaria. Researchers have found evidence that the Plasmodium protozoa do not survive well in G6PD deficient cells. It is believed that the increased frequency of G6PD deficiency may be a way of developing protection against malaria. There are three common G6PD enzyme mutants:

1. **G6PD A+**
   - Affecting approximately 13% of male African-American. In this mutant, the erythrocyte activity reduced to less than 5–15% of normal activity.

2. **G6PD B+**
   - Found in Italian, Greeks and other Mediterranean, Middle-East, African and Asian ethnic groups with incidence ranging from 5 – 40% of the populations.

3. **G6PD Canton**
   - Occurs in 5% of Chinese population.

### ETIOLOGY AND PATHOPHYSIOLOGY

Glucose-6-Phosphate dehydrogenase is an enzyme essential in hexose monophosphate pathway. Synthesis of erythrocyte G6PD is determined by a gene located on the X chromosome. Therefore, the disease involving this enzyme occurs more commonly in male because male has only one X chromosome (XY). Female can act as a carrier (if heterozygous) or affected (if homozygous). Heterozygous females have intermediate enzyme activity, and have two populations of erythrocytes, one is normal and the other is G6PD deficient; most heterozygous females are asymptomatic. This population has an advantage of resistance to Falcifarum malaria.

G6PD catalyses Nicotinamide Adenine Dinucleotide Phosphate (NADP) to its reduced form, NADPH (Nicotinamide Adenine Dinucleotide Phosphate Hydogenase). The role of NADPH is to protect cells from oxidative damage. Since NADPH is not generated in erythrocytes, they are more susceptible to destruction from oxidative stress e.g.: oxidative drugs like primaquine, methylene blue, sulfamethoxazole and oxidative agents like naphthalene/mothball, fava beans or infection. Normal erythrocytes not under oxidative stress generally exhibit G6PD activity at 2% of total capacity, therefore there may be absence of clinical symptoms even with reduced G6PD enzyme activity.

The gene encoding the G6PD is located in the distal arm of X chromosome. Mutation near the amino terminus is associated with chronic nonspherocytic hemolytic anemia. The normal enzyme is designated G6PD B+; G6PD A+ is a normal variant mostly found in African–American. There are over 400 variants of G6PD with a wide spectrum of hemolytic disease.

The most common cause of hemolysis may be infection, even when no drugs given. The exact mechanism is unknown, but it is thought to be the oxidants released by leukocytes during phagocytosis that cause oxidative stress to the erythrocytes.

### Table 1. Classes of G6PD Enzyme Variants

<table>
<thead>
<tr>
<th>Level of Class deficiency</th>
<th>Enzyme activity</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - Severe</td>
<td>Chronic nonspherocytic hemolytic anemia in the presence of normal erythrocyte function</td>
<td>Uncommon, occurs across populations</td>
</tr>
<tr>
<td>II - Severe</td>
<td>Less than 10 percent of normal</td>
<td>Varies, more common in Asian and Mediterranean populations</td>
</tr>
<tr>
<td>III - Moderate</td>
<td>10 to 60 percent of normal</td>
<td>10 percent of black males in the United States</td>
</tr>
<tr>
<td>IV - Mild to none</td>
<td>60 to 150 percent of regular</td>
<td>Rare</td>
</tr>
<tr>
<td>V - None</td>
<td>Greater than 150 percent of normal</td>
<td>Rare</td>
</tr>
</tbody>
</table>

G6PD = glucose-6-phosphate dehydrogenase. Information from references 1 and 7.

(Extracted from [http://www.aafp.org/afp/20051001/1277.html](http://www.aafp.org/afp/20051001/1277.html))

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**Table 2. High risk oxidative drugs to avoid by all variants of G6PD deficiency:**

- Acetylphenylhydrazine
- Aldenosulfone sodium (Sulfoxone)
- Arsine

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**Fig. 1. Hexose monophosphate pathway:** (Extracted from [http://www.aafp.org/afp/20051001/1277.html](http://www.aafp.org/afp/20051001/1277.html))
- Beta-naphtol (2-Naphtol)
- Dapsone
- Dimercaprol
- Flurazolidone
- Glucosulfone
- Vitamin K*
- Methylene Blue
- Pure Naphthalene (Naphthla, Mothball)
- Nirodazole
- Nitrofural (Nitrofurazone)
- Nitrofurantoin
- Pamaquine
- Pentaquin
- Phynyl Hydrazine
- Primacrine
- Probenecid*
- Stibophen
- Sulfacetamide
- Sulfadimidine
- Sulfamethoxazole
- Sulfanilamide
- Sulfasalazine (Salazopyrin)
- Sulfamerazine
- Sulfadiazine
- Sulfacytine
- Quinine
- Quinidine
- Pyrimethamine
- Chlorguanidine, Sulfaguanidine
- Benzhexol
- Antazoline
- Aminopyrine
- Colchicine
- Trimetoprim
- Steptomycin
- Phenytoin
- Phenilbutazone
- L-Dopa
- Isoniazid
- Diphenhydramine
- Vitamin K*

**HIGH RISK DRUGS CONSIDERED SAFE TO TAKE IN NORMAL THERAPEUTIC DOSE**

**Table 4. Miscellaneous agents besides drugs that should be avoided:**
- Fava Beans
- Some Chinese Herbs

**Table 5. Low risk oxidative drugs safe in normal therapeutic dose for G6PD deficient subjects without non-spherocytic hemolytic anemia:**
- Acetaminophen
- Ascorbic Acid (Vitamin C)
- Diphenhydramine
- Isoniazid
- L-Dopa
- Phenilbutazone
- Phenytoin
- Steptomycin
- Trimetoprim
- Colchicine
- Aminopyrine
- Antazoline
- Benzhexol
- Chloroguanidine, Sulfaguanidine
- Procaín Amide Hydrochloride
- Pyrimethamine
- Quinidine
- Quinine
- Sulfacytine
- Sulfadiazine
- Sulfamerazine
- Sulfamethoxypyridazine
- Sulfisoxazole
- Tripletelamin

**CLINICAL MANIFESTATION**

Clinical appearance may vary from absence of symptom to acute hemolytic anemia, chronic non-spherocytic anemia, or neonatal hyperbilirubinemia. Symptoms develop within 24 to 72 hours after exposure to oxidative stressors with resolution within 4 to 7 days. An oxidative agent ingested by a breast-feeding mother may be transmitted in breast milk to her G6PD deficient child and causes an acute hemolysis. In some patients, ingestion of fava beans (may also known as broad beans, bell beans, English dwarf beans, haba beans, fever beans, silkworm beans, tick beans, horse or pigeon beans, in Indonesia: kacang koro), may lead to an acute severe hemolytic symptom called “favism”, which is caused by oxidative products derived from two glycosidic compounds, vicine and convicine. Favism is more common in G6PD Meditteranean (G6PD B-).

Acute hemolytic anemia may present clinically as back or abdominal pain and jaundice secondary to a rise in unconjugated bilirubin. With normal liver function, jaundice occurs after over 50% of erythrocytes hemolyzed. Hemolysis does not continue despite contacted infection or exposure to oxidative agents because older erythrocytes with the worst enzyme deficiency undergo hemolysis first so younger erythrocytes having higher level of enzyme activity dominate; they are able to sustain the oxidative damage without hemolysis. In rare cases, hemolysis is so severe that a blood transfusion is required.

The degree of hemolysis depends on the inciting agent or stressor, the amount ingested, and the severity of enzyme deficiency. Most heterozygous females do not have clinical hemolysis after being exposed to oxidative stressors except in rare cases of random inactivation (Lyon Hypothesis) of the normal X chromosome resulting G6PD deficiency in majority of erythrocytes. Sporadic gene mutation is the common cause of G6PD deficiency that manifests as chronic non-spherocytic anemia. The defect is usually located primarily in the region of NADP binding site near the carboxyl terminus of the protein. The variants that develop chronic non-spherocytic anemia are the Loma Linda, Tomah, Iowa, Beverly Hills, Nashville, Riverside, Santiago de Cuba and Andalas. Hemolysis continues to occur even during normal erythrocyte metabolism. Exposure to oxidative stressors can result in acute hemolysis.

Neonatal hyperbilirubinemia is found mostly in males with gene defect and in homozygous females. This condition is associated with increased risk of kernicterus and death. Newborns of Greeks (G6PD B-) and Chinese ethnic (G6PD Canton) are at higher risk of hyperbilirubinemia. The mechanism of neonatal hyperbilirubinemia is unclear. Although hemolysis may be observed in these cases, hyperbilirubinemia is likely to be secondary to impairment of bilirubin conjugation and clearance by the liver leading to indirect hyperbilirubinemia. G6PD should be suspected in neonates with hyperbili-
rubinemia within the first 24 hours of life, a history of jaundice in a sibling, bilirubin levels greater than the 95th percentile and in Asian females.

LABORATORY FINDINGS
Acute hemolysis results in fall of hemoglobin and hematocrit. In severe cases, the hemoglobin-binding proteins (such as haptoglobin) are saturated, and free hemoglobin may appear in plasma and subsequently in urine. Unstained or supravital preparations of erythrocyte reveal Heinz bodies, which are rapidly removed from the circulation within 3 to 4 days of a hemolysis episode.

DIAGNOSIS
Diagnosis of G6PD deficiency is made by quantitative spectrophotometric analysis. Enzyme activity in affected persons is less than 10% of normal. Screening tests of G6PD deficiency are based on decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH. These screening tests are best to detect homozygous G6PD deficient males and females, but unreliable to detect heterozygous females.

In acute hemolysis, the test may be falsely negative because of domination of reticulocytosis and young erythrocytes having higher enzyme activity. The diagnosis is suspected when G6PD activity is within the low normal range in the presence of a high reticulocyte count. Electrophoretic analysis is used to detect G6PD variants. The G6PD test should be performed in children with a family history of jaundice, anemia, splenomegaly and cholelithiasis, especially of Mediterranean or African ancestry; or children and adults (especially males of African, Mediterranean or Asian descent) with acute hemolytic reaction caused by infection or exposure to a known oxidant agent. WHO recommends neonatal screening in populations with a prevalence of over 3% in males.

THERAPY / TREATMENT
The most important thing is avoidance of oxidative stressors in G6PD deficient persons. Blood transfusion may be required in a severe case of hemolytic anemia. Folic acid and iron can be used as supportive therapy.

SUMMARY
G6PD deficiency is due to inherited genetic mutation on X chromosome. G6PD deficiency increases the vulnerability of erythrocyte to oxidative stress, which may lead to hemolysis. However, most G6PD deficiency subjects are asymptomatic. They can live normal lives, despite bearable hemolysis when exposed to oxidative stressors. Screening for G6PD deficiency (for homozygous G6PD deficient females and males; not reliable in heterozygous females) is important in high-risk neonates to prevent neonatal hyperbilirubinemia, which may lead to kernicterus and death. There is no cure since it is of genetic basis.

REFERENCES