AN ATTEMPT TO UNDERSTAND THE GLUCOSE 6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

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ABSTRACT

G6PD deficiency is one of the most prevalent human enzymopathies, and it is caused by hereditary mutations in the X-linked gene G6PD. G6PD insufficiency has been documented in as many as 400 different genetic variations, with 186 of them having a recognized mutation. Variants are defined by the World Health Organization (WHO) based on residual enzyme activity and illness severity. Red blood cells with a G6PD deficiency are more prone to oxidative damage and thus hemolysis. Almost of G6PD mutations are missense mutations that result in amino acid substitutions that result in a lack of G6PD enzyme function: the protein's stability is compromised, the catalytic activity is reduced, or a combination of both causes occurs. The reasons for glucose-6-phosphate dehydrogenase insufficiency are discussed in this activity, as well as the role of the interprofessional team in evaluating and managing individuals with this illness.

Keywords: Enzyme, Disease, Deficiency, Cells, Treatments.

I. INTRODUCTION

G6PD is the key enzyme in pentose phosphate shunt (PPS) where it catalyzes the entry step ofG6P that forms part of glycolysis and was first described by Warburg and Christian in 1931. In erythrocytes, this alternate anaerobic pathway for glucose metabolism remains the only source for reduced NADP which is required for methemoglobin reductase activity and the maintenance of the level of reduced glutathione (GSH). NADPH and GSH in turn, maintain an effective redox potential protecting cell membrane sulphhydryl groups, enzymes and hemoglobin against oxidative stress and injury. Thus, G6PD activity helps the erythrocyte withstand oxidative stress. Deficient enzyme activity impairs the erythrocyte's ability toremove deleterious oxygen species, thus leading to premature lysis.

G6PD deficiency has been incidental in populations in nearly all geographical locations of the world however, it is frequently found in the belt extending from the Mediterranean area through Southwest Asia, India to South East Asia and the pockets where Plasmodium falciparum malaria had been endemic. Because of its high prevalence among a population where malaria was once endemic, G6PD deficiency is a good example of a balanced polymorphism in which the high rate of mortality caused by this disorder is offset by the protection that it offers against Plasmodium falciparum malaria. Many indigenous ethnic groups have a high prevalence of G6PD deficiency as compared to others. The severity of G6PD deficiency also differs among different populations.

II. BIOCHEMISTRY OF G6PD AND G6PD DEFICIENCY

There are a few obligate surface parasites (such as Mycoplasma genitalium) and intracellular parasites that lack the ancient G6PD enzyme found in all other species, including Archaea, which are predominantly anaerobic (for example, Rickettsia prowazekii). G6PD is an oxidoreductase that catalyses the oxidation of glucose-6-phosphate to 6-phosphoglucono- lactone coupled to the reduction of NAD phosphate (NADP) to reduced NADP (Figure 2). In all mammals, G6PD is ubiquitously expressed, suggesting that it plays an essential housekeeping function: indeed, deletion of the G6PD gene is deadly early in embryonic development. A common name for G6PD is the first enzyme in the pentose phosphate pathway,highlighting its significance in producing the pentose sugars needed for nucleic acid synthesis (but pentose can also be produced through the alternative transketolase-transaldolase

pathway). NADPH, produced by G6PD and named its coenzyme, is the electron donor in processes essential for the production of deoxyribonucleotides, fatty acids, and steroids; it is also the coenzyme of cytochrome P450, central to the metabolism of many drugs and other xenobiotics. NADPH's reducing power is necessary for a process known as protection against oxidative assaults.

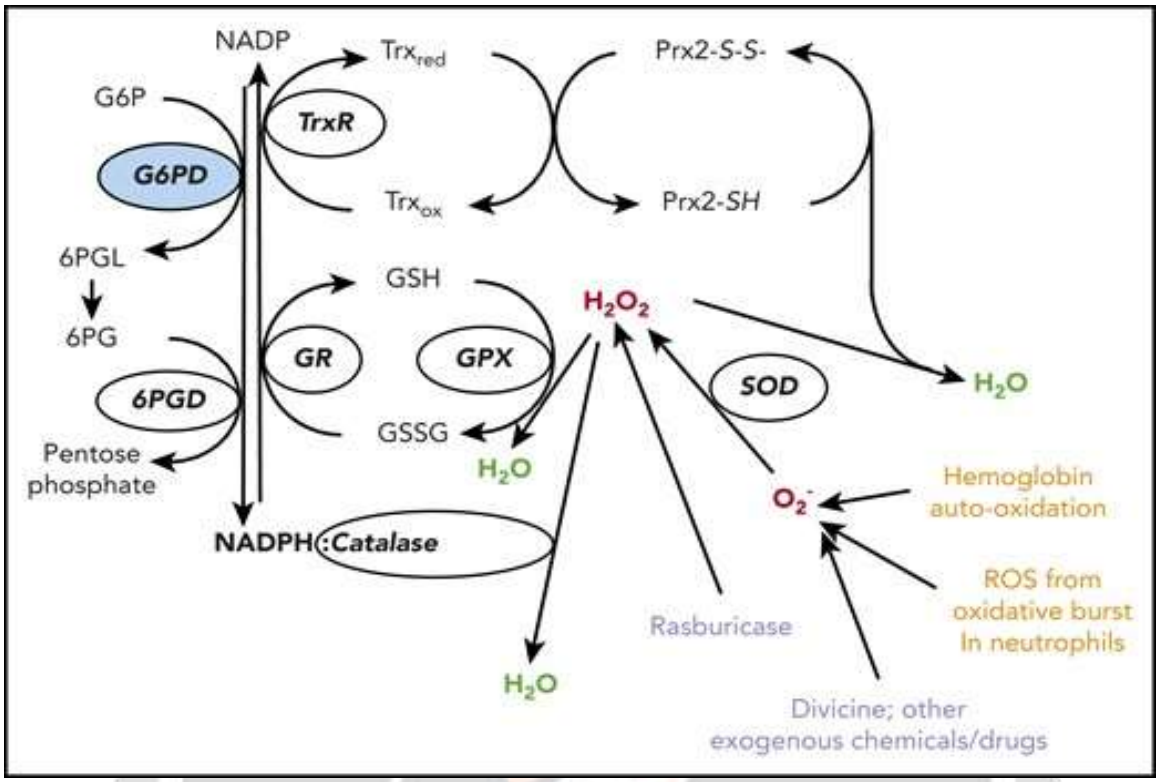

Figure 1: Biochemistry of G6PD

In adult red cells, there is no nucleus, and so no DNA or RNA synthesis, no fatty acid synthesis, no endoplasmic reticulum, and thus no cytochrome P45029: hence, all of these components are unimportant in their physiology, except for the final function, which is crucial. Because the concentration of haemoglobin (Hb) in red cells is less than 5 mM, red cells are constantly subjected to an endogenous oxidative stress. The reversible binding of O2 to Hb's four heme residues is a physical chemistry marvel, yet no physical device is faultless. Occasionally, spontaneous conformational variations in the heme pocket of HbO2 allow water or a tiny anion to enter , resulting in an electron transfer from iron to oxygen, resulting in methemoglobin and superoxide radicals: this auto-oxidation process impacts 2% to 3% of total Hb per day. NADH cytochrome b5 reductase 3 (also known as methemoglobin reductase) rapidly converts methemoglobin (Fe^{3+}) to Hb (Fe^{2+}), whereas superoxide radicals form hydrogen peroxide (H2O2), a potent oxidising agent, via superoxide dismutase. It is here that NADPH is required: three enzymatic pathways in the red cell can eliminate H2O2, and NADPH plays a role in all three. G6PD is the first line of defence against oxidative stress in red cells.

G6PD activity declines as red cells age due to the lack of protein synthesis in adult red cells. Reticulocytes have a high level of G6PD activity, but the oldest red cells have only around one-tenth of that; yet, this amount is still sufficient for the demands of G6PD normal red cells.

III. SYMPTOMS AND CAUSES OF G6PD DEFICIENCY Symptoms

The majority of patients with G6PD deficiency show no symptoms. If a large number of RBCs are destroyed, others may experience signs of hemolytic anaemia.

These can include the following:

- paleness (in darker-skinned kids, paleness is sometimes best seen in the mouth, especially on the lips or tongue)
- extreme tiredness or dizziness
- fast heartbeat
- fast breathing or shortness of breath

- jaundice (the skin and eyes look yellow)
- an enlarged spleen
- dark, tea-colored pee

Mild symptoms don't generally necessitate medical attention. Anemia will improve when the body produces new red blood cells. If a child's symptoms become more severe, he or she may require hospital treatment.

Causes

Section Collapse

Mutations in the G6PD gene cause glucose-6-phosphate dehydrogenase deficiency. This gene codes for glucose-6-phosphate dehydrogenase, a glucose-6-phosphate dehydrogenase enzyme.This enzyme is required for appropriate carbohydrate digestion. It also shields red blood cells from the detrimental effects of reactive oxygen species, which are produced as a consequence of regular physiological operations. In red blood cells, chemical events involving glucose-6- phosphate dehydrogenase produce chemicals that prevent reactive oxygen species from reaching lethal levels.

This enzyme can no longer fulfil its protective role if mutations in the G6PD gene lower the amount of glucose-6-phosphate dehydrogenase or change its structure. Reactive oxygen species can build up as a result, causing damage to red blood cells. Infections, some drugs, and consuming fava beans can raise reactive oxygen species levels, leading red blood cells to be damaged faster than the body can replace them. The signs and symptoms of hemolytic anaemia are caused by a decrease in the amount of red blood cells.

People with the G6PD mutation may be somewhat protected against malaria, an infectious disease spread by a certain species of mosquito, according to researchers. The parasite appears to have a harder time invading red blood cells when the number of functioning glucose-6- phosphate dehydrogenase is reduced. Glucose-6-phosphate dehydrogenase deficiency is most common in malaria-affected areas of the world.

IV. TREATMENTS THAT ARE COMMONLY USED

G6PD deficiency treatment consists of removing the trigger that is triggering symptoms. If the condition was brought on by an illness, the infection must be treated as well. Any drugs that may be causing red blood cell destruction are likewise stopped. Most people can recover from an episode on their own in these situations.

More intensive treatment may be required once G6PD deficiency has advanced to hemolytic anaemia. To replace oxygen and red blood cell levels, oxygen therapy and blood transfusions are sometimes used. You'll have to stay in the hospital while getting these therapies since severe hemolytic anaemia requires continuous monitoring to ensure a full recovery without problems.

The majority of those who are impacted do not require therapy. Preventative actions are frequently the best way to deal with G6PD deficiency. Before taking certain drugs, such as antibiotics, antimalarials, and other medications known to cause hemolysis in G6PD-deficient people, people should be tested for the G6PD defect. Hemolytic anaemia from fava beans or recognized drugs should not arise in G6PD-deficient patients because exposure may be avoided.

If an episode of hemolytic anaemia is caused by the use of a certain medication, it should be stopped under the guidance of a physician. If the episode is caused by an underlying infection,

the infection should be treated as soon as possible. Some adults may require short-term fluid therapy to prevent hemodynamic shock (an insufficient supply of blood to the organs) or, in severe cases where hemolysis is occurring at a high rate, blood transfusions. Blood transfusions are more common in children than in adults, and they can save lives in children with favism.

Jaundice in newborns is treated by exposing the baby to specific lights (bili lights) that help to reduce the condition. An exchange transfusion may be required in more serious situations. The blood of an afflicted newborn is removed and replaced with fresh donor blood or plasma during this surgery. Patients and their families may benefit from genetic counselling.

In India, the prevalence of G6PD deficiency varies between 0-27% in different caste, tribe, and ethnic groups. The

prevalence is higher among the tribes as compared to non-tribal caste populations. Incidence of G6PD deficiency has also been reported in urban and hospital attending heterogeneous populations of selective regions in India.

In G6PD-deficient patients, common drugs to avoid or use with caution include:

- Acetaminophen
- Acetylsalicylic acid
- Chloramphenicol
- Chloroquine
- Colchicine
- Diaminodiphenyl sulfone
- Diphenhydramine
- Glyburide
- Isoniazid
- L-Dopa
- Methylene blue
- Nitrofurantoin
- Phenazopyridine
- Primaquine
- Rasburicase
- StreptomycinSulfacetamide
- Sulfanilamide
- Sulfapyridine
- Sulfacytine
- Sulfadiazine
- Sulfaguanidine
- Sulfamethoxazole
- Sulfisoxazole
- Trimethoprim
- Tripelennamine
- Vitamin K

V. CONCLUSION

G6PD deficiency is a ubiquitous genetic characteristic that can protect heterozygotes from malaria death (save in the very small fraction of individuals who have CNSHA). AHA in a G6PD-deficient kid or adult, on the other hand, is a medical emergency that can be fatal if not treated swiftly and effectively. Ingestion of fava beans is the most common cause of AHA worldwide: favism is seen in at least 35 countries, with thousands of cases reported each year. Iatrogenic deaths have been observed with both primaquine and rasburicase, and these deaths are preventable in both the United States and other nations. Favism can be avoided through population screening and health education, as well as the introduction of fava bean varieties with no or low vicine and convincing levels.

G6PD-deficient individuals have taught us a lot as haematologists. G6PD's biology is eminently interdisciplinary, having served as a model system in biochemical genetics and in understanding how the red cell responds to oxidative attack; a tool for studying X-chromosome inactivation (the most spectacular epigenetic event in human development); a tool for studying clonal populations for years; a pioneer in the molecular genetics of enzymopathies; and the best-characterized example in humans of an X-linked genetic polymorphism balanced by Darwinian selection exerted by malaria.

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