Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency Disease - A Brief Overview

Purnima Ashok* and Blessy Maria Thomas
KLE College of Pharmacy, 2nd Block Rajajinagar, Bengaluru, Karnataka, INDIA.

ABSTRACT
G6PD Deficiency is considered as the most frequently seen enzymopathy affecting the erythrocytes. It has high prevalence rates in the regions of tropical Africa, the Middle East, tropical and subtropical Asia. Severe G6PD deficiency is more common in males, inheriting hemizygous G6PD mutations will have defect in all their RBC’s showing abnormal signs and symptoms. Triggering factors for haemolytic anaemia in G6PD deficient patients include medications and other chemical substances, fava beans, infections, etc. These patients show a spectrum of disorders including, acute massive hemolysis, neonatal icterus, renal failure, chronic haemolytic anaemia, etc. There are several tests available for diagnosing G6PD deficiency, genetic testing can be done to confirm the condition. After diagnosing, the patients should do routine checkups for good prognosis. Every G6PD deficient patient does not need treatment always, however identification and discontinuation of the triggering factors is very important to manage hemolysis. Treatment of the condition mainly focuses on the symptoms. All the hospital should utilize computerized supporting tools so that the patients with less common disease conditions like G6PD deficiency will receive rationalized treatment and will help to control this genetic disorder.

Key words: G6PD Deficiency, Enzymopathy, Haemolytic anaemia, Neonatal icterus, Fava beans.

INTRODUCTION
Glucose-6-Phosphate Dehydrogenase (G6PD)-deficiency is considered as the most common enzymopathy. It is an X-linked genetic disorder; basically, an abnormality of the gene on the X chromosome that controls the production of G6PD in cells. In 1950s, 3 enzyme deficiencies that produce disease in human erythrocytes was identified. These enzymes were galactose-1-phosphate uridylytransferase, catalase and glucose-6-phosphate dehydrogenase. Out of these 3 enzymes, only G6PD deficiency produces a hematologic disorder, namely hemolytic anemia. In 1973, approximately 300 million people worldwide were G6PD deficient and the recent studies show an estimate of 400 million. Whatever the actual number was then, the number of affected individuals is greater now, but propitiously the clinical penetrance is extremely low. In this article we will inquire into the basic physiology of G6PD deficiency and further will discuss on the critical role of health care professionals in rationalizing the treatment of the G6PD-deficient patients.

G6PD Deficiency Disease
G6PD Deficiency is considered as the most common enzymatic disorder affecting the RBCs. To understand the basics of G6PD deficiency, one must understand the enzyme’s normal physiologic functions. In human cells, mitochondria undergo aerobic respiration and produce the energy currency of life, ATP (adenosine triphosphate). The byproducts of this reaction include free radicals and Reactive Oxidative Species (ROS) like superoxide, hydrogen peroxide and hydroxyl radical. These byproducts cause cellular damage and cell lysis in DNA, lipoproteins and cell membranes and this state is commonly known as oxidative stress. To reduce the oxidative stress, human cells have a number of mechanisms to
neutralize the harmful free-radical species by synthesizing antioxidants.\(^1\)

G6PD is commonly referred to as the first enzyme of the hexose monophosphate shunt, or the pentose phosphate pathway, but the main role of G6PD is to produce the reduced form of Nicotinamide Adenine Dinucleotide Phosphate (NADPH). NADPH has an important role in preventing oxidative damage to proteins and other molecules in all cells.\(^1\) In case of red blood cells again the issue is crucial, due to the lack of mitochondria it solely depends on the cytosolic pentose phosphate pathway and generation of reduced glutathione for protection from oxidative stress. In addition, due to the methemoglobin formation oxygen free radicals are continuously generated in the red blood cells making it more vulnerable to oxidative damage and eventual death.\(^1\)

In general, the highly reactive oxygen free radicals either disintegrate spontaneously or converted to hydrogen peroxide (\(\text{H}_2\text{O}_2\)) in the cells. This highly toxic \(\text{H}_2\text{O}_2\) is then converted to \(\text{H}_2\text{O}\) by the enzyme catalase and by glutathione peroxidase (GSHPX). NADPH plays an important role in the functioning of both these enzymes; in catalase, it is a structural component whereas it is required as a substrate by glutathione reductase for oxidizing GSSG to GSH by GSHPX (Figure 1).\(^3\) On the other hand, Glucose-6-phosphate (G6P) gets converted to 6-phophogluconolactone (6PG) catalyzed by the enzyme G6PD and generates reduced NADPH, which is utilized for regenerating glutathione. When a glutathione molecule reduces a free radical, it should be regenerated in a pathway by utilizing NADPH. Other mechanism for producing cellular antioxidants involve carotenoids, ascorbate and alpha-tocopherol.\(^1\)

RBCs solely depend on G6PD activity for oxidative protection. For the patients with G6PD deficiency, the reduced form of GSH is not regenerated, as a result the SH group of RBC membrane undergoes oxidation causing denaturation of the hemoglobin and may precipitate in the RBC inclusions and will result in intravascular hemolysis. The denatured hemoglobin is called as Heinz bodies and can be observed under peripheral blood smear.

**Epidemiology**

G6PD deficiency have high prevalence rates in the regions of tropical Africa, the middle east, tropical and subtropical Asia, some areas of the Mediterranean and Papua new guinea.\(^4\) It has never been reported in Amerindians.\(^3\) Most commonly seen in Africa, the Middle East and Southeast Asia, about one in 10 African-American males are affected in the United States.\(^1\)

**Etiology**

G6PD deficiency is a sex-linked disorder, following an inheritance pattern similar to haemophilia. Severe G6PD deficiency is more common in males, inheriting hemizygous G6PD mutations will have defect in all their RBC’s showing abnormal manifestations.

Females usually inherit a heterozygous G6PD mutation; are generally carriers.\(^4\) Hence, commonly they don’t have severe haemolytic anaemia. In few cases females also will have symptoms if they inherit homozygous G6PD mutation and if their normal X chromosome gets inactivated. Majority of females are asymptomatic carriers.\(^3\)

The degree of severity depends on the expression of the specific G6PD alleles. Several number of G6PD variants has been identified depending on the variations in the G6PD allele, hence the enzyme levels also vary depending on the variants and thereby the sensitivity to oxidants also varies. Extremely low levels of the enzyme will cause chronic haemolytic anaemia.

Hereditary nonspherocytic haemolytic anaemia due to G6PD deficiency is usually seen in infants and children. It is one of the rare types of G6PD deficiency.\(^4\)

**Triggering factors**

There are several triggering factors for haemolytic anaemia in G6PD deficient patients, these include-

- **Medications and other chemical substances**

Several drugs have the potential to cause hemolysis in G6PD deficient patients. Drugs to be avoided include-

- Oxidant drugs, such as the antimalarial drugs primaquine, chloroquine, pamaquine and pentaquine
- Nalidixic acid, ciprofloxacin, niridazole, norfloxacin,

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*Figure 1: G6PD and the glutathione (GSH) cycle.*
methylen blue, chloramphenicol, Rasburicase, phenazopyridine and vitamin K analogues

- Sulfonamides, such as sulfanilamide, sulfamethoxypyridazine, sulfacetamide, sulfadimidine, sulfapyridine, sulfamerazine and sulfamethoxazole
- Nonsteroidal anti-inflammatory drugs (NSAIDs), nitrofurantoin and phenazopyridine
- Isobutyl nitrite, phenylhydrazine, Dapsone, Flutamide, Furazolidone, Methylene Blue, Nalidixic acid, Thiazolesulfone, Toluidine blue, Trinitrotoluene (TNT), Urate oxidase and acetanilide.

### Other agents which cause hemolysis include

- Ingestion/inhalation of moth balls.
- Use of herbal medicines and remedies.
- Topical application of henna (particularly in G6PD deficient newborns)
- High doses of ascorbic acid, etc.

#### Food exposure

Fava beans (Vicia faba) - Patients with G6PD deficiency were found to develop haemolytic anaemia induced by ingestion of the fava bean. Favism was most commonly seen in severe deficient variants of G6PD.

#### Infections

Many different types of infections may cause clinically significant hemolysis in G6PD deficient patients. The exact mechanism of hemolysis is unknown. During phagocytosis the leukocytes releases active oxygen species to its environment and it will damage the erythrocytes. Some studies have revealed fever, gastric upset, abdominal pain and vomiting are associated with severe hemolysis.

### Clinical presentation

G6PD deficient patients shows a spectrum of disorders including, acute massive hemolysis, neonatal icterus, renal failure, chronic haemolytic anaemia, etc. the severity of clinical presentation mainly depends upon.

- Degree of enzyme deficiency
- Nature, dose and duration of exposure to oxidative agents
- Host factors (age, gender, level of haemoglobin, presence of any infection).

Due to the reduction in the RBC count, G6PD deficient patients will have fatigue and in severe conditions they may have shortness of breath, dizziness, headache, dark urine, rapid heart rate, cold extremities, pallor and chest pain. Back / abdominal pain is seen in case of acute hemolysis; whereas in severe conditions it may cause jaundice and acute kidney injury. Other symptoms include reduction in haemoglobin, hemoglobinuria, hyperbilirubinemia and reticulocytosis.

In case of Hereditary nonspherocytic haemolytic anaemia, the patients generally presents with splenomegaly and neonatal icterus, hemolysis usually associated with febrile illnesses or by the administration of drugs.

### Diagnosis

The first step for diagnosing G6PD deficiency is to collect the patient’s family history and details about the geographical area. There are several diagnostic tests available detecting the condition. G6PD enzyme activity level can be identified by doing quantitative laboratory assay. If the enzyme activity level is less than 5 units/gm of Hb, indicates G6PD deficiency. To confirm the diagnosis genetic testing can be done. In the current scenario, routine testing for the disease is not in current practice. However, the physicians can consider certain susceptible individuals such as patients with haemolytic anaemia from tropical Africa, the Middle East, Asia, some areas of the Mediterranean and Papua New Guinea, should consider newborns with severe jaundice, especially males with a family history of jaundice, splenomegaly and cholelithiasis.

Patients with G6PD deficiency should frequently check complete blood count with reticulocyte count. Urine dipstick test helps to detect the hemoglobinuria as this will indicate evidence of persistent brisk hemolysis, which if left untreated will cause acute renal failure due to the blockage of renal tubules. Hence it will indicate immediate blood transfusion even if the hemoglobin level is 9 gm/dl or more. Liver function tests and renal function tests can be done to rule out the other symptoms. Peripheral blood smear test will detect the presence of Heinz bodies. Blood grouping and cross matching has to be done in case of blood transfusion.

### Management

Every G6PD deficient patients do not need treatment always. However, they should avoid all the triggering factors causing hemolysis. Identification and discontinuation of the triggering factors is very important to manage hemolysis in patients with G6PD deficiency.

Haemolytic anaemia is always self-limiting, will resolve in 8 to 14 days. Management of anaemia depends on its severity; rarely in severe conditions do we prefer blood
transfusion. Splenectomy is usually ineffective. Patients with chronic hemolysis or nonspherocytic anaemia should take daily folic acid supplements. Some studies have revealed antioxidant properties of vitamin E in reducing hemolysis in these patients.

Haemodialysis is generally recommended in case of acute kidney injury. The prognosis for G6PD deficient patients is generally quite good. They can live a normal life if they avoid all triggering factors.

G6PD deficient infants with prolonged neonatal jaundice should receive phototherapy with a billilight. Exchange transfusion is suggested in case of severe neonatal jaundice or haemolytic anaemia. Tin Mesoporphyrin, a heme analogue is found to be effective in inhibiting bilirubin production in newborns. Studies are still going on regarding its safety and effectiveness.

Hematopoietic stem cells (from peripheral blood, bone marrow, umbilical cord blood) are taken from G6PD deficient donors for transplantation. Following the engraftment, a recipient of HSCs graft from a G6PD deficient donor will convert to the G6PD status of the donor. After transplantation, the recipient should repeat G6PD screening approximately for 6 months, especially when they have received HSCs from heterozygous female donors.

Application of Technology in patient care
Information technology has become an important part of the health profession. Now a day’s many hospitals are utilizing patient specific data in the electronic medical record (EMR). Along with EMR several supporting tools are also used like clinical decision support (CDS), which will help to ensure better patient care and medication safety. Many hospitals use Computerised Prescriber Order Entry (CPOE) along with other supporting tools. In case of any drug-disease interactions or drug-drug interactions, electronic disease screening tools will generate essential safety alerts for clinicians. This system will be very helpful especially in case of less common disease condition like G6PD deficiency. By chance, if any drugs which cause hemolysis are prescribed for a patient, during prescription verification it will generate the alert. Hence all the hospital should utilize these technologies so that the patients with less common disease conditions like G6PD deficiency can receive a better therapy and care.

There is no cure for this condition, but we can minimize its symptoms by avoiding all the triggering factors. Hence it is the responsibility of the health care professionals to plan awareness programs on this condition and adequate measures have to be taken to improve neonatal health. With the help of recent studies, the health care professionals can plan strategy for the successful management and to control this genetic disorder.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

ABBREVIATIONS
G6PD: Glucose-6-Phosphate Dehydrogenase; RBC: Red Blood Cells; ATP: Adenosine triphosphate; ROS: Reactive Oxidative Species; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; H₂O₂: Hydrogen peroxide; GSHPX: Glutathione peroxidase; GSSG: Oxidized glutathione; GSH: Reduced glutathione; G6P: Glucose-6-phosphate; 6PG: 6-phophogluconolactone; -SH: Sulfhydryl group; HSC: Hematopoietic Stem Cells; EMR: Electronic Medical Record; CDS: Clinical Decision Support; CPOE: Computerised Prescriber Order Entry.

SUMMARY
Implementing electronic medical record for all hospitals will provide a systematic approach towards the treatment and is especially important in rare conditions like G6PD deficiency. Softwares and clinical decision supporting tools are found to be effective in creating alert and hence prevent health hazards from such uncommon clinical conditions.

REFERENCES


