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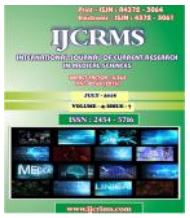

Review Article

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Update on Glucose -6- Phosphate Dehydronase Deficiency

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Abstract

Glucose 6 phosphate dehydrogenase (G6PD) deficiency is a metabolic disorder as a result of the deficiency of G6PD in the glycolytic pathway and this enzyme is essential in the maintenance of red blood cell membrane integrity to ensure its biconcave nature. This condition results in haemolytic anaemia whenever the patient is exposed the fava beans, oxidants, drugs, some chemicals, infection and many others. It is a neglected area in medicine and is area of concern for the public. This paper was written to enlighten the world on the need to have adequate knowledge of this disorder and the test should be included among routine tests to rule it before commencement of treatment to avoid haemolytic anaemia.

Keywords: Glucose 6 phosphate dehydrogenase deficiency, haemolytic aneamia, origin, agents, pathophysiology, management

Introduction

It was reported that Glucose-6-phosphate dehydrogenase was discovered by Alving and colleagues in the year 1956, when they studied the unusual haemolytic reaction that happened in black subjects following the introduction of primaquine. Primaquine is an 8-aminoqunoline which is used for radical treatment of malaria[1].

Glucose 6 phosphate dehyrogenasese deficiency discovery was as a result of a study of haemolytic anemia happening in some subjects treated for malaria with primaquine. Cordes stated that the manifestation of sudden haemolysis in such subjects in 1926, but 3 decades passed before the process of haemolysis was cleared [1]. The studies that led to the discovery of glucose 6 phosphate dehyrogenases deficiency were the result of so many occurrences. Meanwhile, the major pathways via red cells metabolize sugar were carefully studied by researchers such as Warburg, Embden, and Meyerhof [2]. The equipment present then seem incredibly antiqued today, but by 1950,

virtually every step in red cell glycolysis was studied, an amazing mental accomplishment. Second, the discovery of isotopic methods enabling the precise measurement of red cell life span was crucial. Although in 1919 Ashby released her resounding way of determining erythrocyte life span through numbering the inagglutinable cells, this way was too complex and not really reproducible to ensure the solution of the case [3]. Clinical studies of why 8-amino quinoline antimalarials caused haemolysis were gotten when volunteer prisoners in the Illinois State Penitentiary at Joliet were recruited. The recent knowledge of the case started with the study of subjects who showed susceptibility to primaquine [4, 5].

.A study by Akanni et al in Oshogbo, Nigeria among eighty six jaundiced new born showed G6PD deficiencies of 19.5% and 47.7%, respectively [6]. The modern understanding of the condition began with the analysis of patients who exhibited sensitivity to primaquine [5]. The discovery ofG6PD deficiency was strongly supported by the testing of prisoner volunteers at Illinois State Penitentiary, although presently such researches cannot be done. When some prisoners were given the drug primaquine, some developed hemolytic anemia but others did not. After studying the mechanism through Cr^{51} testing, it was conclusively shown that the hemolytic effect of primaquine was due to an intrinsic defect of erythrocytes [5].

Pentose Phosphate Pathway

In most animal tissue, the major catabolic fate of glucose-6-phosphate is the glycolytic breakdown to pyruvate which is then oxidized via citric acid cycle, the respiration chain that result leads to the formation of ATP.Glucose-6-phosphate is oxidized to pentose phosphates by pentose phosphate pathway. In the oxidative pathway, $NADP^+$ is electron acceptor resulting to NADPH. Rapidly dividing cells such as skin bone marrow and intestinal mucosa use pentose to make RNA,DNA,and coenzymes such as ATP (Adenine Triphosphate),and co-enzyme A. In other tissue, the essential product of the pentose phosphate pathway is NADPH which is needed for reductive biosynthesis or to counter the damaging effects of oxygen radicals. Tissue that have enough fatty acid synthesis like liver, adipose, lactating mammary gland or tissue with very active synthesis of cholesterol and steroid hormone like adrenal gland, liver and gonads require NADPH provided by pentose phosphate pathway.

In practice, since majority of G6PD-deficient persons are normally asymptomatic they are referred to as mild simple or common (class 11 and 111), persons who have CNSHA are referred to as having rare, sporadic (class 1).

Pathophysiology

G6PD enzyme is part of the pentose monophosphate shunt. It stimulates the oxidation of G6PD and the decrease of nicotinamide adenine dinucleotide phosphate (NADP+) to nicotinamide adenine dinucleotide phosphate (NADPH). NADPH ensures glutathione is reduced, which functions as a scavenger for dangerous oxidative metabolites. The pentose monophosphate shunt is the only source for NADPH in red blood cells. Therefore, red blood cells depend on G6PD activity to generate NADPH for protection. Thus, erythrocytes are more sensitive to oxidative stresses than other cells.

Gene that codes for G6PD is posit iionedn the distal long arm of the X chromosome at the Xq28 locus.*G6PD* gene is 18 kilo bases (kb) long with 13 exons, and the G6PD enzyme has 515 amino acids. More than 60 changes in the *G6PD* gene have been documented. Many are single-base mutations that occur in an amino acid replacement. G6PD deficiency is an X-linked recessive disorder, with an inheritance pattern resembling to that of hemophilia and color blindness: males usually show the aberration and females are carriers. The allele for *G6PD* has been used to show clonality. Specific *G6PD* alleles are linked to G6PD variants with different enzyme levels and thus, different levels of clinical manifestations. The change in G6PD degrees leads for differences in susceptibility to oxidants. Chronic haemolysis occurs with extremely low enzyme levels. The G6PD A+ variant is linked to

high enzyme levels and there is no haemolysis. G6PD A- is related to lower enzyme levels and acute intermittent haemolysis. G6PD A- happens in elevated frequency in African, Mediterranean, and Asian variants. Mediterranean G6PD A- is marked by enzyme deficiencies that are more serious than in the other G6PD A- alleles. Fava bean haemolysis usually occurs in Mediterranean G6PD deficiency disorders.-G6PD B is the wild type of allele.

Persons with G6PD deficiency are at increased risk of haemolytic anemia when in oxidative stress. Oxidative stress can emanate from infection and from chemical exposure to medication and certain foods. Broad beans, e.g., fava beans, contain high levels of vicine, divicine, convicine and isouramil, all of which produce oxidants. The molecules are reducing agents they reduce oxygen to hydrogen peroxide. The remaining reduced glutathione is consumed; enzymes and other proteins (including hemoglobin) are then destroyed by the oxidants, causing cross-bonding and protein deposition in the red cell membranes. Destroyed erythrocytes are phagocytosed and sequestered in the reticuloendothelia system. The hemoglobin is metabolized to bilirubin. The erythrocytes rarely disintegrate in the circulation, so hemoglobin is rarely excreted directly by the kidney, but this can happen in serious conditions, resulting to acute kidney failure.

The degree of G6PD deficiency determines the clinical expression of the disorder. Individuals with minimally reduced enzyme levels do not experience haemolysis. Others with a greater degree of deficiency have episodes of brisk hemolysis triggered by infections, taking drugs that increase oxidative stress, ingesting fava beans, or ketoacidosis. Haemolysis due to oxidant stresses is usually self-limiting within 8 to 14 days [7].

In 1967, cardiovascular parameters in association with G6PD deficiency were examined among 1,473 black American men. This study found a higher incidence of hypertension and idiopathic cardiomyopathy among those with G6PD deficiency.. This shows that G6PD deficiency may lower cardiovascular-associated death [8]. The second research was a case-control research which showed that among 314 cases of Sardinian men with coronary artery disease, 11.8% were G6PD deficient, whereas among 424 controls, 18.6% were G6PD deficient. These studies showed that G6PD deficiency defends against coronary heart disease. Also, despite the role of G6PD in defending against oxidative destruction in cell and tissue based researches, limited population researches do not encourage an dangerous role for G6PD deficiency in human heart disease.

A protective cardiovascular role for G6PD deficiency is conceivable in light of the effects of G6PD deficiency on cholesterol synthesis [9].

Epidemiology of G6PD Deficiency and Malaria Selection

It has been showed that G6PD deficiency is the highest human enzyme defect, present more than 400 million people worldwide G6PD deficiency resulted in 4,100 deaths in 2013 and 3,400 deaths in 1990' African, Middle Eastern and South Asian people are affected the most, including those who have these ancestries [10].

Favism

It was strongly showed that Fava beans are special among other beans as they contain increased levels of two glycosides, vicine and divicine; and their respective aglycones, convicine and isourami and are strong stimulators of oxidative stress that leads the marked haemolytic crisis. Consumption of fava bean has long been shown to be able to lead to haemolysis and the phenomenon is regarded as favism.lt is widely known that favism is usually linked to Mediterranean variant of G6PD deficiency, though not all subject with G6PD undergo favism after consuming of fava bean. The response of the individual is associated to the amount of the fava bean ingested [11].

The proposed mechanism of the cause of favism is that the compounds contained in fava beans undergo redox cycling. This increases the activity

of the hexose monophophate shunt and reduced glutathione (GSFI), leading formation of free radicals and hydrogen peroxide which facilitates haemolysis in G6PD deficient patients. In favism acute haemolytic anaemia usually occur 24 hours after ingestion.

Haemoglobinuria is more severe in favism than haemolytic crises caused by infection or drugs. Anaemia is usually acute leading to acute renal failure in some patient,due to ischaemia or to precipitation of haemoglobin casts. The oxidative damage that takes place in patients with favism causes series of changes in erythrocyte,leading to rapid clearance of these cells from the circulationhaemolytic events in patient with favism can be either intravascular or extravascular (in the spleen) patient undergoing severe haemolyticanaemia attack may require transfusion [11].

Management

When hemolytic episodes occur in G6PD-deficient individuals, agent that triggers anaemia such as drug or infection and fava bean should be avoided. However, in patients who have class 3 variants such as G6PD A-, it may be possible to continue essential drug therapy with careful monitoring of the blood count. Blood transfusion is only occasionally required. To support patients who have undergone severe hemolytic episodes, usually in patients with favism. It has been suggested that attacks of favism may be ameliorated by the administration of desfemoxamine. In a study it has been discovered that patients with favism who received a single 500-mg dose of desfemoxamine and packed RBC transfusions had a shorter duration of haemoglobinuria, greater rise in Hb level and more rapid drop in reticulocyte count than control patients who received packed cells alone. However, it was not clear that both groups received the same volume of transfusion. To permit NADPH to be synthesised via a different route, xylitol administration has been assumed as a way to prevent or treat haemolysis of G6PD deficiency. Clinical studies in which two severely G6PD-deficient volunteers were pretreated with 10 g xylitol per day and then given primaquine and 20 g xylitol per day showed no protection against haemolysis. It has been suggested that vitamin E, by virtue of its antioxidant effect, might protect against chronic haemolysis in G6PD deficiency causing chronic hemolytic anemia. Some studies have shown a favorable response to this vitamin [12-19].

Mortality/morbidity

Most persons with G6PD deficiency are asymptomatic. Symptomatic patients can present with jaundice in new born and acute anemia associated with [20]. Kernicterus is a rare complication of neonatal jaundice, but can occur in certain populations and can be fatal. Other mechanisms may contribute to hyperbilirubinemia in G6PD deficiency, such as an underlying defect in uridinediphosphoglucoronate-glucuronosyltransferase, the enzyme affected in Gilbert syndrome. Sudden acute hemolytic anemia can occur due to oxidation induced by exposure to certain drugs or chemicals (including some anesthetic agents, infections, ketoacidosis, or the ingestion of favabeans. Chronic hemolysis occurs in severe G6PD deficiency. Fatality rarely occurs [21].

Conclusion

Glucose 6 phospahet dehydrogenase is a very important enzyme in glycoltic pathway of metabolism and its deficiency leads to metabolic disorder that causes haemolytic anaemia in the affected person because of deranged red cell membrane integrity when exposed to some substances such as fava beans, primaquine, stress, chemical and many others. This condition may be among the reasons so many patients' conditions become worse after receiving some treatments in the hospital especially in the developing world. It is important that before starting any treatment on a patient that test to check G6PD status is done to rule out its deficiency to avert the danger associated with such disorder. The test should also be done at early stage of life to prevent jaundice in children which may be disastrous and will help the person to know foods and drugs to avoid.

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