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Original Article

Outcomes of paediatric malarial hepatopathy: a study from Eastern India

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Abstract

Background Severe malaria causes multi-organ involvement, including hepatic dysfunction. Jaundice in severe malaria is found more commonly in adults than in children. It is important to assess the factors associated with malarial hepatopathy, the varied clinical presentations, as well as the complications in order to initiate early interventional measures. There are a limited number of studies in the pediatric population on malarial hepatopathy.

Objective To assess the factors associated with malarial hepatopathy, the varied clinical presentations, as well as its complications.

Methods This prospective study was conducted in the Department of Paediatrics, Sardar Vallabh Bhai Patel Post Graduate Institute of Paediatrics (SVPPGIP), Cuttack, Odisha, India from January 2010 to June 2013, and included 70 children with malaria and jaundice, aged 6 months to 14 years. Malaria was confirmed by microscopic examination of blood smears. Detailed clinical evaluations and investigations were carried out to find multi-organ afflictions, with a special emphasis on hepatic involvement.

Results Of 218 children with malaria admitted during this period, 70 (32%) children had fever and jaundice on presentation. All children who had both *Plasmodium falciparum* and *vivax* infection had malarial hepatopathy. Complications, including acute kidney injury (AKI), disseminated intravascular coagulation (DIC), cerebral malaria, and mortality, were significantly higher among children with malarial hepatopathy compared to children without hepatopathy. However, there was no significant difference of hypoglycemia, respiratory distress syndrome (RDS), convulsions or severe anemia, between children with and without hepatopathy.

Conclusion Hepatopathy is more common with mixed malaria infections. The incidence of AKI, DIC, cerebral malaria, and mortality are significantly higher in patients with hepatopathy. Malarial hepatopathy should be considered in patients presenting with acute febrile illness and jaundice so that specific treatment can be initiated early to prevent increased morbidity and mortality. **[Paediatr Indones. 2014;54:256-9.]**

Keywords: *malaria, hepatopathy, plasmodium falciparum, cerebral malaria*

Malaria remains a serious health problem in many parts of the world. It causes high morbidity and claims many lives in developing countries each year. Humans are generally infected by four species of malaria parasites,[1] although infections with a fifth parasite, *P. knowlesi,* are known to occur in humans on the islands of Borneo and peninsular Malaysia.[2] Malaria is a major public health problem in India and one which contributes significantly to the overall malaria burden in Southeast Asia, with an estimated 24 million cases per year, followed by Indonesia and

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Myanmar.[3] In the Southeast Asia region, India shares two-thirds of the burden (66%), followed by Myanmar (18%) and Indonesia (10%).[4] In India, the state of Odisha has the most malaria cases. Although Odisha has a population of 36.7 million (3.5%), it contributes 25% of the total 1.5 to 2 million reported annual malaria incidence, 39.5% of *P. falciparum* malaria infections, and 30% of deaths due to malaria in India.[5] P*lasmodium falciparum* malaria affects all age groups with multiple systemic complications. Hepatopathy is one of the complications of *P. falciparum* malaria. The diagnosis of malarial hepatopathy is made in the presence of malarial infection with at least a three-fold increase in transaminase levels with or without conjugated hyperbilirubinemia and in the absence of clinical or serological evidence of viral hepatitis.[6]

There is a paucity of data related to malarial hepatopathy at the global level.[6] Hence, we decided to conduct this study at our tertiary care pediatric referral centre to assess the pattern, spectrum of biochemical parameters as well as complications and outcomes of hepatopathy in the endemic area of Odisha, India.

Methods

We conducted a prospective study from January 2010 until June 2013, at the Department of Paediatrics at SVPPGIP and Sriram Chandra Bhanja (SCB) Medical College, Cuttack, Odisha, India. The study involved children aged 6 months to 14 years. Malarial parasite slides were taken by our in-house malarial technician and these smears (thick and thin) were stained with Jaswant Singh Battacharya (JSB) stain and examined at bedside by an experienced microbiologist. The microbiologist examined 100 microscopic fields of thick smear before classifying a smear as negative.

During the study period, a total of 218 cases were admitted with malaria, as confirmed by microscopic blood smear examination. Other common causes jaundice, such as viral hepatitis was ruled out in these patients by relevant tests. Seventy children met the definition of malarial hepatopathy and were included in the study. Their demographic, clinical, and laboratory data at the time of presentation were documented and analyzed. Detailed, clinical evaluations and investigations were carried out to detect multi-organ dysfunction, with special emphasis on hepatic involvement. The definitions and criteria for severe malaria can be found in **Table 1**.

Data were stored and analyzed by *Microsoft Excel* and *SPSS version 21.0* software using Chi-square test. A P value of < 0.5 was considered as statistically significant. All patients with malaria were treated with parenteral artesunate and other complications were managed according to the WHO standard guidelines. Patients were asked to return for follow up 3 after months of discharge for assessment of hepatopathy resolution. During follow up, their clinical status and liver function tests (LFT) were noted.

Results

Of 218 malaria cases during the period of study, a total of 70 (32.1%) cases had hepatic involvement. Their mean age at presentation was 6.6 (SD 3.6) years. Forty-six (65.7%) were males, with a male to female ratio of 1.9:1 (**Table 2, Figure 1**).

The most common age group involved was 6-10 years with the youngest patient aged seven months. *Plasmodium falciparum* was present in 52 (74.3%) cases, *Plasmodium vivax* in 6 (8.5%) cases, and mixed infection of both falciparum and vivax in 12 (17.1%) cases. All children who had both *Plasmodium falciparum* and *vivax* infection had malarial hepatopathy. Fever and icterus were present in all cases. Liver function tests showed hyperbilirubinemia in all cases with mean total bilirubin of 7.4 (SD 5.2) mg/dL with conjugated bilirubin being the dominant type. Aspartate transaminase (AST) was increased in 97% of cases with a mean of 250 (SD 183.2) IU/L. Alanine transaminase (ALT) was increased in 85% of cases with a mean of 182.7 (SD 217.2) IU/L.

Table 1. The definitions and the criteria for severe malaria

- Hepatopathy: characterized by a rise in serum bilirubin along with the rise in serum alanine transaminase (ALT) levels to more than three times the upper limit of normal.
- AKI: serum creatinine of >1.5 mg/dL with or without oliguria (<1 mL/kg/hr)
- Hypoglycemia: blood glucose concentration <40 mg/dL
- Severe anaemia: hemoglobin of <5 g/dL
- Cerebral malaria: any altered sensorium for a minimum of 1 hour not attributable to any other cause in a patient with *Plasmodium falciparum* malaria.
- DIC: spontaneous bleeding from nose, gums, gastrointestinal tract, and /or substantial laboratory evidence of DIC.

Prothrombin time was increased in 7 (10%) cases and mortality occurred in 9 cases (12.8%). The incidence of cerebral malaria (P=0.004), acute kidney injury/AKI (P=0.007), disseminated intravascular coagulation / DIC (P=0.008) and death (P=0.003) were significantly higher in patients with malarial hepatopathy than those without. However, no significant difference was found between those with and without hepatopathy, with respect to convulsions, hypoglycemia, severe anemia or RDS (P>0.05). Comparison of malarial complications between hepatopathy and non-hepatopathy groups can be seen in **Table 3.**

Table 2. Spectrum of malarial hepatopathy in our study (n=70)

Characteristics	n	%
Total cases of malarial hepatopathy	70	32
Male to female ratio	1.9:1	
Most common age group involved, years	6-10	45.7
Number of *Plasmodium falciparum* cases	52	74.3
Number of mixed cases (*P.falciparum and P. vivax*)	12	17.1
Mean bilirubin (SD), mg/dL	7.4 (5.2)	
Mean age(SD), years	6.6 (3.6)	
Mortality	9	12.8

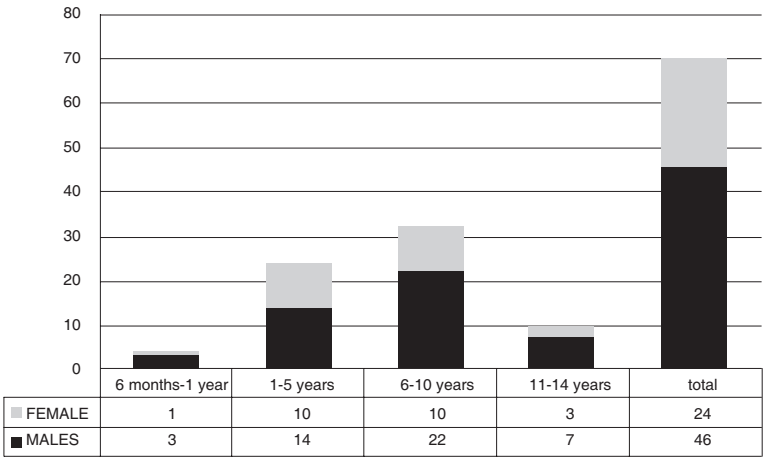

Figure 1. Age distribution of malarial hepatopathy cases in the study group (n = 70)

Table 3. Comparison between children with malarial hepatopathy and children without hepatic involvement

Clinical entity present	Malarial hepatopathy (n=70)		Malaria without hepatopathy (n=148)		P value
	n	%	n	%	
Cerebral malaria	40	57.1	54	36.5	0.004
AKI	16	22.8	14	9.5	0.007
DIC	7	10	3	2	0.008
Convulsions	13	18.6	28	18.9	0.95
Hypoglycemia	12	17.1	40	27	0.101
Severe anemia	63	90	128	86.5	0.46
RDS	03	4.3	18	12.2	0.066
Mortality	09	12.8	07	4.7	0.03

Discussion

Malaria affects all ages with multiple, systemic complications which vary among age groups.[7] Predominanting age groups differ according to geographic area as shown in various studies.[8,9] In our study, most of the affected children were aged 6-10 years.

Jaundice in malaria is multifactorial and its incidence varies among regions. It is important to assess the incidence and factors associated with malarial hepatopathy as well as its complications to understand the pattern of disease presentation in order to undertake appropriate interventional measures.[10] Hepatic dysfunction and jaundice in malaria are explained due to bilirubin excretion failure, endotoxemia, ischemia, acidosis or a combination of the above-mentioned factors which may coexist in the same patient.[11]

Plasmodium falciparum infection (either alone or with *P. vivax*) is the leading cause of malarial hepatopathy, and patients with malarial hepatopathy have increased incidences of hypoglycemia and thrombocytopenia.[12] In our study, all patients with mixed infections had malarial hepatopathy and about 52% of them were *P. falciparum*-positive, predominantly with conjugated hyperbilirubinemia. The causes of malarial hepatopathy are multi-factorial. The most common complications of malaria are cerebral malaria, DIC, AKI, hypoglycemia, severe anemia, shock, RDS, and malarial hepatopathy.[1,5,7,10,13,14] In our study, cerebral malaria, DIC, AKI, and mortality were found to have significant associations in children with malarial hepatopathy as shown in **Table 3,** but we did not find any such significant associations with respect to convulsions, hypoglycemia, severe anemia or RDS.

It is already a well-established fact that *P. falciparum* malaria can cause multiorgan dysfunction and that malarial hepatopathy is more common with *P. falciparum* infection.[15] Hepatopathy in malaria is predominantly manifested as conjugated hyperbilirubinemia with raised liver enzymes. Our study revealed that children with mixed infection (i.e., both *Plasmodium falciparum* and *vivax*) are at higher risk for hepatic involvement. We did not find increased incidence of hypoglycemia in our study cohort, but children with malarial hepatopathy had an increased risk of mortality, cerebral malaria, AKI and/or DIC.

References

1. Elsheikha HM, Sheashaa HA. Epidemiology, pathophysiology, management and outcome of renal dysfunction associated with plasmodia infection. Parasitol Res. 2007;101:1183-90.
2. Cox-Singh J, Davis TM, Lee KS, Shamsul SS, Matusop A, Ratnam S, *et al*. Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. Clin Infect Dis. 2008;46:165-71.
3. World Malaria Report 2012 FACT SHEET. Available at: http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_factsheet.pdf. Accessed on 28/10/2013.
4. World Health Organization. World Malaria report 2011. Available at: www.who.int/malaria/world_malaria_report 2011. Accessed on 28/10/2013.
5. Estimation of true malaria burden in India. Available at: http://www. mrcindia.org/MRC_profile/profile2/Estimation%20of%20true%20malaria%20burden%20in%20India.pdf; page 93. Accessed on 28/12/2013.
6. Saya RP, Debabrata G, Saya GK. Malarial hepatopathy and its outcome in India. N Am J Med Sci. 2012;4:449–52.
7. Hussain K, Shafee M, Khan N, Jan S, Tareen A, Khan M. Seroprevalence of pediatric malaria in Quetta, Baluchistan, Pakistan**.** Iran J Parasitol. 2013; 8:342–7.
8. Murtaza G, Memon IA, Memon AR, Lal MN, Kallor NA. Malaria morbidity in Sindh and the *Plasmodium* species distribution. Pak J Med Sci. 2009;25:646–9.
9. Fazil A, Vernekar PV, Geriani D, Pant S, Senthilkumaran S, Anwar N, *et al*. Clinical profile and complication of malaria hepatopathy. J Infect Public Health. 2013;6:383-8.
10. Anand AC, Puri P. Jaundice in malaria. J Gastroenterol Hepatol. 2005;20:1322-32.
11. Satapathy SK, Mohanty N, Nanda P, Samal G. Severe falciparum malaria. Indian J Pediatr. 2004;71:133-5.
12. Biemba G, Dolmans D, Thuma PE, Weiss G, Gordeuk VR. Severe anemia in Zambian children with Plasmodium falciparum malaria. Trop Med Int Health. 2000;5:9-16.
13. Ahmed S, Adil F, Shahzad T, Yahiya Y. Severe malaria in children: factors predictive of outcome and response to Quinine. J Pak Med Assoc. 2011;61:54-8.
14. White NJ. Malaria. In: Cook GC, Zumla AI, editors. Manson's tropical diseases. China: Saunders Elsevier; 2009. p.1201-300.
15. Kochar DK, Kochar SK, Agrawal RP, Sabir M, Nayak KC, Agrawal TD, Purohit VP, Gupta RP. The changing spectrum of severe falciparum malaria: a clinical study from Bikaner (Northwest India). J Vector Borne Dis. 2006;43:104-8.