

Glucose- 6-phosphate dehydrogenase deficiency: A review

Sanjeewa Sumathipala

Correspondence:

Dr. Sanjeewa Sumathipala.
Family Medicine Consultant
Primary Health Care Corporation
Qatar

Email: sansumathipala@gmail.com

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic disorder affecting people at any age and is thought to affect 400 million people worldwide. It is normally asymptomatic but can lead to significant morbidity and mortality. There are recognized factors that need to be avoided. Detection of the disorder, avoidance of provoking factors, management of the symptoms and any complications are essential to ensure that people with G6PD deficiency can remain as healthy as possible.

Key words: Glucose-6-phosphate dehydrogenase; G6PD deficiency; Red blood cells; Hemolysis; Neonatal jaundice; Fava beans; Malaria; Primaquine.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest enzymatic disorder affecting red blood cells, estimated to affect 400 million people worldwide (1). Since complete absence of G6PD is incompatible with survival, the deficiency is incomplete (2). The deficiency can arise from a reduction in the quantity of enzyme, a qualitative change caused by a change to its structure, or both (1). It is normally asymptomatic but serious complications can occur from presentations like neonatal jaundice or through episodes of acute hemolysis.

The global distribution of the disorder reflects areas where malaria was once endemic, suggesting that the disorder provides selective advantage against that infection. The Middle East is thought to contain a high frequency of this disorder (3). Concern also exists that G6PD deficiency can increase susceptibility to COVID-19 infection (4) and the risk of acute hemolysis from using medications suggested as treatment for that infection (5).

History

Acute hemolysis was detected in some patients treated for malaria with 6-methoxy-8-aminoquinoline drugs in 1926 (6). G6PD was identified in yeast cells in the 1930s and, in 1956, researchers discovered that volunteer prisoners from Illinois State Penitentiary developing hemolytic anemia after taking primaquine had low levels of G6PD activity in their red blood cells (7). At the same time, a similarity was noted between the severe hemolytic anemia associated with ingestion of fava beans and the hemolytic anemia induced by primaquine (8).

Genetic basis

G6PD deficiency is inherited recessively as an X-linked disorder (9). The encoding gene is found on the distal arm of the X chromosome (band Xq28), near to genes that code for hemophilia A, dyskeratosis congenital and colour blindness (10). It was the first gene to be cloned in human beings (11).

Being X linked, G6PD deficiency affects the two genders differently (12). Males who inherit the mutated gene are homozygous for the disorder and all their red blood cells are G6PD deficient.

Females can be:

- a. Homozygous normal, or
- b. heterozygous deficient, or
- c. homozygous deficient, or
- d. compound heterozygous for two mutations on the G6PD gene (13).

In heterozygous females, one copy of the G6PD gene is randomly inactivated during embryogenesis through a process called lyonization. Hence, heterozygous females have one group of red blood cells with normal G6PD activity and another G6PD-deficient group (14). The relative ratio of these red blood cell groups determines the G6PD activity, and the ratio can vary, but is typically 30% to 80% of normal G6PD activity (15).

Function of G6PD

G6PD functions as a housekeeping enzyme in all cells but in varying amounts according to the tissue type (16). It is the rate-limiting enzyme in the pentose phosphate pathway maintaining the level of nicotinamide adenine dinucleotide phosphate (NADPH). NADPH enables glutathione to remain in a reduced state within cells. Reduced glutathione protects cells from oxidative damage.

Since red blood cells lack mitochondria, the only source of reducing power comes from the pentose phosphate pathway (17). In red blood cells, G6PD operates at only 1–2% of its maximum potential and, therefore, a large reserve of reductive potential exists (18). However, when the reduced glutathione store is depleted, hemoglobin becomes vulnerable to damage through oxidation and hemolysis can result.

Distribution of affected people

Over 400 variants of the G6PD enzymes have been identified and the majority are due to single amino acid substitutions (19). G6PD's stability and effectiveness are reduced to varying degrees through these mutations (10).

The most frequent G6PD variants are found in people from the Middle East and the Mediterranean region (G6PD Mediterranean type), areas of Africa (G6PD A-) and parts of India and South East Asia (17).

G6PD deficiency is common in areas where *Plasmodium falciparum* malaria is endemic, suggesting that G6PD deficiency confers a type of defense against malaria (18). Although the exact mechanism for that advantage is not yet known, in heterozygotic females, red blood cells with normal G6PD function were 2 - 80 times more likely to be infested than their G6PD deficient cells (20).

Severity of G6PD Deficiency

The World Health Organization has categorized the deficiency into five classes according to the degree of enzyme deficiency and hemolysis (21).

Class 1: severe enzyme deficiency (less than 10% of normal) and is associated with chronic non-spherocytic hemolytic anemia;

Class 2: severe enzyme deficiency (less than 10% of normal) and is associated with acute hemolytic anemia. G6PD Mediterranean is the classic variant.

Class 3: moderate-to-mild enzyme deficiency (10%-60% of normal). G6PD A- is the classic variant.

Class 4: very mild or no enzyme deficiency (60%-150% of normal). Typically, these variants are not clinically significant.

Class 5: increased enzyme activity (greater than 150% of normal). Typically, these variants are not clinically significant.

Presentation of G6PD Deficiency

Most people with G6PD deficiency are asymptomatic. The most frequent clinical manifestations of G6PD deficiency are neonatal jaundice and acute hemolytic anemia. G6PD-deficient variants can also cause chronic hemolysis, leading to congenital non-spherocytic anemia (1).

Neonatal jaundice

Neonatal jaundice most commonly presents 2–3 days after birth (22). It has variable severity but can lead to kernicterus and death (23). The condition is thought to result more from impairment of bilirubin conjugation and clearance by the liver than from hemolysis (10). Inheritance of the mutation of the uridine-diphosphate-glucuronosyltransferase 1 gene promoter (24) responsible for Gilbert syndrome, increases the risk of neonatal jaundice (24). The hyperbilirubinemia can require phototherapy or exchange transfusion (25).

G6PD deficiency should be considered in neonates who develop hyperbilirubinemia within the first 24 hours of life, or have a history of jaundice in a sibling, bilirubin levels greater than the 95th percentile, or are from ethnicities where the G6PD is prevalent (26).

The WHO recommends that neonatal screening be performed when G6PD deficiency affects more than 3–5% of males in a population (21). Heterozygote females are considered to have less severe clinical manifestations than G6PD deficient males (27). However, those females are also at risk of kernicterus because hemolysis of their G6PD deficient cells can result in hyperbilirubinemia (28).

Acute hemolytic anemia.

Hemolysis can occur after exposure to a variety of provoking agents. The degree of hemolysis is dependent on several factors, including the variant of G6PD deficiency (the Mediterranean variant is most frequently affected), as well as the age of the individual, dose of the provoking agent and coexisting morbidities. As such, the episode of hemolysis can range from mild to life-threatening (29). Treatment such as blood transfusions and renal dialysis may be required in serious cases. The most common provoking agents are infection, fava beans and certain medications (21). Rarer causes include exposure to naphthalene (30) and henna (31).

Clinically detectable hemolysis and jaundice typically arise within 24–72 hours of exposure. Hemoglobinuria causes characteristic dark urine. Anemia worsens until days 7–8. After exposure to the provoking agent ends, the hemoglobin concentrations start to recover from 8–10 days (1). Depending on the severity of the hemolysis, the patient may complain of a number of symptoms including lethargy, headache, lumbar pain, jaundice, and dark urine.

A normochromic, normocytic anemia with anisocytosis and reticulocytosis will appear in laboratory tests. Heinz bodies, which are denatured hemoglobin precipitates and a classic finding, may be present (1).

Fava Bean

Pythagoras is claimed to have forbidden his students from eating fava beans. He eventually preferred to be captured by his enemies who were pursuing him rather than enter a field of fava beans as he was trying to escape (32). Divicine and isouramil, chemicals present in fava beans, are thought to be responsible for acute hemolysis (termed favism) through their oxidizing actions (10).

Favism most commonly affects young children (33). After ingestion of fava beans, symptoms of favism occur within 5 to 24 and include nausea, headache, back pain and fever, followed later by jaundice and hemoglobinuria (34). It is believed that all patients with favism have G6PD deficiency, but not all G6PD-deficient individuals develop hemolysis when they eat fava beans (2) and so there may be an additional property to fava beans and their consumption that results in the risk of hemolysis. Furthermore, passive transmission, through breast feeding when mothers had ingested fava beans has been described (35).

Infection

Although the exact mechanism of susceptibility is not known, it is considered that the lack of glutathione in its reduced form results in the cells inability to withstand the oxidative damage that infections cause (36). Another suggestion is that during phagocytosis, leukocytes discharge active oxygen species that damage erythrocytes in their environment (37).

The most frequent infections causing hemolysis include Salmonella, Escherichia coli, beta-hemolytic streptococci, rickettsial infections, viral hepatitis, and influenza A (26). Hence, G6PD deficient patients need to be aware to seek medical attention promptly when they become ill.

G6PD deficiency has been found to enhance infection of cells with human coronavirus 229E (HCoV 229E). Viral gene expression was higher in G6PD deficient cells compared with control cells. G6PD-deficient cells were more susceptible to HCoV 229E-mediated cell death (38). There are suggestions that SARS-CoV-2 may have a similar effect on cells in G6PD-deficient patients although a definitive association has yet to be made (4).

Medications

A variety of medications can cause acute hemolytic crisis in people with G6PD deficiency (39). These include antimalarial medications such as primaquine or aminoquinoline drugs, and combination medication containing sulphamide. There have also been concerns regarding the use of hydroxychloroquine as a treatment for COVID 19 without ensuring that the recipients did not have G6PD deficiency (5).

The ability of the medication to cause hemolysis is not always predictable. Inherited differences such as acetylator status or if the medication shortens the life span of the red blood cell will affect the severity of hemolysis (2).

WHO recommends testing of all patients routinely for G6PD deficiency before considering primaquine therapy (40). If the G6PD status is unknown and testing to determine it not available, patients given primaquine are recommended to receive close medical supervision and instructed to stop taking primaquine if signs or symptoms of hemolytic anemia appear (41).

Benefits of G6PD Deficiency

It is thought that G6PD deficiency, particularly the G6PD A- variant, confers a defense against malaria. In G6PD A- heterozygous females, red blood cells with normal G6PD activity had more parasitic growth than G6PD-deficient red-blood cells (20). There is some evidence that G6PD deficiency has a positive effect on longevity and can prevent cancer progression (42).

Detection of G6PD Deficiency

G6PD deficiency can be assessed using a fluorescent screening test or quantitative spectrophotometric analysis to assess the activity of the enzyme. Alternatively, DNA sequencing can be used to detect the actual gene mutation (17).

Tests for measuring G6PD activity are based on detecting the rate of reduction of NADP to NADPH. The tests rely upon certain characteristics of NADPH: (10)

- 1 Light absorption at 340 nm.
- 2 Fluoresces when subjected to long wavelength UV light (approximately 340 nm).
- 3 Decolorizes or leads to the precipitation of certain dyes.

Screening for G6PD deficiency, using a fluorescent spot test or dye decolorization method, are relatively easy to use and can yield results quickly, allowing them to be employed as point of care tests (17).

The British Society for Haematology (10) recently suggested criteria to undertake screening:

- Before commencing medication able to cause oxidative damage to red blood cells.
- History of non-immune hemolytic anemia or neonatal jaundice that is prolonged or severe.
- If hemolysis has occurred and is associated with infection or medication considered to oxidize red blood cells, or following haemopoietic stem cell transplantation if donor is G6PD deficient or status unknown
- History of favism
- Family history of G6PD deficiency or favism.
- Detection of red blood cell morphology suggesting oxidant damage or positive Heinz body stain
- The presence of congenital non-spherocytic hemolytic anemia, hemoglobinuria, sickle cell disease or thalassemic disorders

If the screening test yields an abnormal or equivocal result, or the subject is female, then quantitative analysis is required. Quantitative assays provide an actual measure of G6PD activity normalized for either hemoglobin concentration or red blood cell count and provide the definitive diagnosis of G6PD deficiency (44).

If a female is suspected to be heterozygous for G6PD deficiency, a cytochemical test should be undertaken even if the quantitative assay is normal. Staining allows visualization of G6PD normal and G6PD deficient red blood cell groups, thereby identifying heterozygote females (10).

Attempting to diagnose G6PD deficiency during an acute hemolytic episode is likely to lead to inaccurate results (1). During these episodes young red cells and reticulocytes have more G6PD activity than mature red cells leading to false negative results; hence, the assay should be undertaken 2 -3 months following the hemolytic episode (10).

Management of G6PD Deficiency

The most effective strategy is to avoid oxidative stress to red blood cells. Dietary restrictions need to be followed for those with G6PD deficiency. Medication considered unsafe in the presence of G6PD deficiency should be avoided.

Neonatal jaundice due to G6PD deficiency is treated in a similar fashion to neonatal jaundice from other causes. When rising concentrations of unconjugated bilirubin, phototherapy and a blood transfusion may become necessary (43).

Any agent, such as medication, provoking hemolysis should be discontinued, and supportive care instituted (44). Fortunately, most episodes of acute hemolysis are short lived, however, in severe cases, blood transfusions and renal dialysis may be required (45).

Class 1 G6PD variants, leading to congenital non-spherocytic anemia, can develop gallstones (46) and require surgical intervention. Splenomegaly can also occur although splenectomy is not considered to confer any benefit (47). Very rarely, congenital non-spherocytic hemolytic anemia is transfusion-dependent and iron-chelation treatment is required (1).

Summary

G6PD deficiency is the most common enzyme disorder affecting red blood cells. It is inherited in an X linked recessive manner and there are over 400 variants identified. It has a global distribution and includes areas where malaria has been endemic.

The disorder is considered to render red blood cells vulnerable to oxidative damage from a variety of agents, chief amongst these being infection, certain dietary factors, and medications.

The disorder is normally asymptomatic but common presentations include neonatal jaundice and acute hemolysis. Neonatal jaundice typically occurs 2 – 3 days post-partum and is worsened if there is co-existent Gilbert syndrome. Acute hemolysis can present with lethargy, back pain, jaundice, and dark urine. Chronic hemolysis, leading to gallstones and splenomegaly can also be a presentation of G6PD deficiency.

Treatment depends on the nature of the symptoms, co-existing conditions, and the degree of hemolysis. Particular caution needs to be exercised in neonatal jaundice where there is a risk of kernicterus and death.

Identification of G6PD deficiency can begin with screening tests but definitive tests are required to diagnose the condition. Once diagnosed, people with G6PD deficiency need to avoid any agent that can provoke oxidative stress upon the red blood cell and seek medical attention if symptoms develop suggesting hemolysis.

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