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G6PD Deficiency - Prevalent and Little Publicized Disease

SUMMARY

Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency (G6PD) is a disorder linked to the X chromosome, with a worldwide prevalence of between 400 and 500 million people, with multiple clinical presentation, with this enzyme representing an essential function in the hexose monophosphate cascade and the production of intraerythrocyte glutathione, a protective factor against oxidizing agents. Its genetic etiology is located on the long arm of the enzyme. The events that progress after exposure to oxidants and the reduction of glutathione are the formation of methemoglobin, denaturation of globin, followed by the formation of heinz bodies in the erythrocyte membrane, causing the escape of hemoglobin and as the main event, hemolysis, with destruction by the reticuloendothelial system. The patient's clinical condition is variable, depending on the degree of enzyme deficiency, most of them are asymptomatic, without anemia or cellular destruction, and there may be a shortening of the lifespan of the red blood cell, however, acute hemolysis can be triggered by medications; food , mainly fava beans, a type of bean consumed in the Middle East and infections, with the Mediterranean variant being more common compared to variant A, explained in the introduction. Its classic presentation is that of a patient after administration of primaquine, a medication for malaria, with emphasis on G6PD A, present in individuals of African descent, symptomatic with jaundice; pallor and choluria, associated with a drop in hemoglobin; other contraindicated medications are antibiotics from the Fluoroquinolone class (ciprofloxacin;moxifloxacin and norfloxacin); methylene blue; sulfonylureas, such as glipizide and glibenclamide, medications for the treatment of type 2 diabetes mellitus and anti-uremic medications, such as rasburicase. Diagnostic tests can be qualitative or quantitative, being screening or confirmatory, such as the direct antiglobulin test; G6PD enzyme activity and NADP reduction; and the NADPH production rate spectrophotometrically, the latter being a confirmatory test, with the indications of: assessment of jaundice or unexplained hemolytic anemia; asymptomatic individuals at high risk for deficiency before administering medications, or for family members of an affected individual. This narrative review of the literature proposes to offer a general panel on the disease, as well as the epidemiology and complications, due to its dietary restrictions, - medications and pathologies that can cause hemolysis, as it is also an endemic country for malaria and its medications also cause hemolysis, it is necessary to promote health and encourage the importance of the disease to obtain better resources for testing.

Keywords: Deficiency;G6PD;Definition and Hemolysis

ABSTRACT

The Glucose-6-Phosphate- Dehydrogenase (G6PD) Deficiency is a chromosome-X linked disorder, affecting about 400 to 500 million people worldwide, with several clinical presentations and this enzyme represents an important role in hexose monophosphate pathway and production of glutathione within the red blood cell, as a protective agent against oxidant substances. Their genetic etiology is located in the long arm of the X-chromosome in the region 28, with greater severity registered in males than females, as this sex does not have a complete de-
efficiency of this enzyme. The sequence of events that follows after the oxidant agent contact and glutathione
decrease are the methaemoglobin production;globin denaturation and the Heinz Corpuscles formation on red
cell membrane, resulting in hemoglobin leaking and as main event, hemolysis with destruction in the
reticuloendothelial system. Clinical manifestations are wide, depending on degree of enzyme deficiency, the majority are asymptomatic, without anemia or cell destruction, but, it may occur a life-shortening of half-
- life in red blood cell, however, acute hemolysis can be triggered by medications; foods, mainly fava beans, a type of bean consumed in Middle East, and infections, with this event occurring commonly in Mediterranean variant than in A, described in Introduction. Their classical presentation is from a patient after primaquine intake, medication for malaria infection, with highlight for G6PD A variant, mainly present for African-descendant

individuals, symptomatic with jaundice;pallor and dark-urine, associated by hemoglobin fall, other contraindicated medications are antibiotics from Fluoroquinolone class (ciprofloxacin;moxifloxacin and norfloxacin);methylene blue;sulphonylurea like glipizide and glibenclamide, medications used for type-2 diabetes treatment and anti-uremic medication like rasburicase. Diagnostic tests can be qualitative or quantitative, for screening or confirmatory tests, like the direct antiglobulin; the G6PD activity rate and reduction of NADP;the production of NADPH in spectrophotometric method, in which this last test is a confirmatory way to diagnose the pathology, indications for the tests are: jaundice evaluation or hemolytic anemia without a specific cause;asymptomatic patients with high risk of deficiency before drug administration or family members of an affected individual. This narrative review of literature proposes to offer a general panel about the pathology, as well as about epidemiology and complications, because of their diet; medications and pathologies limitations that can cause hemolysis, additionally as Brazil is an endemic country for malaria and their medications also can cause hemolysis, it is important to do the health promotion and stimulate the disease importance to obtain better resources for testing.

Keywords: Deficiency;G6PD;Definition and Hemolysis.

INTRODUCTION

Glucose-6-Phosphate Dehydrogenase Enzyme Deficiency (G6PD) is a disorder linked to the , from the oxidation of glucose-6-phosphate to 6-phosphoglucolactone and reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH, glutathione is an important element for protection against oxidizing agents, mainly hydrogen peroxide and superoxide anion , in addition to exogenous substances, such as medicines.

Under normal conditions, oxidation is prevented due to the chemical reaction with glutathione peroxidase and reduced glutathione, as a result, hemolysis does not occur.

Regarding its genetic bases, the q28 portion was sequenced and is expressed in male patients with variant genes, while heterozygous female patients present absence of the pathology, due to half of their cells expressing the enzyme and the other half not containing it, mothers can transmit the pathology to sons or daughters, while the father transmits the gene to his daughter, special attention should be paid to first-degree relatives who may be carrying the gene that causes the disease, mainly mothers; father of affected daughter; daughter of affected fathers; sons of affected mothers and brothers of the affected patient, as men are homozygous, they will all affect their red blood cells, conferring greater severity.

Its classification is based on the risk of hemolysis and the magnitude of enzyme deficiency, graded from I to III, respectively: severe deficiency; severe deficiency and hemolysis associated with drugs, chemicals or infections; and moderate deficiency, together with hemolysis generally caused by infections. ;drugs or chemical substances.

According to its pathophysiology and clinical characteristics, hemolysis is dependent on the G6PD variant, with the enzyme decaying as the red blood cell ages, and its variants, such as G6PD A, which has a half-life of 13 days, G6PD Mediterranean, unstable in nature, with 27 hours.

These data are related to the severity of hemolysis, and form A is characterized by mild hemolysis and restricted to senile red blood cells, with similar frequencies in West and Central Africa but in the Mediterranean variant, characteristic on the European continent and the Middle East, all cells are deficient, thus causing a more intense hemolytic condition

Variant A contains mutations in its nucleotides, with its main changes in regions 376, with the exchange of the nitrogenous base Adenine to Guanine, in addition to the change in 202, from Guanine to Adenine.

in, the B form, normal or in its wild form and the Mediterranean variant, consists of a change of the nitrogenous base Cytosine to Thymine.

The events that progress after exposure to oxidants and the reduction of glutathione are the formation of methemoglobin, denaturation of globin, followed by the formation of Heinz bodies in the erythrocyte membrane, causing the escape of hemoglobin and the main event, hemolysis, with destruction by the reticuloendothelial system.

The patient's clinical condition is variable, depending on the degree of enzymatic deficiency, most of them are asymptomatic, without anemia or cell destruction, and there may be a shortening of the lifespan of the blood

However, acute hemolysis can be triggered by medications, foods, especially fava beans, a type of bean consumed in the Middle East, and infections, with the Mediterranean variant being more common compared to the A variant.

Its classic presentation is that of a patient after administration of primaquine, a medication for malaria, with emphasis on G6PD A, present in individuals of African descent, symptomatic with jaundice; pallor and choluria, associated with a drop in hemoglobin; other contraindicated medications are antibiotics from the Fluoroquinolone class (ciprofloxacin;moxifloxacin and norfloxacin); methylene blue; sulfonylureas, such as glipizide and glibenclamide, medications for the treatment of type 2 diabetes mellitus and anti-uremic medications, such as rasburicase.

Foods such as Fava are the most common reason for hemolysis, with the 2 main beta-glucosidases, vicine and convicine within it, the hydrolysis resulting from digestion results in divicine and isouramil, which generates free radicals and hydrogen peroxide, oxidative compounds that reduce the amount of glutathione, causing hemolysis, the symptoms of provoked hemolysis occur between 5-24 hours with headache; nausea; back pain; fever; hemoglobinuria and jaundice.

Infections such as pneumonia, diabetic ketoacidosis and viral hepatitis can also cause hemolysis, with mechanisms that are not fully understood, possibly due to the production of free radicals and oxidative compounds.

Diagnosis is indicated for evaluation of jaundice or unexplained hemolytic anemia; asymptomatic individuals at high risk for deficiency prior to medication administration, or for family members of an affected individual, an important but nonspecific test is direct antiglobulin. , also called Coombs, other rapid screening tests are those that provide qualitative access to the enzyme, analyzing its normal function and reduction of NADP.

The assessment of G6PD activity on NADPH is carried out by monitoring a fluorescent spot under ultraviolet light, this being a semi-quantitative test, if negative for the first time, carried out after 3 months due to the possibility of a hemolytic episode reducing the enzyme and if negative for the second time, consider other hemolytic etiologies.

The confirmatory test can be used as an initial test depending on the institution, carried out by adding a compound that will cause hemolysis of red blood cells, associated with a substrate (glucose- - 6-phosphate) and NADP, this test analyzes the formation rate of NADPH, the oxidized form of NADP, spectrophotometrically, with values ranging from: 5.5 to 8.8 units per gram of hemoglobin to 25oC and 8 to 13.5 units per gram of hemoglobin to 37oC, it is important to highlight that the enzyme contains greater activity in newborns, representing young red blood cells with reticulocytosis.

Differential diagnoses that must be made include hemoglobinopathies such as thalassemia; sickle cell disease; hereditary spherocytosis and hemolytic disease of the newborn.

This narrative review of the literature proposes to offer a general panel on the disease, as well as the epidemiology and complications. Brazil is a mixed-race country and awareness is needed, due to its dietary restrictions, medications and pathologies that can cause hemolysis, by treating If you are also from a malaria-endemic country and your medications also cause hemolysis, it is necessary to promote health and encourage the importance of the disease to obtain better resources for testing.

METHODOLOGY

This is a narrative review of the literature based on databases that include:*Pubmed*;*Lancet;The New England Journal Of Medicine*and UpToDate with the following descriptors: GLUCOSE-6-PHOS-PHATE-DEHYDROGENASE DEFICIENCY**AND**DEFINITION**AND**MANAGEMENT, with inclusion criteria: articles from 2018 onwards in English and/or Portuguese with 5 years of publication date; without restriction from study design to visualization; with article denoting aspects such as definition;etiology;fi-physiopathology and management.

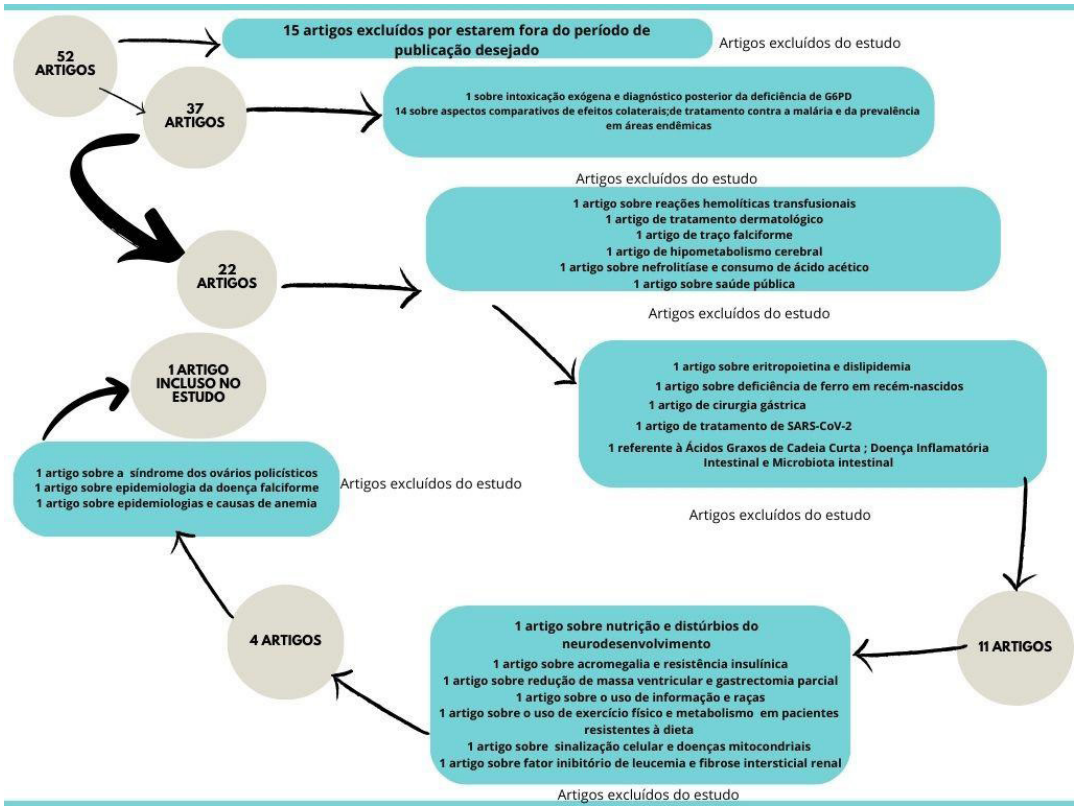
Exclusion criteria: articles prior to the period; articles on a different topic to that proposed and titles outside the proposed theme

RESULTS AND DISCUSSION

From the survey in the aforementioned databases, 3 articles were found in the*Pubmed*; 33 articles in the Magazine*The Lancet*and 16 articles in the magazine*The New England Journal Of Medicine.*

The number of articles selected and those excluded from the narrative review are arranged in the diagram

Next, on UpToDate, 3 main articles were selected based on the title, which include: “Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency”; “Gene test interpretation: *G6PD” and* “Genetics and pathophysiology of glucose-6-phosphate dehydrogenase (G6PD) deficiency”



Favism, a condition caused by the ingestion of fava beans, previously explained, mainly in raw form, the epidemiology is explained mainly where there are high rates of deficiency and the food is cultivated, in Southeast Europe and the Middle East. In Gaza, with 1 .9 million inhabitants, 223 children were admitted over a period of 6 years, with an annual incidence of 1 case per 50,000 inhabitants, thus denoting only a portion of cases that are clinically significant, but mild, important cases are also not counted for the development of preventive and therapeutic measures. The classic clinical picture is of a male patient, 2-10 years of age with pallor; abdominal pain; fever and jaundice, with signs of splenomegaly, generally without methemoglobinemia; mild management is based on hydration and symptomatic treatment , in the severe form, blood transfusion may be necessary with hemoglobin levels below 9g/dL with persistent hemoglobinuria or hemoglobin levels equal to 7g/dL.

Regarding the topic of resistance to malaria, hemoglobinopathies such as sickle cell disease, thalassemia and G6PD deficiency seem to have a protective effect against malaria.*Plasmodium falciparum*, however, individuals must be tested before administering medications, in order to avoid hemolytic anemia.

CONCLUSION

From the information presented, a lack of information was discovered regarding the explanation of the pathology, only obtaining information on the UpToDate platform and 1 article on*The New England Journal Of Medicine*. In 94 individuals originating from the Amazon, with G6PD A, heterozygous and/or homozygous, treated with primaquine, 59% had severe anemia, 48% with hemoglobinuria and 28% with Renal Injury Acute, 50% of them required a blood transfusion; 4 sent to the Intensive Care Unit and 1 death, thus highlighting the need for testing in vulnerable populations and/or with a family history

Management of mild neonatal jaundice due to G6PD deficiency generally does not require treatment, intermediate may require phototherapy and severe, with blood transfusion, in acute hemolysis, the causative agent must be removed, in addition to promoting hydration and, if necessary, offering blood transfusion; in chronic hemolysis, supplementation with folic acid may be necessary

It is important to highlight that the doctor has the important role of explaining; advising and preparing the family of the patient who has recently been diagnosed with the disability, whether at birth or after an episode

hemolytic due to medications; contraindicated foods or infections, in order to offer a better quality of life, avoiding medications or, if necessary, administering medications with intense surveillance in the Intensive Care Unit if the benefit is greater than the harm, studies are necessary to offer the Brazilian prevalence of the pathology and allow greater accessibility of diagnosis in the territory.

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