

Case Report

Hazardous Effects of Malaria for Patients Residing in Low-probability Malaria Areas: A Case Report and Critiques of the Literature for Cerebral Malaria

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Abstract

Despite decades of global and country commitments towards eradicating malaria, malaria remains the most hazardous parasitic disease and the most common cause of fever for humans, especially in tropical countries. *Plasmodium falciparum* causes 90% of malaria cases. Coma [Cerebral Malaria (CM)], acidosis, hypoglycemia, severe anemia, renal dysfunction, and pulmonary edema are the most common complications of malaria caused by *Plasmodium falciparum* and the most common cause of death related to malaria. People from less prevalent malaria areas are at high risk of developing these complications. A 16-year-old male from a low malaria transmission area was diagnosed with CM. Prior to developing CM, he was treated with Coartem. CM is a medical emergency and one of the forms of severe malaria. CM has high mortality and morbidity rates. Yet, international health-related agencies, funders, and policy-makers are unfamiliar with it. The continuous occurrence of CM validates the considerable need for global investment in malaria control and elimination programs. Early administration of Artesunate to all patients suspected of having severe malaria would reduce global malaria-related mortality and morbidity. Simple tests, such as the determination of malaria parasitic density either with thin or thick blood smears, may influence the proper management of all severe malaria cases. However, in clinical practice, the determination of malaria parasitic density is not routinely done. Further commitments are needed to ensure routine determination of malaria parasitic density for all suspected severe malaria cases. Moreover, further commitments are needed to guarantee the proper management of CM because it is a major cause of reversible encephalopathy in tropical countries.

Introduction

Since antiquity, malaria has been the most dangerous parasitic disease and the most common cause of fever and death for human beings. For many years, the World Health Organization (WHO) and various countries have had ambitions of eradicating malaria completely. However, malaria has only been eliminated in a few countries, such as the United States of America (USA), Canada, Europe, and Russia. Malaria causes approximately 2000 deaths each day, especially across the tropical and subtropical world [1]. A total of 198 million cases (within a range of 124 million to 283 million) of malaria were reported in 97 countries, territories, and areas in 2013, putting about 3.2 billion people at risk. About 584,000 (range: 367,000 - 755,000) persons died from the illness in sub-

Saharan Africa that same year, most of them youngsters under the age of five [2]. The vision of the Global Technical Strategy for Malaria 2016 - 2030 is to have "a World free of malaria" [3]. Reductions in malaria mortality rates of at least 40% worldwide by 2020 compared to 2015, reductions in malaria case incidence of at least 40% worldwide by 2020 compared to 2015, by 2020 elimination of malaria in at least 10 countries from which malaria was transmitted in 2015, and prevention of the re-establishment of malaria in all countries that are malaria free were stated as expected milestones in the battle against malaria. Regarding these milestones, many more are still required in order to completely eradicate malaria because, globally, there were estimated 241 million cases of malaria in 85 countries with malaria endemicity in 2020, up from 227 million in 2019, with the majority of this increase

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coming from nations in the WHO African Region. Malaria case incidence decreased from 81 in 2000 to 59 in 2015 and 56 in 2019, then increased to 59 in 2020 [4,5]. Possibly, the COVID-19 pandemic interrupted malaria healthcare-related services and provoked the spike in malaria in 2020. Six *Plasmodium* species, namely: 1) *Plasmodium falciparum* (*P. falciparum*), 2) *Plasmodium vivax*, 3) *Plasmodium ovale curtisi*, 4) *Plasmodium ovale wallikeri*, 5) *Plasmodium malariae*, and 6) *Plasmodium knowlesi*, cause malaria [6,7]. In Africa, *P. falciparum* predominates [8], whereas in many parts of Asia and the Americas, *P. vivax* is more common [1]. 93% of malaria deaths and 99.7% of malaria cases in Africa are due to *P. falciparum*, according to estimates of the global prevalence of malaria [5]. Coma [Cerebral Malaria (CM)], acidosis, hypoglycemia, severe anemia, renal dysfunction, and pulmonary edema are the most common complications of malaria associated with *Plasmodium falciparum* and, in fact, the most common cause of death associated with malaria. People from low-prevalent malaria areas are at high risk of developing these conditions because, in areas where malaria prevalence is low, full protective immunity for malaria is not acquired.

Kabale district is one of the 135 districts of Uganda. Kabale district is located in the south-western part of Uganda and in the greater Kigezi sub-region. The temperature in Kabale ranges from 9 to 23 °C. Its altitude is about 2000 m. Sporogony refers to the asexual reproductive phase of a malaria parasite that occurs outside the host. Classically, the completion of the malaria parasite's life cycle takes place within the anopheles mosquitoes—from gametocyte ingestion to subsequent inoculation, and this process lasts about 8 days - 30 days. High ambient temperatures are a responsible factor for the completion of sporogony [1]. In order to transmit malaria, the mosquito must survive for >7 days [1]. Sporogony is not completed at cooler temperatures (<16 °C for *P. vivax* and <21 °C for *P. falciparum*), thus transmission does not occur below these temperatures or at high altitudes [1]. Like other tropical and subtropical countries, in Uganda, malaria remains a dangerous parasitic disease. For the financial year (FY) 2020 - 2021, malaria was still the foremost condition among all Outpatient Department (OPD) diagnoses for all ages, accounting for 29.1% of all OPD attendances [9]. Moreover, in that FY, about 635,586 (39.5%) malaria cases were admitted, and malaria took about 5,017 (10.9%) lives of Ugandans, both male and female, young and adults [9]. The 2019 pediatric malaria-related data revealed a prevalence of 34% in Karamoja and 22% in West Nile, while the prevalence of malaria in the Kigezi region was less than 1% [10]. Low ambient temperatures and higher altitudes have been malaria-protective factors in the Kigezi region, including the Kabale district. However, outbreaks and transmissions of malaria have occurred in the Kabale district. Moreover, because some people of Kabale travel to malaria-endemic areas; malaria is commonly encountered in healthcare facilities that are in

Kabale district. Dangerously, the people from Kigezi Region who contract malaria are at higher risk of developing severe malaria because they have not fully acquired protective immunity specific to fighting malaria parasites. We report a 16-year-old male from Kabale district that presented with a one-week history of fever and a one-day history of altered mental status, and he was diagnosed with CM.

Case presentation

A 16-year-old male presented with a one-week history of fever and a one-day complaint of altered mental status. Further, history revealed that one week prior to developing these fevers, he had returned from Tungamo district. Because of his fever, he visited a nearby clinic; a positive Malaria Rapid Diagnostic Test (MRDT) was noted, and he was started on an antimalarial drug (Coartem). The patient's attendant reported adherence to the prescribed Coartem. However, the patient's condition did not improve. The fever remained high; the patient was again taken to the nearby Health Center II and later to Health Center III. At Health Center III, the patient developed altered mental status along with difficulty breathing. He lost the ability to walk, and he could not sit unaided. Emergently, the patient was referred to Kabale Regional Referral Hospital. He was admitted to the internal medicine department. A physical examination revealed a very sick-looking young male in respiratory distress. Temperature: 38.5 °C, Respiratory Rate: 24 cycles per minute, Oxygen Saturation: unstable with a fluctuation within the range of 80% - 92% at room temperature. Blood Pressure: 105/65 mmHg, Pulse Rate: 88 beats per minute. The malaria rapid diagnostic test was repeated and came back positive. The Complete Blood Count (CBC) results revealed a hemoglobin level of 6 g/dl; other parameters were normal. CM was diagnosed. Oxygen therapy, transfusion of 2 units of packed red blood cells, paracetamol, and IV Artesunate that was administered at 2.4 mg/kg at 0, 12, and 24 hours, and then every 24 hours until he could tolerate oral antimalarial medication, were instituted. While on the ward, he had five episodes of nose bleeding, which promoted intravenous administration of 2 g of tranexamic acid. On the second admission day, post-transfusion CBC revealed an Hb of 7 g/dL. Thus, another two units of packed red blood cells were transfused (though somehow not necessary). Profuse sweating was noted; however, the patient had regained appetite. He could drink sugar-containing drinks and eat, so sweating stopped. On day three, the patient regained the ability to walk and sit; respiratory distress stopped, and his mental state became normal. He improved, and on day four, he was discharged on an oral antimalarial drug.

Discussion

The main purpose of this case report and review of literature is to demonstrate that malaria has potentially hazardous clinical effects for people residing in low malaria transmission areas such as the 16-year-old male who contracted malaria.



Currently, few well-performed studies indicating the clinical outcomes for malaria patients who come from Kigezi Region have been done. Malaria can mimic other infectious diseases. At all levels of healthcare in the Kigezi region, healthcare professionals are always troubled in terms of probing malaria and other conditions that mimic malaria manifestations. Such trouble may be happening due to the lack of a clear case definition of malaria in relation to Kigezi people who contract malaria. Catastrophic outcomes have been observed for some patients who present with manifestations similar to those of malaria and are treated as malaria cases. Thanks to all Kigezi healthcare professionals who consider malaria and institute anti-malaria treatment for some suspected malaria cases. Developing clear case definitions for malaria in the Kigezi region may save many lives because that may help health workers differentiate malaria from other treatable conditions that mimic malaria.

The clinical manifestations of malaria are nonspecific, and they may include fever, lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches [1]. Closer scrutiny of the possible causes of symptoms and signs (such as fever) that mimic those of malaria is very important. Another diagnosis should be thought of in some cases of headache, chest pain, abdominal pain, cough, arthralgia, myalgia, or diarrhea [1]. For instance, for a patient who may present with headache, fever, photophobia, and a stiff neck, meningitis should be first thought of rather than malaria, because rarely does malaria cause stiff necks. CM, acidosis, severe anemia, renal dysfunction, and pulmonary edema are the most common causes of death linked to *P. falciparum* infections. Our patient had evidence of CM, anemia, and acidosis. Acidosis was ascertained with respect to being in respiratory distress, but the gold standard for objective confirmation of acidosis is to perform arterial blood gas tests. CM was evidenced by an altered mental state and extreme body weakness manifested by an inability to walk and sit unaided. Anemia was evidenced by weakness, low Hb, and respiratory distress. Having had nose bleeding may indicate that he was developing disseminated intravascular coagulation (the deadliest condition) because it is more common in low-transmission settings. Luckily, he recovered. Cytoadherence, rosetting, and agglutination are central to the pathogenesis of *P. falciparum* malaria, which results in signs, symptoms, and complications that develop due to the alteration of normal human physiology [6,11-14]. They lead to the sequestration of red blood cells containing mature forms of the parasite in vital organs (particularly the brain), where they hinder microcirculatory flow and metabolism. Those disturbances, in conjunction with the production of cytokines, activation of second messengers, and opening of the Blood-Brain Barrier (BBB), may lead to CM development. However, all these are reversible when appropriate management interventions are instituted as early as possible. CM caused by *P. falciparum* is the first cause of parasitic-related death worldwide, but it is a potentially

reversible encephalopathy [11] when early treatment is ensured. Other postulated hypotheses that describe how CM occurs include: 1) the permeability hypothesis which states that parasites generate toxic substances that increase the permeability of the BBB; thus, toxic substances enter into the brain and result in edema, coma, and death. 2) The cytokine hypothesis describes that, as a result of the breakdown of the merozoites, a glycolipid similar to an endotoxin is released, which provokes the production of cytokines. The presence of a high concentration of TNF-alpha in the serum of patients with CM supports this theory [12]. 3) Mechanical hypothesis states that the genesis of an obstruction via complex processes induced by *P. falciparum* and impairment of circulation could explain the coma.

Strongly, the use of microscopy with properly stained thick and thin blood smears is the gold standard for diagnosing malaria. The examination of the peripheral blood smear will give an indication of the parasite density as well as the species of parasite. Patients with high levels of malaria parasitemia (more than four percent or equal to or more than three + or more than 100,000 asexual parasitized red blood cells/ μ l) should be treated as severe malaria [15]. Rapid diagnostic tests (such as MRDT), which detect parasite antigens in the blood, are also effective in terms of diagnosing malaria. Specifically, histidine-rich protein II (HRP II) is an antigen produced by *P. falciparum*, and it is detected by MRDT, thus, if it is positive, confirms malaria caused by *P. falciparum*. Other malaria parasites or species produce Plasmodium Lactate Dehydrogenase (PLDH) and aldolase, a pan-malaria antigen for non-*P. falciparum* malaria which can also be used to detect them [10]. It has been confirmed that “the Pan RDTs can detect both *P. falciparum* and non-*P. falciparum* species but cannot differentiate between *P. vivax*, *P. ovale*, and *P. malariae*, nor can they distinguish pure *P. falciparum* infections from mixed infections that include *P. falciparum*. *P. falciparum* predominates in most countries in Africa, including Uganda, and that has led to a preference for the use of HRP II RDTs, which are specific to *P. falciparum*.”

After confirmation of malaria, treatment interventions depend on its severity, age, effectiveness, and availability of antimalarial drugs. It is much more important to holistically treat a whole patient than malaria. Thus, maintaining of airway, breathing, circulation, hypoglycemia (ABC) [16], and control and reversal of acid-base disturbance protocols are very important for all malaria cases. The World Health Organization asserts that all non-complicated malaria species should be treated with artemisinin-based combination therapy [17]. Coartem is the most commonly used artemisinin-based combination therapy to treat uncomplicated malaria. The most preferred combination is Artemether 20 mg-lumefantrine 120 mg (Coartem) = 1 tablet. These drugs interfere with the growth of parasites in the red blood cells of the human body. The patient should receive the initial dose, followed by the



second dose 8 hours later, and then 1 dose per oral Twice a day for the following 2 days. This patient had received Coartem prior to developing severe malaria. Adherence to the prescribed course was ensured. It was not clear whether non-responsiveness was due to malaria parasite resistance to Coartem, a higher density of malaria parasites (most likely this was the cause), or whether other factors were the cause of his apparent life-threatening CM. Other available combinations include Atovaquone 250 mg, and proguanil 100 mg (Malarone) = 1 adult tablet. By following WHO recommendations for severe malaria management [13,18], this patient was treated with intravenous Artesunate administered at 2.4 mg/kg at 0, 12, and 24 hours, and then every 24 hours until he tolerated oral antimalarial medication. He improved and was discharged on oral anti-malaria drugs.

Conclusion

Globally, malaria remains the most commonly occurring infectious disease. Dwellers in areas with higher malaria transmission may acquire immunity that may be important for fighting malaria. However, dwellers in low malaria transmission areas do not acquire such immunity. CM is a medical emergency and one of the forms of severe malaria. CM has high mortality and morbidity. Yet, international health-related agencies, funders, and policy-makers are unfamiliar with it. This case report describes a 16-year-old male from Kabale (Uganda) diagnosed with CM. Prior to developing CM, he was treated with Coartem, but that did not stop him from developing CM. The author firmly believes that non-responsiveness to Coartem was not due to malaria parasite resistance but rather because of the high density of malaria parasites. The continuous occurrence of CM validates the considerable need for global investment in malaria control and elimination programs. Early administration of Artesunate to all patients suspected of having severe malaria would reduce global malaria-related mortality and morbidity. Simple tests, such as the determination of malaria parasitic density either with thin or thick blood smears, may influence the proper management of all severe malaria cases. However, in clinical practice, the determination of malaria parasitic density is not routinely done. Further commitments are needed to ensure routine determination of malaria parasitic density for all suspected severe malaria cases. Moreover, further commitments are needed to guarantee proper management of CM because it is a major cause of reversible encephalopathy in tropical countries.

Ethical consideration

Permission to publish this case was obtained from the patient and his parents after explaining to them the goal and

possible benefits of publishing this case. They were assured that their names would not appear in a publication, and that publication would be for academic purposes.

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