AMPATHCHAT no. 95 version 2

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

Dr Wilmaré Gouws, Dr Mada Ferreira

INTRODUCTION

G6PD is a critical housekeeping enzyme in red blood cells (RBCs). It catalyses the oxidation of glucose-6-phosphate to 6-phosphoglucono-lactone, coupled to the reduction of NAD phosphate (NADP) to reduced NADP (NADPH).[1,2] NADPH is critical in preventing damage to cellular structures caused by oxygen free radicals (Figure 1).[1,2,3]

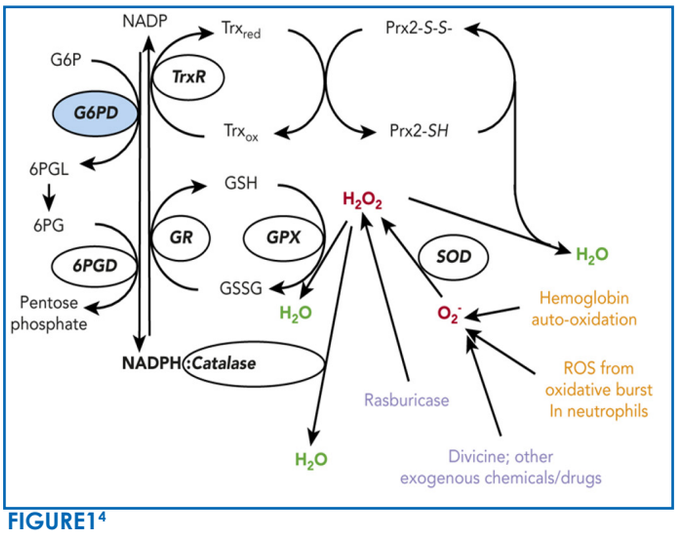

FIGURE1[4]

GENETICS

G6PD deficiency is the most common human enzyme defect affecting over 400 million people worldwide.[1,4,5] G6PD deficiency is an X-linked genetic disorder, females have two alleles and males only one.[1,6] More than 200 mutations have been identified in the G6PD gene.[1,2,4,5] Males can either be hemizygous deficient or hemizygous normal. Females can be homozygous deficient, heterozygous (intermediate) deficient or homozygous normal.[1,3]

PRESENTATION

The RBCs in G6PD-deficient individuals are more susceptible to haemolysis when exposed to oxidative stress.

The majority of G6PD individuals may only become aware of their condition when a haemolytic episode is triggered by certain medication, food substance or infection (Table 1).[1,3]

Medication that may trigger a haemolytic episode should be avoided in G6PD deficient females (homozygous and heterozygous/ indermediate states) as well as hemizygous deficient males.

TABLE 1: TRIGGERS FOR A HAEMOLYTIC ANAEMIA EPISODE IN INDIVIDUALS WITH G6PD DEFICIENCY

Medication to avoid/use with caution[3,7,8,9]

Analgesics/antipyretics
- Aspirin (caution in high doses >1g/day)
- Paracetamol (caution)

Antimalarials
- Dapsone
- Primaquine
- Chloroquine (caution)
- Quinine (caution)

Anti-bacterial
- Co-trimoxazole
- Nitrofurantoin
- Quinolones (e.g. ciprofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin)
- Sulfadiazine
- Sulfasalazine (caution)

Other
- Pegloticase
- Rasburicase
- Niridazole
- Methylene blue
- Chloramphenicol (caution)
- Isoniazid (caution)
- Ascorbic acid (caution)
- Vitamin K (caution)
- Isosorbide (caution)
- Dinitrate (caution)
- Glibenclamide (caution)

Food

Legumes e.g., fava beans (broad beans), soybeans, peanuts, peas and chickpeas

Infections[1,10]

Hepatitis A or B, pneumonia, typhoid fever

G6PD-deficient individuals can experience haemolytic episodes ranging from mild to life-threatening. The degree of haemolysis depends on several factors, including the G6PD deficiency variant, the dose and duration of the triggering factor, the age of the patient and coexisting morbidities.

G6PD DEFICIENCY IN NEONATES

Neonates may present with neonatal jaundice peaking 2-3 days after birth. Severity varies, but without adequate treatment, it can lead to bilirubin encephalopathy (kernicterus), permanent neurological damage, or death. More than half of all neonates develop jaundice from multiple causes in the first week of life.

The level of hyperbilirubinemia due to G6PD deficiency is often higher than in jaundice due to other causes, resulting in a higher demand for exchange transfusion in these G6PD-deficient neonates.[1]

Neonates with a coexisting mutation of the uridinediphosphate-glucuronosyltransferase 1 (UGT1A1) gene promoter, responsible for Gilbert syndrome, have an increased risk of developing severe neonatal jaundice.[3]

Indications for G6PD testing[3]

- Prior to treatment with offending drugs (Table 1)
- Haemolysis after intake of offending drugs (Table 1)
- Haemolytic anaemia in neonates (non-spherocytic)
- Congenital non-spherocytic haemolytic anaemia in males or females
- Prolonged or severe neonatal jaundice
- Red cell morphology is suggestive of oxidative damage (bite cells)
- Sickle cell disease
- Thalassaemic disorders
- Favism
- Family history of G6PD deficiency and favism
- Before starting Rasburicase in an oncology patient
- Acute haemolysis following haematopoietic stem cell transplant if the donor is G6PD deficient

DIAGNOSTIC TESTING FOR G6PD DEFICIENCY

G6PD deficiency can be diagnosed by either using qualitative or quantitative assays.

Qualitative/Screening G6PD testing

- Rapid and commonly used test which detects the fluorescence of NADPH (generated from NADP) proportional to G6PD levels.
- Although the screening test can identify severe G6PD deficiencies, discrimination between intermediate and normal G6PD levels may be problematic.[11]

Quantitative/Confirmatory testing for G6PD

The Standard Biosensor G6PD point of care analyzer uses a colorimetric detection system where a diaphorase reaction yields a violet colour, directly proportional to the G6PD concentration in the sample. Colour intensity is measured by photometry.

This quantitative assay employs semi-quantitative interpretation to distinguish between three clinically significant G6PD levels: deficient, intermediate and normal (Table 2).

Table 2: Interpretation of G6PD levels

Male (u/g Hb)		
Normal	**Deficient**	
≥4.1	0-4	
Female (u/g Hb)		
Normal	**Intermediate-deficient**	**Deficient**
≥6.1	4.1-6	0-4

Test information

Mnemonic	**G6RET**
Specimen type	1 x EDTA tube
Turnaround time	24h (please arrange with the haematopathologist if urgently required)
Frequency of test	daily

Conclusion

G6PD deficiency is the most common human enzyme deficiency. A high index of suspicion is needed to adequately diagnose these patients to prevent haemolysis by minimising or avoiding drug triggers. Quantitative G6PD testing is furthermore imperative in diagnosing and managing neonates presenting with jaundice.

References

1. Gonzalo J. Domingoa, Nicole Advania, Ari W. Satyagrahab, Carol H. Sibleyc, Elizabeth Rowleya, Michael Kalnokya, Jessica Cohena, Michael Parkerd and Maureen Kelley. Addressing the gender-knowledge gap in glucose-6-phosphate dehydrogenase deficiency: challenges and opportunities. Int Health 2019; 11: 7–14
2. Lucio Luzzatto,1,2 Mwashungi Ally,1 and Rosario Notaro3 Glucose-6-phosphate dehydrogenase deficiency Blood. 2020;136(11):1225-1240)
3. David Roper,1 Mark Layton,1 David Rees,2 Chris Lambert,3 Tom Vulliamy,4 Barbara De la Salle,5 Carol D'Souza. Laboratory diagnosis of G6PD deficiency. A British Society for Haematology Guideline. British Journal of Haematology, 2020, 189, 24–38
4. Nkhoma ET, Poole C, Vannappagari V et al. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. Blood Cells Mol Dis 2009;42(3):267–78.
5. Gomez-Manzo S, Marcial-Quino J, Vanoye-Carlo A et al. Glucose-6-phosphate dehydrogenase: update and analysis of new mutations around the world. Int J Mol Sci 2016;17(12).
6. Beutler E, Yeh M, Fairbanks VF. The normal human female as a mosaic of X-chromosome activity: studies using the gene for C-6-PD deficiency as a marker. Proc Natl Acad Sci USA 1962; 48:9–16.
7. Italian G6PD Deficiency Association can be found at www.g6pd.org.
8. Frank JE. Diagnosis and management of G6PD deficiency. Am Fam Physician. 2005;72(7):1277-1282
9. Sansone S, Rottensteiner J, Stocker J, Rosanelli C, Wiedermann CJ. Ciprofloxacin-induced acute haemolytic anaemia in a patient with glucose-6-phosphate dehydrogenase Mediterranean deficiency: a case report. Ann Hematol (2010) 89:935-937
10. Beutler E. G6PD deficiency. Blood 1994;84(11):3613–36.
11. LaRue Nicole, Kahn Maria, Murray M, Leader BT, Bansil, P, McGray S, Kalnoky, M, Zhang, H, Huang H, Jiang H, Domingo, GJ. Comparison of Quantitative and Qualitative Tests for Glucose-6-Phosphate Dehydrogenase Deficiency. Am J Trop Med Hyg. 2014 Oct 1;91(4):854-861
12. Richardson SR, O'Malley GF. (2022, September 26). Glucose-6-Phosphate Dehydrogenase Deficiency. In Stat Pearls Publishing. Retrieved March 19, 20325, from https://www.ncbi.nlm.nih.gov/books/NBK470315