Overview

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an x-linked recessive disorder that is characterized by the deficiency of G6PD in red blood cells. The condition is characterized by excessive intravascular hemolysis which is induced by certain oxidative stressors, such as the ingestion of fava beans, the development of an infectious illness or the exposure to certain drugs.
**Genetics of G6PD**

The gene that is responsible for G6PD is located on the X chromosome (band Xq28). Despite females having two X chromosomes, females and males have the same enzyme activity as one of the X chromosomes in female embryo are inactivated.

**Epidemiology of G6PD Deficiency in Children**

G6PD deficiency is recognized as the most common enzyme deficiency in humans and has been described in all races and ethnicities. The condition is most common in African Americans in the United States. The estimated prevalence of G6PD deficiency in black boys is around 10%.

G6PD deficiency is more prevalent in geographic regions that have malarial epidemics; therefore, the highest prevalence of G6PD genetic mutations is seen in tropical Africa, followed by the Middle East, tropical and subtropical Asia, and least commonly in Papua New Guinea.

The condition has been found to confer some partial protection against malaria, which explains the persistence of the mutation. Neonates with G6PD deficiency who develop kernicterus due to hyperbilirubinemia have a significantly increased mortality and morbidity risk. Otherwise, older children who have the mutations are usually asymptomatic until they are exposed to a triggering oxidative stressor, such as an infection, ketoacidosis, or the ingestion of certain drugs and fava beans. The condition in this group of children is very rarely fatal.

In addition to the differences in the prevalence of G6PD deficiency among different ethnicities all over the world, the severity of the condition is also dependent on the ethnicity of the child. African American children with G6PD usually have a milder disease compared to those from the Mediterranean descent.

**Pathophysiology of G6PD Deficiency**

The gene that codes for G6PD is located on the long arm of the X-chromosome at Xq28 locus. Different mutations have been noted in the G6PD deficiency and the severity of the condition seems to be dependent on the type of the mutation involved. Approximately, 60 mutations have been recorded so far in this gene that has been linked to a G6PD enzymatic relative or absolute deficiency. Most of these mutations are single-base changes that result in a single amino-acid substitution which renders the enzyme inactive.

The term G6PD B allele has been used to describe the wild type allele or the normal variant. G6PD A+ allele is a variant that is associated with minimal enzymatic deficiency and is usually asymptomatic. The most common allele variant in African Americans and the Mediterranean region is the G6PD A-. This abnormal variant is rarely associated with chronic hemolysis.

The different G6PD allele variants have been further classified by the World Health Organization into five different classes depending on the severity of the condition. Patients who have severe and chronic hemolysis are classified as G6PD class I. G6PD class II is the term preferred for children who have G6PD and are of Mediterranean descent. G6PD class III is the most common form of G6PD deficiency, where children are usually asymptomatic until they are exposed to a known stressor.
Those with G6PD abnormal variants that are always completely asymptomatic are considered as class IV or V.

The G6PD enzyme is responsible for the oxidation of the glucose-phosphate and the reduction of the nicotinamide adenine dinucleotide phosphate (NADP+) to NADPH. NADPH is needed to maintain glutathione in its reduced form, which is needed to neutralize oxidative metabolites that the cell can be exposed to. This enzymatic pathway is the only source of NADPH in red blood cells; therefore, red blood cells that lack G6PD or have a G6PD enzyme of diminished activity lack the ability to produce NADPH and are therefore prone to oxidative damage.

Oxidative stressors can denature hemoglobin and cause intravascular hemolysis in patients with G6PD deficiency. Denatured hemoglobin is visualized as Heinz bodies in peripheral blood smears stained with supravital staining.

Clinical Presentation of G6PD Deficiency in Children

Most patients with G6PD deficiency are asymptomatic until they are exposed to an oxidative stressor. Neonatal jaundice within the first 24 hours of life can be seen in newborns with G6PD deficiency. Neonates who develop early jaundice due to G6PD deficiency need blood transfusions.

Older children with G6PD deficiency usually do well until they are exposed to a known trigger. The most common triggers of hemolysis in G6PD deficiency include the ingestion of fava beans or acquiring an infectious disease. Hemolysis is usually not immediately after exposure but happens one day up to three days after the exposure.

<table>
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<th>Common oxidative stressors in children</th>
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<td><strong>Drugs</strong></td>
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<tr>
<td>• Sulfas (TMP-SMX)</td>
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<td>• Quinolones</td>
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<tr>
<td>• Nitrofurantion</td>
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<td>• Aspirin</td>
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Patients who have frequent intravascular hemolysis can complain of right upper quadrant abdominal pain due to cholelithiasis. Therefore, any child who has gall bladder stones should be evaluated for G6PD deficiency among other possible etiologies of gallbladder stones in this age group, such as sickle cell disease.
The typical symptoms of acute hemolytic anemia are **non-specific and include darkened urine, skin pallor, conjunctival pallor and shortness of breath with or without tachycardia**. Signs and symptoms of a possible triggering oxidative event should be sought. The patient might have an **acetone-like breath, vomiting and abdominal pain due to diabetic ketoacidosis**. The child might have symptoms and signs suggestive of an **ongoing infectious illness such as a cough, chest pain, fever, or urinary tract symptoms**. Finally, a recent drug intake history should be examined because **many drugs, including the sulfa group of antibiotics, can induce hemolysis** in children with G6PD deficiency.

- Acute, irritability, fatigue
- Signs of infection if that's a trigger
- Cola colored urine (hemoglobinuria)
- Pallor, tachycardia, murmur
- Jaundice
- Hepatosplenomegaly
- Shock in severe cases

**Diagnostic Workup for G6PD Deficiency in Children**

It is not feasible to examine all children with hemolytic anemia for a possible G6PD deficiency; therefore, the treating physician should **look for certain clues that point towards G6PD deficiency** as the etiology of hemolytic anemia in the child.

Children who **develop acute hemolysis only when they are exposed to oxidative stress** but are otherwise asymptomatic should be evaluated for a possible G6PD deficiency. Additionally, neonates with early and unexplained hyperbilirubinemia should undergo specific testing to exclude G6PD deficiency.

The first test in the evaluation of the child with suspected G6PD deficiency is a **complete blood count with reticulocyte count**. Children usually have a **reduced number of red blood cells** due to hemolysis and an **elevated reticulocyte count**. Lactate dehydrogenase levels are also elevated in children with intravascular hemolysis due to G6PD deficiency.

<table>
<thead>
<tr>
<th>CBC shows anemia and evidence of hemolysis:</th>
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<tbody>
<tr>
<td>↓ Elevated</td>
</tr>
<tr>
<td>↑ Low</td>
</tr>
<tr>
<td>• Indirect bilirubin</td>
</tr>
<tr>
<td>• LDH</td>
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<tr>
<td>• Haptoglobin</td>
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A peripheral blood smear is indicated in children with suspected G6PD deficiency. The peripheral blood smear **can reveal bite cells which occur because of the splenic removal of the denatured hemoglobin**. Heinz bodies can be also visualized on the
peripheral blood smear.

Children with G6PD deficiency-induced intravascular hemolysis also have **decreased haptoglobin levels, hematuria, and the urinary hemosiderin**.

To confirm the diagnosis of G6PD deficiency, one can either **quantify NADPH or the G6PD enzyme in red blood cells**. **Beutler test** is used to quantify NADPH. The quantitative analysis of G6PD activity in leukocyte-depleted blood samples can confirm the diagnosis of G6PD. These tests should not be used during the acute stage of hemolysis.

![Image: Prevalence and molecular basis of glucose-6-phosphate dehydrogenase deficiency in Afghan populations: implications for treatment policy in the region: “G6PD fluorescent spot test under ultraviolet light (365nm) (Beutler test) [18]. The left filter paper shows a severe deficiency, and the two on the right show a normal reaction.” by Leslie T, Moiz B, Mohammad N, Amanzai O, Ur Rasheed H, Jan S, Siddiqi AM, Nasir A, Beg MA, Vink M - Malar. J. (2013). License: CC BY 2.0](image)

**Treatment of G6PD Deficiency in Children**

Fortunately, the hemolysis associated with G6PD deficiency is **usually mild and children do not need any treatment**; therefore, it is more important to **focus on the prevention of future episodes of hemolysis**, rather than treating the current episode.

Children with ongoing hemolysis should be evaluated for a possible ongoing oxidative stress and that **stress should be eliminated**. For example, ongoing infections should be treated, diabetic ketoacidosis should be corrected and any possible offending drugs should be withdrawn.

In contrast to intravascular hemolysis due to spherocytosis, **splenectomy has no role in the management of G6PD deficiency**.
Neonates who develop jaundice due to G6PD deficiency should receive phototherapy. **Exchange blood transfusion should be attempted to correct severe neonatal jaundice.** Children from Mediterranean descent, who develop severe intravascular hemolysis due to the ingestion of fava beans, might also need a blood transfusion.

The most common causative drugs of hemolysis in children with G6PD deficiency are the **antimalarial drugs** primaquine, chloroquine, pamaquine and pentaquin. **Fluoroquinolones** can also cause hemolysis. **Sulfonamides** should be avoided in this group of children. **Nonsteroidal anti-inflammatory drugs** have been linked with an increased risk of hemolysis in some patients with G6PD deficiency.

**References**


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