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ORIGINAL ARTICLE

Urinary bile casts in bile cast nephropathy secondary to severe falciparum malaria

Manoj Kumar Mohapatra[1], Ashok Kumar Behera[1], Purna Chandra Karua[1], Prafulla Kumar Bariha[1], Ashutosh Rath[1], Kailash Chandra Aggrawal[2], Snigdha Rani Nahak[2] and Santosh Shankar Gudaganatti[2]

[1]Department of Medicine, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India and [2]Department of Pathology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India

Correspondence and offprint requests to: Manoj Kumar Mohapatra; E-mail: mohapatra.manoj@rediffmail.com

Abstract

Background: Severe cholestatic jaundice may complicate with bile cast nephropathy (BCN) causing severe acute kidney injury (AKI). In this study, we investigate BCN in severe falciparum malaria complicated with jaundice and AKI.

Methods: This prospective study was conducted in a tertiary health care institution with high prevalence of malaria. A cohort of 110 patients with falciparum malaria complicated with cerebral malaria, jaundice and AKI were enrolled. Species diagnosis was made from peripheral blood smear or rapid diagnostic test. Severe malaria was diagnosed from WHO criteria. BCN was diagnosed with the detection of bile casts in urine or in biopsy. The recovery pattern and outcome with and without BCN was assessed.

Results: Out of 110 patients, 20 (18.2%) patients had BCN and 15 (13.6%) patients had hepato-renal syndrome. Patients with BCN had high conjugated bilirubin (26.5 ± 4.1 mg/dL), urea (75.9 ± 10.3 mg/dL) and creatinine (7.2 ± 0.8 mg/dL), longer duration of illness (6.4 ± 1.1 days), higher mortality (25.0%) and prolonged recovery time of hepatic (9.6 ± 2.4 days) and renal dysfunction (15.1 ± 6.5 days) compared with patients without BCN.

Conclusions: Prolonged duration of illness and increased bilirubin cause BCN among patients with severe falciparum malaria with jaundice and AKI, which is associated with high mortality and morbidity.

Key words: bile casts, cholemic nephrosis, hepato-renal syndrome, jaundice-related nephropathy

Introduction

Malaria, which is a protozoal disease caused by infection with the parasite of genus *Plasmodium* and is transmitted to humans by the bite of certain species of infected female anopheline mosquitoes, remains a major global health problem, affecting about 200 million people and resulting in about 80 000 deaths annually [1].

Out of all species of *Plasmodium* that cause human malaria, *Plasmodium falciparum* is notorious for its potential to develop various complications leading to severe malaria and death [2, 3]. Cerebral malaria, anemia, jaundice and acute kidney injury (AKI) are common clinical variants of severe malaria, which can manifest alone as single organ dysfunction or in combination as

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multiorgan dysfunction. AKI is invariably associated with jaundice and cerebral malaria and is reported to have high mortality that ranges from 20 to 40% [4–6].

Apart from malaria, many acute and chronic diseases of the liver also cause renal dysfunction without any structural changes, which is known as hepatorenal syndrome (HRS) [7]. In contrast, obstructive jaundice with AKI exhibits tubulointerstitial nephropathy on biopsy, which is described as 'cholemic nephrosis' (CN) or bile nephrosis [8, 9].

Cholestasis, which may be extrahepatic or intrahepatic, has been implicated in CN [10, 11]. Extrahepatic cholestasis is characterized by mechanical obstruction to bile flow in the biliary tract causing CN, which has been proved experimentally in common bile duct ligated (CBDL) dogs and rats, and recently in mice [12–14]. Intrahepatic cholestasis is functional in nature and is the consequence of disturbances in canalicular excretion and sinusoidal uptake of bile, and found in advanced liver failure [15]. Therefore, it had not been linked to CN until some clinical studies revealed tubular abnormalities in kidney among patients with jaundice [11]. Furthermore, this was supported by an autopsy study that showed 30% of patients with HRS with advanced liver diseases had structural changes in kidney similar to CN [16]. The condition has been re-described as jaundice-related nephropathy (JRN), bile cast nephropathy (BCN) and cholemic nephropathy [11, 14, 16]. BCN has been described in various liver diseases including cirrhosis of liver, subacute hepatic failure, infectious mononucleosis, alcoholic liver disease, stanozolol toxicity and as a complication of colo-rectal malignancy [16–22]. The aforementioned studies are limited to case reports and autopsy. However, no prospective data are available as regards its occurrence and outcome in any particular disease condition. Because of the frequent occurrence of AKI and jaundice in severe malaria, we undertook this prospective study to find out the incidence and prognostic significance of BCN in patients with severe falciparum malaria.

Materials and methods

Study site

We carried out this prospective, observational study in the Department of General Medicine, VSS Institute of Medical Science and Research, Burla, Sambalpur, Odisha, India, from October 2014 to September 2015. The state of Odisha is situated along the Bay of Bengal and extends from 17.49°N to 22.34°N latitude to 81.27°E to 87.29°E latitude, and the study site is situated between the geographical co-ordinates of 21.50 N and 88.37 E. Malaria is endemic in this state, and the maximum number of deaths due to falciparum malaria in India have been reported from this state [23].

Case selection, case definition and exclusion criteria

We enrolled 110 consecutive patients of severe falciparum malaria with cerebral malaria, jaundice and renal failure for this study. The diagnosis of falciparum malaria was made by detection of the asexual form of the parasite in a Giemsa-stained peripheral blood smear or by the rapid diagnostic test. Cerebral malaria, jaundice and renal failure were diagnosed when the Glasgow Coma Scale was <11, serum bilirubin was >3.0 mg/dL and serum creatinine was >3.0 mg/dL or blood urea >20.0 mg/dL, respectively, according to the WHO guidelines [2]. The diagnosis of BCN was made by the detection of bile casts in the urine and/or kidney biopsy showing bile casts in Hall's stain [16]. Cholestatic jaundice was defined when conjugated bilirubin was more than 50.0% of total bilirubin with raised alkaline phosphatase and exclusion of surgical obstruction by abdominal ultrasonography [24]. HRS was diagnosed according to International Ascites Club criteria, 2005 [25].

On the day of admission, we carried out the clinical examination and investigations of all enrolled patients, and recorded the data. We assumed the day of fever as the onset of malaria and the time of hospitalization as the initiation of treatment, and the interval between the two as the fever to treatment interval.

Patients with severe falciparum malaria without jaundice and renal failure, suffering from chronic kidney disease, chronic liver disease, acute viral hepatitis, sickle cell disease, *Plasmodium vivax* malaria or mixed species malaria were excluded from study.

Investigations

On admission, blood was drawn for complete blood count, glucose, urea, creatinine, bilirubin, alanine-amino transferase (ALT), aspartate-amino transferase (AST), alkaline phosphatase (ALP), sodium and potassium. For detection of bile casts, 10 mL of urine was centrifuged at 2000 r.p.m. for 20 min and examined under a microscope after discarding the supernatant. The number of bile casts was calculated in 10 high power fields. Fifty high power fields were examined before declaring that the urine sample was negative for bile casts. We examined the urine twice daily for 3 days. An autopsy was done in one case, and post-mortem biopsy was done in two cases. The tissue was stained with HE stain and Hall's stain for detection of bile casts.

The parasitic count was calculated from the numbers of parasitized cells per 200 leukocytes in a thick film stained with Giemsa stain, i.e. number of parasites × total leukocyte count/200, and was expressed as number of asexual parasites per microliter of blood.

Treatment and follow-up

All patients were treated with an injection of Artesunate at the dose of 2.4 mg/kg body weight intravenously at the time of admission, then at 12 and 24 h, then once a day until the patient could take medication orally [26]. Hemodialysis was done as per requirement. Electrolyte abnormalities and acid–base imbalance were treated appropriately.

All patients were followed up weekly for 6 weeks after discharge from the hospital and subjected to clinical examination, parasitological test and renal function tests during each visit.

The statistical analysis was performed using IBM SPSS Statistics Version 20. The comparison between groups was made with the *t*-test. A P-value of <0.05 was considered to be statistically significant.

Results

Study participants

We enrolled 110 cases (80 males and 30 females) of severe falciparum malaria with cerebral malaria, jaundice and renal failure. Of these, BCN and HRS were present in 20 (18.2%) and 15 (13.6%) patients, respectively. The remaining 75 (68.2%) patients had other causes of AKI. Patients with severe malaria with bile casts are classed as Group A ($n = 20$, 18.2%) and without casts, including the patients with HRS, are classed as Group B ($n = 90$, 81.8%). The biochemical investigations showed that patients of Group A have increased blood urea, serum creatinine, serum bilirubin, conjugated bilirubin and ALP compared with Group B (Table 1). The serum albumin was comparable in both groups. With further analysis of Group A patients ($n = 20$), we found that 16 (80.0%) patients had bilirubin >20.0 mg/dL (26.5 ± 4.1 mg/dL) and 4 (20.0%) patients had serum bilirubin <20.0 mg/dL (15.8–18.8 mg/dL with mean 17.3 ± 1.1 mg/dL) with presence of bile

Table 1. Demographic and biochemical parameters of patients

Variables	Bile cast present (Group A), $n = 20$	Bile cast absent (Group B), $n = 90$	P-value
Age (years)	30.3 ± 6.8	29.4 ± 6.6	0.6
Sex (M/F)	12/8	68/22	
Hemoglobin (g/dL)	7.4 ± 1.4	7.4 ± 0.96	0.7
Parasite (no/cmm)	6095.0 ± 1680.7	5745.0 ± 1153.2	< 0.01
Bilirubin total (mg/dL)	24.7 ± 5.2	7.8 ± 3.1	<0.001
Bilirubin direct (mg/dL)	14.2 ± 5.3	4.2 ± 1.9	<0.001
AST (IU/L)	106.0 ± 14.4	97.5 ± 10.5	0.5
ALT (IU/L)	104.7 ± 15.5	95.0 ± 10.1	0.4
ALP (IU/L)	290.5 ± 13.9	221.5 ± 20.1	<0.01
Albumin (g/dL)	3.6 ± 0.4	3.7 ± 0.3	0.7
Blood urea (mg/dL)	75.9 ± 10.3	54.4 ± 17.8	<0.001
Serum creatinine (mg/dL)	7.2 ± 0.8	5.4 ± 0.7	<0.001
CRT (days)	4.1 ± 0.6	3.9 ± 0.9	0.8
JRT (days)	9.6 ± 2.4	6.4 ± 1.4	<0.001
RFRT (days)	15.1 ± 6.5	10.0 ± 3.9	<0.001
Death [n(%)]	5 (25.0)	9 (10.0)	<0.001

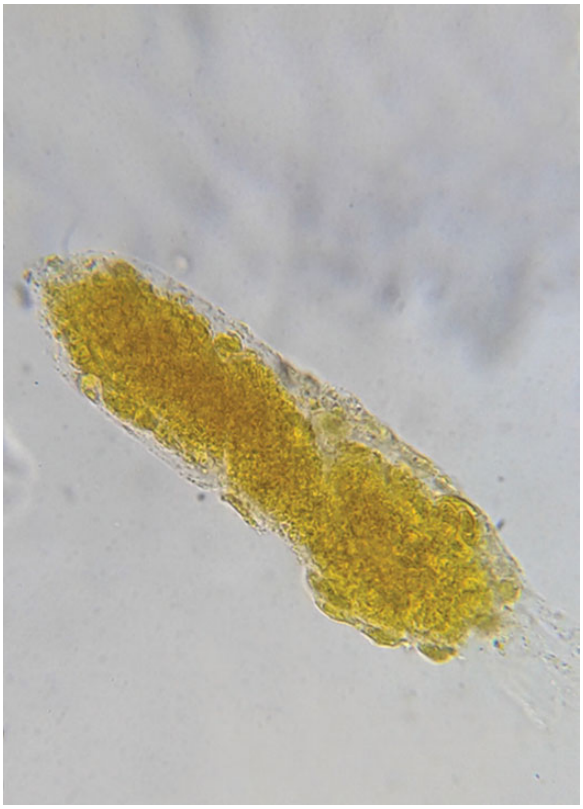

Fig. 1. Bile cast in urine.

cast. The latter patients had lower serum albumin (2.5 ± 0.3 g/dL) than the former (3.8 ± 0.4 g/dL) (P < 0.01). The parasitic count was comparable in both groups.

Urine analysis and histopathology

Urine analysis showed dark yellow urine, with proteinuria of variable degree, bile salts and urobilinogen. Microscopy of the centrifuged sample of urine showed bile-stained casts in all patients of Group A (Figure 1). The number of bile casts varied from 1 to 6 (3.8 ± 1.6, median 3) in 10 high power fields. Bile casts were detected within the first 24 h in 14 (70.0%) patients and within 48 h in the other 6 (30.0%) patients. We examined 50 high power fields before stating that the urine sample was negative for bile casts. We could not detect bile casts in urine after the onset of dialysis.

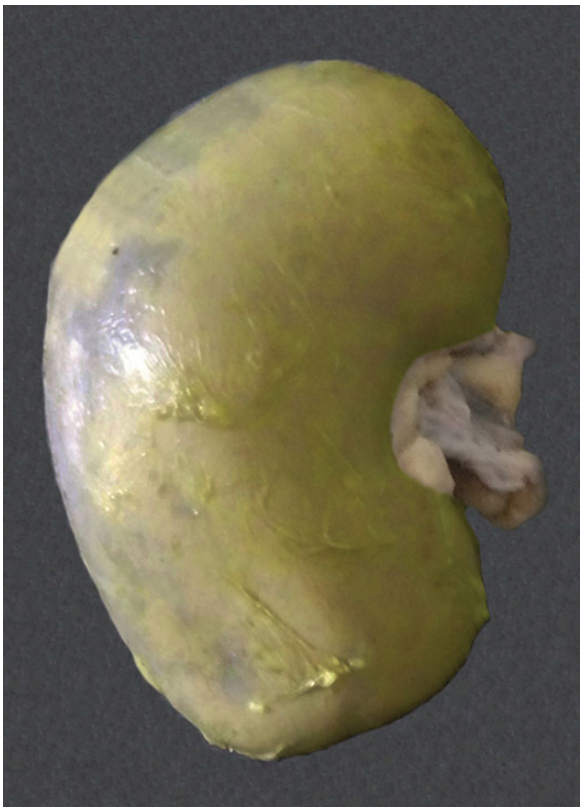

Fig. 2. Greenish yellow discoloration of kidney with BCN.

Autopsy was done in one patient. Formalin-preserved kidney showed green discoloration due to conversion of bilirubin to biliverdin. On longitudinal section, renal pyramids also looked yellowish green in color due to a higher concentration of bilirubin. Linear dark green streaks consistent with bile casts are present throughout the cortex and medulla (Figure 2).

Histopathology with HE stain showed numerous tubular casts at low magnification. In the high power field, the glomerular architecture was maintained. There was degeneration and attenuation of tubular epithelial lining suggestive of acute tubular necrosis. Some tubules contained bile casts and necrotic cellular deposits. Hall's stain showed yellow green acellular tubular casts in the distal nephron characteristic of bile cast.

In addition to Artesunate and other supportive measures, hemodialysis was performed in all cases (100.0%) of Group A ($n = 20$) and 58 (64.4%) patients of Group B with a total of 78 (70.9%) patients from both groups. The patients were subjected to dialysis daily for 3 h until the onset of diuresis.

Onset of BCN and outcome

The fever to treatment interval among subjects of Group A was prolonged (5–8 days, with a mean of 6.4 ± 1.1 days) compared

with Group B (3–5 days, 3.6 ± 1.2 days). The recovery pattern of different complications showed that coma recovery time (CRT) was comparable in both the groups (4.1 ± 0.6 days versus 3.9 ± 0.9 days, P = 0.6). Jaundice recovery time (JRT) was longer in Group A (9.6 ± 2.4 days) compared with that in Group B (6.4 ± 1.4 days, P < 0.01). Renal function recovery time (RFRT) was also prolonged. The complete recovery of renal failure took 15.1 ± 6.5 days in Group A compared with 10.0 ± 3.9 days in Group B (P < 0.001). The phase of oliguria was also prolonged in Group A, with a mean duration of 5.5 ± 1.4 days compared with 3.5 ± 0.8 days in Group B (P < 0.001).

The percentage of deaths in Group A (25.0%, 5/20) was more than that in Group B (10.0%, 9/90) (P < 0.001). The overall mortality was 12.7% (14/110). On follow-up, we found three (15.0%) patients with BCN had persistence of renal dysfunction up to 6 weeks, whereas all patients from Group B had recovered completely by that time.

HRS in severe malaria

Although the patients with HRS were included in Group B, we separated a few variables for further evaluation. The mean serum bilirubin, conjugated bilirubin and fever to treatment interval was 7.5 ± 1.9 mg/dL, 4.1 ± 1.1 mg/dL and 3.1 ± 0.8 days, respectively, among patients with HRS, which were significantly (P < 0.001) less than in patients with BCN (serum bilirubin 24.7 ± 5.2 mg/dL, conjugated bilirubin 14.2 ± 5.3 mg/dL and treatment interval 6.4 ± 1.1 days). Urinary bile casts were not detected in any patient. All patients recovered with antimalarial drug, supportive treatment and dialysis when required (5 of 15 with HRS).

Discussion

The current study provides a new perspective on BCN. It shows that 18.2% of patients with severe falciparum malaria with jaundice and renal failure are complicated with BCN, which is the result of prolonged duration of illness and increased conjugated bilirubin above a critical level. BCN is also linked to higher mortality and morbidity. The diagnosis can be made simply with detection of bile casts in urine.

The mechanism of AKI in falciparum malaria is multifactorial. The main factors are fluid loss, alteration in renal microcirculation due to sequestration of parasitized erythrocytes, pigment-associated nephropathy, and immune-mediated glomerular and tubular pathology [6, 27]. The present study shows that BCN and HRS are present in 18.2 and 13.6% of patients with severe malaria with jaundice and AKI. HRS has been reported in about 40.0% of patients with cirrhosis of the liver; however, its incidence in acute hepatic dysfunction is not known because in clinical practice it may be difficult to differentiate from other causes of AKI [7, 25]. BCN was found in 30.0% of diagnosed patients with cirrhosis of the liver with HRS, which has been attributed to advanced liver failure associated with cholestasis [16]. In this study, none of the patients with falciparum malaria with HRS had urinary bile casts, which conveys that HRS and BCN are mutually exclusive. However, this kind of association between HRS and BCN in acute liver disease has not been described previously.

The association between renal dysfunction and obstructive jaundice is well established and the incidence varied from 9.0 to 47.0% with mortality ranging from 9.1 to 76.0% [8–10]. Only limited information is available on BCN in nonobstructive causes because the available studies are limited to retrospective autopsy study and case reports [16–22]. The autopsy study that included 44 specimens of kidney from patients with jaundice of varied etiology showed that BCN was present in 24 of 44 (54.5%) patients, of which 16 were mild and 8 were severe in nature [16]. Increased conjugated bilirubin, i.e. >20.0 mg/dL, is the notable finding in all studies. The present study showed that BCN was present in 18.2% of cases of severe falciparum malaria with jaundice and was associated with higher mortality (25.0%) compared with patients without BCN (10.0%), with overall mortality of 12.7%. In addition, the recovery of hepatic and renal dysfunction was also delayed, increasing the morbidity and length of hospital stay. Furthermore, persistence of AKI was found in three (15.0%) patients, suggesting that AKI in malaria is not completely reversible if complicated with BCN. It is well documented that the mortality was higher (39.5%) in patients with falciparum malaria with AKI compared with patients without AKI (13.9%) [27]. It is still higher in patients with malaria with AKI and jaundice [6]. In the present study, the mortality is lower than in other studies because of early intervention and dialysis.

BCN is a clinico-pathological entity that encompasses a spectrum of renal derangement which ranges from intrarenal bile cast formation and tubular injury to renal fibrosis leading to AKI [16]. In the past, experiments with CBDL dogs showed the above-described changes, but similar experiments with rats in later years did not show much change in the kidney [12, 13]. However, a landmark study showed that renal tubular epithelial injury, intratubular cast formation and tubulointerstitial fibrosis can occur in CBDL mice, which is not only related to the duration of ligation but also to the toxic effect of bile acids [14].

Cholestasis is the predominant factor for the pathogenesis of BCN [14, 16]. It is characterized by increased serum concentration of conjugated bilirubin, bile acids and bile salt, and all are nephrotoxic [24]. Bilirubin itself is a potent vasodilator that can lead to obligatory loss of water up to 1.5 L along with salt loss [10]. In the animal model, it is found that conjugated bilirubin is toxic to cells. It causes uncoupling of oxidative phosphorylation, giving rise to less production of ATP per glucose, hence cellular hypoxia. It sensitizes the renal parenchyma to ischemic damage [10, 11]. After glomerular filtration, free conjugated bilirubin can enter the tubular cells from the lumen causing direct damage. Increased levels of conjugated bilirubin, typically >20.0 mg/dL, precipitate bile cast formation inside the distal tubules, causing BCN. Serum albumin has the capacity to bind bilirubin up to 20.0 mg/dL and beyond it, bilirubin forms intratubular casts triggering AKI [11].

Bile acids and salts are carcinogenic and a similar model has been postulated in AKI with jaundice [28]. Infusion of bile acids to animals precipitated renal failure with formation of bile casts in kidney, which could be detected in urine [12, 29]. In CBDL mice, it was demonstrated that bile acids are toxic to renal tubules and play a pivotal role in the genesis of BCN [14]. Low water solubility of bile acids within an acidic microenvironment of the distal nephron facilitates cast formation that causes tubular obstruction and subsequent AKI [16]. Bile salts cause natriuresis and diuresis, leading to a diminished effective plasma volume [30]. From the above information, it can be concluded that both high bilirubin and bile salts are responsible for formation of bile cast, which is *sine qua non* of BCN [14, 16, 31].

From this study, we concluded that the duration of illness and increased conjugated bilirubin (>20.0 mg/dL) are two important factors responsible for the genesis of BCN in malaria. The beginning of bile cast formation during the development of cholestasis in malaria is not known precisely. Unlike mouse models that showed tubular epithelial injury after 3 days and demonstrable BCN after 8 weeks of ligation of the common bile duct, the present study showed that in malaria BCN is possible within 6.4 ± 1.1 days of illness.

In falciparum malaria, cytoadherence and sequestration of parasitized red blood cells to capillary endothelium causes tissue hypoxia leading to severe malaria [2]. Further delay in treatment brings many hemodynamic alterations that include electrolyte disturbances, acidosis, metabolic changes, anemia and hypovolemia, which further enhances hypoxia leading to multiorgan dysfunction [2–4]. Subsequently, as the disease progresses, liver dysfunction deteriorates, increasing cholestasis. Conjugated bilirubin and bile salts further enhance volume depletion and cause direct damage to tubular epithelium of the kidney. In an already dysfunctional kidney, both bile acid and conjugated bilirubin form intratubular bile cast causing tubular obstruction and AKI as explained in previous studies [11, 14]. Thus, the BCN is superimposed on the previously compromised kidney.

BCN is a pathological diagnosis, but in a critical condition like severe malaria, when biopsy is not possible, it can be diagnosed with detection of bile casts in urine. It has been recommended that in patients with jaundice-related renal dysfunction, urine analysis is more practical and useful for diagnosis rather than invasive investigations [7]. Liver injury in animals demonstrated AKI and passage of bile casts in urine within 24 h [12]. Urine of both dogs and humans with jaundice showed bile-stained casts subsequent to intratubular bile cast formation, and detection of a single bile cast in urine is diagnostic of BCN [12, 29].

This notion has a major implication for future research in the prevention of AKI in malaria by treating cholestasis with drugs like ursodeoxycholic acid, which prevented BCN in mouse models [14].

A limitation of this study is that kidney biopsy was not performed due to the patients being critically ill. Therefore, we could not compare the diagnostic value of bile casts in the urine with the histology. In spite of this limitation, this is the first prospective study to analyze BCN in any non-obstructive jaundiced malaria patients. Its recognition is clinically significant for the prevention of mortality and morbidity with early intervention.

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