THE ATLANTIC Journal of Medical Science and Research

Atlantic J Med Sci Res. 2023;3(2):76-80
DOI: 10.5455/atjmed.2023.02.09

Case Report

Chukwunonyerem Precious Duke-Onyeabo, Ngozi Nancy Onu, Chukwunonso Chigozie Iheji, Nneka Ogochukwu Nwokoye, Ikenna Kingsley Ndu

Enugu State University Teaching Hospital, Department of Paediatrics, Parklane, Enugu

Received: 06 February, 2023
Accepted: 03 April, 2023
Published: 17 May, 2023

Corresponding Author: Chukwunonso Chigozie Iheji, Enugu State University Teaching Hospital, Department of Paediatrics, Parklane, Enugu
Email: gozieprimenet@yahoo.com

CITATION
Duke-Onyeabo CP, Onu NN, Iheji CC, et al. Blackwater fever following artemether-lumefantrine administration in children in a malaria holoendemic region: A case series. Atlantic J Med Sci Res. 2023;3(2):76-80. DOI: 10.5455/atjmed.2023.02.09

Blackwater fever following artemether-lumefantrine administration in children in a malaria holoendemic region: A case series

Abstract

Aim: Blackwater fever is one of the severe forms of malaria that is infrequently reported. The association of blackwater fever with quinine is supported by its disappearance following the replacement of quinine with chloroquine. However, there seems to be a resurgence with recently introduced artemisinin-based antimalarials.
Case Presentation: This is a case series of four males aged 3 – 11 years who presented to our facility with features of intravascular hemolysis following the intake of appropriate doses of Artemether/Lumefantrine for malaria treatment. Two of the cases were transfused, and one had two sessions of hemodialysis, however, all recovered fully and remained stable during follow-up visits.
Conclusion: These cases underscore the need for a high index of suspicion for early detection of blackwater fever while using Artemether/Lumefantrine and the need for more post-market surveillance of the drug.

Keywords: Blackwater fever, artemether/lumefantrine, malaria

INTRODUCTION

Blackwater fever, characterized by acute intravascular hemolysis that presents clinically with dark-colored urine (hemoglobinuria), jaundice, fever, anemia, and renal failure, is one of the severe forms of malaria that is infrequently reported (1). Other features may include scanty or absent parasitemia on the peripheral blood smear, nausea, vomiting, circulatory compromise, and epigastric pain (1).

This syndrome was first reported among non-immune European expatriates living in malaria-endemic areas and with a history of irregular intake of quinine as a chemoprophylactic drug and inadequate treatment of attacks of P. falciparum malaria (2). Its disappearance supports the association between blackwater fever and quinine after 1950 with the replacement of quinine by chloroquine (3). Blackwater fever seemed to reappear at the end of the 1990s following the reintroduction of quinine as P. falciparum resistance to chloroquine developed (3). In the past, blackwater fever was rare in the indigenous population (2). However, recently, cases have been reported in people living in areas with stable malaria transmission who are supposed to have sufficient immunity against malaria (1,4). Studies across different malaria endemic regions have reported prevalence ranging from 2%-17% (1,5-7). In Nigeria, a prevalence rate of 3.7% was reported in Maiduguri and 19.1% in Ibadan (8,9).

The pathophysiology of blackwater fever is complex and not fully understood. It has been hypothesized that the hyper-hemolytic process characterizing blackwater fever may be an immune-mediated response to erythrocytes altered by quinine or the parasite, or both (double red blood cell sensitivity to antimalarial and P. falciparum), and accounting thus for the low or even absence of parasitemia (10).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency has also been implicated in the etiology of blackwater fever; however, its role is not clearly demonstrated, as blackwater fever has been reported in patients with normal erythrocyte G6PD levels (1). Cases of blackwater fever have been reported with other synthetic aryl amino alcohol antimalarials such as halofantrine, mefloquine, and lumefantrine (11,12). More recently, blackwater

fever has been recorded in patients taking artemisinin for malarial treatment (13). These case series highlight cases of blackwater fever in children treated with Artemether-Lumefantrine for malaria and demonstrate that early intervention improves the outcome in patients with this condition.

MATHODOLOGY

The admission case notes of four children who presented with a passage of cola-colored urine following administration of Artemether-Lumefantrine and managed at the Children's Emergency Room of Enugu State University Teaching Hospital (ESUTH), Enugu, South-east Nigeria over a three-month period, from July – August 2022 were reviewed. Relevant sociodemographic data, symptoms and signs, investigation results, treatment, and outcome were obtained (Table 1).(percent). SPSS 25 was used for statistical analysis.

CASE REPORT

Case 1

BD, an eleven-year-old boy, presented to the children's emergency room of ESUTH with a ten days history of high-grade intermittent fever with chills and rigors, three hours history of cola-colored urine, and abdominal pain. Two days following the onset of the fever, he was given Artemether-Lumefantrine (appropriate dose for weight) with minimal improvement. Following this, he was noticed to be passing cola-colored urine on account of which he was brought to the children's emergency room by his mother.

Examination at presentation revealed a male child conscious but lethargic, pale, and icteric with an axillary temperature of 40.4oC, epigastric tenderness, non-tender hepatomegaly, and blood pressure 105/66 mmHg. The malaria rapid diagnostic test done was reactive. A diagnosis of severe malaria with blackwater fever was made. The hemoglobin genotype was AS. Urinalysis showed urobilinogen (2+) and no RBC on microscopy. The total white blood cell count was 5,100/mm3, with 80% granulocytes, 18% lymphocytes, and 2% monocytes. The platelet count was 56,000/mm3 and hematocrit was 8.1g/dl. Thick blood film was positive for malaria. Initial Serum electrolyte showed elevated urea (118.8mg/dl) and elevated creatinine (5.04mg/dl). He was commenced on intravenous Artesunate and omeprazole.

Table 1. Patient characteristics and laboratory findings

CASES	AGE (YRS)	SEX	CLINICAL FEATURES				HB (g/dL)	MP BLOOD FILM
			FEVER	COLA-COLORED URINE	PALLOR	ICTERIA		
1	11	M	YES	YES	YES	YES	8.1	+
2	6	M	YES	YES	YES	YES	4.7	+
3	7	M	YES	YES	YES	YES	8.5	+
4	3	M	YES	YES	YES	YES	6.3	+

MP = Malaria Parasite; + = Positive

While on admission, the passage of cola-colored urine persisted; by the 5th day, he developed severe oliguria with a urine flow rate of 0.2mls/kg/hour. Serum urea and creatinine levels rose (urea;118.8mg/dl, creatinine; 141.6mg/dl). He had two hemodialysis sessions with normalization of urine output and serum urea and creatinine. He spent 24 days on admission and had normal urine output, serum electrolyte, urea, and creatinine levels at the 4-week follow-up visit.

Case 2

EP, a six-year-old male, was brought to the children's emergency room of ESUTH with a week's history of high-grade intermittent fever, six hours of history of the passage of dark-colored urine, and 2 hours of history of the paleness of the body. At the onset of symptoms, the patient was given oral antimalaria (Artemether-Lumefantrine).

Examination findings at the presentation showed a well-nourished male child in obvious respiratory distress, febrile, icteric, severely pale, tachypnea, and non-tender hepatomegaly. A diagnosis of severe malaria with black water fever was made. Urinalysis showed urobilinogen (2+), MRDT done was reactive, and urgent PCV was 14%. Hemoglobin genotype was AS, thick blood film was positive for malaria, and Serum electrolytes, urea, and creatinine were normal. Blood pressure 105/65mmHg. He was commenced on intravenous artesunate, transfused with sedimented red blood cells, and given full daily maintenance fluid. Urine output was good throughout admission. The patient improved with the resolution of all symptoms and was discharged home after spending one week in the hospital. He is yet to be seen on the follow-up visit.

Case 3

OB, a seven-year-old male, was brought to the children's outpatient clinic of ESUTH, with a one-week history of high-grade continuous fever, five-day history of abdominal pain and non-projectile, postprandial vomiting, and three days history of dark-colored urine, yellowish discoloration of eyes and progress paleness of the body. He was taken to a private hospital where he received a blood transfusion, intravenous fluid, and oral Artemether-Lumefantrine before presentation to our facility.

At presentation, he was conscious but irritable, febrile with an

axillary temperature of 38.5oC, moderately pale, and icteric. He had epigastric tenderness and non-tender hepatomegaly. His blood pressure was 119/77mmHg. A diagnosis of severe malaria with blackwater fever was made. Blood glucose was 88mg/dl, total white cell count was 6600/mm3, 61% granulocytes, 26% lymphocytes, and 3% monocytes. Platelet 50,000/mm3. Hematocrit was 8.5mg/dl. MRDT and thick blood film were positive for malaria parasites. He was placed on intravenous fluid and intravenous Artesunate. Urine output remained optimal throughout the hospital stay. Over the course of a five-day admission, his symptoms gradually resolved, and he was discharged in stable clinical condition. At the follow-up, two weeks after discharge he was in good condition.

Case 4

CC, a three-year-old male, was admitted through the children's emergency room of ESUTH with a seven-day history of high-grade intermittent fever. On account of this, he was given a tablet Artemether-Lumefantrine gotten from a patent medicine dealer without relief of symptoms. Five days into the illness, he was noticed to be unconscious as he stopped responding to calls, was passing cola-colored urine with a reduction in urine output, and also had yellowness of the eyes. He was taken to a private hospital where he received a blood transfusion and was subsequently referred to our facility.

At presentation, he was unconscious with GCS 7/15, tachypneic (54bpm), febrile with an axillary temperature of 39.2oC, moderately pale, and severally icteric. He had tachycardia (pulse rate of 154bpm) and a tender liver that was palpable 7cm below the coastal margin. His blood pressure was 95/61mmHg. MRDT and blood film were positive for malaria. A diagnosis of severe malaria anemia with blackwater fever was made.

Blood glucose was 109mg/dl, total white blood cell count was 22,180/mm3, neutrophils 78%, lymphocytes 20%, monocytes 2%, platelets 247,000/mm3. Hematocrit was 6.3mg/dl. Urinalysis was positive for urobilinogen. Serum electrolytes, urea, and creatinine were within normal limits. Liver transaminases were also normal. Cerebrospinal fluid analyses were not suggestive of CNS infections. He was commenced on intravenous artesunate, Ceftriaxone (discontinued after the CSF analyses result), and maintenance fluid. In the 10-day course of inpatient care, he had two more blood transfusions and maintained an optimal urine output. He was discharged upon recovery and is yet to be seen at the follow-up clinic.

DISCUSSION

Black water fever, previously an infrequently reported complication of malaria, especially among children in high transmission settings, appears to be on the rise (1,2,4,9,10,13). The four cases seen within three months in our center reflect the increasing number of cases reported among African children. While some authors have suggested the reintroduction of quinine in the treatment of multidrug-resistant malaria as a potential reason for this (1,3,10), others have linked this resurgence of black water to the introduction of artemisinin-based combination therapies (13,14).

Most of our patients were aged more than five years, consistent with earlier reports from Ibadan, Southwest Nigeria, Uganda, and DRC (2,9,14,15). This is difficult to explain as malaria severity tends to be worse in children under five. A plausible explanation for this is a hypothesis put forward by Rogier et al. (4) linking previous repeated exposure to antimalarial drugs to black water fever. Notably, all four patients in our case series were males. Gobbi et al. (1) and other researchers have noted a similar male preponderance among children presenting with black water fever (1,2,14). Previous reports, especially among adult populations, showed no gender predilection (3,16-18). However, considering the link between the male gender and G6PD deficiency and the hypothesized overlap between malaria, antimalarial administration and G6PD deficiency, black water fever may not necessarily be a separate entity from G6PD-related hemolysis and hemoglobinuria (1,4). Our inability to assay for the G6PD status was a major limitation of this study, as this may have lent further credence to this hypothesis. This may be the basis for more advanced studies in the future.

Clinically, all the patients in our study presented with fever, the passage of cola-colored urine, jaundice, some degree of anemia, and hepatomegaly. Similarly, most previous studies on blackwater fever reported hemoglobinuria, jaundice, and pallor as major manifestations (1,4,18,19). Acute renal failure was seen in the oldest (11 years) of our patients and this was severe enough to require hemodialysis. In 2014, among Congolese children, Bodi et al. (20) reported a higher preponderance of development of acute renal failure in the presence of black water fever among older children who were semi-immune to malaria compared to younger children. Cases of black water fever-related acute renal failure have also been documented in adult populations (16-18). This renal dysfunction probably occurs due to massive intra-vascular hemolysis, sudden onset of hypovolemia, and the deposition of hemoglobin pigments in the renal tubules (20).

The presence of fever, positive MRDT, and thick blood films positive for malaria in our patients suggest high malaria parasitemia (21,22). This, however, is at variance with early reports (2,4,19,23). Gobbi et al noted low or absent malaria parasitemia among Burundi children with black water fever (1). Similarly, Bodi et al. (2) observed a low level of malaria parasitemia among Congolese children with black water fever. These conflicting observations shed light on the complexity and poor understanding of the pathogenesis of the clinical entity known as black water and call for further work in this regard.

Artemether-Lumefantrine was the implicated medication in all our patients. Most reports on black water fever have solely attributed it to quinine (1-4,10,15-19). It has been postulated that contact of RBC with plasmodium and quinine metabolite produces

a neo-antigen which leads to the synthesis of autoantibodies named hemolysin responsible for the intravascular hemolysis and consequent hemoglobinuria was seen in black water fever (24). Another postulated mechanism of quinine-associated black water fever is the host/genetic mediated oxidative response to quinine metabolites (11). Artemisinin derivatives such as artemether, are known to have an endoperoxide bridge that can release free radicals when reacting with iron and thus may trigger oxidative stress-related intravascular hemolysis in susceptible individuals (11). More so, Lumefantrine which is a component of Artemether-lumefantrine is an aryl-amino-alcohol compound and has been implicated in the pathogenesis of black water fever (11,12). The exact mechanism for this remains elusive.

Our management included intravenous artesunate, blood transfusions, adequate fluid management, and hemodialysis for the child with acute renal failure. With these, we were able to achieve minimal morbidity and zero mortality among our patients. Currently, there are no standardized protocols/guidelines for the prevention and management of black water fever, thus leading to inconsistency in its management across various settings (14,17). Some authors have reported, in addition to the standard management of severe malaria, the use of parenteral steroids increases the likelihood of steroid complications (1,14,18). Therefore, there is a need to develop a standardized protocol for its management. The authors suggest the need to identify possible predictors of black water fever, such as G6PD deficiency, amongst others, following the administration of artemether-lumefantrine. Subsequently, the literature for this medication may need to be updated to reflect the need for caution before its use.

CONCLUSION

Black water fever is on the rise among children in malaria holoendemic regions. The WHO-recommended pharmacotherapy to treat uncomplicated malaria is increasingly implicated in its pathogenesis. A high index of suspicion is paramount in early detection and management. There is a need to develop a standardized protocol for its management. An adequate understanding of the pathogenetic mechanism underlying black water fever will guide the emergence of its treatment protocol. Furthermore, more elaborate post-market surveillance of Artemether-Lumefantrine should be instituted to detect and document black-water fever as a possible adverse effect of the drug.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

REFERENCES

1. Gobbi F, Audagnotto S, Trentini L, et al. Blackwater fever in children, Burundi. Emerg Infect Dis. 2005;7:1118-1120.
2. Bodi JM, Nsibu CN, Longenge RL, et al. Blackwater fever in Congolese children: a report of clinical, laboratory features and risk factors. Malaria J. 2013;12:1-7
3. Bruce-Chwatt LJ. Quinine and the mystery of blackwater fever. Acta Leiden. 1987;55:181-96.
4. Rogier C, Imbert P, Tall A, et al. Epidemiological and clinical aspects of blackwater fever among African children suffering frequent malaria attacks. Trans R Soc Trop Med Hyg. 2003;97:193-7.
5. Idro R, Aloyo J, Mayende L, et al. Severe malaria in children in areas with low, moderate and high transmission intensity in Uganda. Trop Med Int Health. 2006;11:115-24.
6. Gbadoe AD, Kini-Caussi M, Koffi S, et al. Evolution of severe pediatric malaria in Togo between 2000 and 2002. Med Mal Infect. 2006;36:52-4.
7. Ekvall H, Arese P, Turrini F, et al. Acute haemolysis in childhood falciparum malaria. Trans R Soc Trop Med Hyg. 2001;95:611-7.
8. Sabine G, Bala YH, Suleimon M, Gunnar H. Malaria prevalence and outcome in the in-patients of the Paediatrics Department of the State Specialist Hospital (SSH), Maiduguri, Nigeria. J Trop Paed. 1998;44:109-13.
9. Ajetunmobi WA, Orimadegun AE, Brown BJ, et al. Haemoglobinuria among children with severe malaria attending tertiary care in Ibadan, Nigeria. Malar J. 2012;11:336.
10. Niyomwungeri R, Nyenyeri LD, Menelas N, et al. Blackwater fever: Re-visiting this nearly forgotten complication of malaria. Rwanda Med J. 75:1-3.
11. Huggan PJ, Ng CH, Ho J, et al. A case of blackwater fever with persistent plasmodium falciparum parasitaemia detected by PCR after artemeter-lumefantrine treatment. Malaria J. 2018;17:1-8.
12. Merat S, Lambert E, Vincenti-Rouquette I, et al. Case report: combination artemether-lumefantrine and haemolytic anaemai following a malarial attack. Trans R Soc Trop Med Hyg. 2003;97:433-4.
13. Olupot-Olupot P, Engoru C, Uyoga S, et al. High frequency of blackwater fever among children presenting to hospital with severe febrile illnesses in eastern Uganda. Clin Infect Dis. 2017;64:939-46
14. Paasi G, Ndila C, Okiror W, et al. Characterising childhood blackwater fever and its clinical care at two tertiary hospitals in eastern uganda. 2021.
15. Kunuanunua TS, Nsibu CN, Bodi JM, et al. Severe malaria in children: A descriptive report from Kinshasa, the Democratic Republic of Congo. J Trop Pediatr. 2015;61:272-8.
16. Mahamadou D, Hassane DM, Zeinabou MT, et al. A report of four cases of blackwater fever after quinine treatment at Zinder National Hospital, Niger Republic. Case Rep Infect

Dis. 2019.

17. Van den Ende J, Van den Ende J, Coppens G, et al. Recurrence of blackwater fever: triggering of relapses by different antimalarials. Trop Med Int Health. 1998;3:632-9.
18. Brunee F, Gachot B, Wolff M, et al. Resurgence of blackwater fever in long-term European expatriates in Africa: report of 21 cases and review. Clin Infect Dis. 2001;32:1133-40.
19. Chau TT, Day NP, Van Chuong L, et al. Blackwater fever in southern Vietnam: a prospective descriptive study of 50 cases. Clin Infect Dis. 1996;23:1274-81.
20. Bodi JM, Nsibu CN, Aloni MN, et al. Black water fever associated with acute renal failure among Congolese children in Kinshasa. Saudi J Kidney Dis Transpl. 2014;25:1352.
21. Ogunfowokan O, Nwajei AI, Ogunfowokan BA. Sensitivity and specificity of malaria rapid diagnostic test (mRDT CareStatTM) compared with microscopy amongst under five children attending a primary care clinic in southern Nigeria. Afr J Prim Health Care Fam Med. 2020;12:1-8.
22. Sani UM, Jiya NM, Ahmed H. Evaluation of a malaria rapid diagnostic test among febrile children in Sokoto, Nigeria. Int J Med Sci. 2013;3:434-0.
23. WHO: World Malaria Report. 2011, Geneva: World Health Organization, http://www.who.int/malaria/world_malaria_report_2011/en/
24. Bodi JM, Nsibu CN, Hirayama K. Immunogenetic Mechanisms of Black Water Fever: Article Review. Gene Technol. 2021;10:1-8.