Original article:

Renal and hepatic derangements in malaria with clinical outcome

Dr. B G Shivakumar ; Dr. Sai Sekhar P

Name of the Institute/college: JJM MEDICAL COLLEGE, Davangere , India

Corresponding author : Dr. B G Shivakumar

Abstract:

Background:. India accounts for two third of the cases in South East Asia. The clinical pattern of malaria has changed worldwide including India in last decade.

Methods: 100 cases of malaria diagnosed by peripheral smear or rapid spot test were included in the study. Patients with urea (>35mg%) and creatinine (>1.5 mg%) and urine output (<400 ml/day), patients with total bilirubin > 3mg% were categorized into predominant conjugated jaundice if direct bilirubin >15% of total.

Results: Renal dysfunction was seen in the form of raised blood urea 30% of cases, raised serum creatinine 16% of cases and proteinurea 21%, haematuria 16%, oliguria 9% and ARF 5%. 30% had biochemical jaundice.

Conclusion: Renal and Hepatic dysfunction is common in malaria and associated with bad prognosis if left untreated. Acute renal failure is common and conjugated bilirubinemia predominates biochemical jaundice in malaria.

Keywords: Urea, Creatinine, Jaundice, Malaria

Introduction:

Malaria is an important parasitic disease of mankind known to exist in India for thousands of years. In spite of phenomenal progress in medical science in latter half of the century, malaria still continues to be a major killer of mankind especially in developing and developed countries. India contributes to about two thirds of malaria cases in the South East Asian Region of WHO. Although annually India reports about two million cases and 1000 deaths attributable to malaria, the true burden of malaria in India is not certain.[1]

There is an increasing trend in the proportion of Plasmodium falciparum as the agent, but the pattern of clinical presentation of severe malaria has also changed and while multi-organ failure is more frequently observed in falciparum malaria, there are reports of vivax malaria presenting with severe manifestations and multiorgan failure.[2,3]Plasmodium falciparum is known for its dreaded complication of renal dysfunction. An upsurge in the incidence of acute renal failure in malaria has been reported in India and varies from 13% to 17.8%.[4] This can be due to increasing problems of drug and insecticide resistance.[5]

Jaundice is common in adults with severe malaria and there is other evidence of hepatic dysfunction with increase in serum bilirubin, Serum transaminases and 5-nucleotidase, fall in serum albumin and

prolonged prothrombin time. Jaundice in malaria is caused by hemolysis, hepatocyte injury and cholestasis.[6] Hepatic dysfunction contributes to hypoglycemia, lactic acidosis and impaired drug metabolism.

Methodology:

This study consists of 100 patients, both male and female with malaria getting admitted to Bapuji Hospital and Chigateri Government Hospital, attached to J.J.M. Medical College, Davangere during the period of 2012-2013. A cross sectional clinical study consisting of 100 new cases of malaria is undertaken to study the renal and hepatic derangements.

Inclusion criteria :

- Patients of age greater than 16 years and both sexes
- Patients positive for malarial parasites either by thick and thin smear or by Rapid spot malarial antigen test.

Exclusion criteria :

- Patients in whom renal and hepatic dysfunction might already be present were excluded from the study.
- Known hypertensive
- Known diabetics
- Patients with known renal disease
- Patients with urinary tract infections
- Patients with chronic liver diseases, alcoholics
- Patients who are on anti tubercular treatment.

100 patients, with malaria admitted in Bapuji Hospital and Chigateri Government Hospital studied using random sampling methods over a period of one and half years in 2012-2013. Patient studied with the following investigations.

a) Peripheral blood smear/ rapid spot test for malarial parasite
b) Complete haemogram
c) Blood urea and serum creatinine
d) Serum sodium and serum potassium
e) Random blood sugar
f) Urine for protein, sugar, white blood cells and red blood cells
g) Liver function tests which includes prothrombin time, total protein, albumin, total bilirubin, direct and indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkalaine phosphtase (ALP).

The following patients were taken as having acute renal failure.

Patients with serum creatinine levels of more than 3 mg/dl

Oliguric acute renal failure :

Patients with serum creatinine > 3mg/dl and urine output ≤ 400 ml/day

Non oliguric acute renal failure :

Patients with serum creatinine > 3mg/dl and urine output >400 ml/day.

Patients were followed up until blood examination was negative for malarial parasites.

Results:

The study consisted of patients admitted in the medicine wards of Bapuji Hospital and Chigateri General Hospital (District Hospital) Davangere attached to J.J.M. medical college, during the period from 2012 to 2014.

This study consisted of 100 cases satisfying inclusion and exclusion criteria.

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Table 1: Proportion for malaria paraistes

	No.of cases
Vivax	61
Falciparum	39

Table 2 : Age distribution

Age (years)	**No.of cases**	**Percentage**
< 20	7	7
21 – 40	52	52
41-60	32	32
> 60	7	9
Total	**100**	**100**

Majority of patients were in the age group between 21-40 years (52%). The youngest patient was 18 years and the oldest was 80 years.

Table 3 : Blood urea (N=30)

BLOOD UREA (MG/DL)	**VIVAX**	**FALCIPARUM**	**TOTAL**	**PERCENTAGE**
35 – 50	7	6	13	43.3
50 – 100	3	7	10	33.3
>100	2	5	7	23.3
Total	**12**	**17**	**30**	**100**

Renal dysfunction in the form of raised blood urea (≥ 35 mg/dl) was seen in 30 patients.Majority of the patients with raised blood urea had falciparum malaria 17 patients (56%).

Renal dysfunction in the form of raised serum creatinine (>1.5 mg/dl) was seen in 16 patients. Majority 62% of patients had P.falciparum malria.

- Out of 100 patients, acute renal failure was seen in 5 patients (5%).
- 4 Patients (80%) had P. falciparum malaria, while 1 patient (20%) had P. Vivax.
- In all the 5 patients blood urea was above 100 mg/dl.
- Hyperbilirubinemia (> 3mg/dl) was seen 4 patients (80%).
- Dialysis was done in 3 out of 5 patietns (60%), while 1 patient (20%) was managed conservatively.
- Moratality was seen 1 patient (20%) in ARF.

Fever, nausea or vomiting, headache and altered sensorium were the predominant features. One patients had persisting hiccups. Thromboc-ytopenia, heamaturia were predominant findings.Oliguric renal failure was seen in four

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patients (80%) while the other one patient (20%) had non-oliguric reneal failure.

Liver enzymes:

Table 4 : Serum alkaline phosphatase (ALP)

ALP	Vivax	Falciparum	Total	Percentage
Serum alkaline phosphtase (ALP)	4	4	8	8

Serum Alkaline phosphatase (ALP): ALP levels above 4 times the upper limit were taken to be suggestive of significant cholestatic jaundice.8 (8%) cases had a serum ALP value above 4 times normal i.e. >360U/L. But only 6 of these values were seen in jaundiced cases. Hence 6 (6%) of 100 cases had a significant cholestatic component to the jaundice. These 6 cases 4 were caused by falciparum malaria and 2 caused by vivax malaria..The 2 cases without associated jaundice could signify a transient cholestasis without bilirubinemia. 1 caused by vivax malaria and 1 by falciparum.

Table 5 : Serum alanine aminotransferase (ALT)

ALT	No.of Cases	Percentage
≥120	21	21
≥ 120 with TB >3 mg%	10	10

Serum ALT(>3 times) elevated in 21(21%) patients among them jaundice is seen in 10(10%) patients.

Discussion

In this study renal dysfunction was seen in the form of raised blood urea (30%), raised serum creatinine (16%) proteinuria (20%), heamaturia, (16%), oliguria (9%), acute renal failure (5%).Raised blood urea was seen in 30 patients (30%) and majority of them (17 patients) had falciparum malaria. Study done by Nityanand et, al.,[7] also showed raised blood urea in 32% with majority of them having falciparum malaria.

Raised serum creatinine was seen in 16 patients majority of them, 10 patients 62% had falciparum malaria. Out of these 16 patients, 5 of them develop acute renal failure, of which 1 died. In a study by Nityanand et. al.[7] raised serum creatinine was seen in 32% and majority of the had falciparum malaria.Rise in blood urea and serum creatinine in malaria have been attributed to various factors like dehydration, increased catabolism and impaired real function.[8]

Acute renal failure is one of the dreaded complication of severe malaria. Out of 100 patients in our study, 5 patients 5 progressed to Acute renal failure, of which 4 patients (80%) had falciparum malaria, 1 patients (20%) had vivax. Mehta et al[71] also showed a similar incidence of Acute renal failure in malaria of

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about 5.9%, predominantly (66%) with falciparum malaria.

Acute renal failure was associated with hyperbilirubinemia in 4 patients (80%), which is almost similar in the study done by Habte B. et al.,[12] (92%). Another study conducted by V.B. Kute, et al., Jaundice is seen in 74.5%.[13] The presence of jaundice indirectly increases renal injury by increasing vascular reponse of catecholamines, increase in Plasma Renin Activity (PRA), hypreuricemia.

All the 5 patients (80%) in our study had thrombocytopenia. Milind Y. Nadkar[40] in his study has shown such a high (100%) incidence of thrombocytopenia in patients with severe malaria.It has been suggested that platelet consumption, as part of disseminated intravascular coagulation (DIC) is a possible mechanism. Sequestration and destruction of platelets in the spleen, in conjunction with spleenomegaly is though to be another possible mechanism. Electron microscopic confirmation of intra platelet parasitism suggests that this is also a possible cause of decreased life span of platelets.

Acute renal failure was associated with altered sensorium in 3 patiens (60%), Acute Respiratory Distress Syndrome (ARDS) in 1 patient 20%. Study done by Prakash J.et al.[14] showed altered sensorium in about 38.4% of the patients with acute renal failure. Study conducted by Tran Thi My et al[10] showed Acute Respiratory Distress Syndrome (ARDS) in 11% and lower.Altered sensorium in severe malaria have been attributed to various factors like renal dysfunction, hepatic dysfunction or electrolyte imbalance.Dialysis was done in 3 out 5 patients (60%) and one patient (20%) was managed conservatively, in the study done by Mehta et al[11], dialysis rate was 92% in patients with acute renal failure.

In this study the incidence of jaundice in malaria was 30%. Other studies as reviewed show the following. There is a wide variation in the report of jaundice in malaria. In a study of 732 patients with falciparum malaria in an endemic area, it was shown that jaundice occurs in 5.3% of all such cases. Mehta et al. in a study of 425 cases of falciparum malaria have also reported jaundice in only 2.58%. In epidemics, the reported incidence of jaundice is higher and varies from 11.5% to 62%. Murthy et al. found jaundice in 62% of patients with falciparum malaria. Wilairatana et al. from Thailand reported an incidence of jaundice in 32% of falciparum malaria although the bilirubin was predominantly unconjugated. Harris et al. from South India found that 37% of cases of falciparum malaria had hyperbilirubinemia. In children, Bag et al. found 'hepatitis' in 8% children with complicated falciparum malaria.

The incidence of jaundice can vary a lot. It can as low as ~2% and as high as 100%.

Jaundice in falciparum vs. jaundice in vivax:

Jaundice has been found to be more common in falciparum as compared to vivax malaria. Hazra et al. found an association of jaundice in 40% and 9.09% cases with P. falciparum and P. vivax, respectively, from Calcutta. Echeverri et al. in a study of vivax malaria from Colombia have reported an incidence of jaundice in 15%. Seth et al. found jaundice in 7.7% cases of falciparum malaria while they did not find jaundice in vivax

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malaria.At least 10% of patients in this study had malarial hepatitis. This entity seemed to be occurring even in Vivax malaria.

The remaining 11 cases showing ALT elevation >three times a had some component of hepatic injury, but it was not amounting to produce hyperbilirubinemia.

Serum Aspartate aminotransferase (AST):

AST is found in the liver, heart, skeletal muscle, kidneys, brain, and red blood cells. AST too is most commonly found in the liver as is seen to rise with hepatocyte injury. However to prevent confusion from distinguishing an elevated level due hemolysis of RBCs from an elevated level due hepatic injury with ALT>120IU/L was used.The results in this study showed an increase in AST >120IU/L in 40%.

However, only 20% had an elevated AST (>3 times) with conjugated hyperbilirubinemia. Comparing with other studies:

Serum Alkaline phosphatase (ALP):

Alkaline phosphatase is a hydrolase enzyme used to indicate cholestasis. Levels above 360IU/l (>4times the upper limit of normal) associated with conjugated hyperbilirubinemia usually imply cholestasis.

In this study ALP was found to be elevated more than 360IU/L in 8% of the cases, but the elevation was associated with conjugated bilirubinemia only in 6% of the cases.

So cholestatic component of jaundice was present in at least 6% of the total cases.

Conclusion

- The peak incidence of renal dysfunction was seen in 3rd to 5th decade.
- Renal dysfunction was seen in the form of raised blood urea (30%), raised serum creatinine (16%), proteinuria (20%), haematuria (16%), oliguria (9%), acute renal failure(5%).
- Though the incidence of acute renal failure in malaria was 5% but renal dysfunction was seen in almost 36% of patients.
- The presence of jaundice was a bad prognosis in malaria.
- The mortality was 1% in this study.

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