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Malaria by *Plasmodium vivax* and Deficiency of Glucose-6-phosphate Dehydrogenase: The Venezuela Case

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Abstract

Plasmodium vivax malaria is an important public health problem in Venezuela where the therapeutic regimen administers primaquine as the only drug available to prevent recurrence of *P. vivax* malaria. However, Primaquine is an oxidative drug that can cause hemolysis in subjects deficient in the enzyme Glucose-6-Phosphate Dehydrogenase. The objective of this paper is to show concisely what was done and found about this enzyme defect in Venezuela. Based on the review of the scientific literature of virtual data (Bireme/OPS, Medline, PudMed, Scielo) from descriptors or related keywords, the objective of this research was achieved. The information found is located in three chapters: Malaria as a public health problem; treatment of *P. vivax* malaria and G6PD deficiency; and G6PD deficiency in Venezuela. It is concluded that the researchers have advanced progressively and firmly in obtaining information about G6PD deficiency in Venezuela, a country considered endemic for *P. vivax* malaria, in order to provide key information for the treatment of such an important health problem.

Keywords: Malaria; *Plasmodium vivax*; Primaquine; Hemolytic anemia; G6PD

Introduction

Plasmodium vivax malaria is an important public health problem in Central American and South American countries, including Venezuela. The therapeutic guideline recommended by the World Health Organization and adopted by most countries with transmission of *P. vivax*, administers chloroquine and primaquine. The latter acts against hypnozoites and is the only drug available to prevent recurrence of malaria due to *P. vivax*. However, primaquine is an oxidative drug that can cause hemolysis in subjects deficient in the enzyme Glucose-6-Phosphate Dehydrogenase (G6PD), recessive Erythroenzymopathy linked to the X chromosome, with wide global distribution and high genetic and biochemical heterogeneity [1-6]. The knowledge on the prevalence of this deficiency in Venezuela appears as fundamental in the fight against such an important sanitary scourge, in this sense the object of the present writing is to show concisely what has been done and found about this enzymatic defect in that country, then of an update or of the description of the state of the art about what was found by researchers in response to this sanitary problem.

Methodology

Based on the review of the scientific literature of virtual data (Bireme/OPS, Medline, PudMed, Scielo) from descriptors or related keywords, the objective of this research was achieved, that is, a description of the state of art in relationship with *P. vivax* malaria and G6PD deficiency in Venezuela in order to show clearly and accurately to the scientific community what has been done about it.

Malaria as a public health problem

Malaria is the parasitic disease of greatest severity and prevalence in the world, especially affects people living in tropical and subtropical countries, so 2.4 billion people are exposed to the risk of contracting the disease. Each year, malaria causes between 300 and 500 million clinical cases and 1.5 to 2.7 million deaths. They do not escape to such situation America and the Caribbean, 38% of the population of the region lives in areas of active transmission of malaria [1-3].

The etiological agents are four species of the genus Plasmodium: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. The most dangerous is *P. falciparum*, to which most of the severe cases and deaths due to malaria are attributed, predominates in Africa where more than 90% of the world casuistry occurs; *P. vivax* prevails in South America (>70%), in Central America (>80%) and in the Eastern Mediterranean (>80%) and shows high frequency in Southeast Asia and the Western

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Pacific (49%). Although *P. vivax* infection is rarely fatal, recurrences of the disease produce high morbidity. As for *P. malariae* and *P. ovale,* the first one is irregular and sporadic ovale in Africa, South America and some countries of the Far East. However, in Venezuela and according to sources of the Ministry of Popular Power for Health, 80% of malaria cases are caused by *P. vivax* [7,8].

Treatment of *Plasmodium vivax* malaria and glucose-6-phosphate dehydrogenase deficiency

The therapeutic guideline recommended by the World Health Organization and adopted as a health policy by Venezuela for the radical cure of malaria by *P. vivax* administers 25 mg of the base of chloroquine for three days and 15 mg of the base of primaquine day for 14 days. Chloroquine fulfills the purpose of eliminating parasites from the blood circulation and primaquine destroys hypnozoites and consequently avoids relapses [9-11].

In this sense, Primaquine, an 8-Aminoquinoline, is currently the only drug available in clinical practice for the radical cure of malaria by *P. vivax* [12-14]. It is effective against the hepatic stages of all Plasmodium species, which is why it is also used in primary prophylaxis, since by destroying the parasites in the liver it prevents them from reaching the bloodstream and causing the disease. Also, primaquine is used in terminal prophylaxis, when it is administered together with schizontocidal drugs in prevention of possible recurrences, particularly in travelers to endemic areas of malaria [15]. However, the discovery of hemolytic accidents in subjects with G6PD deficiency who had received antimalarial treatment with primaquine dates from 1954, when the labeling of erythrocytes with ^{51}Cr revealed that the haemolytic effect resulted from intrinsic anomalies to the erythrocytes of these subjects [16]. In people with G6PD deficiency the hemolytic activity of the PQ is attributed to the oxidative stress caused by the active metabolites of this drug, specifically 5-Hydroxyprimagine (5-HPQ), which forms disulfide bridges between the hemoglobin and cytoskeletal proteins, which disrupt the interaction of the molecules that make up the erythrocyte cell membrane and lead to the transformation of the erythrocyte into a senescent cell that is removed from the circulation [17-20]. Subsequently, it was shown that human erythrocytes with deficient activity of G6PD were in turn deficient in glutathione, the only intra erythrocytic buffer of reactive oxygen species [21].

Several studies have confirmed the accidents of hemolytic anemia caused by the conventional dose of primaquine in the endemic areas of *P. vivax* malaria and its relationship with G6PD deficiency [21-24]. The problem becomes more complicated because in several tropical regions the total dose (210 mg) of primaquine administered according to the 15 mg/day/14 day schedule does not have the efficacy necessary to prevent recurrence of the disease [25]. Objective that can be achieved by increasing the total dose, for example: 420 mg [26-30]. However, this also increases the risk of producing hemolytic accidents in subjects with G6PD deficiency, since the oxidative effect of primaquine is dose-dependent, which is why the evaluation of different primaquine administration protocols requires prior information about the population risk of G6PD deficient [29,30].

It is well known that G6PD deficiency is more common in Africans and Asians than in Europeans and North Americans; the severity of the G6PD deficiency varies among races, the most severe forms are found in Mediterranean populations and the mildest in the African population [31]. In the American continent it is reported that between 11% and 13% of people of African descent born in North America show G6PD deficiency; that in Mexico, the G6PD deficiency ranges between 0.4% and 4% and predominates among the mestizo of the Gulf and Pacific coasts; and that in Brazil there is a G6PD deficiency of 0% in Amerindian populations and 9.6% in the descendants of Africans [32-34].

G6PD deficiency in Venezuela

From Venezuela the official information begins with, of De Acquatella [35] who investigated the deficiency of G6PD in 300 donors of the blood bank of the University Hospital of Caracas, in 123 Paraujano Indians and in 56 individuals belonging to the black population of Tapipa (Miranda state), finding 2% deficient among the donors of the blood bank, no deficient subjects in the samples belonging to the group of the Paraujano Indians (of the Venezuelan Guajira) and apparent predominance of the enzymatic deficiency in the women (13.3%) about men (11.5%) of the population of Tapipa.

Years later, G6PD deficiency was reported in Bolivar State in 5.3% of 650 subjects who attended the Malariology Service (Zone III) due to clinical suspicions of malaria. Of the 35 deficient subjects, 19 were clearly deficient (17 men and 2 women) and 16 showed partial deficiencies (12 men and 4 women) [36]. Muller [37] also found G6PD deficiency in 13.1% of 2,338 patients with congenital hemolytic anemia, who had been referred to the Institute of Oncology and Hematology of the Ministry of Health and Social Development in a period of 15 years. According to the biochemical classification, 4.9% belonged to class I, 45.7% to class II and 49.4% to class III. Navarro et al. [38] also found a deficiency of the G6PD enzyme in a 6-year-old boy from the Sucre state with a diagnosis of *P. vivax* malaria and treated with primaquine, who after the treatment had developed hemolytic anemia.

Recently, a study carried out in the Cajigal municipalities of the state of Sucre and Sifontes of the Bolívar state, with high transmission of *P. vivax* malaria, found 3.6% of intermediate or class III G6PD deficiency, predominant in the Cajigal municipality and in Men, also the molecular characterization of the G6PD gene, by means of PCR/RFLP and automated DNA sequencing, showed a predominance of the variant A-(202 G →A/376A→G). This study constitutes the first finding of the genetic variants of G6PD in the Venezuelan population [39]. Due to reports of acute hemolytic anemia in indigenous Piaroas of the municipality of Atures of Amazonas state exposed to *P. vivax* malaria. Bastidas et al. [40] performs a field study to determine the activity of G6PD by biochemical tests, its results do not show the deficiency enzymatic in none of the subjects included in the study, concluding that the anemia is of deficiency origin in indigenous Piaroas and that the limited gene flow is maintained in relation to the enzymatic defect reported previously for Venezuela and other countries.

Conclusion

The review reveals that researchers have progressively and steadily advanced in obtaining information on G6PD deficiency in Venezuela, a country considered endemic for *P. vivax* malaria, in order to provide key information for the treatment of this important problem.

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