

## An Unlikely Malaria Case: Report of a Patient with G6PD Deficiency and Travel to a Non-Endemic Region of Africa

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### Abstract

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency which overlaps with malaria endemicity supports the protection hypothesis against malaria. The aim of this case study is to present a case where the protective association did not help prevent the occurrence of the disease. Further, the patient contracted the disease during travel to a non-endemic area of Africa (Cape Town, South-Africa) and the patient having taken drug prophylaxis namely doxycycline. Lastly, during his first passage to the emergency room, in spite of obvious clinical manifestations, the diagnosis of malaria was not made based on traditional laboratory results being negative (rapid testing and staining microscopy). The second passage to the ER with similar symptoms and laboratory testing repeated twice ultimately confirmed malaria. The patient was successfully treated with artemisinin derivatives. This report serves again to point to the complexity of factors that makes for disease manifestation, to the challenges of diagnosis for the doctor, and to assess the presence and extent of protective association between G6PD and malaria. Further, the patient was closely monitored for 24 hours in hospital with strict observation of doses of artemisinin derivatives due to lack of evidence of the extent of toxicity and hemolytic anaemia due to G6PD.

**Keywords:** *Glucose-6-Phosphate Dehydrogenase Deficiency; Malaria Protection; Malaria Endemicity; Artemisinin-Based Therapy; Malaria Testing; Malaria Prophylaxis; Diagnostic Strategy; South-Africa*

### Introduction and Background

Malaria is a serious and sometimes fatal parasitic disease characterized by clinical symptoms of high fever, chills and eventually anaemia of varying severity [1]. Over 3,2 billion people in the world are at risk of malaria and a wide range of anti-malarial drugs are used to prevent and treat malaria [2]. Globally, > 200 million infected individuals develop clinical symptoms, and > 400,000 die because of severe malaria, primarily children in Sub-Saharan Africa [3]. There are five types of malaria possible in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. Of these, *P. falciparum* has been known to be the most dangerous and causing the highest fatality in different subgroups, but especially in children and pregnant women [4].

Glucose-6-Phosphate Dehydrogenase (G6PD) is an enzyme that catalyzes a reaction in the pentose phosphate pathway that generates reduced form of NADPH, which in turn is responsible for glutathione (GSH) homeostasis [5]. GSH is an antioxidant, and together, these processes make cells more able to resist and control oxidative stress [5]. G6PD is indispensable for the survival of red blood cells (RBCs) [6]. Inability of RBCs to maintain GSH homeostasis results in oxidative stress and affects the integrity of the RBCs, giving rise to hemolysis [5]. For *Plasmodium* species to survive, replicate and develop, it has been hypothesized that they need optimum RBC redox status, which is diminished in G6PD deficient cells, and thus supporting the malaria hypothesis [5].

Deficit of G6PD is a genetic abnormality that is responsible for hemolytic anemia from hemolysis from oxidative stress due to the consumption of food or certain medications [6]. G6PD deficiency is an incomplete hereditary X-linked hemolytic disease that is widespread in the tropical and sub-tropical regions of the world, and which overlaps with malaria endemicity, supporting the protection hypothesis against malaria. This points to the hypothesis that G6PD deficiency may have arisen, spread, or maintained in frequency through the natural selection by malaria [5]. Epidemiological studies have yielded confusing results. It has been very recently proposed after thorough research that heterozygous girls might be the driving force for the positive selection of G6PD deficiency alleles [7]. Homo- or hemizygous males, as the disease is X-linked, on the other hand, are not only unprotected, but are prone to more severe forms of malaria [5]. The following case illustrates this hypothesis.

### Clinical Case Presentation

A 50-year old male travelled to Cape Town, South-Africa for 3 days via Amsterdam and Johannesburg, and was back in Belgium in June 2017. He took drug prophylaxis of doxycycline 100mg once per day. After two weeks upon arrival, or 24 days after arrival in Africa, he developed flu-like symptoms with headaches, joint pain and chills. He visited the Emergency Department (ED) of CHIREC Clinic where his vital parameters were normal (Heart rate: 72/minute, Blood pressure: 126/65 mmHg, and temperature: 36,5°C) and the laboratory tests for malaria by rapid antigen testing [1] as well as thick and thin blood films were negative. Past medical history included G6PD deficiency, alpha-thalassemia, hypercholesterolemia and familial leucopenia. The patient had no medication history. In his blood test, the C reactive protein was at 81,4 mg/dL, platelet count was 92,000/mm<sup>3</sup>, haemoglobin at 15 g/dL and total white cell count at 3100 x 10<sup>6</sup>/mm<sup>3</sup>. With the concertation of the infectious disease expert, the patient was diagnosed with a viral infection and prescribed acetaminophen 1g four times/day.

After five days, due to the persistence of symptoms and more intense chills, he was brought again by his wife to the ED. At presentation, he was febrile (40°C), tachycardic (98/minute) and hypotensive (104/65 mmHg); there were no meningeal signs and the Glasgow Coma Scale was normal (15/15). Index of suspicion for malaria was high as fever with chills were at the forefront of the symptoms. Oxygen saturation while breathing ambient air was 97%, the respiratory examination and a chest radiograph were both normal. Laboratory investigations were as follows: haemoglobin 9,9 g/dL, red blood cell count 4,33 x 10<sup>6</sup>/mm<sup>3</sup>, total white cell count 3,9 x 10<sup>6</sup>/mm<sup>3</sup>, platelet count was at 101 x 10<sup>3</sup>/mm<sup>3</sup>. The coagulation parameters were within normal range. Hypokalemia was present (3,4 mmol/L) as well as increased values of C reactive protein (78 mg/L), total bilirubin (2,5 mg/dL) and lactate dehydrogenase 556 U/L. Serum concentrations were slightly above normal range for glucose at 117 mg/dL and liver enzymes at 50 U/L for GOT and 48 U/L for GPT. Other values of urea and creatinine were within normal ranges. Testing for dengue was not performed.

Thin and thick blood films were carried out initially as well as the rapid antigen testing for pan-*plasmodium* were all negative, a problem with the antigen kit which was confirmed eventually and the Center for Tropical Diseases in Antwerp was informed. As the suspicion for malaria was high, the patient was hospitalised in the general medical floor for surveillance and active cooling procedure with acetaminophen, aspirin and wet towels. The second thick blood film came back positive for *Plasmodium falciparum* with a count of 20:00. The film was proofread the next morning by the laboratory clinician. The patient was put through the three day regimen of Riamet (Artemether 20 mg + lumefantrine 120 mg) with a loading dose of 2 x 4 pills in 4 hours followed by 2 x 4 pills per day. At treatment inception, platelet count was 101 x 10<sup>3</sup>/mm<sup>3</sup> without haemorrhagic manifestations.

Thick blood films were diagnostic of *P. falciparum* infection. Further, the samples were sent for the Center for Tropical Diseases in Antwerp where malaria was confirmed by PCR. The rapid antigen test remained negative, surprisingly. Blood and urine cultures were obtained, but gave negative test results. Platelet counts showed a rapid increase soon after the treatment with Riamet. Haemoglobin level

also showed an increase following treatment. The total bilirubin level showed a decrease and the renal function (urea/creatinine values) remained normal. After receiving 3 doses of 4 pills of Riamet and upon normalizing of body temperature, the patient was discharged on the second day of hospitalisation in good clinical condition with platelet counts in the normal range and rising haemoglobin levels confirming the absence of hemolytic anemia due to G6PD. Further thick and thin films were not carried out.

### Discussion

In this report, a man returning from South-Africa, with increasing cases of malaria [8], with imported *P. falciparum* malaria was initially classified as suffering from a common viral infection and allowed to return home. The patient's clinical course was eventually more classic for malaria as he returned with very high fever. The classical presentation of malaria is fever cycles associated with chills and rigors, although these are seen only in 50 - 70% of patients with malaria [9]. Malaria can be associated with a variety of manifestations ranging from simple febrile syndrome to lethal complications [9]. Atypical features include migraine, cough, bradycardia, postural hypotension, anaemia, thrombocytopenia, pancytopenia, cerebral involvement and rarely rupture of spleen in cases of huge splenomegaly [9]. Low platelet counts are commonly encountered in all types of malaria [10]. The patient showed a sharp increase of platelet numbers upon treatment.

This report serves to point to the complexity of disease manifestation and to the challenges of diagnosis for the doctor. Among *Plasmodium* species, *P. falciparum* is responsible for severe and fatal malaria [9]. The symptoms and signs of malaria can be wide and pose problem for the diagnosis. Malaria can present with unusual features and should be considered in front of any acute febrile illness unless excluded by lack of exposure and repeated negative thick and thin blood films.

Further, given the considerable geographical overlap between *P. falciparum* and G6PD deficiency, this report also serves a case in point to assess the presence and extent of protective association between G6PD and malaria. More than 400 million people are thought to be G6PD deficient in the world [5]. The global prevalence of X-linked G6PD deficiency is thought to be a result of selection by malaria, but studies have been unconvincing [7]. It has been found recently from a study in Tanzania that heterozygous girls, who were protected from severe and complicated *P. falciparum* malaria, might be the driving force for the positive selection of G6PD deficiency alleles [7]. Conversely, subjects homozygous for G6PD deficiency were found to be at a significantly higher risk of severe anaemia [7]. Although the patient had no criteria for intensive care admission, the possibility exists that he would perhaps not have contracted any malaria were him not G6PD deficient.

He also has alpha-thalassemia in his past medical history from testing during childhood in Great Britain, but laboratory testing revealed this to be negative. The G6PD trait was nevertheless confirmed. It has been hypothesised that there might exist a concordance between the several hemoglobinopathies and incidence of malaria parasite disease [11]. A better understanding of the factors associated with immunity and protection from malaria may contribute to better treatment by the development of vaccines and other therapies [11]. Furthermore, the occurrence of disease in spite of having taken drug prophylaxis and during travel to a non-endemic region namely the southern tip of Africa remain question marks that are unaccounted for in this case report.

The rapid diagnostic tests are based on detection of parasite HRP-2 (histidine rich protein-2), LDH (lactate dehydrogenase) and aldolase [12]. The SD Bioline Malaria Ag Pf/Pan test kit contains a membrane strip precoated with mouse monoclonal antibodies specific to HRP-II of *P. falciparum* on test line Pf region and with mouse monoclonal antibodies specific to LDH of *Plasmodium* species Pan (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*) on test line Pan region respectively [1]. The sensibility of the tests is evaluated at 88 - 99% for *P. falciparum*, which is even more difficult if parasitemia is low. In spite of such high values for sensibility, the patient's rapid tests revealed to be repeatedly negative, which was attributed to a lot defect confirmed by the company. These should be carefully analysed and points to

the need to keep doing initial and confirmatory tests with thick and thin slide films with a minimum of three at regular intervals of 6 - 12 hours in order to confirm the diagnosis or cure. In our network of hospitals in Brussels capital region in Belgium, 31 cases of malaria were treated in 2017. The defective kit used during a period of two months in the middle of 2017 was replaced.

### Conclusion

This report shows the multiple factors that intervene for malaria disease manifestation upon infection as well as to point to the challenges of diagnosis of the parasite infection. Furthermore, once malaria was confirmed, pharmacological treatment was also a challenge as the safety profile given the G6PD deficiency and the consequent need for strict monitoring was important. The unlikelihood of events leading to the disease as well as occurrence makes this case a rare one. In a context of increasing international travel for tourism and trade in which distant exotic regions are easier to reach, the relevance of proper prophylaxis should be highlighted in order to obtain individual protection. But even then, the protection is not disease-proof. As South Africa is not known as a cradle of malaria, patients going to this area should take chemoprophylaxis, with attention to screening for G6PD to be safely treated subsequently. Last but not least, patient and family anxiety regarding the course of the disease should not be ignored.

### Learning Points

- G6PD deficiency is a complex trait which can protect females but render males susceptible to more severe forms of malaria.
- G6PD deficiency can protect against uncomplicated malaria in African countries, but not severe malaria.
- South Africa, in spite of being a non-endemic area, is a country where chemoprophylaxis should strongly encouraged while visiting.
- Malaria diagnosis remains a challenge for the doctor from a semiological perspective.
- Platelet level is a reliable indicator of malaria presence and severity.
- Doxycycline prophylaxis is not disease proof.

### Disclosure

The authors have no conflict of interest to disclose

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