Prevalence and Determinants of Black Water Fever in Malaria

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ABSTRACT

BACKGROUND

Study on black-water fever in malaria is less common in India. Early diagnosis and treatment can save the life of the patient. Therefore, we studied the clinical features, risk factors and outcome of black-water fever with malaria.

METHODS

The study was carried out at Department of Medicine, VIMSAR, Burla, Sambalpur, Odisha. All patients of fever with black water fever with in 7 days duration were enrolled investigated for malaria, Biochemical investigations were done, and clinical feature and outcome were analysed. Diagnosis of malaria was done by blood smear and black water fever was diagnosed by ortho-tolidine test. G6PD deficiency test was also done.

RESULTS

During the study period, 100 patients of malaria were evaluated out of which 10 patients of black-water fever were found. The age group mostly affected was 20-40 years; among them 60% were male, and 40% were female. 80% of patients were cured and 20% patient died.

CONCLUSIONS

Among black water fever patients, *Plasmodium falciparum* was most common cause. It was seen in more than the cases i.e. 60% and *Plasmodium vivax* species was found in 20% of cases.

KEYWORDS

Blackwater Fever, *Plasmodium falciparum, Plasmodium vivax*, G6PD Deficiency

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BACKGROUND

Malaria is a common vector-borne disease in India, Malaria is transmitted by Anopheles mosquito and the parasite responsible are *Plasmodium falciparum* and *Plasmodium vivax* species. Black water fever is one of the complications of malaria. It was estimated that malaria causes more than 228 million cases in year 2018.[1] BWF is commonly associated with *Plasmodium falciparum* but it is also associated with *Plasmodium vivax*.[2] Recurrence of blackwater fever or triggering of relapses by different anti-malarials (five cases of BWF) were described all of whom had history of recent quinine therapy. In two cases a second haemolytic crisis was induce by halofantrine.[3] A case of blackwater fever with persistent *Plasmodium falciparum* parasitaemia which was detected by PCR after artemether-lumefantrine treatment. Blackwater fever is a complication of malaria infection characterised by a syndrome of febrile intravascular haemolysis. Falciparum malaria can be complicated by black water fever. BWF is a severe clinical syndrome characterised by intravascular haemolysis, haemoglobinuria, and acute renal failure from massive quinine induce haemolysis.[4] there is a report of four cases of blackwater fever after quinine treatment at Zinde National Hospital Niger Republic. BWF is a rare but serious complication of malaria that is a consequence of anti-malaria treatment.[5]

There is resurgence of black water fever in long-term European expatriates in Africa. BWF is a clinical syndrome characterized by intra vascular haemolysis, haemoglobinuria and acute renal failure. In blackwater fever, acute intravascular haemolysis has almost disappeared since quinine is no longer used in malaria chemoprophylaxis. A study reports a case of intravascular haemolysis after treatment with Halofantrine of *Plasmodium falciparum.*[7] G6PD deficiency is also associated with BWF which is reported in a study.[6] in a prospective study of 50 Vietnamese patient with BWF, all patients had fever and haemoglobinuria. BWF was associated with quinine ingestion in 28 patients. G6PD was seen in 27 patients and concurrent malaria infection in 16 patients.[8] But studies on Blackwater fever are less in number in India and are limited to few case reports. Therefore, we wanted to determine the incidence, risk factors, clinical presentation, and outcome of malaria with black-water fever.

METHODS

We have conducted the study at VIMSAR, Burla, Odisha, India, during the period July 2016 - Aug 2018, after taking clearance from the ethical committee. During the study, period all patients who attended the OPD of Department of Medicine and Emergency Department with history of fever with black-water fever of <7 days duration were included in the study. All patients were investigated for malaria and black-water fever and were admitted for observation. The diagnosis of malaria was made with peripheral blood smear (thick and thin) stained with Giemsa stain for detection of malaria parasite. And diagnosis of black-water fever was done using ortho-tolidine test.

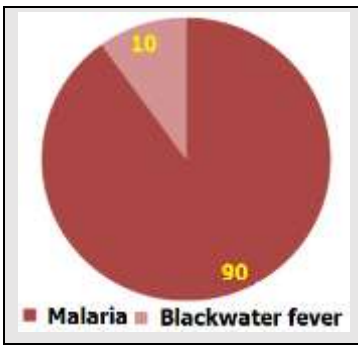

Figure 1

Detailed history was obtained. Detailed clinical examination was done. Relevant laboratory investigations were done in all cases. We collected blood at the time of admission for complete blood count (CBC), fasting blood glucose, blood urea, serum creatinine, sodium, potassium, bilirubin, serum glutamate-oxaloacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT) and alkaline phosphate (ALP), HIV, HBsAg, HCV, serum LDH, Coombs test, G6PD screening test, sickling test, urine test for colour, urine sugar, albumin and phosphate. Microscopic examination of urine for haemoglobin, and ortho-tolidine test for confirmation of black colour urine were also done. The parasite count made from the peripheral blood smear was expressed as the number of asexual parasites per micro litre of blood and was calculated from the number of parasitized cells per 200 leucocytes in a thick film i.e. number of parasites x total leucocyte count/200. CBC and parasitic count were repeated every 24 hrs. till the normalization of the platelet count, normalization of colour of urine and to know the parasitic clearance. Temperature was recorded every 12 hrs. to assess fever clearance time. All patients were followed up for 2 weeks.

During the period of study 100 patients of malaria were included. Patients of sickle cell anaemia, incompatible blood transfusion, snake bite, vigorous exercise, leptospirosis statin treatment were excluded from the study. Patients with history of treatment with quinine or lumefantrine were included in the study out of which 10 patients were diagnosed black water.

RESULTS

Predominant age group affected was 20-40 years, male patients were 60% and female were 40%. *Plasmodium falciparum* was the most frequently observed species it was seen more than half of the cases i.e. 60%, *Plasmodium falciparum, vivax* species were found in 20% of cases. Mixed infection consisting of both *P. falciparum* and *P. vivax* was observed in 20% of cases.

Patients treated with quinine were 50% and patients treated with Lumefantrine were 20% among those who developed black water fever and G6PD deficiency was seen in 30% who developed black water fever.

Sl. No.	Age in Year	Male	Female	Total
1.	20-25	1	1	2
2.	26-30	2	2	4
3.	31-35	1	1	2
4.	36-40	2	0	2
	Total	6	4	10

Table 1. Age and Sex Distribution

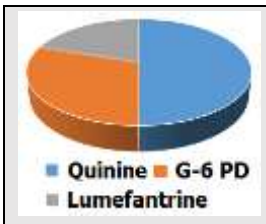

Figure 2. Risk Factor for Black Water Fever

Fever was present in almost all patients. Second most common symptom was chills and rigor in 70% of cases. Headache was presents in 60% of cases. Nausea and vomiting were present in half (50%) the cases. Muscular pain was present with 30% of patients and 30% of cases presented with pain abdomen. Black colour urine was the constant finding. It was seen in all patients. Pallor is the second most common finding seen in 80% of cases. Icterus was present in 70% of cases. Half (50%) of the patients had hepatomegaly and 40% patients had splenomegaly. Mean haemoglobin is 7.4 and mean haematocrit is 26.90. This indicates that most of patients developed anaemia due to black-water fever. 86.7 was the mean platelet count; mean leucocyte count was 17.1; leukocytosis may be due to other concomitant infection.

From literature we know that quinine is associated with black-water fever. In this study it was found in 30% of cases. Chau THH et al[8] found that 56% had h/o quinine use. Lumefantrine was associated with 20% cases seen in study by Fabrice Brunnel et al.[6]

Symptom / Physical Finding	No. & (%) of Patients
Fever	10 (100)
Chills and Rigor	7 (70)
Headache	6 (60)
Nausea and Vomiting	5 (50)
Muscular pain	3 (30)
Pain abdomen	3 (30)
Pallor	8 (80)
Icterus	7 (70)
Hepatomegaly	5 (50)
Splenomegaly	4 (40)

Table 2. Symptoms and Physical Findings in BWF

Fever was present in all patients(100%) in our study the same as study conducted by Chau THH et al[8], chills and rigors were present in 70% of cases, whereas it was present in 77% of cases in their study, headache was present in 60% in our study where as it was present 78% in Chau TTH et al study,[8] nausea and vomiting was present in 50% cases in our study it was 45% in their study. Percentage of nausea and vomiting was high because of treatment with oral drugs that might have led to gastritis. Muscular pain was present in 30% of cases; it was present in 40% in study Black colour urine was present in both studies. Pallor was present in 80% of cases where as it was present in 50% of cases in Chau THH et al study.[8] It may be due to more haemolysis in this study in compare to Chau THH et al study.[8] Icterus was comparable in both study hepatomegaly was present 50% of cases in both the studies, 40% patient had splenomegaly in our study where as it was 34% in Chau THH et al study[9] mean serum creatinine in black water fever (BWF) was 3.68, mean serum bilirubin was 3.88, mean serum LDH of 1919.70 indicate intra vascular haemolysis. Most common outcome in BWF was anaemia it was present 90% of cases out of which 66% received blood transfusion jaundice was second most common outcome is seen in 70% of cases. 50% of patient developed acute kidney injury (AKI), out which 60% of patient required haemodialysis (HD),[9] blood Transfusion (BT) in 66% of patient, Inj. Artesunate given to all patients as per WHO guidelines,[10] cure rate was 80% and 20% patient were died in this study.

Outcome	Present Study	Chautth et al[9]
Anaemia	90%	88%
Jaundice	70%	80%
AKI	50%	42%
Haemodialysis (HD)	60%	15.6%
Blood transfusion (BT)	66%	46%
Cure	80%	98%
Death	20%(2)	2%(1)

Table 3. Showing Outcome and Comparison in Different Studies

DISCUSSION

The present study showed that blackwater fever is not an uncommon complication. Prevalence of blackwater fever in this study was 10% whereas in the study conducted by Chau TTH et al[8] it was found in 32%, and one case was reported in the study by SN Biswas et al.[11] Black water fever a rarely encountered clinical entity by Chatterjee KD[12] In this study G6PD deficiency was found to be a risk factor of blackwater fever with odds ratio of 4.33. 30% patients of (BWF) had G6PD deficiency. Whereas study conducted by Chau THH et al[8] found G6PD deficiency in 54% cases but no patient were reported with G6PD deficiency in study Bruneel F et al.[6] Anaemia was the most common clinical feature in our study same with Chau TTH et al study,[8] percentage of blood transfusion was more in our study compare to Chau TTH et al study.[8] This may be due to more percentage of patients requiring blood transfusion during haemodialysis. In this study jaundice was present in 70% of cases whereas it was 80% in the study of Chau THH et al[8] percentage of patients developing acute kidney injury (AKI) was comparable in both the studies, but percentage of patients requiring haemodialysis was more in this study. This may be due to a greater number of patients in oliguric renal failure in our study, out of 10 patients 8 (80%) were responded to Inj. Artesunate and Blood transfusion and haemodialysis and cured and 2 patients died. mortality rate was 20% in this study. Study by Chau TTH et al[8] found the mortality rate was 2%. It may be due to less no of patient in our study.

CONCLUSIONS

There are very few studies from India studying blackwater fever in malaria. Prevalence is higher in males with most

people in the age group of 2nd to 4th decade of life. Though *Plasmodium falciparum* is the most common malarial species with which it is seen, it is also seen in *Plasmodium vivax* infections. BWF is also associated quinine, lumefantrine and G6PD deficiency. 80% of the patients responded to artesunate treatment and mortality rate is 20%.

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