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Malarial Hepatopathy

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ABSTRACT

Introduction: Liver is the first organ to be affected in a case of malaria. The term malarial hepatopathy appears to be a more appropriate one to describe hepatocellular dysfunction in cases of malaria. The purpose of this research is to evaluate the clinical & biochemical changes in patients of malaria with hepatopathy and patients of malaria without hepatopathy so that specific treatment can be provided. Methods: - A total number of 40 patients both male & female irrespective of age and suffering from jaundice & evidence of malaria on peripheral smear & positive malaria antigen card test were selected as a study group. The malaria was tested by: Peripheral smear, malaria antigen card test. Complete blood picture, platelet count was done by fully automatic cell counter. Evidence of jaundice & hepatopathy was tested by estimating serum levels of Total Bilirubin, Direct & Indirect bilirubin, SGOT, SGPT, Alkaline phosphatase, Total protein, Albumin, Globulin. Urea, creatinine, sodium & potassium levels were also measured. Chi square test x^2 = 1.343 was used to calculate p value which was considered insignificant when the value were > 0.05 Results: The total serum bilirubin levels were < 3 in 42 % patients and > 3 in 58 % patients. The conjugated bilirubin levels were raised to > 3 in 90 % patients. The mortality observed with malaria hepatopathy in our study was 6 %. Conclusions: The mortality too was higher in patients with 'malarial hepatitis. The mortality associated with conjugated bilirubin & malaria hepatopathy is significant.

KEYWORDS: Activities, Important, House, Occupation and Profession.

INTRODUCTION

Over last few years there has been a rise in incidence of fatal malaria in urban areas of India. The most common clinical presentation in patients of malaria was fever & jaundice[1].The presence of jaundice often led to an initial diagnosis of acute viral hepatitis & acute hepatic failure[2]. This has to be differentiated clinically & by lab tests so as to treat the actual cause of hepatitis. Malaria with hepatopathy is associated with increased mortality, prolonged illness & hospitalization as compared with malaria without hepatopathy[3].

Approximately 500 million people are affected annually by malaria & approximately 3 million, mostly children die of malaria each year[3]. The liver plays a key role in the life cycle of malaria parasite & in some cases it is seriously affected. Although hemolytic jaundice is not uncommon in malaria, there are reports of derangements of liver function tests to those leading to liver failure as a complication of malarial infection[4].

Although unconjugated hyperbilirubinemia is common in malaria[5-7], hepatocellular jaundice or malarial hepatitis with an incidence of 2.6% was reported from North East India[8]. Higher incidence of malarial hepatitis was reported by a number of authors[9, 10]. While hepatomegaly & mild elevation of enzymes can be observed in a significant proportion of patients, involvement of liver leading to liver cell necrosis is a relatively uncommon complication in falciparum malaria[11-16].

Hepatocellular dysfunction ranging from conjugated hyperbilirubinemia with or without mild elevation in trasaminases has been described in malaria[12,13]. Although, jaundice in malaria is multifactorial and is due to one or several of the following:

A. Intravascular hemolysis of parasitized and non-parasitized RBCs.
B. Shock and disseminated intravascular coagulation leading to microangiopathic hemolysis.
C. Hepatocyte dysfunction.
D. Co existent malnutrition.

Raised unconjugated bilirubin, due to hemolysis, is often seen in cases of malaria[17,18]. But, hemolysis alone does not cause severe jaundice or predominantly conjugated hyperbilirubinemia.[19] Even if bile pigment production reaches to its maximum of 1500 mg daily (6 times normal), serum bilirubin rises only to about 2-3mg%. Some studies have suggested that mild jaundice may result from hemolysis alone, but very high bilirubin concentration indicate hepatocyte dysfunction[20, 21]. Moreover, hemolysis alone can produce predominantly unconjugated hyperbilirubinemia which usually does not exceed more than 10 mg%[22]. In patients having serum bilirubin levels of more than 10 mg%, there are more chances of associated hepatocellular injury as compared to the patients having serum bilirubin levels of less than 10 mg%, in whom the hemolysis and disseminated intravascular coagulation may be the important factors[22]. Therefore, patients with serum bilirubin levels more than 10mg% are likely to have a proportion of raised conjugated bilirubin, along with raised liver enzymes, indicating hepatocellular injury.

The term 'malarial hepatitis' (MH) has been used in the literature to describe the occurrence of hepatocellular jaundice in patients with Plasmodium falciparum infection. However, histologically, the hepatitis or the actual inflammation in the liver has never been demonstrated[23]. The term malarial hepatopathy appears to be a more appropriate one to describe hepatocellular dysfunction in cases of malaria.

Alteration in liver function has also been observed by many earlier workers, in India as well as other part of Asia hence the present study was designed to evaluate the clinical and biochemical changes in liver in patients with malaria with jaundice[8, 24].

AIMS: To evaluate the clinical profile & biochemical changes in patients of malaria with hepatopathy and patients of malaria without hepatopathy.

Material & methods: A total number of 40 patients both male & female irrespective of age and suffering from jaundice & evidence of malaria on peripheral smear & positive malaria antigen card test & malaria hepatopathy were selected as a study group. The same number of patients who were suffering from jaundice & malaria without hepatopathy were selected as control group. The patients with liver disease due to viral hepatitis, alcoholism, abscess, liver enlargement, fatty liver, cirrhosis, portal hypertension, taking hepatotoxic drugs were excluded from the study.

Ethical Consideration:

The specimen used for this study (i.e. blood and pleural fluid) will be obtained as a byproduct of various different investigations routinely carried out on the patients in the hospital wings.

(A) Selection of subjects/patients: The present study was done in Global Gastroenterology Centre, Bhopal. Fifty (50) subjects were selected for this study from OPD and Indoor ward of the centre during 2010 &2012. It included patients of both sexes & different ages.

(B) The samples were be collected and divided in two groups as follows:

Group I – Newly Diagnosed Patients Of Jaundice With Malaria Hepatopathy.
Group Ii— Controls Of Patients with Malaria With-out Hepatopathy.
Inclusion criteria: Patients of all age group in with definitive diagnosis of malaria were considered for the study. The diagnosis was made by clinical history, clinical examination, peripheral smear examination for parasitemia, malaria antigen test & other biochemical blood tests. Because, this study is focussed on assessment of malaria with or without hepatopathy, those patients which were malaria positive for slide test of malaria &/or with positive malaria antigen test were included.

Exclusion criteria: Exclusion criteria for test group included the presence of clinical & serological evidence of hepatitis due to other causes eg. Drug or viral hepatitis.

For all participant patients requisition proforma was filled including their age, sex, diagnosis, & other medical complaints. All patients and control subjects gave formal consent for the study.

(B) *Blood Samples:* Five (5) ml of blood was obtained from each patient and control & collected in EDTA & Plain tubes.. Aliquot of samples were kept for analysis. Blood samples were centrifuged and serum separated for the analysis to be carried out.

(C*) Biochemical analysis:*
Tests carried out were,

1. Serum total Bilirubin 2. Serums direct Bilirubin 3. Serum indirect Bilirubin 4. Serum Alanine Aminotransferases (AST) 5. Serum Aspartate Aminotransferases (ALT) 6. Alkaline Phosphatase. 7. Serum protein. 8. Serum Albumin. 9. Serum Globulin. 10. Serum Urea. 11. Serum Creatinine. 12. Serum Electrolytes (Sodium & Potassium). 13. Complete Blood picture. 14. Malaria antigen card test. 15. Smear examination for malaria.

The above biochemical parameters were determined. Biochemical analysis of all these serum samples was done on Biosystem A25 fully automated analyzer using Biosystem kits. Complete blood picture was done on fully automated cell counter. Malaria antigen card test was done by antigen cards by morpean. Frequency tables & chi square tests were done to compare and to measure the mortality in malaria with hepatopathy & without hepatopathy.

All patients were treated by IV/oral quinine, Artemesinin compounds using standard regimen, whereas specific complications were treated according to the WHO protocol. Adequate care was taken for management of hypoglycemia. Chi square test $x^2 = 1.343$ was used to calculate p value which was considered insignificant when the value were > 0.05

RESULTS

The age of the patients ranged between 15-60 years. Apart from the fever and jaundice, which were present in all the patients, other signs and symptoms were related to individual complications. The important finding was icterus in all the Patients .The serum bilirubin levels were < 3 in 42 % patients and > 3 in 58 % patients. The conjugated bilirubin levels were raised to > 3 in 90 % patients. The mortality observed with malaria hepatopathy in our study was 6 %.

The mortality associated with conjugated bilirubin & malaria hepatopathy is significant i.e. 0.0001 according to Pearson chi square test.

Frequency Table

Serum bilirubin (mg%)					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<3	21	42.0	42.0	42.0
	3-10	16	32.0	32.0	74.0
	>10	13	26.0	26.0	100.0
	Total	50	100.0	100.0	

The serum bilirubin levels were raised in a majority of patients with malaria. The serum bilirubin levels < 3 were 42 %, those between 3 – 10 were 32 % & serum bilirubin >10 were 26 %.

Unconjugated					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<3	31	62.0	62.0	62.0
	3-10	15	30.0	30.0	92.0
	>10	4	8.0	8.0	100.0
	Total	50	100.0	100.0	

Conjugated					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<3	30	60.0	60.0	60.0
	3-10	15	30.0	30.0	90.0
	>10	5	10.0	10.0	100.0
	Total	50	100.0	100.0	

The conjugated bilirubin levels were raised between 3 – 10 in 30% patients % were >10 in 10 % patient

SGOT

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<40	15	30.0	30.0	30.0
	40-100	19	38.0	38.0	68.0
	>100	16	32.0	32.0	100.0
	Total	50	100.0	100.0	

The SGOT levels were raised in > 40 in 70 % patients.

SGPT					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<40	19	38.0	38.0	38.0
	40-100	22	44.0	44.0	82.0
	>100	9	18.0	18.0	100.0
	Total	50	100.0	100.0	

SGPT which is more liver specific enzyme was elevated in 82% patients. Hemoglobin level					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<5	4	8.0	8.0	8.0
	>=5	46	92.0	92.0	100.0
	Total	50	100.0	100.0	

Hemoglobin levels < 5 were observed in 8 % patients.

Mortality					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	47	94.0	94.0	94.0
	Yes	3	6.0	6.0	100.0
	Total	50	100.0	100.0	

The Percentage mortality observer with patients of malaria hepatopathy was 6%.

Count					
<3		Mortality- conjugated			Total
		3-10	>10		
Mortality	No	31	14	2	47
	Yes	0	1	2	3
Total		31	15	4	50

Chi-Square Tests			
	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	15.721[a]	2	.000
Likelihood Ratio	9.804	2	.007
N of Valid Cases	50		

a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is .24.

DISCUSSION

Serum bilirubin is elevated and it is the conjugated fraction which is dominant in patients with hepatopathy[22]. According to the WHO, serum bilirubin levels in patients with severe falciparum malaria remain in the range of 7–10 mg/dL but in a study, 29 out of 86 patients had serum bilirubin levels greater than 10 mg/dL with a maximum value of 48.2 mg/dL[25]. Another study found 14 of 31 patients with serum bilirubin levels greater than 14 mg/dL with predominantly conjugated hyperbilirubinemia [24]. Anand et al.[8] studied 39 patients, out of whom 13 had serum bilirubin in the range 16 ± 6.3 mg%, and most had predominantly conjugated hyperbilirubinemia.

In a study of 50 cases of falciparum malaria 18 patients had serum bilirubin < 3mg%, 20 patients had serum bilirubin 3-10 mg% and 12 patients had serum bilirubin >10 mg %[7].In this study 21 patients (42%) had significant conjugated hyperbilirubinemia. This study also observed raised serum enzyme levels in some of these patients and 9 out of 12 patients having serum bilirubin levels of more than 10mg% also had very high levels of serum enzymes. In another study by Kochar et al[15] The AST/ALT levels were 158.11 ± 76.79 IU/l and 202.98 ± 120.00 IU/l, respectively, in patients with serum bilirubin < 10 mg%, vs. 563.03 ± 303.13 IU/l and 669.83 ± 368.08 IU/l, respectively, in patients with serum bilirubin > 10 mg%.

Hepatocellular damage in malaria is also proven histopathologically in some studies. In a study of 50 patients with proven Plasmodium falciparum malaria with jaundice, histo-pathological examination was done in 20 patients with serum bilirubin level 3-10 mg%. It showed evidence of swollen hepatocytes in 100%, malarial pigment deposition in 75%, inflammatory infiltrates in 60%, congestion of hepatocytes in 50% and associated centrizonal necrosis in 25% of cases and fatty change in 10% of cases[23]. Another study of 60 patients of slide positive falciparum malaria, age more than 18 years, who were subjected to liver biopsy also showed liver involvement[26]. The specific histopathological changes in liver due to P. falciparum observed in this study were RE cell proliferation - 90%,haemazoin pigmentation - 90%, congestion 80%, portal infiltration - 75%, sinusoidal infiltration and dilatations - 71.6%, cholestasis- 40%, while minor changes in the form of nuclear vacuolation - 23.3%, liver cell necrosis - 18.3%, and vacuolated cytoplasm in10%, of cases were also seen.

CONCLUSION

It has been observed that higher serum bilirubin levels are associated with increased incidents of complications and mortality. The mortality too was higher in patients with 'malarial hepatopathy. The mortality associated with conjugated bilirubin & malaria hepatopathy is significant.

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