Study of hepatic profile in falciparum malaria in children of the age group of 1–10 years

Anubhav Prakash[1], Richa Richa[2], Bhupendra Narain[3], Anil Kumar Jaiswal[4]

From [1]Senior Resident, Department of Pediatrics, Sri Krishna Medical College Hospital, Muzaffarpur, [2]Junior Resident, Department of Pathology, [3]Associate Professor, [4]Professor and Head of Department, Department of Pediatrics, Patna Medical College Hospital, Patna, Bihar, India

Correspondence to: Dr. Bhupendra Narain, Mr. Rama Shankar Singh, Flat no-201, Maheshwari Complex, Biscoumaun Colony, PO-Gulzarbagh, PS-Alamgunj, Patna, Bihar - 800 007, India. E-mail: brnarain@gmail.com

Received - 22 December 2019 Initial Review - 16 January 2020 Accepted - 30 January 2020

ABSTRACT

Background: Severe falciparum malaria (FM) has more predilections to affect the liver resulting in raised serum transaminases. When the levels are more than 3 times the upper limit, it is known as malarial hepatopathy (MH). The liver function test is an important tool to predict complications and prognosis in patients with FM, which should be done at the earliest. **Objective:** The objective of the study was to study the patient characteristics, presenting features, and complications of malaria in patients with MH and to compare these with patients who had normal liver enzymes. **Materials and Methods:** This case–control study was carried out on 76 children of the age group of 1–10 years suffering from FM admitted in the department of pediatrics of a tertiary hospital of Bihar. All admitted children suffering from FM were divided into two groups based on the presence of MH as cases and controls. Various parameters were compared between these two groups and the results were interpreted. Data were collected and the results were analyzed by SPSS v23 software. **Results:** Baseline characteristics were comparable in both groups. Among cases, 90.9% had an altered level of consciousness and 72.7% had convulsions at admission, in comparison to 50.0% and 25.9% among controls. A total of 68.1% of cases of MH presented with icterus, compared to 3.7% of the controls ($p<0.0001$). Patients of MH who suffered from renal failure were 18.1%, compared to 1.8% among controls ($p=0.0321$). Among cases, 36.3% suffered from hypoglycemia, compared to 12.9% among controls ($p=0.0251$). The mean hemoglobin (Hb) levels among cases were lower as compared to controls ($p=0.0002$). A total of 36.3% of cases and 12.9% of controls expired due to the disease ($p=0.0251$). **Conclusion:** MH is associated with a higher incidence of complications such as altered sensorium, seizures, icterus, raised bilirubin levels, renal failure, increased chances of hypoglycemia, and lower mean Hb levels and a poor outcome.

Key words: *Falciparum malaria, Hepatic profile, Malarial hepatopathy*

Plasmodium falciparum (Pf) is the most prevalent malaria parasite in Africa, accounting for 99.7% of estimated malaria cases and in the Southeast Asia region (50%). In 2018, there were an estimated 0.40 million deaths from malaria globally. Children aged under 5 years are the most vulnerable group affected by malaria. In 2018, they accounted for 67% (0.27 million) of all malaria deaths worldwide, most of them due to Pf [1]. Falciparum malaria (FM) is a potentially lethal disease, and despite treatment, mortality is about 15–20%. The common and important forms of complicated malaria in children include cerebral malaria, severe anemia, hypoglycemia, and respiratory acidosis [2]. Others are renal failure, circulatory collapse, and shock, blackwater fever, spontaneous bleeding, hepatic dysfunction, etc.

The WHO describes severe malaria as a Pf positive patient, who presents with one or more of the manifestations of the initial WHO criteria (1990) [3] or the added WHO criteria (2000) [2]. Hepatic dysfunction in malaria has been known for many years, but hepatic encephalopathy is unusual. The incidence of jaundice in malaria varies between 10 and 45% in different reports and is seen more in adults than in children [4]. Patients with hepatocellular dysfunction in malaria are more prone to develop complications but have a favorable outcome if hepatic involvement is recognized early and managed properly. In adults, the reported incidence of hyperbilirubinemia in severe malaria varies from 32 to 37%, the majority of which is predominantly unconjugated hyperbilirubinemia [5,6].

The term "malarial hepatopathy (MH)" has been used to describe hepatocellular dysfunction in a patient with severe malaria; however, actual inflammation of the liver parenchyma is rarely seen [7]. MH is characterized by a rise in serum bilirubin along with the rise in alanine transaminase (ALT) levels to more than 3 times the upper limit of normal [4]. Shoukier *et al*. explained MH as hyperbilirubinemia (>3 mg/dl) and elevated liver transaminases more than 3 times the normal limit [8]. This in the absence of evidence of exposure to hepatotoxic drugs and the absence of clinical or serological evidence of viral hepatitis makes MH a unique entity. It is very common in children during

severe infection and the incidence is reported to vary from 8% [9] to 32% [10].

The present study was conducted to look for the hepatic involvement in children of the age group of 1–10 years and to study the patient characteristics, presenting features, and complications of malaria in patients with elevated liver enzymes and to compare these with patients of FM who had normal liver enzymes.

MATERIALS AND METHODS

This case–control study was done on 76 patients of FM admitted in the department of pediatrics of a tertiary hospital of Bihar, from January 2015 to November 2017. As per the inclusion and exclusion criteria, 76 patients from 1 to 10 years of age were divided into two groups, cases with hepatopathy (n=22) and controls without hepatopathy (n=54). All the involved study subjects were investigated within few hours at the time of admission for complete blood count, blood sugar, liver function test (LFT), kidney function test, serum electrolytes, peripheral blood smear (PBS), and rapid diagnostic test (RDT) for malaria parasite and if found altered, which were repeated after 3 days until it came to normal.

Patients who were Pf positive by PBS examination and positive histidine-rich protein 2 kit during the selected period were included in the study. The controls included those suffering from FM with normal liver enzymes and without evidence of MH, while cases included those with FM who had elevated liver enzymes (>3 times of normal limits). Patients with viral hepatitis were excluded from the study. Patients who presented with raised liver enzymes due to septicemia, drugs, or other identifiable causes were also excluded from the study.

The diagnosis of MH was made if a patient fulfilled all the following criteria [7,11]: (1) Demonstration of Pf infection by PBS examination or antibody-based RDT, (2) at least three-fold rise in transaminase levels either ALT or aspartate transaminases with or without conjugated hyperbilirubinemia, and (3) absence of clinical or serological evidence of viral hepatitis.

The present study was conducted as per the current version of the Declaration of Helsinki. The Institutional Ethics Committee approval was obtained. Informed written consents were taken from guardian/parents of children involved. All of the patients that were included in the study were treated with intravenous artesunate or oral artesunate combination therapy. The patients were put on conservative management for the treatment of complications.

Data were collected using pre-structured pro forma, and the results were analyzed by SPSS v23 software using Student's t-test, odds ratio (OR), and Z-value. Statistical data were expressed in mean and standard deviation and $p<0.05$ was considered as a statistically significant.

RESULTS

Patients of the age group of 1–10 years were enrolled in the study with a mean age of 5.0±2.3 years among cases and 5.5±2.7 years among controls (p=0.4905). Among cases, there were 17 (77.3%) males and five (22.7%) females with male:female ratio of 3.4:1. Among controls, there were 29 (53.7%) males and 25 (46.3%) females with the male:female ratio being 1.16:1. All the 76 (100%) patients of Pf complained of fever with/without chills and/or rigor. Among cases, 20 (90.9%) had altered levels of consciousness, either semiconscious or unconscious, and two (9.1%) were conscious at the time of admission. Among controls, 27 (50%) presented with an altered state of consciousness and 27 (50%) were conscious. The demographic details of the study population are shown in Table 1.

Laboratory parameters between the two groups are compared in Table 2. Eight (36.3%) cases suffered from hypoglycemia compared to seven (12.9%) controls (OR – 3.8, 95% confidence interval [CI]: 1.1–12.4). The mean hemoglobin (Hb) level was significantly lower among cases than in controls. Eight (36.3%) patients with MH expired among cases including four patients with renal failure, while seven (12.9%) patients without MH also expired, including one patient with renal failure (OR – 3.8. 95% CI: 1.1–12.4, p=0.0251).

DISCUSSION

Among the enrolled age group of 1–10 years, the most commonly affected age group was below 5 years. According to the World Malaria Report 2019, under 5 years is the most vulnerable age group which accounted for 67% of malarial death worldwide in 2018 [1]. A similar age incidence was also noted by Prasad *et al*. [12]. Deen *et al*. found that chronically malnourished children under 5 years of age were at a greater risk of developing malarial episodes [13].

Our study found a significant correlation of MH with an altered level of consciousness (p=0.0036) and convulsion (p=0.0004) at admission. Severe impairment of the sensorium is very common in severe malaria but is multifactorial and other contributing factors being hypoglycemia, hypoxia, uremia, and hepatic encephalopathy due to the MH itself [4,14]. Kochar *et al*. found strong evidence of hepatocyte dysfunction and hepatic encephalopathy in their study subjects involving patients of malaria with no obvious non-malarial explanation [14].

Our study found a strong correlation between MH and seizures at admission, which is perhaps the first such study to date. It may have occurred due to the combination of multiple factors such as cerebral malaria, hepatic encephalopathy, MH, or dyselectrolytemia. However, additional tests are required to be done to find the exact etiology of increased chances of seizures in the case of FM with hepatopathy.

Krishnan and Karnad found that seizures in FM patients were associated with poor outcomes [15]. They also illustrated that cerebral dysfunction was the most common organ system involved and was associated with maximum deaths. Lalloo *et al*. found that cerebral dysfunction and renal failure were associated with poor outcomes [16], which occurred more in patients of MH which is in accordance with our study.

Table 1: Demographic details of the study population

Characteristics	Cases (n=22) (%)	Controls (n=54) (%)	Odds ratio (95% confidence interval)	p value
Age (years)	5.0±2.3	5.5±2.7		0.491
Fever	22 (100)	54 (100)		
Altered consciousness	20 (90.9)	27 (50)	10.0 (2.1–47.0)	0.0036
Convulsions	16 (72.7)	14 (25.9)	7.6 (2.4–23.3)	0.0004
Renal failure	4 (18.1)	1 (1.8)	11.7 (1.2–112.3)	0.032
Icterus	15 (68.1)	2 (3.7)	55.7 (10.4–296.9)	<0.0001
Hepatomegaly	19 (86.3)	43 (79.6)	1.6 (0.4–6.4)	0.495
Splenomegaly	20 (90.9)	43 (79.6)	2.5 (0.5–12.6)	0.249
Pulmonary edema	1 (4.5)	2 (3.7)	1.1 (0.1–13.7)	0.894

Table 2: Laboratory parameters among study groups

Investigations	Cases (n=22)	Controls (n=54)	p value
Total serum bilirubin (mg/dl)	4.8±1.8	0.8±0.8	
ALT (IU/L)	346.4±141.0	45.0±50.6	
AST (IU/L)	343.5±136.0	47.0±44.3	
INR	1.47±0.13	1.18±0.14	
Alkaline phosphatase (IU/L)	297.9±69.7	176.4±29.6	
Blood sugar (mg/dl)	8 (36.3)	7 (12.9)	0.0251
Mean hemoglobin levels (g/dl)	4.5±2.0	6.8±2.4	0.0002

AST: Aspartate transaminase, ALT: Alanine transaminase

Our study observed a significant positive correlation between icterus and cases of MH (p<0.0001), which is attributed to raised hepatic transaminases. This was in accordance with the study of Kausar *et al*. who found a strong significant correlation of bilirubin with liver enzymes [17]. Ahsan *et al*. also found that rising bilirubin was significantly associated with impaired consciousness, acute renal failure, and adverse outcomes [18].

Our study found a significant increase in the number of acute renal failure in MH patients in comparison to the control group (p=0.0321) which is in accordance with the studies conducted by Bhalla *et al*. as well as the other authors [4,5,11,15,16,18-21]. The present study established a significant correlation between hypoglycemia at admission and MH (p=0.0251). A total of 36.3% of cases of MH suffered from hypoglycemia with a whole blood sugar <40 mg/dl [3], compared to 12.9% among controls which are in accordance with the other studies conducted in the past, which also suggest hypoglycemia as a poor prognostic sign [5,11,15,21-23].

Our study demonstrated significantly lower Hb levels in patients of the MH group when compared to controls (p=0.0002). The present study found a significant correlation between MH and the final outcomes (p=0.0251). A total of 36.3% of cases of MH suffered from the grave outcome, in contrast to 12.9% among controls, which is in accordance with the study by Murthy *et al*. who found that mortality was higher in the patients of MH than those without it (40% vs. 17%) [4,19]. We found no significant correlation between cases of MH and the occurrence of hepatomegaly (p=0.495), splenomegaly (p=0.249), and pulmonary edema (p=0.894).

The present study had a few limitations. First, the sample size was relatively small, with a total of only 76 patients. Second, we did not follow-up on the time taken after the initiation of therapy for the resolution of hepatopathy. Third, they were not followed up for the possibility of chronic liver disease.

CONCLUSION

MH is associated with a higher incidence of complications such as altered sensorium, seizures, icterus, raised bilirubin levels, renal failure, hypoglycemia, and anemia. The LFT is necessary in patients of Pf malaria to find out cases of MH at an early stage so that early therapy can be instituted to prevent complications and thereby mortality.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Prakash A, Richa R, Narain B, Jaiswal AK. Study of hepatic profile in falciparum malaria in children of the age group of 1–10 years. Indian J Child Health. 2020; 7(2):50-53.

Doi: 10.32677/IJCH.2020.v07.i02.002