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MAJOR CLINICAL ASPECTS OF G6PD DEFICIENCY, CHALLENGES IN MANAGEMENT

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Abstract:

The pathophysiology, diagnosis, and medication-use implications of glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most common enzyme deficiency in humans, are reviewed. We performed detailed search through electronic databases; PubMed, and EMBASE, for studies published in English language and human subjects thought instant to 2018. Glucose-6-phosphate dehydrogenase deficiency is a hereditary disorder that happens virtually solely in males. This problem mainly impacts red cell, which lug oxygen from the lungs to tissues throughout the body. In affected people, a problem in an enzyme called glucose-6-phosphate dehydrogenase causes red blood cells to break down prematurely. This destruction of red cell is called hemolysis. If transformations in the G6PD genetics decrease the quantity of glucose-6-phosphate dehydrogenase or change its structure, this enzyme can no more play its safety function. As a result, reactive oxygen species can build up and harm red blood cells.

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INTRODUCTION:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an incomplete hereditary X-linked hemolytic disease. This enzymopathy prevails in the tropics and subtropics, integrating with endemic or formerly endemic malaria; which indicates that G6PD deficiency might have developed, spread out, or maintained in frequency through natural selection by malaria [1]. Although it is difficult to identify G6PD deficient patients as the majority of induced individuals are asymptomatic up until they are exposed to triggers, more than 400 million people are thought to be G6PD deficient [1].

G6PD catalyzes the reaction in the pentose phosphate pathway that generates decreased form of NADPH, which is in turn responsible for glutathione (GSH) homeostasis [2]. GSH is an antioxidant, and together, these processes make cells much more able to withstand and control oxidative stress [1]. Incapability of the erythrocytes to maintain GSH homeostasis leads to oxidative stress and impacts the integrity of the RBCs, generating hemolysis. Most favorable RBC redox status is necessitated by malaria parasites for their survival, replication, and advancement [2]. This factor is diminished in G6PD deficient RBCs, sustaining the security theory.

Although inconclusive evidence collected to support the theory that G6PD deficiency is protective versus serious mortal malaria [3]. Some scientists also argued that perhaps malaria may not be the only factor impacting the deficiency gene locus [3]. It continues to be to be defined whether a straight association exists between G6PD deficiency and defense from malaria.

The pathophysiology, diagnosis, and medication-use implications of glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most common enzyme deficiency in humans, are reviewed.

METHODOLOGY:

We performed detailed search through electronic databases; PubMed, and EMBASE, for studies published in English language and human subjects thought instant to 2018. Studies discussing the glucose-6-phosphate dehydrogenase (G6PD) deficiency, management approaches, following keywords are used in search process: “G6PD”, “G6PD deficiency”, “hemolytic anemia”, “treatment”, “Management”. We excluded case reports. Moreover, references of included studies were scanned for more relevant articles.

DISCUSSION:

- **Classification and Pathophysiology of G6PD Deficiency**

G6PD deficiency is an X-linked genetic disorder with 187 well-known allelic mutations [4] G6PD, an important enzyme in the pentose phosphate pathway, exhibits diminished activity in these patients, causing inadequate production of safety intracellular thiols throughout oxidative stress [4]. While the deficiency is ubiquitous throughout cell types, erythrocytes are specifically insecure to oxidative stress in the G6PD-deficient state, and the disease has been connected with neonatal hyperbilirubinemia, acute hemolysis, and chronic nonspherocytic hemolytic anemia. The World Health Organization (WHO) has categorized G6PD deficiency according to the magnitude of the enzyme deficiency and hemolysis intensity [5]. Class I through Class III describe deficiency states ranging from one of the most extreme chronic nonspherocytic hemolytic anemia to moderate deficiency that reveals hemolysis only with exposure to certain metabolic conditions, infections, medicines, and foods. Classes IV and V define nondeficient and high-enzyme-activity states.

Hemolytic anemia is one of the most prevalent severe manifestation of G6PD deficiency. In a normal program, patients present with discoverings of jaundice, fatigue, pain in the back, tachypnea, and tachycardia. Pertinent laboratory discoveries consist of decreased hemoglobin and red blood cell counts, reticulocytosis, enhanced lactate dehydrogenase, and boosted unconjugated bilirubin.

To comprehend the biochemistry of G6PD deficiency, one must initially know the enzyme's normal function. The mitochondria of human cells are accountable for producing energy (adenosine triphosphate) using aerobic respiration, the by-products of that include free radicals and reactive oxidative species (ROS) from the "leaky" electron transport chain [6]. Free radicals such as superoxide, hydrogen peroxide, and hydroxyl radical can hurt DNA, lipoproteins, and cell membrane layers, causing cellular damages and cell lysis. This state is typically referred to as oxidative stress [5]. Human cells utilize multiple techniques to neutralize the damaging free-radical species by synthesizing antioxidants to combat oxidative stress. One such in vitro antioxidant is the thiol glutathione. In its reduced (cell-protective) type, glutathione feeds on free-radical species to prevent cell damage. Nevertheless, when a glutathione molecule minimizes a free radical, it has to be re-growed in a path making use of the lowering coenzyme NADPH. The pentose phosphate pathway produces a supply of

NADPH with a reaction depending on G6PD. In the pentose phosphate pathway, G6PD catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconolactone and in the process creates decreased NADPH used to regenerate glutathione. Various other procedures for generating cellular antioxidants entail ascorbate, alpha-tocopherol, and carotenoids [7].

The primary trouble with G6PD deficiency is that patients cannot restore ample quantities of protective glutathione. In the majority of cells, this deficiency is irrelevant, since other mitochondrial processes sustain a supply of natural antioxidants to remove damaging ROS. However, erythrocytes naturally shed organelles, consisting of mitochondria, throughout cell maturation and depend exclusively on the cytosolic pentose phosphate pathway and generation of decreased glutathione for oxidative defense [7]. G6PD deficiency, nevertheless, reduces these cells' capability to restore glutathione, leaving red blood cells sensitive to oxidative damage and ultimate fatality.

Table 1. Classes of G6PD Enzyme Variants [5],[6].

Class	Level of Deficiency	Enzyme Activity	Prevalence
I	Severe	Chronic nonspherocytic hemolytic anemia in the presence of normal erythrocyte function	Uncommon; occurs across populations
II	Severe	Less than 10 percent of normal	Varies; more common in Asian and Mediterranean populations
III	Moderate	10 to 60 percent of normal	10 percent of black males in the United States
IV	Mild to none	60 to 150 percent of normal	Rare
V	None	Greater than 150 percent of normal	Rare

- **Difficulties in diagnosis**

The gold standard for medical diagnosis of G6PD deficiency is spectrophotometric measurement of enzyme activity; molecular review may be required to establish the diagnosis in females homozygous for the ailment.

The medical diagnosis of males and homozygous females with G6PD deficiency is apparent and can be determined by the measurement of enzyme activity. Identification of heterozygous women, nonetheless, is much more challenging (Table 2). Because of X chromosome inactivation, these patients have 2 separate RBC populaces, which are generally found in a 50:50 ratio; however, that proportion can vary. If enzyme activity is evaluated, they can have activity varying from typical to deficient, which can possibly cause a false negative outcome [8], [9]. In a female patient, if an enzyme detection test outcome is intermediate or borderline or if G6PD deficiency is supposed yet the result of enzyme detection testing is typical, molecular analysis is recommended to prove or rule out G6PD deficiency [8], [9].

Acute hemolysis can similarly lead to troubles in identifying G6PD deficiency. Patients whose enzyme activity is tested during an episode of acute hemolysis might be wrongly identified as having normal G6PD activity because of the discerning devastation of older RBCs with the lowest G6PD activity [8], [9]. The younger RBCs that remain have normal to near normal G6PD activity. It is typically recommended that the test be performed once more at the very least 2 weeks after a hemolytic episode; however, some sources suggest waiting at the very least 2-3 months [8].

Table 2. Genotypes associated with various Glucose-6-phosphate Dehydrogenase (G6PD) Phenotypes [10].

G6PD Phenotype	Males	Females
Chronic nonspherocytic hemolytic anemia	Class I	Class I/Class I
Deficient (<10% to 60% of normal G6PD activity)	Class II or III	Class II/Class II Class III/Class III Class II/Class III
Normal (>60% of normal G6PD activity)	Class IV	Class IV/Class IV
Variable (<60% or>60% of normal G6PD activity)	Not applicable	Class I/Class IV Class II/Class IV Class III/Class IV

- **Clinical implication**

Every health care specialist needs to beware in managing the G6PD-deficient patient. As was pointed out in the past, swallowing of fava beans, specific drugs, infections, and metabolic disorders can cause hemolysis. Poor management of those G6PD-deficient individuals who develop acute hemolytic anemia can bring about permanent neurologic damage or fatality.

First of all, a variety of medicines, as noted in Table 3 can precipitate hemolysis in G6PD-deficient subjects. These medicines can interact with hemoglobin and oxygen, bring about the intracellular accumulation of hydrogen peroxide (H2O2) and other oxidizing radicals. As these oxidants accumulate within enzyme-deficient cells, hemoglobin and other proteins are oxidized, causing loss of function and cell death [11], [9].

Table 3. Medications that should be avoided by persons with G6PD Deficiency* [12].

Drug name	Use
Dapsone	Antimicrobial for treatment of leprosy
Flutamide (Eulexin)	Antiandrogen for treatment of prostate cancer
Mafenide cream (Sulfamylon)	Topical antimicrobial
Methylene blue (Urolene Blue)	Antidote for druginduced methemoglobinemia
Nalidixic acid (NegGram)	Antibiotic used primarily for urinary tract infections
Nitrofurantoin (Macrodantin)	Antibiotic used primarily for urinary tract infections
Phenazopyridine (Pyridium)	Analgesic for treatment of dysuria
Primaquine	Antimalaria agent
Rasburicase (Elitek)	Adjunct to antineoplastic agents
Sulfacetamide (Klaron)	Antibiotic (ophthalmic and topical preparations)

Drug name	Use
Sulfamethoxazole (Gantanol)	Antibiotic used in combination preparations (i.e., trimethoprim-sulfamethoxazole [TMP-SMX; Bactrim, Septra])
Sulfanilamide (AVC)	Antifungal agent for treatment of vulvovaginal*Candida albicans* infection

G6PD = glucose-6-phosphate dehydrogenase.

*—Classes I, II, and III.

Altikat et al. examined the impacts of certain anesthetic agents such as halothane, isoflurane, ketamine, sevoflurane, prilocaine, diazepam, and midazolam on enzymatic activity of G6PD [13]. They identified that although isoflurane, sevoflurane, diazepam, and midazolam had an inhibitory result on G6PD activity in vitro, halothane, ketamine, and prilocaine had none. On the other hand, no recorded cases were discovered to show that benzodiazepines, codeine/codeine derivatives, propofol, fentanyl, or ketamine can trigger hemolytic crisis in the G6PD-deficient patient in vivo.

Nonetheless, hemolytic crises induced by inhalational general anesthetic agents are still being researched, especially because some authors have vaguely related G6PD deficiency to deadly hyperthermia [14]. Clearly, insufficient research study has been done to research the impacts of inhalational anesthetic agents on the G6PD-deficient patient.

Of vital note, methylene blue is ineffective in patients with G6PD deficiency who might request exchange or hyperbaric treatment, due to the fact that these patients lack the ability to return hemoglobin to the ferrous kind [15]. As a result, drugs such as benzocaine, lidocaine, articaine, prilocaine, and silver nitrate, which are recognized to generate methemoglobinemia, must additionally be stayed clear of [16].

Infection is most likely the most common aspect prompting hemolysis in G6PD-deficient subjects [17], [18]. In one study, for instance, a sudden fall in hemoglobin concentration happened in about 20% of G6PD-deficient topics with pneumonia [17]. A variety of other infectious agents, including Escherichia coli, rickettsiae, viral hepatitis, dental caries, salmonella, and beta-hemolytic streptococci, have been implicated [16-18]. Quereshy et al. define an instance of a G6PD-deficient patient who created hemolytic anemia secondary to a maxillofacial infection due to a blatantly carious tooth [19].

The aspects in charge of increased damage of G6PD-deficient red cells during infection are not known. One feasible explanation is that the red cells are affected by oxidants created by phagocytosing macrophages - a system similar to that seen with drug-induced hemolysis [20].

Certain metabolic conditions, such as diabetic ketoacidosis, additionally seem with the ability of activating damage of G6PD-deficient red cells [13]. Both acidosis and hyperglycemia are potential precipitating variables, and modification of the abnormalities is associated with turnaround of the hemolytic process [21]. In some diabetic people, occult infection may be an usual trigger for generating both acute hemolysis and ketoacidosis.

Postoperatively, the G6PD-deficient patient can provide specific medical indications that may trigger the need for additional assistance or therapy. In general, hemolysis is seen 1 to 3 days after contact with triggering factors. Acute hemolysis is self-limited, but in unusual circumstances it can be severe sufficient to require a blood transfusion [22]. The patient might establish cyanosis, headache, fatigue, tachycardia, dyspnea, lethargy, lumbar/substernal pain, stomach pain, splenomegaly, hemoglobinuria, and/or scleral icterus [23]. Also, the break down products of hemoglobin will collect in the blood, causing jaundice, and they can be eliminated in the urine, causing dark brownish staining [9].

Peripheral blood smear microscopy may include pieces of red cell "schistocytes" and reticulocytes. Denatured hemoglobin involvements within the red cell are called Heinz bodies. Lactate dehydrogenase (LDH) will certainly rise in blood. Unconjugated bilirubin in the blood is elevated, resulting in jaundice. Haptoglobin degrees are decreased. The straight Coombs test is favorable, if hemolysis is triggered by an immune process. Nonetheless, because hemolysis in G6PD deficiency is not an immune procedure, the straight Coombs outcome should be negative. Hemosiderin in the urine indicates chronic intravascular hemolysis. Urobilinogen is also existing in the urine.

Grant E. Sklar described a case in which a G6PD-

deficient patient experienced a decline in hemoglobin concentration of practically 4 g/dL and a rise in unconjugated bilirubin consistent with the advancement of hemolysis second to acetaminophen overdose [22]. On the other hand, according to a much more current article in Lancet, the association between acetaminophen and hemolysis in the G6PD-deficient patient is uncertain [9].

General anesthetic commonly covers up the instant signs of hemolysis, making it difficult to identify a hemolytic crisis while the patient is asleep. Even hypotension, which could be an outcome of hemolysis, may be credited to various other causes in an anesthetized patient. The appearance of free hemoglobin in plasma or urine is presumptive evidence of a hemolytic reaction. Therapy includes discontinuation of the offending agent and maintenance of urine result by infusion of crystalloid solutions and diuretics such as mannitol and/or furesomide [23].

In contrast to the trouble in establishing a hemolytic problem while the patient is under general anesthesia, clinical signs and symptoms are a bit extra apparent. Medical signs and symptoms of hemolysis generally emerge within 24 to 72 hrs of medication application, and anemia worsens up until concerning day 7 [9]. This makes it difficult for the health expert to recognize a hemolytic crisis in patients who undertake outpatient or short hospital stay (less than 24 hour) treatments. As a result, the practitioner must educate the risky patient and his/her caretaker to look for signs and symptoms of a hemolytic crisis (cyanosis, headache, dyspnea, exhaustion, lumbar/substernal ache, jaundice, scleral icterus, dark urine). An easy postoperative call to check on the patient before the follow-up consultation could be important to his or her health. It is thought that after removal of the offending hemolytic agent, hemoglobin concentrations start to recuperate after 8 to 10 days; therefore, rarely (except in youngsters) does acute hemolysis bring about serious anemia calling for a blood transfusion [9].

The most vital management method is to stop a hemolytic crisis in the first place by avoiding the oxidative stress factors [9]. Nevertheless, acute hemolysis in G6PD-deficient adults is brief and generally does not call for particular treatment. Nonetheless, in case of a hemolytic crisis, the offending agent needs to be eliminated, and the patient needs to be monitored closely. Table 4 summarizes the research laboratory examination results in patients with acute hemolysis [9], [24]. At minimum, a day-to-day complete blood count should be complied with to check the requirement for a blood transfusion.

Table 4. Laboratory Evaluation in Patients With Acute Hemolysis [24],[9]

Laboratory Evaluation	**Findings**
Complete blood count	Anemia
Reticulocyte count	Increases by day 4-7
Peripheral blood smear	Heinz bodies, schistocytes, reticulocytes
Haptoglobin	Decreased
Liver function tests	Elevated bilirubin
Urinalysis	Brown color,hemosiderin,urobilinogen
Coombs test	Positive
Lactate dehydrogenase	Elevated

CONCLUSION:

Glucose-6-phosphate dehydrogenase deficiency is a hereditary disorder that happens virtually solely in males. This problem mainly impacts red cell, which lug oxygen from the lungs to tissues throughout the body. In affected people, a problem in an enzyme called glucose-6-phosphate dehydrogenase causes red blood cells to break down prematurely. This destruction of red cell is called hemolysis. If transformations in the G6PD genetics decrease the quantity of glucose-6-phosphate dehydrogenase or change its structure, this enzyme can no more play its safety function. As a result, reactive oxygen species can build up and harm red blood cells. Aspects such as infections, particular medications, or ingesting fava beans can increase the degrees of reactive oxygen species, causing red blood cells to be damaged faster than the body can change them. A reduction in the number of red blood cells causes the symptoms and signs of hemolytic anemia.

The clinical presentation and timespan for drug-induced hemolysis in the G6PD-deficient patient has been described by various authors. The most usual

existing signs and symptom is exhaustion as a result of the decreased red blood cell count. Acute hemolysis may also cause back or ventral ache. Very reduced erythrocyte counts may result in shortness of breath, dizziness, headache, cold extremities, pallor, and upper body pain. If hemolysis is serious enough, jaundice might happen.

The most efficient management method is to stop hemolysis by preventing oxidative stress factors. For that reason, management for pain and stress and anxiety ought to include medications that are safe and have not been revealed to trigger hemolytic crises, such as benzodiazepines, codeine/codeine derivatives, propofol, fentanyl, and ketamine. In severe hemolysis, blood transfusions might be called for; hemodialysis may be needed if acute kidney injury takes place. Neonates should be evaluated for G6PD deficiency when family history, ethnic or geographic origin, or the timing of the look of neonatal jaundice proposes the probability of G6PD deficiency. Generally, the prognosis for G6PD-deficient patients is quite good. Most patients live fairly typical lives as long as they stay clear of triggers.

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