Clinical aspects of hemolysis in patients with *P. vivax* malaria treated with primaquine, in the Brazilian Amazon

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ABSTRACT

This report describes the development of hemolysis in eighteen glucose-6-phosphate dehydrogenase deficient patients treated for *Plasmodium vivax* malaria with chloroquine and primaquine. The most frequent findings accompanying hemolysis were fever and leukocytosis, in addition to anemia requiring red blood cell transfusion, and development of acute renal failure. Hemolysis in patients using primaquine is not infrequent and contributes to the morbidity of infection caused by *Plasmodium vivax.*

Keywords: malaria, *Plasmodium vivax*, treatment, primaquine, hemolysis.
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INTRODUCTION

In 2007, Brazil reported 457,659 cases of malaria, mostly in the Brazilian Amazon, with 85% caused by *P. vivax* infection.[1] Because of its ability to promote relapses from hypnozoites in the liver, the radical treatment of *P. vivax* infection requires the use of chloroquine (blood-stage schizonticidal drug) and primaquine, an 8-aminoquinoline that remains the only licensed tissue-stage schizonticidal drug.[2] The recommended dosage of chloroquine is 10 mg/kg/day in the first day followed by 7.5 mg/kg/day in the second and third days; the dosage of primaquine is 0.5 mg/kg/day for 7 days, according to the Brazilian Antimalarial Therapy Guidelines.[3] Despite of a slightly lower efficacy compared to the 14-day regimen (0.25 mg/kg/day) recommended by the World Health Organization, the 7-day regimen (0.5 mg/kg/day) adopted by the Brazilian Ministry of Health leads to better compliance.[4] Primaquine however, has hemolytic anemia a notable adverse effect in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[5] This is an X-linked recessive enzymatic defect in the hexose mono-phosphate shunt, which prevents cellular damage from oxidative stress.[6] Therefore, the majority of affected cases are males. Homozygous symptomatic women are rare. The common African variant G6PD A- is usually a mild/moderate deficiency (10−15% of normal activity in hemizygous males). In contrast, the G6PD Mediterranean variant is more severe (< 1% of normal activity).[7]

In Manaus (Western Brazilian Amazon), an association between G6PD deficiency and methemoglobinemia without significant severity was detected.[8] In spite of the widespread use of primaquine in tropical areas highly endemic for *P. vivax* species, the clinical aspects of hemolysis triggered by its use are poorly described in the literature, sometimes leading to inappropriate management of these cases in the health system.

PATIENTS AND METHODS

We report a series of 18 male patients with *P. vivax* infection referred to the Tropical Medicine Foundation of Amazonas, a tertiary-care unit for infectious diseases in Manaus, Brazil, from August 2006 to August 2007. All of these patients had been treated by primaquine and developed hemolysis (indirect bilirubin > 1.0 mg/dL). They were all ultimately diagnosed with G6PD-deficiency, by the qualitative Brewer´s test.[9] This test was repeated after 120 days in all patients with an initial negative G6PD deficiency test because of the transitory G6PD increase related to reticulocytosis during an acute hemolytic crisis.

RESULTS

The major clinical symptoms of these patients were: jaundice (18/18), pallor (17/18), dark urine (14/18), fever (12/18), vomiting (10/18), dehydration (6/18), cyanosis (3/18), and low urinary output (1/18). Table 1 details some clinical and laboratory characteristics. No patient was treated with antibiotics, despite the presence of fever and leukocytosis.

DISCUSSION

In a smaller patient sample, Silva *et al*. detected similar clinical manifestations among G6PD-deficient patients using primaquine in the State of Pará (Eastern Brazilian Amazon).[10] Most of our patients were already negative for Plasmodium parasites when admitted to the hospital, reflecting an adequate response to chloroquine. The onset of symptoms related to hemolysis emerged 1-6 days after starting primaquine, supporting the need for routine follow-up of male patients during this interval, since patients are not tested routinely for G6PD deficiency before the prescription of antimalarials in Brazil. Eleven out of the 18 patients still complained of fever, despite negative peripheral parasitemia, and 12 had leukocytosis (leukocyte count > 12,000/mm^3), which could be attributed to the hemolytic crisis itself. Likewise, in two American soldiers returning from Iraq who developed hemolytic anemia and leukocytosis while receiving primaquine prophylaxis for malaria, routine wide spectrum antimicrobials were not started.[11] The most clinically relevant complication in these patients was anemia, which required red blood cells transfusion in 12 of the 18 patients, leading to a substantial increase in hospitalization costs. Three patients who developed acute renal failure resolved favorably and did not require hemodialysis. One patient developed severe acute renal failure that required hemodialysis. This patient was not included in the analysis because he was lost to follow-up and the diagnosis of G6PD deficiency could not be reliably ascertained (data not shown). Therefore, acute renal failure in the tropics should raise the consideration of primaquine-triggered hemolysis in G6PD-deficient individuals.[12] Rhabdomyolysis as the cause of acute renal failure was not investigated in our patients because none referred significant myalgia.

Table 1. Clinical and laboratory characteristics of 18 patients with* P. vivax *infection with primaquine-induced hemolysis

Patient number	Age (years)	Type of malaria	Fever (admission)	Peripheral parasitemia (admission)	Time on primaquine (days)	Leukocytes /mm^3	Hgb (g/dL)	Creatinine (mg/dL)	Indirect bilirubin (mg/dL)	Time of hospitalization (days)	Need for RBC transfusion
1	19	P.v.	+	-	3	13,600	10.3	N/A	3.04	7	-
2	10	P.v.	-	-	6	16,400	6.1	0.9	1.40	3	-
3	17	P.f. + P.v.	+	-	1	15,300	6.8	1.2	7.47	11	+
4	12	P.v.	+	-	5	9,800	8.0	0.5	4.98	3	-
5	21	P.v.	+	-	3	17,000	10.0	0.9	3.85	3	+
6	14	P.v.	-	-	5	24,700	9.0	5.9	1.22	9	+
7	32	P.v.	-	+	2	6,600	12.7	1.0	8.60	2	-
8	39	P.v.	+	-	2	5,800	10.9	1.8	5.68	4	-
9	12	P.v.	+	-	5	12,500	6.1	0.5	3.62	4	+
10	23	P.v.	-	-	4	12,700	5.9	2.2	4.56	5	+
11	21	P.v.	-	-	5	11,400	9.1	1.3	3.54	8	+
12	15	P.v.	-	-	5	17,200	6.3	2.1	5.03	7	+
13	17	P.v.	+	-	3	12,800	7.9	0.7	6.44	2	+
14	11	P.v.	+	-	4	26,400	7.0	0.6	1.83	5	-
15	8	P.v.	+	-	5	10,400	5.2	N/A	1.43	3	+
16	12	P.v.	+	-	5	12,100	6.4	N/A	3.92	2	+
17	31	P.f. + P.v.	+	+	5	15,300	9.9	0.9	4.77	3	+
18	19	P.v.	+	-	4	6,400	8.4	0.9	3.10	3	+

P.v., *Plasmodium vivax*; P.f., *Plasmodium falciparum*; Hgb, hemoglobin; RBC, red blood cells; N/A, non-available.

A better characterization of hemolysis could have been achieved with the reticulocyte percentage and haptoglobin level estimates. However, these laboratorial tests are not always available in most of the malaria endemic areas.

Further studies are needed to determine the magnitude of this problem in the primary care units in malaria endemic areas, especially in Latin America where *P. vivax* predominates and G6PD deficiency is estimated to be around 3%.[13] A better understanding of this hematological complication will support the development of guidelines reinforcing the correct clinical management of hemolysis developing in patients during treatment for malaria.

REFERENCES

1. Brazilian Ministry of Health. Epidemiology of Malaria in Brazil, 2007. Available at: http://portal.saude.gov.br/portal/arquivos/pdf/folder_malaria_2008_final.pdf. Accessed 17 November 2009.
2. Krotoski WA. The hypnozoite and malarial relapse. Prog Clin Parasitol 1989; 1:1-19.
3. Brazilian Ministry of Health. Brazilian Antimalarial Therapy Guideline. Available at: http://portal.saude.gov.br/portal/arquivos/pdf/manu_terapeutica_malaria.pdf. Accessed 19 March 2009.
4. Krudsood S, Tangpukdee N, Wilairatana P *et al*. High-dose primaquine regimens against relapse of *Plasmodium vivax* malaria. Am J Trop Med Hyg 2008; 78:736-40.
5. Baird JK, Hoffman SL. Primaquine therapy for malaria. Clin Infect Dis 2004; 39:1336-45.
6. World Health Organization. Glucose-6-phosphate dehydrogenase deficiency. Bull World Health Organ 1989; 67:601-11.
7. Beutler E, Duparc S. Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. Am J Trop Med Hyg 2007; 77:779-89.
8. Santana MS, Rocha MA, Arcanjo AR *et al*. Association of methemoglobinemia and glucose-6-phosphate dehydrogenase deficiency in malaria patients treated with primaquine. Rev Soc Bras Med Trop 2007; 40:533-6.
9. Brewer GJ, Tarlov AR, Alving AS. The methemoglobin reduction test for primaquine-type sensitivity of erythrocytes. A simplified procedure for detecting a specific hypersusceptibility to drug hemolysis. JAMA 1962; 180:386-8.
10. Silva MC, Santos EB, Costal EG *et al*. Clinical and laboratorial alterations in *Plasmodium vivax* malaria patients and glucose-6-phosphate dehydrogenase deficiency treated with primaquine at 0.50 mg/kg/day. Rev Soc Bras Med Trop 2004; 37:215-7.
11. Carr Jr. ME, Fandre MN, Oduwa FO. Glucose-6-phosphate dehydrogenase deficiency in two returning Operation Iraqi Freedom soldiers who developed hemolytic anemia while receiving primaquine prophylaxis for malaria. Mil Med 2005; 170:273-6.
12. Sakhuja V, Sud K. Acute renal failure in the tropics. Saudi J Kidney Dis Transplant 1999; 4:247-60.
13. Santana MS, Lacerda MVG, Barbosa MGV e*t al.* Glucose-6-phosphate dehydrogenase deficiency in an endemic area for malaria in Manaus: a cross-sectional survey in the Brazilian Amazon. PLoS ONE 2009; 4:e5259.