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P. falciparum Malaria induced Renal impairment

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Abstract

Introduction: The involvement of the kidney in falciparum malaria has been known for decades. In 1944, Spitz observed acute renal failure due to falciparum infection in soldiers during World War II. This observation was later supported by other workers who detected oliguria developing in patients with black water fever. The initial clinical pattern is that of reversible renal dysfunction or pre-renal azotemia, which rapidly progresses to acute tubular necrosis if treatment is not started early. Patients with malaria induced renal failure are hypercatabolic with blood urea and serum creatinine levels rising rapidly.Oliguric as well non-oliguric renal failure are observed and duration of oliguric renal failure ranges from a few days to several weeks depending on the severity of renal dysfunction. Acute renal failure in falciparum malaria is usually associated either with acute intravascular haemolysis or heavy parasitemia. Acute renal failure in falciparum malaria is also observed in patients with severe intravascular haemolysis resulting in haemoglobinuria. It may be induced by malarial fever or by anti-malarial drugs in a patient with or without G6-PD deficiency. **Materials and Methods:** This is a hospital based cross sectional study carried out in a total of 50 cases of acute renal failure who were selected from diagnosed patients of *P. falciparum* malaria. Cases were confirmed either by *P. falciparum* antigen test and/or peripheral blood smear test(both thick and thin smear).Malarial ARF (MARF) is diagnosed when serum creatinine level > 3 mg/dl, and/or urine output < 400 ml/24hrs despite adequate rehydration. **Result:** Out of 174 cases of falciparum malaria 50 patients (28.7%) had acute renal failure in falciparum malaria. 36 (72%) cases were males and 14 (28%) were females, indicating a much higher incidence in males. Approximately 78% of the cases in the present study were below the age of 40 years. The youngest was 15 years old and the oldest was 61 years old (Mean age – 32 ± 11.6 years). All were febrile (100%) and a majority had oliguria or anuria (72%); jaundice was detected in 30 (60%) patients on presentation. Hepatomegaly & Splenomegaly were found in 76% & 66% of the cases respectively. Out of the total 50 cases of malaria induced ARF, 14 cases (28%) had pre-renal ARF while in the majority, 72% the clinical course was that of ATN. The pathogenesis of ATN in the 36 cases was found to be heavy parasitaemia in 40% of the cases, IV hemolysis with haemoglobinuria in 3 (6%) of cases; and cholestatic jaundice in 26% of falciparum patients. Examination of the urinary sediments revealed that albumin was present in urine in 40 cases (80%). Majority of the patients had significant rise in blood urea level with a mean value of 177 mg. S. creatinine levels ranged between 3.2 - 13.6 mg with a mean value of 7.83 mg. The mean creatinine clearance rate was 11.71 ml/min. The overall mortality rate was 26%. **Conclusion:** AKI is common in Falciparum malaria. The pathogenesis of AKI is largely unknown but may be related to the erythrocyte sequestration and agglutination within the renal microcirculation interfering with flow and metabolism. Clinically and pathologically, this syndrome manifests as Pre-renal azotemia and acute tubular necrosis. Acute renal failure may occur simultaneously with other vital-organ dysfunction (in which case the mortality risk is high) or may progress as other disease manifestations resolve. Early dialysis or hemofiltration considerably enhances the likelihood of a patient's survival, particularly in acute hypercatabolic renal failure. Severity of oliguria and presence of one or more associated complications like pulmonary oedema, acidosis, and altered sensorium have considerable influence on the outcome of the patients.

Keywords: Blood Urea Nitrogen (BUN), Acute Tubular Necrosis (ATN), Acute Kidney Injury (AKI), Malarial Acute Renal Failure (MARF), Acute Renal Failure (ARF).

INTRODUCTION

The overall prevalence of ARF in falciparum malaria is less than 1%, but could go upto 60% in severe infection. The reported incidence in India included: 13% North East India, 17.2% in Orissa and 17.8% in Delhi. Overall mortality among those with renal failure was 45%, compared with 10% in those without (WHO, 2000).

ARF is more common in adults than children. Malarial acute renal failure is diagnosed when serum creatinine level rises above 3 mg/dL (265 mol/L) and/or when urinary output is less than 400 ml in 24 hours. Renal involvement varies from mild proteinuria to severe azotaemia associated with metabolic acidosis.

Acute renal failure is mediated through several mechanisms. These may be due to the effect of the parasitized RBC (pRBC) on the microcirculation, hypovolaemic shock, or non-specific effects of

inflammation.

a. Effect of pRBC on the microcirculation:

The entry of parasite into the RBC produces changes in the surface of the pRBC causing formation of knob-like processes, which helps in anchoring the endothelium and adhesion between RBCs. This tight pack of RBCs impedes the microcirculation to various vital organs. There occurs cytoadherence due to thrombospondin formation from vascular endothelium. This is specifically seen in *P. falciparum* and not in *P. vivax* or *P. malariae*. Hence, acute renal failure is seen in falciparum. Inability of pRBCs to deform according to the need of microcirculation leads to sluggish blood flow and consequently to renal ischaemia.

b. Hypovolaemia:

In severe infection, vascular permeability is increased by chemical including kinins, prostaglandins, leukotrienes, histamine, serotonin, adenosine & probably other unidentified substances. Fluid leaks from the intra-vascular compartment and lead to hypovolaemia.

Vascular endothelial damage induced by anoxia, complement activation and oxygen radicals released during the inflammatory process and circulatory reflow further increases fluid leakage from the intra-vascular space. Blood volume thus decreases in severe infection. Hypovolemia is also attributed to increased insensible loss and sweating from pyrexia, decreased fluid intake and increased capillary permeability. Hypovolemia thus decreases the renal blood flow, and by catecholamine release through the activation of the sympathetic nervous system, renal blood flow is further compromised leading to renal ischaemia and renal failure.

c. Non-specific effects of inflammation:

Several pathophysiologic alterations that occur in falciparum malaria can lead to renal ischaemia and tubular injury. These alterations are the nonspecific consequences of infection, but are important factors in the pathogenesis of renal failure.

1 Intravascular coagulation (DIC):

The role of intra-vascular coagulation in the pathogenesis of renal failure deserves consideration. Alteration in coagulation factors, prolonged prothrombin time, thrombocytopenia & the presence of fibrin degradation products are common in severe falciparum malaria. The fibrinogen half life is diminished and fibrin is deposited in the vascular bed.Occasionally, disseminated intravascular coagulation occurs in severe cases & is associated with cerebral, pulmonary and renal complications.Recent study has suggested that malarial thrombocytopenia is the result of splenic pooling of platelets aggravated by a decrease in platelet life span.

In most patients, however the classic picture of disseminated intravascular coagulation is not present generally; only regional or low grade intra- vascular coagulation is present and its contribution to the development of renal failure is probably minimal.

1. *Intravascular haemolysis*:

Haemolysis is usual phenomenon in malaria and it ranges from mild to severe. Severe intravascular haemolysis in black water fever is a well recognized clinical entity and is one of the causes of acute renal failure. Several factors including membrane changes,immunologic reactions, alteration of charges on the erythrocyte surface and interference with erythrocyte ATP and sodium-potassium ATPase have been incriminated in causing haemolysis. But, except for patients with glucose-6-phosphate dehydrogenase deficiency or those receiving multiple drug treatment, haemolysis is usually mild. In the majority of the cases, haemoglobin cannot be detected in the plasma and serum haptoglobin is normal.

2. *Hyperviscosity:*

Significant increase in blood viscosity has been observed during the acute phase of falciparum malaria due to combined effect of the elevation of plasma fibrinogen and alteration in the rheologic property of the infected red blood cells.Decreased deformability of parasitized red blood cells with increased viscosity has been shown in experimental malaria. The rise in blood viscosity is of significant degree when compared with that of uncomplicated falciparum malaria with milder elevation of plasma fibrinogen and lesser degree of parasitaemia. The increase in blood viscosity could, according to Poiseuille's law, significantly decrease the flow in the micro-circulation. Hyperviscosity coupled with hypovolemia compromises the renal blood flow and favour intra-vascular coagulation.

3. *Catecholamine effects:*

Studies by various workers has shown that in the early stage of renal failure in falciparum malaria, infusion of phenoxybenzamine is followed by the increase in urine flow and urine sodium excretion. However, when acute tubular necrosis sets in, phenoxybenzamine has no effect.

In humans with falciparum malaria during the early stage of renal failure, evidence of renal ischaemia is indicated by a decreased urine volume, very low urine sodium concentration, increased urine osmolality and decreased glomerular filtration rate. Following phenoxybenzamine infusion, the urine flow, urine sodium concentration and glomerular filtration increase along with the reduction in urine osmolality.

These findings indicate increased catecholamine activity. Catecholamine release is attributed to sympathetic stimulation and stimulation of the adrenal gland by kinin . Although a malarial toxin has long been postulated, but it has never been found. Catecholamine, along with rennin-angiotensin activation by hypovolemia, contribute to the decreased renal blood flow along with leukocyte mediated activation of the kallikrein-kinin system in increasing vascular permeability. Catecholamine also can directly increase vascular permeability.

4 *Hyperbilirubinaemia:*

High levels of bilirubin have also a contributory effect in the pathogenesis of acute renal failure. Haemolysis is invariably present in cases of *P. falciparum* malaria. It can cause alteration in renal haemodynamics in addition to depression in cardiac function. Hyperuricaemia induced by severe jaundice may further compromise renal function in the presence of decreased acid urine. Black water fever is occasionally associated with acute renal failure, and is caused by G-6-PD deficiency in these patients.

5 Bacterial endotoxaemia:

May potentiate ischaemic renal injury.Cachectin can cause haemoconcentration, shock, and tubular necrosis.The angiostudies depict decreased blood flow to the cortical areas of kidney in the acute stage. But glomerulonephritis is very rare (WHO, 2000).

Aims and Objectives

To find out the incidence ,presentations and outcome of acute renal failure in falciparum malaria.

MATERIALS AND METHODS

This cross sectional Hospital based study was carried out among the hospitalized patients. A total of 50 cases of acute renal failure were selected from patients diagnosed to be suffering from falciparum malaria. Cases of *P. falciparum* malaria, confirmed by detection of *P. falciparum* antigen and/or in peripheral blood smear (thick and thin

films) were taken up for the study. Acute renal failure cases were selected based on the fulfillment of the following basic criteria:

1. Malarial ARF (MARF) is diagnosed when serum creatinine level > 3 mg/dl, and/or urine output < 400 ml/24hrs despite adequate rehydration.
2. No past history of renal failure or insufficiency.
3. Normal kidney morphology on USG.

Patients' ≤ 12 years were excluded from the study.

RESULTS

All the available and relevant literature on the subject of acute renal failure in falciparum malaria has been reviewed.

Fifty cases of acute renal failure selected from amongst 174 diagnosed cases of falciparum malaria were studied.

The cases of acute renal failure were diagnosed on the basis of serum creatinine concentration > 3mg/dl (>265µmol/L) and/or 24-hour urine output < 400 ml, despite adequate rehydration, occurring within a few hours to days during the course of the malarial fever.

Patients with past history of renal disease or insuffiency, and age less than 12 years were excluded from the study. Cases were followed up in the hospital with respect to management and prognosis.

The results and observations of the study are summarized below:

- Out of the total of 174 cases of falciparum malaria only 50 cases (28.7%) had clinical and biochemical features of renal failure, while the 124 cases (71.3%) had no evidence of renal involvement.
- Study of the age and sex distribution of the patients with acute renal failure revealed that most of the patients were under 40 years of age and the majorities were males.
- The clinical presentations of the cases were typical with fever present in all the cases. Jaundice was found to be the most frequently associated features with renal failure (60%) followed by altered sensorium 42%. Metabolic acidosis (34%) and pulmonary oedema (28%) were the cases major complications of acute renal failure at the time of presentation. Also patients' presenting with oliguria (72% cases) and 28% had non-oliguric renal failure.
- Analysis of the patients with acute renal failure revealed that pre-renal azotemia secondary to volume depletion or hyper catabolism was present in 14 cases (28%), and in 36 patients (72%), the cause of acute renal failure was acute tubular necrosis. All the patients with pre-renal azotemia had low urinary Na+ excretion of less than 10 mmol/L with either normal or minimal increase in proteinuria, no significant abnormality in urinary sediments and rapid reversal of renal dysfunction following correction of the hypovolemia with intravenous fluids. On the contrary, increased urinary sodium excretion (> 20 mmol/L) was present in cases of acute tubular necrosis.
- Study of the pathogenesis of acute renal failure revealed that severe intravascular haemolysis with haemoglobinuria was the cause of renal failure in 3 patients (6%). Severe malarial infection was the cause of massive IV haemolysis. The majority, 20 (40%) patients developed acute renal-failure due to heavy parasitaemia and 13 patients (26%) due to cholestatic jaundice.
- Severity of the 29 cases of acute tubular necrosis were judged and graded on the basis of serum creatinine levels, duration of renal dysfunction and type of management of the cases. The serum creatinine level in patients with severe renal failure averaged 10.11 mg%, and duration of oliguria ranged between 8 to 15 days, whereas in patients with mild renal failure, serum creatinine level was usually below 5mg%, and duration of oliguria was comparatively of shorter duration ranging between 4 to 7 days. Mean duration for serum creatinine levels to return to normal was 13 days compared to mean duration of 22 days in cases of severe renal failure. Haemodialysis was required in 29 cases of severe renal failure and only 2 cases of mild renal failure. Rest of the cases recovered with conservative treatment.
- Study of the glomerular filtration rate revealed that majority of the patients (90%) had very low GFR (Mean value – 9.68 mmol/L) which indicated severe renal dysfunction. Patients with less severe form of renal failure had moderate fall of GFR (Mean value – 25.59 mmol/L) observed in 10% cases.
- Out of 30 patients with jaundice, 8 patients showed unconjugated hyperbilirubinemia with normal liver enzymes. 22 patients showed features of development of malarial hepatitis or cholestatic jaundice with marked rise in bilirubin level, predominantly conjugated forms along with 3 to 4 fold rise in serum transaminase and alkaline phosphatase levels.
- 29 cases (58%) received Quinine and rest (42%) received Artesunate.
- Dialysis was required in all cases with the severe form of acute tubular necrosis. No dialysis was required in patients with pre-renal azotemia. Patients with relatively milder form of acute tubular necrosis were managed with conventional treatment with quinine infusion, diuretics and dopamine infusion, except in two cases that required haemodialysis. Haemodialysis was done in the total 62% cases. The remaining 19(38%) patients were treated conservatively. Among 31 patients requiring the haemodialysis 24 (86%) were oliguric and 07(14%) non-oliguric. Compared with nonoliguric subjects, the oliguric patients had higher need of dialysis. On average, four haemodialysis sessions were performed, with a per patient minimum of two to a maximum of 14 sessions.
- Overall mortality rate in the present study was 26%. There was 27.8% mortality in cases with severe renal failure. While 78.6% survival was noted in patients with pre-renal azotemia. Fatal outcome was observed especially in the severely oliguric patients and those with other potentially lethal complication such as cerebral oedema, pulmonary oedema and jaundice.

DISCUSSION

In this study of 50 patients with falciparum malaria, there was an overall male preponderance, with 36 cases (72%) were male. Male patient outnumbered female patients in ratio a of 2.57: 1. Previous studies including Dutta et al (1975), Buck et al (1983), and Wilairatana P et al (1994) reported the incidence of malaria in male as 78.3%, 74%, 74.75% respectively. Hence the sex profile in the present study is comparable to the above studies. Frequent travel history, more outdoor activities and less clothing in males compared to females could be the reason for high incidence in male (Park K, 1997). It was observed that the maximum number of patients with falciparum malaria, were in the age group (21-30) years (32%), followed by 26% cases in the age group of 31-40 years. While, 78% of the cases were below the age of 40 years. Tasmin A et al (1993) in his study observed age ranging from 23-63 years and mean age was 38 years. Joshi YK et al (1986) carried

out a study with age group ranging from 19-63 years. So, the present study compares well with the above mentioned studies. Fever was present all the 50 patients in the present study at the time of admission. Renal failure sets within 4 to 8 days from onset of the fever. Fever, as a presenting symptom was observed in 37 out of a total of 42 patients studied in one series (Stone et al., 1972). Similarly, Ramachandra S et al (1976) studied 65 patients of malaria and all the patients presented with fever. Murthy GL et al (1998) studied 20 patients & all of them presented with fever. These time interval almost similar with the present study. Majority of the cases (72%) were oliguric at the time of admission with urine output less than 400 ml per 24 hours. Stone et al., (1972) have reported 85% oliguric renal failure. Similar findings have been reported by V. Boonpucknavig et al., (1979). Habte B et al., (1990) in their study of 72 patients with severe falciparum malaria, observed oliguric renal failure in 45% of cases. Non-oliguric renal failure has also been recognised by other workers (Sitprija et al., 1988). A fewer incidence of complications and a better prognosis associated with non-oliguric renal failure has been observed in various studies by other workers. A fatal outcome was associated significantly with anuria (Trang TT, White MJ et al., 19921). In the present study, 30 patients (60%) out of the total 50 ARF patients with falciparum malaria presented with jaundice. Stone et al. (1972) detected Jaundice in 67% cases of renal failure due to falciparum malaria. Association of jaundice with renal failure verifies the role of hyperbilirubinemia in further compromising the already impaired renal function in severe falciparum malaria (Bloom D, McCalden, 1975; SM Agrawal et al. 1984). The decrease in serum bilirubin is accompanied by increased urine output and improvement of renal function, suggesting the adverse effect of jaundice on renal function (Aoyagi T et al. 1968). So, the present study compares well with the above mentioned studies. In the present study, 21 patients (42%) had altered sensorium, ranging from drowsiness to loss of consciousness. Convulsions were noted in 8% of these patients.Stone et al., (1972) detected altered sensorium in approximately 55% of the cases. Similar study done by Habte et al. (1990) observed a higher incidence of altered sensorium (83%) associated with acute renal failure. The cerebral manifestations suggest reduced blood flow, due to sequestration of parasitized erythrocytes in the microcirculation in falciparum malaria (DA Warrel, 1987. In the present study, anaemia was detected in 35 cases (70%). Ohno T et al. (1996) were observed in 70% of ARF patients developed anaemia and severe anaemia developed up to 40% of the patients. It is typically hemolytic, although blood loss may also contribute. Kochar D et al. (1997) in a study of 532 cases of falciparum malaria has reported severe anaemia in 5.83% cases. In the present study, hepatomegally was found in 38 cases (76%) and Splenomegaly in 33 cases (66%). Almost similar percentages of organomegally were found in the following study; Gupta GC et al. (1991) observed Hepatomegaly in 81.25% cases & Splenomegaly in 71.8% cases. Analysis of the 50 cases of acute renal failure with falciparum malaria revealed two groups:Acute renal failure secondary to volume depletion or hyper catabolic state due to the high fever was noted in 14 patients (28%). There was moderate rise of urea and creatinine with low urinary sodium excretion of less than 10 mEq/L Renal failure was rapidly reversed by correction of the hypovolemia with intravenous fluids. The majority, i.e. 36 patients (72%) developed renal failure; the clinical course resembled that of acute tubular necrosis. The urinary Na+ excretion in these patients was found to be greater than 20 mEq/L.In a study by Sitprija V et al., (1970) on patients with malaria induced renal failure, pre-renal azotaemia was detected in 40% of the patients and acute tubular necrosis developed in 60% cases. A comparatively higher incidence of acute tubular necrosis of 72% in the present study is attributed to the fact that most of the patients were from rural background and were admitted to the hospital rather late during the course of the illness. Occurrence of renal involvement leading to proteinuria has been commonly observed in falciparum malaria by various workers (Sitprija V. 1988; Rath, Patel DK, 1990). Rath et al., (1990) observed proteinuria ranging between 0.4 to 1.5 g/24 hours in all their cases of renal failure. 29 cases (58%) received Quinine and rest (42%) received Artesunate. The reasons behind used more artimisinine derivatives were hypotension with or without multi-organ failure. J Prakash et al. (2002) was used Quinine in majority 78.7% of patients and remaining 21.3% cases were treated with artimisinine derivatives. In this study Quinine was used more number of patients than the present study. Dialysis was required in total of 31 patients (62%) due to rapid renal shutdown with development of complications. All cases Haemodialysis was performed for restoration of normal renal function. The remaining 19 patients (38%) were treated conservatively. Similar observation has been made by Stone et al., (1972) and Weber MW et al., (1991) in their study of malaria induced renal failure. Dialysis was required in 69.2% and 70% of their cases respectively. In the current study, out of the 50 cases with acute renal failure, 13 cases succumbed showing an overall mortality rate of 26% and survival rate of 74%. Excellent prognosis has been observed in the 11 patients with pre-renal azotemia showing 78.6% survival rate. Habte B. et al., (1990) observed a mortality rate of 29% from their study of twenty four patients with malaria induced renal failure. These findings are consistent with the present findings.

CONCLUSION

A sizable number of cases of falciparum malaria develop acute renal failure in the form of pre-renal azotemia and acute tubular necrosis. Cases of pre-renal azotaemia respond well to Antimalarial therapy and conservative treatment with excellent prognosis. Early and frequent Haemodialysis helps in reducing mortality in most of the cases of acute tubular necrosis. Severity of oliguria and presence of one or more associated complications like pulmonary oedema, acidosis, and altered sensorium have considerable influence on the outcome of the patients. Hence, it is essential to look for these ominous parameters which have adverse outcome in renal failure associated with falciparum malaria. As the study was conducted with small number of cases, further study is necessary with large number of cases to arrive at a conclusion regarding the malady of acute renal failure in falciparum malaria.

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