

Fatal Primaquine-Induced Hemolysis in a Patient With *Plasmodium vivax* Malaria and G6PD A(–) Variant in the Brazilian Amazon

TO THE EDITOR—In 2012, among 17 deaths in persons with a clinical diagnosis of *Plasmodium vivax* infection analyzed post mortem at a reference center in the Brazilian Amazon, we reported that 2 deaths had occurred in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients with primaquine (PQ)-triggered hemolysis [1]. The G6PD enzyme activity was characterized using the phenotypic qualitative Brewer test. These patients were prescribed chloroquine (25 mg/kg in 3 days) and PQ (0.5 mg/kg/d for 7 days), and clinical complications developed after the third day of the recommended PQ dose. Attempts to extract DNA from paraffinized blocks with organ tissues from the autopsies were successful in only 1 patient.

In this patient, a 57-year-old man with the incidental finding of mild alcoholic steatohepatitis, a severe hemolytic crisis had developed, including acute renal failure, respiratory distress, and severe anemia. Polymerase chain reaction-restriction fragment length polymorphism performed to detect common G6PD mutations (143 T/C, 563 C/T and 1003 G/A, 202 G/A and 376 A/G) revealed the presence of both 202 G/A and 376 A/G mutations. These results were confirmed using the TaqMan Master Mix with allele-specific probes on the StepOnePlus Real-Time Polymerase Chain Reaction System (Applied Biosystems) and validated with DNA sequencing of exons III, IV, V, VI and IX (ABI 3100; Applied Biosystems), which did not show any additional mutations. G6PD mutations associated with the A(–) allele (202 G/A and 376 A/G) are the most common in G6PD-deficient individuals of African descent.

To date, a total of 14 deaths due to PQ intake have been reported in an extensive

safety review of 8-aminoquinoline drugs [2]. Twelve occurred in confirmed G6PD-deficient individuals, of whom the only known genotype was one Mediterranean variant (563 C/T) in an 18-year-old man who died of acute renal failure in India. Latin American countries contribute to 4.5% of the G6PD-deficient male population from malaria-endemic countries, corresponding to an estimated 10 million males [3], with about 90% carrying the G6PD A(–) variant [4]. In this continent, PQ-triggered hemolysis is the main complication among G6PD-deficient patients [5], contributing to the increasingly perceived morbidity of *P. vivax* infection. In conclusion, it is important to recognize that G6PD A(–), classified as a class III variant and often referred to as one with “moderate activity” (10%–20%; borderline with class II variants), may result in dangerous or even potentially life-threatening hemolysis on intake of certain triggering agents, as was shown for dapsone-containing formulations in children with the G6PD A(–) variant [6].

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References

- Lacerda MVG, Fragoso SCP, Alecrim MGC, et al. Postmortem characterization of patients with clinical diagnosis of *Plasmodium vivax* malaria: to what extent does this parasite kill? Clin Infect Dis 2012; 55: e67–74.
- Recht J, Ashley EA, White N. Safety of 8-aminoquinoline antimalarial medicines. Geneva, Switzerland: World Health Organization, 2014.
- Howes RE, Piel FB, Patil AP, et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geo-statistical model-based map. PLoS Med 2012; 9: e1001339.
- Howes RE, Dewi M, Piel FB, et al. Spatial distribution of G6PD deficiency variants across malaria-endemic regions. Malar J 2013; 12:418.
- Monteiro WM, Franca GP, Melo GC, et al. Clinical complications of G6PD deficiency in Latin American and Caribbean populations: systematic review and implications for malaria elimination programmes. Malar J 2014; 13:70.
- Pamba A, Richardson ND, Carter N, et al. Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. Blood 2012; 120:4123–33.

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Clinical Infectious Diseases® 2016;62(9):1188

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