

Original Research Article

Hepatic dysfunction in children with complicated malaria

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ABSTRACT

Background: Complicated malaria caused by *Plasmodium falciparum* alone or with *P. vivax* can lead to multi organ dysfunction. There is a paucity of studies about hepatic dysfunction in children with complicated malaria. Hence, this retrospective study was done to find out the clinico-biochemical profile of children with complicated malarial hepatic dysfunction from a malaria endemic region of India. Further, liver function test (LFT) response to Artemisinin-based combination therapy (ACT) i.e. artesunate + sulfadoxine-pyrimethamine therapy in the malarial hepatic dysfunction children was assessed.

Methods: Out of 203 children confirmed to have malaria, 60 children were found to have complicated malaria with jaundice as per WHO malaria guidelines (total serum bilirubin >3 mg%). Physical examination, malaria related biochemical and ultra-sonographic findings were noted. All the children were found to be uniformly on ACT as per institute protocol adapted from WHO guidelines. Biochemical parameters of hepatic function were compared between day 1 and 4.

Results: Presentations were fever, pallor and clinical jaundice in 100%, reddish urine in 63.3%, tender hepatomegaly in 100% and splenomegaly in 81.7% of the study population. Liver function test showed mild to moderate elevation of serum bilirubin and enzymes with remarkable recovery noticed with the use of ACT in all the study subjects.

Conclusions: Clinical presentations of malarial hepatic dysfunction although mimics viral hepatitis, LFT showed mild to moderate elevation only. Further, ACT therapy was found effective in the management of all children with hepatic dysfunction in complicated malaria.

Keywords: ACT, Children, Complicated malaria, LFT, Hepatic dysfunction

INTRODUCTION

Malaria is one of the life-threatening diseases across the globe. Nearly half of the world's populations are under threat for malarial infection. In the year 2015, the morbidity and mortality rates of malaria were around 214 million and 5 lakhs respectively.¹ According to the World Malaria Report 2016, India accounted for 89% of the

total patients in the South East Asia Region of WHO. Among them, *Plasmodium falciparum* accounts for more than 50% of the total malaria patients. Majority of the affected individuals are from Eastern part of India, especially from Odisha which accounts for 25% of total reported annual malarial incidence.² Among the various species of *Plasmodium*, *P. falciparum* is responsible for 30% of malarial deaths in India.³ Children are the most

vulnerable groups affected by malaria and they can deteriorate rapidly. Complicated (severe) malaria is defined as per WHO 2015 guidelines.⁴ Most common clinical profile in children with complicated malaria includes severe anemia, hemoglobinuria, seizures and impaired consciousness. Over the years, the clinical features of falciparum malaria have changed. Acute renal failure and hepatic dysfunction have become more common now especially in older children.³ Very few studies are available with regard to the hepatic involvement in malaria infected children.⁵

In complicated malaria, jaundice is a notable symptom and the extent of hepatic involvement ranges from mild abnormalities in liver function tests to severe hepatic dysfunction. Mortality rate seems higher in group of patients with jaundice (45 versus 17%).⁵ In endemic areas, fulminant hepatic failure may also be caused by other infections such as viral hepatitis.⁶

Complicated malaria with hepatic involvement has a favourable outcome if recognized early and managed properly in malaria endemic areas.⁷⁻¹¹ As pediatric age group is more susceptible for malaria complications, including involvement of liver, this retrospective study provides insight into the clinical profile and outcome. This would facilitate in devising strategies to reduce mortality and morbidity due to the disease.

METHODS

Data was collected from the case records of children admitted from June 2013 to June 2015 in the Department of Pediatrics, Maharaja Krishna Chandra Gajapati Medical College and Hospital, Berhampur, Odisha, India. Of the 203 children in the age group of 1-12 years who were found to have laboratory confirmed malaria, 60 children (male: 39 and female 21) had jaundice (total serum bilirubin >3 mg%) who received 3 days of ACT as per institute protocol adapted from WHO guidelines were taken as study population. Children with evidence of underlying liver disease like viral hepatitis, amoebic liver abscess, chronic liver disease, hemolytic anaemia, history of taking hepatotoxic drugs and past history of jaundice were excluded.

Data on demography, clinical presentations, physical examination findings, malaria related biochemical tests and abdominal sonography were collected. Liver function test (LFT) comprising of serum bilirubin (total and direct), liver enzymes: aspartate amino transamiase (AST), alanine amino transaminase (ALT), alkaline phosphatase (ALP) prothrombin time (PT-INR), were recorded on day 1 and day 4 (excluding 5 expired and 5 discharged against medical advice before the completion of ACT).^{12,13}

These biomarkers of hepatic function were compared and analyzed by one-way ANOVA using SPSS software

version 17. *p*-value less than 0.05 was considered to be significant.

RESULTS

There were 39 (65%) males and 21 (35%) females (1.86:1). The mean age of children was found to be 7 years. Presentations were fever, pallor and clinical jaundice in all 60 (100%), dark/red urine in 38 (63.3%), vomiting in 36 (60%), tender hepatomegaly in 60 (100%) and splenomegaly in 49 (81.7%) of the study population. Other significant signs and symptoms of severe malaria found were hypotension in 12 (20%), respiratory signs of cough and tachypnea in 10 (16.6%), altered sensorium in 20 (33.3%) and seizures in 10 (16.7%) children. Clinical signs of hepatic encephalopathy were never seen in any of the cases. Meningeal signs, diarrhea, pain abdomen, oliguria and gastro intestinal bleed were noted very less frequently (Table 1).

Table 1: Signs and symptoms.

Signs	Number of patients/ percentage of distribution	Symptoms	Number of patients/ percentage of distribution
Pallor	60 (100%)	Fever	60 (100%)
Clinical jaundice	60 (100%)	Jaundice	60 (100%)
Hypotension	12 (20%)	Seizure	10 (16.7%)
Respiratory sign	10 (16.6%)	Altered sensorium	20 (33.3%)
Splenomegaly	49 (81.7%)	Headache	23 (38.3%)
Altered sensorium	20 (33.3%)	Vomiting	36 (60%)
Meningeal signs	2 (3.3%)	Pain abdomen	25 (41.7%)
Brisk deep tendon reflex	3 (5%)	GI bleed	7 (11.7%)
Extensor plantar	4 (6.7%)	Reduced urination	18 (30%)
		Dark/red urine	38 (63.3%)

Signs and symptoms of total malarial hepatic dysfunction patients based on WHO criteria; Total number = 60

Severe malarial anemia was seen in 16.6% of children of the study population. Hypoglycemia (<40mg/dl), thrombocytopenia (<100000/cumm) and nephropathy (serum creatinine >3mg/dl) were also found in nearly 10% of patients (Table 2).

Out of the 60 patients, 11 (18.4%) had bilirubin of 3-5 mg%, 29 (48.3%) had between 5-10 mg%, and 20 (33.3%) had >10 mg% respectively. Further, AST level in plasma was normal in 4 (6.7%), mildly raised (41-100 IU/L) in 42 (70%) and moderately raised (101-1000 IU/L) in 14 (23.3%) patients.

Similarly, ALT level was normal in 9 (15%), mildly raised in 36 (60%) and moderately raised 15 (25%) respectively. Additionally, ALP level was observed normal (<150IU/L) in 5 (8.4%), mildly raised (150-300 IU/L) in 34 (56.6%) and moderately raised (>300IU/L) in

21(35%) patients, (Table 2). Hepatic function assessed (serum total and direct bilirubin, AST, ALT and ALP) for ACT between day 1 and day 4 showed significant positive response ($p= 0.000$) (Table 3).

Table 2: Biochemical and ultrasonographic profile.

Blood Parameters*	Mean ± S.D		No.of patients (%) **
Hemoglobin	7.406±2.155	Severe Anemia (<5 gm/dl)	10 (16.6%)
Random blood sugar	104.780±70.178	Hypoglycemia (<40 mg/dl)	06 (10%)
Platelet count	1.580±0.464	Thrombocytopenia (<100000/cumm)	07 (11.3%)
Serum creatinine	1.689±0.889	Malarial nephropathy (>3 mg/dl)	06 (10%)
PT (INR)	1.3±0.13		
S. Albumin	4.61± 0.79		
Sonographic findings**	No. of cases (%)		
Liver			
Hepatomegaly	60 (100%)		
Altered Echo pattern	15 (25%)		
Gall bladder			
Increased wall thickness	11 (18.4%)		
Lumen with sludge	16 (26.7%)		
Clear lumen	44 (73.3%)		
Splenomegaly	49 (81.7%)		

*values are given in gm/dl, random blood sugar in mg/dl, Serum creatinine in mg/dl and platelet count in lakhs respectively; **values given are in number of patients and within bracket are percentages of distribution among the total study population.

Table 3: Hepatic function response to ACT treatment.

Liver function tests	Day 1	Day 4	p value
Serum bilirubin: total (mg/dl)	9.432 ±5.633	4.458±2.958	0. 00
Serum bilirubin: direct (mg/dl)	5.190±3.634	2.336±1.552	
Aspartate amino transaminase (IU/L)	67.064±26.027	49.606±17.966	
Alanine amino transaminase (IU/L)	68.356±29.527	49.926±20.886	
Alkaline phosphatase (IU/L)	247.784.071±100.222	214.260±79.403	

The sonographic findings recorded shows hepatomegaly with normal architecture in all 60 (100%), altered echo pattern in 25% (15) of study patients respectively. Also, the gall bladder had thickened wall in 11 (18.4%) with luminal sludge in 16 (26.7%) and associated splenomegaly in 49 (81.7%) of the study population (Table 2).

The case fatality rate of 8.3% was seen in school going children with malarial hepatopathy. Among these patients some of the additional abnormalities observed were severe alterations in LFT with prolonged prothrombin time, cerebral malaria, severe malarial anemia, thrombocytopenia and renal impairment.

DISCUSSION

The mean age of affected children was 7 years with higher distribution in boys. The predominant clinical presentations mimics viral hepatitis and includes moderate to high grade fever, vomiting and jaundice with

dark/red urine.¹⁴ The incidence of hepatic dysfunction in children was found to be 29.5% which is comparable to the earlier studies.^{2,15} However, incidence of hepatic dysfunction in adults varies from 8-32%.⁵ The probable cause for the hepatic dysfunction was attributed to the kupffer cell phagocytosis of the infected red blood cells, stagnation of bile in liver and hypertrophy of the hepatocytes.^{11,16,17}

In this study, apart from tender hepatomegaly, splenomegaly was also observed in majority of the study patients. Further, altered sensorium and hypotension which often goes unnoticed, were also observed in considerable number of patients which could be due to associated cerebral malaria and not attributed to hepatic encephalopathy.¹¹

Malarial nephropathy (serum creatinine >3 mg%) was seen in 10% that could be due to mechanical obstruction by infected erythrocytes, immune mediated glomerular and tubular pathology.¹⁸

Although all the study population were found to have clinical pallor, only 16.6% had severe malarial anemia (Hb <5 gm%) which is less when compared to the previous study.¹⁵ But, the degree of decrease in hemoglobin is high in the present study which could be due to rapid hemolysis by heavy parasitemia and dyserythropoiesis, further leading to severe indirect hyperbilirubinemia.¹⁹ Platelet count, prothrombin time and albumin levels didn't find significant variations in our study which is concurrent with an earlier study.⁸

Hypoglycemia was noted in around 10% of the study children which is in accordance to another study where it showed similar findings and it could be due to impaired endogenous glucose production, increased consumption and decreased food intake. On the contrary, age group of children in that study was 0-5 years.²⁰

The sonographic findings reported mainly showed hepatomegaly and splenomegaly. Apart from this, gall bladder wall thickening with luminal sludge is also seen in considerable number of study children. Even though they are seen in other common pathological condition, imaging of the liver and spleen could be helpful as part of a diagnostic support in severe malaria.²¹

ACT is the recommended drug of choice in anti-malarial treatment protocol across the globe. In this study, ACT showed significant (p value <0.000) improvement (near normal levels) of bilirubin and hepatic enzymes by day 4. ACT offers to be a good therapeutic option in varying degrees of hepatic dysfunction in children.²² Although this retrospective study offers good insight into clinical profile of hepatic dysfunction in children of malarial endemic area from India, much remains to be studied differentiating from other similar illnesses causing fever and jaundice in the tropics, including long-term follow up of such children.

CONCLUSION

The study findings conclude that malarial hepatic dysfunction is common among children in endemic areas mimicking viral hepatitis nevertheless with mild to moderate elevations in LFT. It responds well to appropriate ACT treatment unlike viral hepatitis which takes a longer course and severe alterations in LFT. Although much remains to be done, absence of histopathological examination of the liver, incomplete follow up till normalization of liver functions were the limitations of the study. Future studies are required to understand the molecular mechanism for the pathogenesis of hepatic dysfunction in children with complicated malaria.

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