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Peas, beans, and the Pythagorean theorem – the relevance of glucose-6-phosphate dehydrogenase deficiency in dermatology

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- favism
- oxidative stress
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Summary

Glucose-6-phosphate (G6PD) deficiency is a common disease characterized by acute hemolysis induced by oxidative stress. More than 400 million subjects throughout the world carry the hereditary enzyme defect with the highest prevalences in Africa, Asia, and the Mediterranean region.

In individuals affected by the erythrocytic enzymatic disorder, besides infectious diseases and diet, acute hemolytic crisis can be triggered by numerous drugs frequently used for the treatment of dermatoses. Taking into account the increasing number of immigrants from geographic regions with high prevalences of G6PD deficiency, dermatologists should be alert to the presence of disease.

Introduction

Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) affects more than 400 million people worldwide, making it the most common human enzyme defect. Typical signs of this X-linked recessive mutation may be seen in men, homozygous women, and even heterozygous women.

Among the more than 400 known variants especially the Mediterranean and Asian variants, as well as the A⁺ variant, which is widely spread amongst Africans and the African American population in the U.S., are particularly relevant for clinical practice. Patients suffering from one of these variants can have acute and occasionally even life-threatening hemolytic crises. These are nearly always associated with stress such as infection, use of “oxidative” drugs, or after eating certain foods.

In the following we discuss the main features of G6PD deficiency that are relevant for dermatologists and describe a 33-year-old man who was diagnosed with the disease to illustrate its key features. Our patient, who was HIV-positive, was admitted for inpatient antibiotic therapy with recurrent headache symptoms and an incidental finding of secondary syphilis.

Patient history and clinical picture

A 33-year-old man visited our clinic with a recurrent headache that had persisted for several days. He was of Sardinian origin and was HIV-positive. STD tests were performed and included lumbar puncture which revealed neurosyphilis.

The patient reported a penicillin allergy. He also reported having been allergic to

peas and beans since childhood which he said caused abdominal cramps and weakness. Both brothers, his sister, and mother had the same “allergy” with identical symptoms. His father, who had passed away six years previously, had also experienced similar symptoms after eating certain foods. The patient reported that on the island of Sardinia it was commonly known that there is a correlation between pea and penicillin allergy; thus he assumed he was allergic to penicillin. The results of examination of the skin and of the remainder of the body were normal.

Diagnosis

On the basis of patient history we made a presumptive diagnosis of G6PD deficiency. Chemical laboratory tests were performed and showed reduced activity

of G6PD to 0.1 IU/g hemoglobin (Hb) (normal range: 9–14 IU/g Hb) and moderately reduced erythrocyte (Ery) count (Ery 3.7 mil/ μ L, Hb 11.9 g/dl, hematocrit [Hct] 35.1 %). Haptoglobin was 32.7 mg/dl (30–200 mg/dl) and thus in the lower part of the reference range. Lactate dehydrogenase (LDH), bilirubin, and all other tested parameters were unremarkable. RAST testing for specific antibodies to antibiotics (i.e., penicillin G, penicillin V, ampicillin, amoxicillin, and cefaclor) did not show an increase, nor was total IgE (4.76 kU/l) elevated. Thus there was no evidence of a penicillin allergy. Additional allergy testing was not considered necessary.

Therapy and course

We began intravenous benzylpenicillin (4 mil IU 6x/daily). Therapy was continued for 14 days and was well tolerated. Afterward, the patient was given three follow-up intramuscular injections of benzathine benzylpenicillin in weekly intervals. During his hospital stay, mild to moderate headache symptoms were well controlled with paracetamol 500 mg tablets.

Etiology and pathogenesis

G6PD deficiency occurs worldwide and is the most common enzymatic defect in humans. An estimated 400 million people have the disorder [1]. There are ethnic and geographic variations as well as differences in enzyme variants and hence disease severity. The X-linked recessive defect (position Xq28) is especially prevalent among people of Asian and African descent, as well as among African Americans and in Mediterranean populations. The fact that there is a close correlation between the geographic distribution of G6PD deficiency and regions in which malaria is endemic is explained by a selective advantage for carriers of the mutation due to increased resistance to severe *Plasmodium falciparum* infection [2, 3]. High prevalences in Mediterranean regions also reflect previously widespread malaria, which on the island of Sardinia, for instance, was not eradicated until about 50 years ago [4].

There are also reports in the literature on certain gene mutations that are found exclusively in central and northern Europe, including the Aachen, Iserlohn, and Regensburg variants in Germany [5,

6, 7, 8]. Currently, about 140 gene mutations have been identified as causing more than 400 different enzyme variants [9]. These are associated with varying levels of residual enzyme activity [10].

The wild type allele is known as G6PD^B. Pathologic variants may be broadly classified as G6PD^{Canton} among Asians; G6PD^{A-} in West Africans and African Americans; and G6PD^{Mediterranean} in Caucasians (Table 1). The latter type has the lowest residual enzyme activity at less than 10 percent of normal ranges, and is thus considered by the WHO classification [11] to be a severe form of G6PD deficiency.

According to the Lyon hypothesis, in X-linked inherited disorders one of the two X chromosomes is inactivated during embryonic development (and becomes known as the Barr body). The pattern of inactivation is not uniform, however, and thus heterozygous women are mosaic with two different cell lines, one containing the normal, and the other the mutated X chromosome. This explains why in the event of G6PD deficiency, heterozygous women may also be symptomatic or develop hemolytic crises [4]. The antioxidant glutathione protects the cellular integrity of the erythrocytes and other cells by eliminating oxygen-free radicals. The process depends on NADPH; oxidized glutathione is converted into its reduced and hence active form by glutathione reductase. NADPH arises during the breakdown of glucose

in the pentose phosphate pathway (hexose monophosphate shunt) – a process requiring G6PD in cell cytoplasm [12]. If enzyme concentrations are diminished or enzyme activity is inhibited, the resulting deficiency leads to diminished levels of glutathione. Harmful free radicals accumulate (Figure 1) and, depending on the severity of the enzymatic defect, more or less severe acute hemolysis occurs.

As erythrocytes age, there is a physiological reduction in G6PD. This makes older cells especially sensitive to an accumulation of free radicals. If the enzyme still possesses adequate residual activity, as in G6PD^{A-}, moderately increased concentrations of free radicals will tend to cause only hemolysis of these cells, while the patient remains otherwise asymptomatic. In severe forms of G6PD deficiency, such as the Mediterranean variants, enzyme activity is reduced to such an extent that all red blood cells are highly susceptible to minimal oxidative stresses.

Our patient originated from Sardinia which has one of the highest prevalences of G6PD deficiency in the world at 10–15 % [13, 14]. As with most people with G6PD deficiency, he was unaware that he had the disorder. His concerns about a potential reaction to intravenous penicillin for neurosyphilis, similar to what he experienced after eating beans or peas, were unwarranted. Yet drugs with “oxidative” properties are indeed common triggers of typical symptoms of

Table 1: WHO classification of G-6-PD deficiency by enzyme activity [11]. All common, clinically-relevant types belong to class II or III.

Class	Enzyme activity in erythrocytes compared to healthy subjects	Clinical symptoms	Type
I	massive reduced	Chronic hemolytic anemia	CNSHA
II	< 10 %	severe G-6-PD deficiency	G-6-PD ^{Mediterranean}
II	10–60 %	moderate G-6-PD deficiency	G-6-PD ^{A-} , Canton
IV	60–90 % (normal activity)	no G-6-PD deficiency	G-6-PD ^B
V	> 110 % increased activity	no G-6-PD deficiency	

CNSHA – chronic non-spherocytic hemolytic anemia

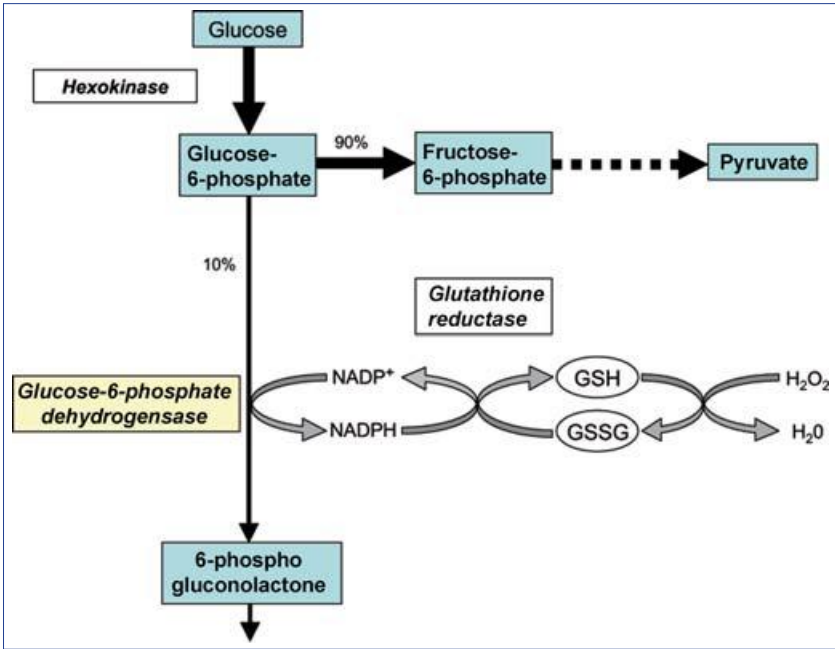


Figure 1: Pentose phosphate cycle (hexose monophosphate shunt). Elimination of harmful oxygen-free radicals (H_2O_2) by glutathione goes hand in hand with its oxidation. NADPH is used to convert oxidized glutathione (GSSG) back into its reduced form (GSH). G-6-PD deficiency leads to diminished concentrations of NADPH and thus accumulation of harmful oxygen-free radicals. Unlike other cells, in erythrocytes the pentose phosphate cycle is the only means of generating NADPH in any significant amount.

G6PD deficiency in people in whom residual enzyme activity is insufficient to eliminate the “oxidative burst” induced by such drugs. In 1928 the tropical medicine physician Wilhelm Cordes of Hamburg [15] was the first to point out the relationship between antimalarial drugs and acute hemolytic anemia in Cubans of African descent. Since then a number of drugs have been identified which are potentially hazardous in patients with G6PD deficiency (Table 2). In addition to aminoquinoline antimalarials, which are often used in the treatment of immune diseases affecting the skin, dermatologists should also be aware of potential complications of using sulfonamide derivatives. Drugs that may induce severe hemolytic crises in patients with G6PD deficiency include dapsone, commonly used in bullous skin disorders, and sulfamethoxazole which is used in HIV-positive patients for the prevention and treatment of *Pneumocystis carinii* and toxoplasmosis infections. Based on a report by Eldad and colleagues [16] of a 20-year-old male soldier who was treated for burn injuries, it appears that even topical therapy with silver sulfadiazine cream is sufficient to cause hemolytic anemia in predisposed patients.

The use of henna, which is often used in the Islamic world for ritual purposes and also as an alternative remedy, can be fatal for people with G6PD deficiency, especially newborns, infants, and small children. Raupp and colleagues [17] present a case report on four children who developed hemolytic crises after applying only small amounts of the dye to the palms of their hands and soles of their feet. In one of the children the hemolytic crisis was fatal. Katar and colleagues [18] report a 7-day-old Turkish newborn who became jaundiced and lethargic a day after application of topical henna to prevent diaper rash. It is still unclear whether fumaric acid esters, which are also commonly used in German-speaking countries for systemic treatment of psoriasis, could potentially induce acute hemolytic anemia. In a recent publication, Lehmann and colleagues [19] reported that the immunosuppressive effects of dimethyl fumarate and diethyl fumarate are partly due to depletion of glutathione in human leukocytes. If reduction of the antioxidant also affects the red blood cells, then it is very likely that fumaric acid esters could trigger hemolytic anemia in predisposed patients. Not only drugs and dyes, but also fava beans (*Vicia faba* or faba bean, thick bean, broad bean, field bean) (Figure 2) cause hemolytic anemia (favism) in

Table 2: Drugs and non-medical substances with potentially oxidative properties [30].

Drug
<i>Analgesics</i>
■ Aspirin
■ Quinine
■ Metamizole !
■ Phenacetin
■ Propyphenazone
<i>Sulfonamide antibiotics</i>
■ Acetazolamide !
■ Sulfacetamide !
■ Sulfadiazine/Silver sulfadiazine
■ Sulfamethoxazole !
■ Sulfapyridine
<i>Antibiotics (without sulfonamides)</i>
■ Chloramphenicol
■ Dapsone !
■ Ciprofloxacin
■ Metronidazole
■ Nalidixic acid !
■ Nitrofurantoin !
<i>Antihypertension drugs</i>
■ Dihydralazine
■ Hydralazine
■ Nifedipine
■ Sodium nitroprusside
<i>Antimalarial agents</i>
■ Primaquine!
■ Pamaquine!
■ Chloroquine!
■ Hydroxychloroquine!
■ Mefloquine!
<i>Immunomodulatory drugs</i>
■ Dapsone !
■ Olsalazine
■ Sulfasalazine
■ (Salazosulfapyridine)
■ Fumaric acid esters (not yet certain, but likely)
<i>Other</i>
■ Doxorubicin (cytostatics)
■ Fosamprenavir (protease inhibitor)
■ Metoclopramide (antiemetic)
■ Methylene blue (antidote in methemoglobinemia)
■ Probenecid (uricosuric)
■ Phytomenadione (Vitamin K_1)
■ Sultiam (antiepileptic)
■ Vitamin C (usual daily doses are considered safe)
<i>Non-medicinal substances</i>
■ Phenylenediamine (hair dye)
■ Naphthalene (ingredient in moth balls) !
■ Henna (dye) !

! = high risk of developing severe hemolytic anemia

susceptible individuals. “Avoid fava beans” advised the Greek philosopher and mathematician Pythagoras who refused to so much as walk on the fields where they were grown [20].

[Pythagoras is better known for his theorem “In a right triangle the sum of the squares of the legs is equivalent to the square of the hypotenuse” as summarized by the formula: $a^2 + b^2 = c^2$.]

The fava bean, which is grown throughout the world and is a very popular foodstuff in the Middle East and Southern Europe, is probably the most common trigger of hemolysis in patients with G6PD deficiency [21, 22]. Yet, for reasons that are still unknown, favism does not affect all people with G6PD deficiency and some patients can eat fava beans without any problems.

Controversy exists as to whether typical symptoms may also be caused by simply inhaling pollen from the plants, or in babies who have been breastfed by mothers who have just eaten the beans. Such findings were reported by Schiliro and colleagues [22] who conducted a study in Sicily, and similar reports have been made by other authors [23]. Yet Meloni and colleagues [24] were unable to confirm these results in a study done in Sardinia. One explanation for these apparently contradictory findings could be that the Mediterranean form of G6PD deficiency has at least 12 different mutations in Sicily alone [25, 26]. It

is agreed, however, that the symptoms related to ingesting fava beans are not caused by an allergic reaction [27].

The significance of other legumes, especially peas, in triggering hemolytic anemia is not exactly known. Although most publications on G6PD deficiency mention only fava beans in favism, patients often report typical symptoms after eating peas. In their analysis of the β -glycosides vicine and convicine which are responsible for favism, Chevion and Navok [28] addressed this question by testing their concentrations in various types of fava beans as well as green beans and chick peas. Their results showed that the two glycosides are found in all types of fava beans studied, but that neither vicine nor convicine is found in peas.

Clinical presentation

Irrespective of whether symptoms are drug-induced or occur after ingesting fava beans, their onset is typically one or two days after exposure. Symptoms may also occasionally appear abruptly within only a few hours after ingesting fava beans [21].

Common symptoms are generalized weakness and feeling unwell, abdominal and/or back pain, red-brown urine, and in severe cases jaundice as an expression of acute hemolysis. Adults are especially at risk of acute kidney failure. Patients with severe acute hemolytic anemia can experience life-threatening shock

symptoms. In newborns, G6PD deficiency can manifest as severe neonatal jaundice with a risk of developing kernicterus.

There is usually no swelling of the liver or spleen in G6PD deficiency. As mentioned before, not only males but also females can develop the signs and symptoms named above. However, other than homozygous female patients, male patients nearly always experience more severe courses.

Diagnosis

If clinical presentation and/or patient history are suggestive of G6PD deficiency, enzyme activity should be measured (normal: 9–14 IU/g Hb). It should be noted that false negatives are possible during or shortly after a hemolytic episode because the destruction of mainly older erythrocytes leads to rejuvenation of the cell population [29]. If there is any doubt, tests should be repeated two or three months later; relatives of the patient may also be tested. Detection of the defect is possible with genetic testing such as PCR.

During hemolysis, or in severe forms of G6PD deficiency (e.g., Mediterranean type, chronic non-spherocytic hemolytic anemia), patients usually have hyperbilirubinemia, even in the absence of oxidative stress. Levels of lactate dehydrogenase are elevated and concentrations of haptoglobin are diminished. Reticulocytosis and reduced hemoglobin content in the erythrocytes are often detectable a short time after hemolysis and in patients with Mediterranean G6PD deficiency.

Differential diagnoses

Symptoms such as weakness, feeling unwell, and abdominal pain can also occur with food intolerance or allergy. G6PD deficiency should be considered if anemia is also present and the patient belongs to one of the commonly affected ethnic groups. Other forms of anemia should also be considered. These include drug-induced hemolytic anemia, autoimmune-hemolytic anemia, and paroxysmal nocturnal hemoglobinuria. While “conventional” neonatal icterus arises from decreased conjugation of water-insoluble bilirubin by the immature liver, in G6PD deficiency it occurs as a result of excessive hemolysis. Further differentials are listed in Table 3.



Figure 2: Fava beans – responsible trigger in favism. The fava bean (lat. *Vicia faba*), or faba bean, broad bean, or thick bean is a legume. Fava beans are popular in Mediterranean countries where normally the seeds (right) are eaten without the skin.

Table 3: Differential diagnoses.

- Food allergy or intolerance
- Drug-induced hemolytic anemia
- Autoimmune hemolytic anemia
- Paroxysmal nocturnal hemoglobinuria
- Pyruvate kinase deficiency
- Physiological neonatal icterus

Therapy

Therapy of the enzyme defect is not yet possible. Avoidance of substances that can trigger symptoms is therefore of the utmost importance. Upon diagnosis for the first time, patients and possibly their relatives should be thoroughly educated about the disorder.

Particular caution should be taken in treating infections as oxidative drugs can dramatically worsen infection-induced acute hemolytic anemia. Still, when visiting regions with a high risk of malaria infection, prophylactic measures (as recommended by the WHO) should be taken. Patients with G6PD deficiency may take atovaquone/proguanil, proguanil, or artemether/lumefantrine. The Center for Pediatric and Adolescent Medicine at the University of Frankfurt/Main (Germany) has compiled a list of drugs, which is available on the Internet, for patients with the disorder [30].

Severe hemolytic anemia is treated symptomatically. In addition to transfusion of erythrocyte concentrate, crystalloid or colloid solutions may be given; forced diuresis and alkalization of the urine may be performed to prevent denatured hemoglobin from clogging the renal tubules [31].

Conclusions

Despite the high incidence of the enzyme defect, severe hemolytic anemia is unusual in affected patients. Even when it does occur, it is often so mild that the patient remains asymptomatic. Yet in those in whom residual enzyme activity is too low to eliminate oxygen-free radicals in the erythrocytes, oxidative stress can pose a high risk of potentially life-threatening acute hemolytic anemia. Thus for patients belonging to commonly affected ethnic groups, it is essential to take a careful patient history, assess enzyme activity, and, if necessary,

advise the patient about potential toxic substances.

With increasing numbers of immigrants, measures such as patient identification cards and screening tests for newborns, such as those already conducted in some Mediterranean countries, would be desirable.

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Note

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Conflict of interest

None.

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