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An Overview of the Most Common Enzyme Defect, Glucose-6-Phosphate-Dehydrogenase Deficiency

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ABSTRACT

Background: Glucose-6-Phosphate-Dehydrogenase **(**G6PD) deficiency is the most common enzyme deficiency globally and is more remarkable in certain parts of the world which had high malaria prevalence in the past. It is an X-linked genetically inherited disorder, where the first presentation can be neonatal jaundice. There are over 300 variants of this disorder based upon the genetics. Although the morbidity and mortality is not very high, the deficiency can be more appropriately managed by proper preventive methods which include screening and avoidance of trigger. Also prompt management of acute hemolysis can save a child from many complications.

Methodology: we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE from January 1987 to March 2017. The following search terms were used: G6PD deficiency, prevalence of G6PD, genetics of G6PD deficiency, management and diagnosis of G6PD

Aim of the work: this study aimed to understand about the etiology, pathophysiology and study various lines of prevention and management of G6PD deficiency in pediatric age group.

Conclusion: proper preventive and treatment methods can avoid negative effects on the child's quality of life and reduce morbidity and mortality, therefore the child's care takers must be well informed.

Keywords: G6PD deficiency, prevalence of G6PD, genetics of G6PD deficiency, management and prevention of G6PD, diagnosis of G6PD.

INTRODUCTION

G6PD deficiency is a hereditary genetic defect, X-linked, caused by mutations in the G6PDgene, creating protein variants with various degrees of enzyme activity, which are associated with an extensive range of clinical and biochemical phenotypes. G6PD deficiency is the most common enzyme deficiency worldwide affecting 400 million people across the globe and one of the most common disorders addressed in the pediatric hematology department, especially in some parts of the world [1]. The highest occurrences are detected in Africa, Middle East, Asia and the Mediterranean region; owing to current migrations, nevertheless, the disorder is also found in areas like North and South America and northern European countries. The most common clinical presentations are neonatal jaundice and acute hemolytic anemia, which often, is triggered by an exogenous agent in most patients. The remarkable similarity between the regions where G6PD deficiency is prevalent and Plasmodium falciparum malaria is widespread gives us circumstantial proof that G6PD deficiency offered resistance against malaria [2].

Historically, a pathological disorder was noticed after ingestion of fava beans (*Vicia faba*), later it was identified as G6PD deficiency. Several doctors in southern Italy and Sardinia, during the beginning of the 20th century, described a clinical picture of what was called favism at that time. However, since the response to fava bean consumption was noted to be inconsistent, common theories on the pathogenesis of favism were associated with allergy or toxic effects. Later in 1956, it was found that patients developing hemolytic anemia triggered by the antimalarial drug primaquine showed a very low amount of G6PD activity in their red blood cells. A similar trend was noted in Sardinia in patients with severe hemolytic anemia associated after consumption of fava beans, or sometimes even inhalation of the plant's pollen. A low activity of G6PD enzyme in

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subjects with a history of favism was consequently reported in Germany and Italy [3].

METHODOLOGY

- Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 1987 to March 2017. The following search terms were used: G6PD deficiency, prevalence of G6PD, genetics of G6PD deficiency, management and diagnosis of G6PD

- Data Extraction

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University.

Classification of G6PD Deficiency

In 1967, WHO made the first recommendations for defining glucose-6-phosphate dehydrogenase deficiency which are constantly updated. G6PD deficiency was defined biochemically by quantifying residual enzyme activity and electrophoretic movement. More than 400 biochemical different types of G6PD deficiency were recognized based upon other criteria, which included physicochemical properties, kinetic variables, pH dependence and use of substrate analogues. G6PD deficiencies were, therefore, classified into five classes according to their enzyme activities and clinical manifestations [4]:

- **Class I:** Severely deficient; related to chronic non-spherocytic hemolytic anemia
- **Class II:** Severely deficient with 1–10% residual activity; it is associated with acute hemolytic anemia
- **Class III:** Moderately deficient with 10–60% residual activity
- **Class IV:** Normal activity (in the range 60–150%)
- **Class V:** Increased activity (more than 150%)

G6PD deficiency can also be classified as sporadic or polymorphic. The G6PD enzyme deficiency can be due to a reduction in the amount of enzyme molecules, a structural variability in the enzyme making it dysfunctional, or both [5].

Pathophysiology

G6PD is an enzyme works by catalyzing the very first reaction in the pentose phosphate pathway, generating the reducing capability to all the cells in the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH). NADPH allows cells to balance against the oxidative stress which is caused by several oxidizing agents, and conserves the reduced form of glutathione. The reduced form of glutathione is crucial for the reduction of hydrogen peroxide and other oxygen radicals, and in order to maintain hemoglobin in the reduced state. As red blood cells do not have mitochondria, their only source of NADPH is the pentose phosphate pathway; consequently, defense against oxidative damage in a red blood cell is entirely dependent on G6PD [6].

Inheritance Patterns

G6PD deficiency displays a typical X-linked pattern of inheritance, which was recognized through favism having a greater occurrence in males than in females. Males are hemizygous for the G6PD gene. Females, on the other hand have two copies of the G6PD gene on each X chromosome and therefore, can be heterozygous or have normal gene expression. Heterozygous females who are G6PD deficient are genetic mosaics as an effect of X-chromosome inactivation; the abnormal cells of a heterozygous female can be as deficient for G6PD as similar to a G6PD-deficient male: consequently, such females can be vulnerable to the equivalent pathophysiological phenotype. While heterozygous females typically have less severe clinical presentations than G6PD-deficient males, yet some may develop severe acute hemolytic anemia [7, 8].

Genetic Mutations and Molecular Aspects:

The G6PD gene is positioned at the telomeric region of the long arm of X chromosome (i.e. band Xq28), near the genes for hemophilia A, color blindness, and congenital dyskeratosis. Wild-type of G6PD is known as G6PD B. All mutations of the G6PD gene that end in enzyme deficiency disturb the coding sequence of the gene. About 140 mutations have been so far been reported, majority are single-base substitutions causing amino acid replacements. In rare cases, a second mutation may be present in cis point mutations range all over the entire coding region [7].

Looking at the three-dimensional model of human G6PD enzyme, it showed that the NADP+ binding site is situated in a part of the enzyme near the N terminus, where there is also the highly conserved amino acid (in 23 species) Arg72. This area plays a direct role in coenzyme binding. The group of mutations around exons number 10 and 11 shows the subunit interface. This cluster of mutation interacts with other important residues positioned elsewhere that are brought near this domain by protein folding. Nearly all mutations in this domain lead to types of G6PD deficiency leading to chronic hemolytic anemia (class I) and affect both hydrophobic and ionic bonds. All the variants caused by mutations of in this location showed a prominent decrease in thermal stability [9].

Aside from mutations that cause enzyme deficiency, numerous polymorphic spots in introns have been recognized, facilitating the description of G6PD haplotypes. These haplotypes aid in understanding the evolutionary history of G6PD gene. Analyzing the linkage disequilibrium in haplotypes with coding sequence polymorphisms, it became possible to date the most common mutations and estimation of the timeframe of malaria selection [10].

Epidemiology of G6PD Deficiency

G6PD deficiency alleles are distributed universally; estimate say that at least 400 million people carry some sort of mutation in the G6PD gene leading to its deficiency. The highest prevalence is found in Africa, the Middle East, southern Europe, Southeast Asia, and Pacific islands. Nonetheless, because of current migration, deficient alleles are quite prevalent in North America, South America, and northern Europe. Recently, molecular analysis was used to map the prevalence of G6PD deficiency across the world [11].

In most regions of high occurrence of G6PD deficiency, numerous polymorphic alleles are found. Tropical areas of Africa are one exemption, where the specific subtype G6PD A– comprises for about 90% of the G6PD deficiency. G6PD A– is also common in North and South America, and in regions where people of African origin inhabit. Furthermore, G6PD A– is quite prevalent in the Middle East, Italy, Spain, the Canary Islands, and Portugal. The second most common subtype is G6PD-Mediterranean, which is prevalent in all the Mediterranean countries. In some populations, such as the countries surrounding the Persian Gulf, both the G6PD A– and G6PD Mediterranean coexist. Other polymorphic subtypes are the Seattle and Union variants, found in southern Greece, Algeria, Italy, Sardinia and the Canary Islands. G6PD Union was also found in China [12,13].

Diagnosis of G6PD Deficiency

The absolute diagnosis of G6PD deficiency is achieved by the estimation of enzyme activity, using quantitative spectrophotometric investigation of the rate of NADPH generation from NADP [14]. Complete biochemical classification of G6PD enzyme is required only for definition of a new variant, as endorsed by WHO, although inter-laboratory variations have led to the new variants being wrongfully identified. Simple molecular methods of diagnosis which includes PCR, direct sequencing, and denaturing gradient gel electrophoresis permit discovery of specific mutations, population screening, family studies and, prenatal diagnosis. The most frequent mutations, which are Mediterranean, A–, Seattle, and Union, can be rapidly identified by restriction enzyme analysis, after G6PD exon is amplified by PCR [6].

Diagnostic Difficulties:

Diagnostic disputes can arise for G6PD subtypes when enzyme activity is measured during an episode of acute hemolysis, or in the occurrence of a high reticulocyte count, since the level of enzyme activity is higher in reticulocytes than in more mature cells giving a false negative report for G6PD deficiency. Troubles can also be faced in the investigation of neonates due to the same explanation. Additionally, none of the screening tests are capable of reliable diagnosing heterozygous females, because mosaicism of X-chromosome leads to only partial deficiency. Heterozygous females have activity fluctuating from hemi zygote to normal. Blood-film smear analysis of individual cells after dye discoloration is preferable. Therefore, molecular analysis is the only method through which a definitive diagnosis can be made of a female patient [14].

When to Test for G6PD Deficiency?

Testing for G6PD deficiency should be done when an acute hemolytic reaction in a child happens following an exposure to a known

oxidative drug, fava beans ingestion, infection, chiefly if they are of African, Asian, or Mediterranean descent. Additionally, boy family members of families which have a history of recurrent jaundice, splenomegaly or cholelithiasis must be tested for G6PD deficiency. Newborn babies should be tested if they have severe neonatal jaundice, predominantly those of Mediterranean or African ancestry, as they are quite probable to have G6PD deficiency [15].

Clinical Manifestations

Signs and Symptoms

Most G6PD-deficient children are asymptomatic and therefore the family could be unaware of their status. The illness usually manifests as acute hemolysis, as a result of some sort of oxidative stress triggered by agents such as infections, drugs, or the consumption of fava beans. G6PD deficiency, fortunately, does not generally affect quality of life of the child, life expectancy, nor affect activity of the patient. G6PD deficiency typically presents the first time as drug-induced or infection-induced acute hemolysis, neonatal jaundice, favism, or chronic hemolytic anemia (non-spherocytic). Despite the cause of the acute hemolysis in G6PD deficiency, it is manifested clinically by fatigue, pallor, back pain, and jaundice. Increased indirect bilirubin, lactate dehydrogenase and increased reticulocytes are markers of the episode [16].

Drug-induced Hemolytic Anemia

G6PD deficiency was first discovered by investigating hemolysis that had developed in patients who had received primaquine. Successively, several drugs were associated to acute hemolysis in G6PD-deficient patients. To decide if a specific drug can directly cause hemolytic crisis in G6PD-deficient patients is often challenging to establish. The reasons could be that, firstly, an agent assumed to be safe for some G6PD-deficient children is not certainly safe for all other children. Second, drugs with possibly oxidant effects are sometimes administered to patients with an underlying clinical condition, where that condition is the cause of hemolysis. Third, patients are generally taking more than one kind of medication. Fourth, hemolysis in G6PD deficiency is a self-limiting phenomenon and, hence does not necessarily produce clinically significant anemia or reticulocytosis [17].

Typically, safe alternative medications are available that the health care provider should be aware of. If no alternatives are available, treatment decisions must be based upon clinical judgment of the risk involved. Clinically noticeable hemolysis and jaundice usually arise within 24–72 hours of drug administration. Dark urine as a result of hemoglobinuria is a distinguishing sign. Anemia worsens up to 7–8 days. After drug cessation, hemoglobin concentrations start to improve after 8–10 days. Heinz bodies which are denatured hemoglobin precipitates situated in peripheral red blood cells are a typical finding [18].

Infection-Induced Hemolytic Anemia

Infection is perhaps the most usual cause of hemolysis in children with G6PD deficiency. The most common agents are hepatitis viruses A and B, cytomegalovirus and conditions such as pneumonia and typhoid fever are all notable causes. The degree of hemolysis can be influenced by many factors, counting concomitant drug administration, age, and liver function. The total bilirubin reading can be increased by hepatitis and also by hemolysis, which can be a potential source of diagnostic error. In severe cases, prompt transfusions can considerably and quickly recover the clinical course. Acute renal failure is a grave probable complication of viral hepatitis and concomitant G6PD deficiency; leading to acute tubular necrosis because of renal ischemia, and tubular obstruction. Some patients with hemolysis may also hemodialysis however, this is rare in children [19].

Favism

The association between fava beans and its clinical consequences was acknowledged many centuries ago, but first officially reported in the 20th century. So-called favism was noted to be present in Mediterranean countries, the Middle East, Far East and North Africa, where the consumption and production of fava beans was widespread. Favism is now generally believed to be most commonly related to the Mediterranean variant of G6PD deficiency [20]. Not all G6PD-deficient children undergo favism after consumption of fava beans and also the individual had an unexpected response, indicating that

various factors lead to the disorder, which includes the pre-existing health of the patient and the quantity of fava beans ingested. Favism can occur after consumption of both dried and frozen beans, but is more likely to develop after eating fresh beans and therefore the disorder is most likely to occur in the season when beans are harvested. The toxic constituents of fava beans are believed to be divicine, isouramil and convicine. These enhance the activity of the hexose monophosphate shunt, consequently leading to hemolysis in G6PD-deficient children. Breastfed babies with g6PD deficiency whose mothers have consumed fava beans are at a risk of acute hemolysis [21].

Favism manifests as acute hemolytic anemia, typically around 24 hours after the beans are eaten. The resultant hemoglobinuria is often more severe than that caused by drugs or infection, even though bilirubin concentrations are lower. Due to hemolysis, the anemia is acute and severe, often resulting in acute renal failure in some patients due to ischemia or cast deposition. The oxidative damage changes the shape of erythrocytes into anisopoikilocytosis and bite cells and they are rapidly cleared from the circulation. Therefore, hemolytic events in patients with favism can be both intravascular and extravascular, such as in the spleen. A child can require a blood transfusion in case of a severe hemolytic attack. Fortunately, prevention campaigns in regions of high G6PD deficiency prevalence, which includes neonatal screening and parental health education, have greatly helped in reducing the incidence of favism [22].

Neonatal Jaundice

Data suggested that about a one-third of all male newborn babies who present with neonatal jaundice have G6PD deficiency; while, the deficiency is less prevalent in female newborns with jaundice. Jaundice often manifests by 1–4 days of after birth. Kernicterus, a rare complication, can lead to permanent neurological damage if not immediately managed. G6PD deficiency and neonatal jaundice can differ greatly in their severity and frequency in various populations. Genetic and environmental factors including maternal exposure to oxidant drugs can be a contributing factor [23].

The mechanism of G6PD deficiency leading to neonatal jaundice is not yet well understood. Hemolysis does not to contribute to jaundice as much as contributed by impaired bilirubin conjugation and hepatic clearance. G6PD-deficient neonates additionally inherit a mutation of the uridine-diphosphate-glucuronosyl-transferase-1 gene promoter, that which causes Gilbert's syndrome, are at remarkably high risk for neonatal jaundice. Assessment of neonates who develop hyperbilirubinemia should be done in places where routine screening for G6PD deficiency is not done, (bilirubin concentrations > 95th percentile [150 μmol/L]) within the first day of life, and also in those babies with a history of neonatal jaundice in siblings [24].

Genetic Modifiers of G6PD Phenotype

Acute or chronic hemolysis associated with G6PD deficiency can be exacerbated by unrelated, co-inherited genetic alterations in erythrocyte, for example red blood cell membrane defects, pyruvate kinase deficiency, thalassemia, glucose-6-phosphate isomerase deficiency, and congenital dyserythropoietic anemia. Quite a few reports have been published about G6PD deficiency in association with hereditary spherocytosis. A surprisingly high amount of indirect bilirubin is noticed in the coinheritance of G6PD deficiency with Gilbert's syndrome. In neonates and G6PD-deficient adults, the bilirubin amount is influenced by the presence of the $TA_{(7)}$ allele in the uridine diphosphate glucuronosyl transferase gene and this gene is G6PD-dose dependent [25].

Management of G6PD Deficiency

The most efficient management approach for G6PD deficiency is to prevention of hemolysis, by avoiding oxidative agents for instance certain drugs and fava beans. This approach, however, requires that the patient is already aware of their deficiency, due to a history of previous hemolytic episode or a screening test. Acute hemolysis in G6PD-deficient individuals is typically brief, and does not require any specific management. However, sometimes in children, severe acute hemolysis resulting in severe anemia can necessitate red blood cells transfusion [14].

Neonatal jaundice which is caused by G6PD deficiency is managed in the same way as neonatal jaundice due to other causes. Some disagreement exists regarding treatment with regards to bilirubin concentrations. Typically, when the concentration of indirect bilirubin exceeds 150μmol/L, newborn

are given phototherapy in order to prevent permanent neurological damage. At higher concentrations >300 µmol/L, a blood transfusion can be required [23]. However a child with congenital non-spherocytic hemolytic anemia can occasionally have a well-compensated anemia which does not necessitate blood transfusions; nevertheless, these patients must be monitored, as any further exacerbating event, for example infection, or oxidant drug intake, can severely deteriorate the degree of anemia. In very few cases the congenital hemolytic anemia can be transfusion-dependent, and so an iron-chelation treatment would be required. Antioxidants including vitamin E and selenium have shown some benefits in patients with chronic hemolysis, but no available consistent data supports this strategy. Some children with congenital non-spherocytic hemolytic anemia can develop splenomegaly, but splenectomy has not shown benefit. Prenatally diagnosed G6PD deficiency has been identified, while this approach is still uncertain with respect to low mortality and morbidity of G6PD deficiency. In severe and refractory cases of the deficiency gene therapy remains a possibility for future research [26].

Management of Neonatal Jaundice

The treatment of this form of jaundice is similar as that of neonatal jaundice due to other causes than G6PD deficiency. In majority of the cases, quick phototherapy is often very effective; conversely, when bilirubin levels are higher than 300 µmol/L, or less in case of premature babies, or babies who have acidosis or other infection, an exchange blood transfusion is vital to prevent neurological damage [24].

Treatment of Acute Hemolytic Anemia Including Favism

A patient with AHA may be a diagnostic problem that, once solved, does not require any specific treatment at all; on the other hand, AHA may in some cases be a medical emergency requiring immediate action. In such cases immediate blood transfusion is imperative and may be lifesaving. Hemodialysis may be necessary if there is acute renal failure [22].

Management of Chronic Non-spherocytic Hemolytic Anemia

Chronic non-spherocytic hemolytic anemia because of G6PD deficiency is not very different from other causes of chronic hemolysis such as pyruvate kinase deficiency. If the anemia is not severe like the acute type therefore, regular folic acid supplements with surveillance will be adequate. It is however important to avoid exposure to potentially hemolytic drugs, which may cause exacerbation requiring a blood transfusion, mostly in accompanied by infection. Rarely anemia is so severe that the patient must be considered as transfusion-dependent. Since, unlike in thalassemia, erythropoiesis in the bone marrow is functional in chronic non-spherocytic hemolytic anemia; therefore a hyper-transfusion regimen to suppress the bone marrow is not specified. Regardless, appropriate iron chelation must be given in patients needing regular transfusions [27]. Although, there is no suggestion of selective red-cell destruction in the spleen, in practice a splenectomy has proven to be beneficial in some severe cases. When chronic non-spherocytic hemolytic anemia is diagnosed, genetic counseling must be presented to the family. An imperative step is to decide whether the mother is a heterozygous; in case if she is, there is a likely chance of disease in every subsequent pregnancy with a male child. DNA analysis can be used to make a prenatal diagnosis if the mutation is first recognized in an affected relative [26].

CONCLUSION

We have seen in this review that proper ways of prevention which included a perinatal screening, and identification and avoidance of trigger can lead to the best form of management in a G6PD deficient child, and ultimately prevent the disorder from affecting the quality of life. In case of a manifestation, prompt treatment depending on the age and severity of the hemolysis can be offered. Parents and care takers must be educated about the child's condition by the health care provider.

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