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Molecular mechanisms, pathophysiology and laboratory investigations of favism

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Abstract: Abstract: Favism refers to a hemolytic episode triggered by consumption of fava bean in person with glucose-6-phosphate dehydrogenase (G6PD) impairment. It is characterized by splenomegaly, anemia, and jaundice. This review describes in detail the molecular mechanisms, pathophysiology, complications, and laboratory investigations of favism. The fava bean contains significant amounts of antinutritional substances, including vicine and convicine, which are responsible for the hemolytic crises observed. Red blood cells with G6PD deficiency are vulnerable to oxidative damage because they lack protection against reactive oxygen species. Hemolysis or erythrophagocytosis of red blood cells can occur when specific agents, such as raw fava beans, sulfonamides, or infections, are activated. However, avoiding raw fava beans can help prevent favism. This is because boiling fava beans has been shown to reduce the negative effects of the antinutritional chemicals vicine and divicine present in the fava beans. G6PD deficiency currently has no treatment. Nonetheless, gene therapy appears to be a promising treatment option for enzyme deficiencies. Data for this research were collected from PubMed, Google Scholar, Springer, Nature, Taylor and Francis, MDPI, BMC, and other related sources.

Keywords: *Fava beans, Favism, Mechanisms, Pathophysiology, G6PD deficiency and hemolysis.*

1. Introduction

In 1843, Mira Franco wrote an article for the Revista Universal Lisbonense in Portugal that contained the first clear mention of favism [1]. The features of the contemporary medical history of "ictero-haemoglobinuric favism," which first appeared in Portugal, Italy, and Greece in the 19th century, were precisely encapsulated in two landmark assessments, one by Luisada in 1941 and the other by Fermi and Martinetti in 1905. Because favism is an ancient literary movement, it is sometimes viewed as a thing of the past. It is most likely still the most common cause of acute hemolytic anemia globally [2]. The red cell and the bean are the two primary players in favism. Rhizobia, nitrogen-fixing bacteria that grow on the roots of this leguminous plant, help it symbiose and reduce the need for fertilizers. Beans from the Vicia faba plant are not only delicious but also contain about 25% protein by dry weight. The beans can be eaten cooked or raw, fresh or dry. Vicia faba has high concentrations of two β-glucosides, vicine and convicine, up to 2% in dry weight [2].

Numerous theories have tried to explain the mechanism of hemolysis in favism. According to the most commonly accepted theory, favism is caused by two β-glycosides, convicine and vicine, which

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contain the pyrimidines isouramil and divicine. In people with G6PD deficiency, hemolysis results from the production of free radicals during auto-oxidation [1]. The enzyme glucose-6-phosphate dehydrogenase (G6PD), which is highly active in red blood cells (RBCs) and plays a crucial role in the pentose phosphate pathway, is biologically deficient in susceptible individuals. Reduced glutathione, supplied by NADPH, eliminates free radicals that cause oxidative damage. Prevalent oxidants harm functional proteins and active enzymes when reduced glutathione levels are low [2]. Favism is most commonly seen in children between the ages of two and five, and it is two to three times more common in boys than in girls. Clinical signs include jaundice, splenomegaly, hepatomegaly, pallor, tachycardia, nausea, vomiting, dizziness, malaise, and stomach discomfort. Laboratory results include anemia, reticulocytosis, elevated bilirubin levels, and, in rare cases, urine urobilinogen and methemoglobinemia. The symptoms are usually self-limited and do not result in sequelae, despite the fact that hospitalization and transfusion are often required [3].

2. Aetiology of Favism

The clinical manifestation of acute hemolytic crises and the susceptibility of a subgroup of individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to broad bean consumption are referred to as "favism." Hemolytic anemia, the most common side effect of G6PD deficiency, can occasionally be lethal [4]. Hemolysis in these individuals is triggered by the following:

Ingestion of fava beans: Favism is triggered by two substances, vicine and convicine, present in fava beans and converted into isouramil and divicine in the colon. They function by producing more free radicals, which in turn oxidize glutathione. The presence of these glucosides differentiates fava beans from other legumes, as other legumes lack them. The presence or absence of a hemolytic crisis and its severity are determined by the levels of vicine and convicine. Only 25% of deficient adults experience a hemolytic crisis after consuming fava beans, and even within the same individual, there is significant variation in the severity of symptoms due to the unpredictability of hemolytic crises. Factors that influence the occurrence of hemolytic crises include the quantity (by mass), quality, and degree of ripeness, which correlate with the amount of antinutritional glucosides present in the legume. Fresh beans contain more beta-glucosides than dried beans because of their green shell. Soaking before cooking reduces the vicine and convicine contents by 56% and 34%, respectively. The amount of beta-glucosides is not significantly affected by cooking [5]. Lastly, the clinical presentation may be influenced by the age of onset [3]. These reasons explain why severe forms of G6PD deficiency are detected in paediatrics, while mild to moderate versions are sometimes diagnosed at an advanced age after a first attack [5].

Glucose 6-phosphate dehydrogenase deficiency: G6PD deficiency is the most prevalent enzymatic disorder in the world. Fava bean consumption is the primary cause of acute hemolytic crises at any age and neonatal jaundice worldwide. An alteration in the constitutive Gd gene causes this frequent erythrocyte enzyme deficiency, which is inherited sex-linked. In addition to being involved in the hexose monophosphate shunt pathway, G6PD maintains the erythrocyte's reducing potential sufficient. Enzymatic variations that arise from genetic alterations in the polymorphic gene exhibit varying degrees of activity, leading to distinct clinical presentations of the deficiency. The majority of deficiency carriers do not exhibit clinical symptoms at steady state; the enzymatic impairment is equivalent to a moderate hemolytic condition that is typically fully compensated for. A hemolytic crisis ensues when red blood cells experience elevated oxidative stress due to an external cause [3]. Certain drugs, viral disorders, or the use of specific foods, especially fava beans, can also cause significant oxidative stress in people with G6PD deficiency. Patients with favism should not take methylene blue, nitrofurantoin, sulfamethoxazole, or primaquine. Hepatitis A and B viruses, cytomegalovirus, any pneumonia-causing bacteria, and *Salmonella typhi* are the infectious pathogens most commonly implicated in a hemolytic crisis. Apart from fava beans, quinine-based beverages, and vitamin C-containing dietary supplements are also forbidden [5]. G6PD insufficiency is more common in Africa, Southeast Asia, the Middle East, Southern Europe, and Oceania, though it can be found in many different groups. G6PD deficiency

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manifests clinically as a variety of symptoms that vary in intensity. G6PD deficiency has been classified by the World Health Organization into classes I–IV based on the severity of the enzyme deficiency. Class II patients, who have a severe enzyme deficit, have G6PD activity less than 10% of the normal value. Class II patients exhibit intermittent hemolytic episodes, typically after being exposed to oxidant stressors like fava beans (like in this case) or oxidant medications. G6PD deficiency can also be classified according to mutations in the G6PD gene that are present in specific ethnic groups, for example, Mediterranean-type G6PD deficiency, a class II deficiency [1].

3. Fava Beans and Their Nutritional Values

The fava bean (Vicia faba), also referred to as the horse bean or broad bean (Figure 1) [6], is one of the oldest crops cultivated worldwide. The Mediterranean region, Egypt, Ethiopia, China, India, Northern Europe, Afghanistan, and Northern Africa are among the countries that produce a lot of fava beans [7]. Of the more than 50 countries that produce fava beans, Asia, the European Union (EU), and Africa account for about 90% of the total production [8]. Faba beans are considered an important crop from an ecological, nutritional, and economic standpoint [9]. Dietary fiber (25.0%), proteins (26.1%), and carbohydrates (58.3%) are all abundant in mature fava bean seeds [10]. Fava beans also contain a variety of bioactive compounds, including total phenolics and flavonoids with demonstrated antioxidant qualities [11]. A range of antinutritional agents, such as saponins, lectins, trypsin inhibitors, condensed tannins, phytic acids, and favism-inducing substances, negatively affected the biological value of fava beans [12].

Figure 1.
Physical Appearance of Fava Beans.
Source: Revilla [12].

3.1. Chemical Composition and Nutritional Profile of Fava Beans

Fava beans are rich in complex carbohydrates, lysine-rich protein, dietary fiber, secondary metabolites that are not of nutritional value, and bioactive substances like phenols, γ-aminobutyric acid, and antioxidants that have been linked to several health benefits [13, 14]. Minerals and other macro- and microelements are also abundant in it [7].

Proteins: Fava beans contain 60% globulins, 20% albumins, 15% glutelins, and 8% prolamins [7]. The amino acid profile of fava beans includes the nonessential amino acids (glutamic acid, aspartic acid, alanine, glycine, arginine, serine and proline) and essential amino acids (leucine, isoleucine, lysine, tryptophan, tyrosine, methionine, phenylalanine, histidine, valine, and threonine) [15].

Carbohydrates (starch, dietary fiber, and sugars): The majority of fava bean seeds (41–58%) are made up of starch, with 51%–68% of the seeds being carbohydrates [10]. Dietary fiber, the amount of

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starch, and the type of sugar are the three primary nutritionally important aspects of fava bean carbohydrates. The primary soluble sugars in the raffinose family are stachyose, verbascose, and raffinose. These oligosaccharides are believed to limit the consumption of Fava beans and to be the cause of flatulence from a digestive standpoint. Fava bean seeds are rich in two soluble sugars, stachyose and verbascose. The two main components of the 22–45% starch found in fava beans are amylopectin and amylose [16].

Minerals and vitamins: Numerous minerals and vitamins, such as sodium, potassium, sulfur, copper, iron, manganese, calcium, cysteine, phosphorus, magnesium, and zinc, are found in fava beans [10, 15]. The high potassium (1,062 mg/100 g) and low sodium (13 mg/100 g) of mature fava bean seeds make them ideal for people with hypertension who are on a low-sodium diet. By contrast, the potassium and salt contents of immature fava bean seeds are 50 and 250 mg/100 g, respectively [10]. Fava beans are rich in folate, an essential cofactor for the synthesis of purines, pyrimidines, and amino acids [17].

Bioactive compounds: Numerous bioactive phytochemicals, including flavonoids, phenolic compounds, terpenoids, and lignans, are found in fava beans. Fava beans contain a variety of free and esterified phenolic compounds, including vanillic acid, dicaffeoylquinic acid, sinapic acid, caffeic acid, salvianolic acid, ferulic acid, cis- and trans-p-coumaric acid, eucomic acid, hydroxyeucomic acid, caffeoylquinic acid, and protocatechuic acid. Fava bean pod extracts of different types had total phenolic contents ranging from about 4.8 up to 13 mg gallic acid equivalent (GAE)/g [11].

Antinutritional factors: A range of antinutrients can be found in fava beans' ripe seeds. Condensed tannins, trypsin inhibitors, phytates, convicine, lectins, saponins, oligosaccharides (raffinose, stachyose), vicine, and protease inhibitors are among them [15, 18]. Hemolytic anemia, or favism, is caused by the main antinutritional compounds in fava beans, vicine and convicine. Favism significantly restricts the use of fava beans due to its health implications [2].

4. Molecular Basis of Favism

A deficiency in glucose-6-phosphate dehydrogenase is the molecular basis of favism. The housekeeping enzyme G6PD, which catalyzes the conversion of glucose-6-phosphate (G6P) to 6-phosphoglucono-d-lactone, is expressed by every cell in the body. The enzyme phosphogluconate dehydrogenase (6PGD) then hydrolyzes the product to 6-phosphoglucono-v-lactone, which is subsequently oxidized and decarboxylated to the pentose sugar ribulose-5-phosphate. Each molecule of G6P that G6PD oxidizes yields two molecules of NADPH because NADP is a cofactor for both G6PD and 6PGD. As pentose is the final product of these reactions, G6PD is sometimes called the first enzyme of the hexose monophosphate shunt pathway (Figure 2). However, the targeted inactivation of G6PD in embryonic stem cells and additional lines of evidence made it clear that the synthesis of NADPH is G6PD's main physiological function. The main electron donor present in most human cells is NADPH. It is essential for many biosynthetic processes, including the synthesis of steroid hormones, cholesterol, and fatty acids, as well as the conversion of ribose to deoxyribose, which is required for DNA synthesis. Since most cells have multiple enzymes that catalyze the dehydrogenase processes that produce NADPH, there may not be a shortage of NADPH even in the absence of G6PD. The situation in red blood cells is very different because during erythroid cell differentiation, the other NADPH-producing enzymes have been sacrificed. However, because of their sacrifice, these cells are nonexistent, so they do not need NADPH for the biosynthetic pathways [18].

However, red blood cells' other main function, protection against oxidative stress or attack, requires NADPH. Since the regeneration of reduced glutathione (GSH) requires a steady supply of NADPH, the glutathione cycle is crucial in mediating this response [19]. The red cell's ability to protect itself from endogenous oxidative stress, even in the absence of an external attack, is crucial because it is a skilled carrier, loader, and unloader of haemoglobin-bound oxygen and can also produce free radicals in the process. It is evident from the above that erythrocytes are more susceptible to the effects of G6PD deficiency than other cells (Figure 2). This disease is caused by genetic abnormalities in the G6PD gene, which are expressed in all cells. However, there is yet another significant explanation for this. As red

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blood cells age in circulation, many of their functions tend to progressively deteriorate because the individual proteins that support those functions degrade exponentially in these ribosome-less cells that are incapable of producing new proteins [20]. As a result, a normal red cell's G6PD activity is about 50 times lower on day 120 when it is ready to be removed than it was when it was a reticulocyte.

This process is further amplified by the great majority of mutations that affect the stability of the G6PD protein in vivo. G6PD insufficiency is never complete because that would be lethal. Therefore, in the steady state, the effects of G6PD deficiency are usually undetectable; the NADPH produced by G6PD activity and the remaining G6PD activity are just enough to maintain the red cell, with a slight reduction in lifespan. However, when an external oxidative stress is applied, as in the case of fava beans, G6PD-deficient red blood cells are unable to increase the generation of NADPH, whereas normal red blood cells do. GSH is rapidly decreased, haemoglobin and other proteins are damaged, and eventually the red cell either hemolyzes entirely or becomes a target for macrophages. The fact that G6PD deficiency is a genetic anomaly that is mostly or completely asymptomatic throughout life may be the most crucial factor to take into account when analyzing its clinical consequences [19]. The World Health Organization has so far found and categorized 217 G6PD genetic variations, ranging from the most severe to the mildest types, into classes I through IV. The diagnosis of favism is not excluded based on age; unlike severe variants that are identified in childhood, mild forms might continue to exhibit only minor symptoms. Given that these mutations are primarily present in Africa, the Mediterranean basin, Asia, and the Middle East, the patient's ethnic origin is crucial information [5].

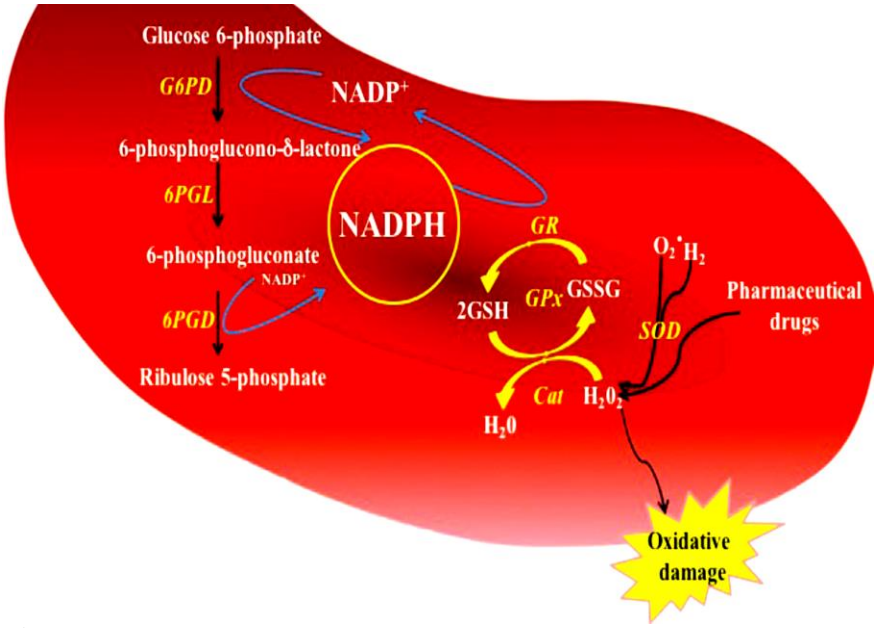

Figure 2.
Significance of G6PD enzyme in the Penton Phosphate Pathway (PPP) in red blood cells.

The enzymes 6-phosphogluconate dehydrogenase (6PGD) and glucose 6-phosphate dehydrogenase (G6PD) work together to produce NADPH in red blood cells that are G6PD-normal. In order to regenerate the oxidized GSSG, NADPH acts as a proton donor. Nicotinamide adenine dinucleotide phosphate, NADPH, glucose-6-phosphate dehydrogenase, and G6PD [2].

5. Pathophysiology of Favism

Despite its complexity, the process of hemolysis in favism has been better understood. Glutathione and NADPH are rapidly oxidized by reactive oxygen species (ROS) such as hydrogen peroxide and

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superoxide anion, produced when divicine and isouramil are absorbed into the bloodstream through the intestinal epithelium. Glutathione peroxidase and catalase detoxify hydrogen peroxide in red blood cells with normal G6PD function. Both of these enzymatic functions depend on NADPH. Because they are unable to reverse glutathione depletion due to a lack of NADPH, red blood cells deficient in G6PD suffer severe oxidative damage. Although intravascular hemolysis occurs in the most severely damaged red blood cells, a significant amount of the hemolysis is extravascular due to the sequence of events that follows (Figure 3) [2]. Iron is released from hemoglobin and ferritin as a result of hydrogen peroxide and ROS attacking the lipids and protein thiol groups in red blood cells. They also change oxyhemoglobin into the powerful oxidants ferryl hemoglobin, methemoglobin, and hemichromes (partially denatured hemoglobin). Hemichromes bind to the membrane cytoskeleton (resulting in the formation of Heinz bodies), cross-bonded stiff hemighosts are produced, and membrane proteins aggregate as a result of the simultaneous oxidation of sulfhydryl groups in cytoplasmic and membrane proteins. This sequence of oxidative events causes autologous IgG and factor C3c to be deposited on clustered band 3 via the complement alternative pathway (tick-over mechanism) in the absence of the protective activity of glutathione and NADPH. Erythrophagocytosis occurs in the opsonized red blood cells. Both intravascular and extravascular hemolysis are implied by the long-standing term "ictero-hemoglobinuric favism" [2].

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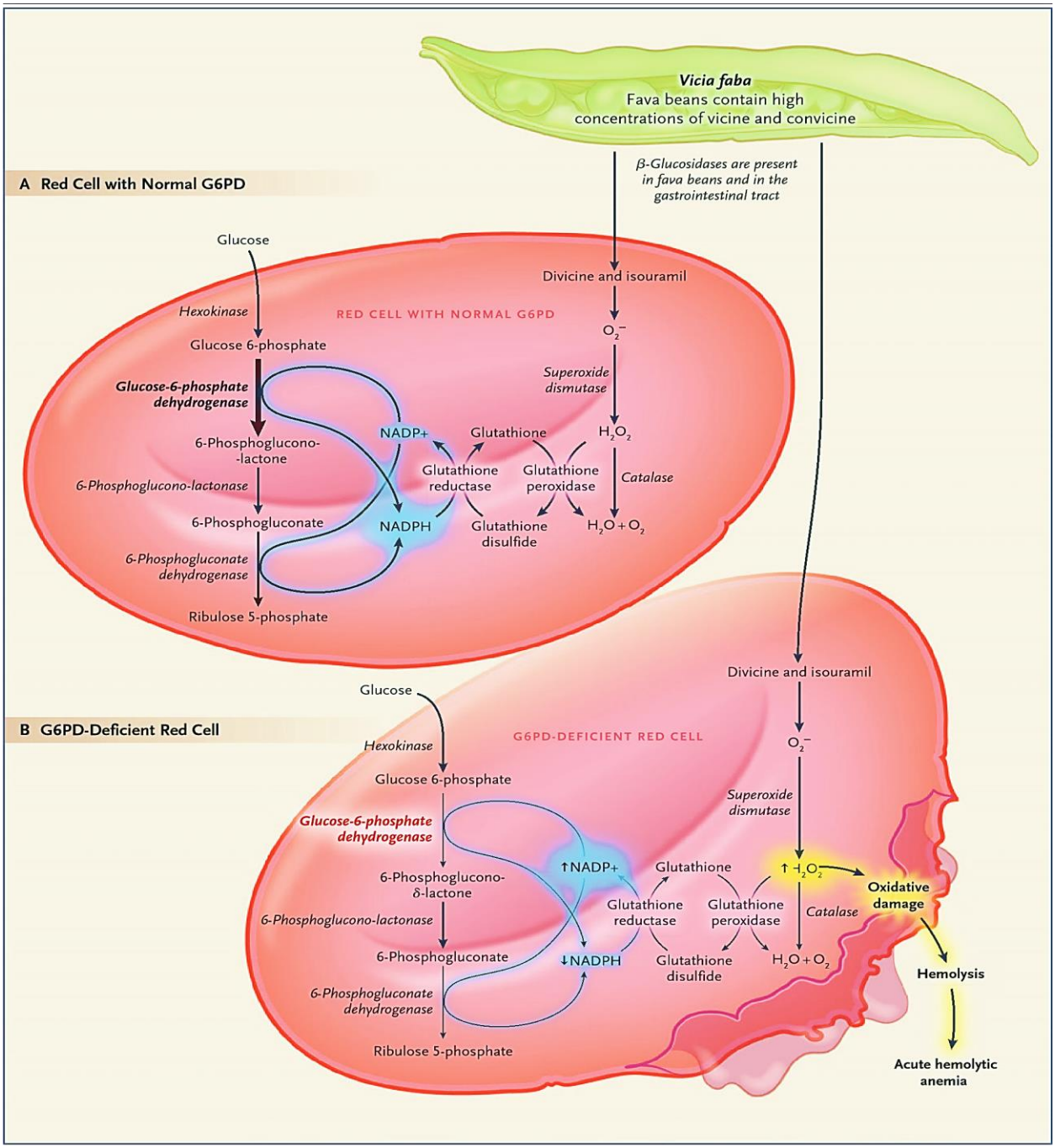

Figure 3.
The sequence of events occurring within red blood cells following consumption of fava beans.

(A); depicts normal red blood cell metabolism following ingestion of fava beans. (B); depicts a G6PD-deficient red blood cell exposed to oxidative stress following ingestion of Vicia fava (containing a high amount of vicine and convicine) [2].

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6. Clinical Presentations of Favism

Individuals with G6PD deficiency are usually asymptomatic, so the acute hemolytic anemia of favism appears suddenly (thus the term "favism attack") [21]. It is a severe form of acute hemolytic anemia that can be lethal. The degree of enzymatic malfunction usually corresponds with the severity of the clinical presentation. Most common clinical presentations of favism include anemia, jaundice, abdominal pain, pallor, fever, hemoglobinuria, and splenomegaly. Peripheral blood smear findings typically demonstrate bite cells (degmacytes), blister cells, polychromasia, anisocytosis, and poikilocytosis. Using supravital staining with methyl violet, Heinz bodies can be visualized (Figure 4).

7. Laboratory Diagnosis of Favism

The laboratory tests listed below can be used to identify favism:

Full Blood Count: RBC count is decreased.

Peripheral blood film findings include Heinz bodies (seen with supravital staining), bite cells (degmacytes), nucleated red blood cells (polychromasia), anisocytosis, and poikilocytosis. Bite cells result from splenic removal of denatured hemoglobin inclusions.

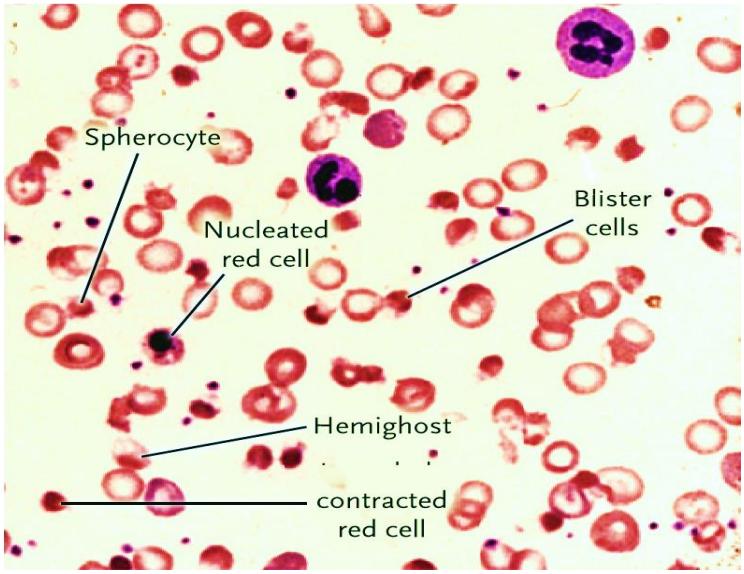

Figure 4.
Morphological Changes seen in severe favic attack: Peripheral blood smear stained with May-Grunwald-Giemsa stain, taken on the first day, reveals nucleated red cells, hemighosts and spherocytes.
Source: Luzzatto and Arese [2].

Reticulocytosis: (from 2% to 65%), a sign of increased bone marrow activity in an attempt to counteract hemolysis.

Increase in serum unconjugated bilirubin levels: indicative of intravascular hemolysis.

Hb estimation: Hb concentration is reduced (2.0–12.0 mg/dL). G6PD enzyme assay: Beautler's fluorescent spot test and spectrophotometry can be utilized for the G6PD enzyme assay. For adults without an enzyme deficit, the normal range is 8.6 to 18.6 units/gram of haemoglobin. < 10% of normal indicates an enzyme deficiency.

Coomb's test: Coombs test is usually negative. This is to distinguish autoimmune hemolytic anemia from favic crises.

8. Complications of Favism

Certain complications have been associated with favism. They include:

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a. Death: Two reported cases of death were likely caused by the high ratio of fava bean consumption to patient weight (infants).
b. Visual impairment: Two cases of blindness and other vision issues have been reported in children.
c. Multiple systolic murmur cases were noted in infants, children, and adolescents.
d. Kidney failure: Three cases of renal failure were linked to favism in adults [3].
e. Syncope: a brief loss of consciousness brought on by a transient decrease in cerebral blood flow is known as syncope. According to the theory, syncope is brought on by a drop in brain oxygenation resulting from an abrupt drop in haemoglobin levels linked to fever [5].

9. Management of Favism

If diagnosed early, acute hemolytic anemia caused by eating fava beans can be effectively treated. Trustworthy diagnostic methods are available, and point-of-care diagnostics are increasingly important when primaquine and its newly released analog, tafenoquine, are used to eradicate malaria [22]. In mild cases, symptomatic treatment and rapid hydration are sufficient. More serious cases, however, require hospitalization. Children and adults with severe favism need immediate medical attention, with blood transfusions being the main treatment. Although there are no official standards, if hemoglobin levels are 7 g/dL or less, or if hemoglobinuria persists and is less than 9 g/dL, indicating brisk hemolysis, an emergency blood transfusion should be administered. Under all conditions, the need for blood transfusions should be periodically assessed. Fortunately, favism's acute hemolytic anemia resolves on its own, unlike other forms of the condition. Hemodialysis might be necessary in cases of acute renal failure, but in patients without prior kidney disease, it resolves spontaneously [2, 21].

10. Correction of G6PD Deficiency

A retroviral vector containing human G6PD cDNA was used to transduce hematopoietic stem cells in primary and secondary recipient syngeneic mice, resulting in consistent expression of human G6PD. Macaque monkeys also expressed human G6PD using a similar vector. Although it hasn't been done yet, allogeneic bone marrow transplantation or gene therapy may treat severe chronic nonspherocytic hemolytic anemia (CNSHA) caused by G6PD deficiency. Although chronic administration is necessary, butyrate or valproate may be able to treat G6PD deficiency [22].

11. Future Perspectives

Wih FDA approval for retinal dystrophy, spinal muscular atrophy, and cystic fibrosis, as well as clinical trials for sickle cell anemia and ß-thalassemia, gene therapy is becoming increasingly popular in treating inherited genetic disorders [23]. The therapeutic challenges posed by the genetic diversity of G6PD deficiency are expected to be addressed by gene treatment. In mice that have received primary and secondary bone marrow transplants, retroviral transduction of the human G6PD gene into human hematopoietic stem cells and mice doubles G6PD activity and results in stable, lifelong expression of human G6PD [24]. This implies that the most severe types of G6PD deficiency require gene therapy.

12. Conclusion

The molecular basis of favism is a deficit of the glucose-6-phosphate dehydrogenase enzyme, the rate-limiting enzyme in the hexose monophosphate shunt pathway that converts NADP to NADPH. Reactive oxygen species (ROS) cause oxidative damage to cells, which NADPH guards against. Glucose-6-phosphate dehydrogenase has a number of mutations that can cause the enzyme to function less or not at all. Hemizygous males are more likely to have G6PD insufficiency, which is inherited as an X-linked trait, though heterozygous females can also have it. G6PD-deficient red blood cells lack defense against reactive oxygen species, making them susceptible to oxidative damage. This syndrome may stay asymptomatic for the rest of a person's life unless it is activated by particular agents such as raw fava beans, sulfonamides, infections, and so on, which cause hemolysis of red blood cells and/or erythrophagocytosis. The severity of the enzyme deficit determines whether hemolysis is intravascular

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or extravascular. The term "favism" refers to hemolytic episodes brought on by fava bean consumption. Clinical manifestations of favism include splenectomy, anemia, and jaundice. Since boiling fava beans has been shown to lessen the negative effects of the antinutritional chemicals vicine and divicine present in these beans, avoiding eating raw fava beans is one way to avoid favism. G6PD deficiency does not currently have a treatment. Nonetheless, gene therapy seems to be a promising treatment option for enzyme deficiencies.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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