



Glucose-6-Phosphate Dehydrogenase Deficiency a Balanced Polymorphism between Resistance to Malaria Infection and Hematological Abnormalities

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Abstract

Background and Aims: constantly showing to the scientific field the paradox between benefit and disadvantage of Glucose-6-phosphate dehydrogenase deficiency in malaria control is the objective of this paper.

Materials & Methods: It was based on the document review based on electronic manuscripts.

Results: The resulting information was grouped into 4 chapters: the enzyme glucose-6-phosphate dehydrogenase and its deficiency, the glucose-6-phosphate dehydrogenase deficiency protects against malaria parasites, need to rule out deficiency of glucose-6-phosphate dehydrogenase before starting treatment of malaria by Plasmodium vivax and conclusions.

Conclusions: It is concluded that this deficiency in malaria has a balanced polymorphism between resistance and infection, because it confers resistance to P. falciparum infections, but produces hemolysis in the treatment with primaquine in P. vivax. In the case of P. vivax malaria, the discarding of glucose-6-phosphate dehydrogenase deficiency, the treatment supervised by health professionals and the use for radical cure of optional schemes, to reduce the risk of hemolysis is imposed.

Keywords: Glucose-6-phosphate dehydrogenase; Polymorphism; Malaria; Infection; Treatment

Introduction

The enzyme Glucose-6-phosphate dehydrogenase (G6PD) protects erythrocytes from oxidative stress caused by the consumption of certain foods and drugs, an action that gives particular attention to endemic areas for parasites that require medications that have oxidizing effects, among them *Plasmodium vivax* malaria, as the radical cure of the same that seeks to prevent relapse caused by dormant stages in the liver (hypnozoite) focuses on the oxidative drug primaquine, capable of producing severe hemolytic crises in people with G6PD deficiency [1].

However, G6PD deficiency in the case of malaria, although it seems paradoxical, confers some degree of protection against the infection of another parasite, *P. falciparum*, in areas where it is endemic. These elements, protection against infection and side effects of the treatment, contents in which the authors call balanced polymorphism of G6PD deficiency, deserve to be shown and discussed, the main objective of this paper in order to stimulate research in this regard as a previous step for the control of this parasite, particularly because worldwide by 2017 there were 219 million new cases of malaria, which indicates that there

have been no significant advances in the reduction of this disease [2,3].

Materials and Methods

This work was based on the documentary review based on electronic manuscripts obtained from the databases: Pubmed, Medline, Scopus, Lilacs, Science Direct, SciELO and Ovid. The specific descriptors were used in the search. The information was analyzed by the authors and the resulting information was grouped into 4 chapters: the enzyme glucose-6-phosphate dehydrogenase and its deficiency, G6PD deficiency protects against malaria parasites, need to rule out G6PD deficiency before starting the treatment of *P. vivax* malaria and conclusions.

Results and Discussion

The enzyme glucose-6-phosphate dehydrogenase and its deficiency

The conversion of glucose-6-phosphate to 6 phosphogluconate with reduction of NADP to NADPH is mediated by the cytoplasmic enzyme G6PD. NADPH is responsible for maintaining the adequate amount of reduced glutathione (GSH), a crucial element in the elimination of hydrogen peroxide from free radicals when the cell is exposed to oxidative stress, a particularly marked event in erythrocytes for two fundamental reasons. Continuous generation of oxygen radicals due to the hemoglobin cycle and frequent exposure of these cells to exogenous oxidizing agents [4-6].

The oxidative damage is irreversible and with cell death in the G6PD deficiency described in 1956 with an inheritance linked to the X chromosome (due to deletions, point mutations and substitutions) determined two years later, in this sense it is indicated that the men who inherit the gene they are always hemizygotes (deficient) and women can be homozygous (normal or deficient) or asymptomatic heterozygotes or with mild or severe manifestations in direct relation to the percentage of cells with the mutated phenotype (result of inactivation of the X chromosome) [7-10]. Because the half-life of the G6PD enzyme does not exceed 60 days, senescent erythrocytes are mostly destroyed in oxidative stress exposures [11-13].

The clinical manifestations, specifically the expression of the deficiency depends on the variant of G6PD and exogenous factors, such as beans, infections and drugs (such as sulfonamides, antipyretics, nitrofurans, primaquine and chloroquine), the clinical conditions include neonatal hyperbilirubinemia, anemia acute hemolytic and chronic non-spherocytic hemolytic anemia, and it is the kernicterus (bilirubin infiltration into the brain) the main complication [4,14,15].

G6PD deficiency protects against malaria parasites

In some populations and despite its clearly adverse effect on health molecular variants of G6PD producing deficiency remain constant and with high frequency in endemic populations for malaria, this strong correlation generates in part of the world scientific community the questioning about whether the deficiency of G6PD confers protection against this infection [16,17]. With the passage of time it has become evident that malaria is a selective force, especially *P. falciparum*, because several polymorphisms are associated with protection against this infection, among them are: genes that encode oligoproteins of the erythrocyte cell membrane (groups blood), globin genes (HbS, HbC, HbE, thalassemias), oxidative stress (G6PD deficiency), cytoadherence and immune system [18,19].

The protective role of G6PD deficiency against malaria is understood or explained if it is based on the fact that any lack of GSH main molecule with erythrocyte-reducing potential negatively affects *Plasmodium* spp. infection. Because they are parasites that break down hemoglobin for nutritional purposes, but iron oxidation is toxic to them, and the reduction corresponds to GSH, so G6PD deficiency confers some protection against malaria, in this sense several findings have been pointed out: strong association between endemic areas of malaria and distribution of G6PD deficiency, inhibition of parasite growth in deficient erythrocytes, reduction of the risk of malaria infection in women and hemizygote men carrying the G6PD A- variant, and allele linkage imbalance (observed in the G6PD A- and Mediterranean variants) that overlaps with the spread of malaria [20-24]. In a clear example of balanced polymorphism, on the one hand resistance to infection and on the other hematological alterations [24,25].

Need to rule out g6pd deficiency before starting treatment of malaria by *P. vivax*

In the radical cure of *P. vivax* malaria, primaquine is used exclusively but this triggers hemolysis in subjects with G6PD deficiency, this is particularly serious in many regions where primaquine is prescribed without prior discarding of this enzymatic deficiency and without medical supervision. In any case it is recommended; in proven G6PD deficiency replace the traditional primaquine scheme from 0.25 mg/kg daily for 14 days to 0.75mg/kg weekly for 8 weeks whose efficacy is 90%. Because the molecular variants and the prevalence of G6PD vary between geographic regions and even among ethnic groups, the determination of G6PD deficiency is recommended in populations where malaria is endemic and the weekly treatment schedule with primaquine [26-29].

The genotypic determination of the molecular variant of G6PD is also recommended, since tests based on the measurement of enzymatic activity sometimes do not rule out G6PD deficiency, especially during or after a hemolytic crisis because old deficient

erythrocytes have already been destroyed and the relatively normal enzyme activity is maintained by young red blood cells [30,31]. It is also recommended that information on G6PD deficiency and effects on erythrocyte hemolysis once exposed to oxidizing agents be made available to as many healthcare professionals as possible and to the general population, but with special emphasis on those who live in endemic areas for malaria, in the first group for being responsible for providing efficient health care and in the second group to seek timely and quality advice [29,32,33].

Conclusion

G6PD has a balanced polymorphism between resistance and infection in malaria, in this sense it confers a certain degree of resistance to *P. falciparum* infections, but produces hemolysis in the treatment with primaquine in *P. vivax*. In the case of *P. vivax* malaria, the discarding of G6PD deficiency, the treatment supervised by health professionals and the use for radical cure of optional schemes with primaquine are imposed, to reduce the risk of hemolysis in patients with deficiency of G6PD.

Conflicts of Interest

The authors report no conflict of interest in relation to this document.

Author's Contribution

All the authors participated in the conception of the work, information search, analysis and writing of the data found.

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