Glucose-6-Phosphate Dehydrogenase Deficiency

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KEYWORDS

• Glucose-6-phosphate dehydrogenase • Hemolytic anemia • Favism
• X-linked genetic polymorphism • Malaria selection

KEY POINTS

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency, expressed in red cells, is mostly asymptomatic; however, G6PD-deficient persons develop acute hemolytic anemia (AHA) when exposed to fava beans, to infection, or to certain drugs, including primaquine.
- The gene encoding G6PD maps to the X chromosome. Therefore, full-blown G6PD deficiency is more common in males, but female heterozygotes are also at risk of hemolysis.
- G6PD deficiency is widespread in the entire world and its epidemiology correlates with that of malaria; different mutant alleles underlie G6PD deficiency in different populations.
- Primaquine is still the only drug that can eradicate *Plasmodium vivax* hypnozoites; to promptly prevent or to treat hemolytic anemia, it is important to test for G6PD before administering primaquine.

INTRODUCTION

G6PD was discovered and biochemically characterized in 1932 by Otto Warburg and Walter Christian[1] in yeast and in red cells as an enzyme with a redox function. It was one of the first enzymes of glucose metabolism to be identified, but, although Warburg did not know that, the clinical manifestations of what later became known as G6PD deficiency had been already described. In the nineteenth century, pediatricians in Greece, Portugal, and Italy observed severe anemia and hemoglobinuria in children who had eaten fava beans – hence, the term *favism*[2]; it was noticed that favism tended to recur in the same persons and also that it ran in families. Subsequently, since the 1920s, it was observed[3] that an adverse side effect of 8-aminoquinolines (primaquine and plasmoquine), used for the treatment and the prophylaxis of malaria, was AHA. No connection to favism was suspected at the time, but again it was reported that it was

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only in certain people that this side effect occurred, and in those people it could happen again on rechallenge with the same drug; this became known as the *primaquine sensitivity syndrome*.

In 1956, Paul Carson's group in Chicago[4] reported that red cells from primaquine-sensitive persons were deficient in G6PD (enzyme activity <15% of normal), and in 1958 Gennaro Sansone's group in Genoa, Italy,[5] found the same deficiency in children with a previous history of favism. It was promptly proved that G6PD deficiency was genetically determined and that its inheritance was X-linked.[6] Almost as soon as Mary Lyon[7] discovered the X-chromosome inactivation phenomenon in mice, Ernie Beutler's group[8] found independently, using G6PD as a marker, that the same applied to humans. At the time this was the first example of a hemolytic anemia due to an inherited abnormality expressed in red cells; hence, the term *enzymopathy* was coined, in analogy to hemoglobinopathy. Reassuringly, however, it was clear that in the absence of an exogenous trigger, G6PD-deficient persons had no pathology; hence, primaquine-induced or fava bean–induced AHA became a prototype of a disease arising from a specific interaction between a gene and an environmental factor, just at the time when the term *pharmacogenetics* was coined.[9]

At approximately the same time, Tony Allison[10] and Arno Motulsky[11] hypothesized that genetically determined G6PD deficiency might have been favored by malaria selection; this spurred a flurry of studies aiming to determine the frequency of this trait in many countries. It quickly emerged that G6PD deficiency was widespread in human populations in all continents; a wealth of epidemiologic data were tabulated by David Livingstone as early as 1967.[12] In the meantime, the World Health Organization (WHO) Human Genetics, then headed by Italo Barrai, was prompt in taking on board the public health implications of such a widespread genetic abnormality; in 1966, a study group was arranged with the remit to review available data and to agree on a measure of standardization for the study of G6PD deficiency.[13]

This article focuses on the essentials of G6PD deficiency as a global health problem and on the essentials of its clinical manifestations, which are a paradigmatic example of a highly specific interaction between an inherited abnormality and exogenous agents that trigger hemolysis. Space does not permit a comprehensive coverage, particularly with respect to management, for which existing literature is referred to.[14,15]

BIOCHEMISTRY OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

G6PD is a housekeeping enzyme, expressed in all cells of the body, that catalyzes the oxidation of glucose 6-phosphate (G6P) to 6-phosphoglucono-δ-lactone (**Fig. 1**), which is then hydrolyzed to 6-phosphoglucono-∂-lactone this, in turn, through the action of the enzyme phosphogluconate dehydrogenase (6PGD), is further oxidized and decarboxylated to the pentose sugar ribulose 5-phosphate.[16] Both G6PD and 6PGD have NADP as coenzyme, and therefore 2 molecules of NADPH are formed per molecule of G6P oxidized by G6PD (see **Fig. 1**). Because the product of these reactions is pentose, G6PD is commonly referred to as the first enzyme of the pentose phosphate pathway. On the other hand, from targeted inactivation of G6PD in embryonic stem cells[17] and from other lines of evidence it became clear that the prime physiologic role of G6PD is the production of NADPH.

In most cells of the human body NADPH is the key electron donor required for many biosynthetic processes, including several reactions in the pathways of fatty acid synthesis, cholesterol, and steroid hormone synthesis, as well as in the formation