Clinical Profile of Acute Renal Failure in Cases of P. Falciparum Malaria in South Gujarat

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ABSTRACT

BACKGROUND: Acute renal failure is a common complication of severe malaria in adults, and without renal replacement therapy (RRT), it carries a poor prognosis. Even when RRT is available, delaying its initiation may increase mortality. We aimed to study the incidence, severity, clinical presentations, prognostic factors, complications and outcome of ARF in P. falciparum malaria cases of Surat, Gujarat. MATERIALS AND METHODS: A prospective study of cases of plasmodium Falciparum malaria has been carried out between August 2005 to October 2006. The cases were studied in terms of demographic, clinical features, laboratory data, urine output, requirement for Renal replacement therapy and outcomes including death. RESULTS: Acute Renal failure was observed in 10% cases of P.falciparum malaria.60% patients of ARF had proteinuria and granular cast in urine examination.60% had oliguric renal failure.20% cases had hyperkalemia and associated with high mortality.70% of the patients of ARF required dialysis. There was 30% mortality in cases of ARF with P. falciparum malaria Grade ++++ parasitemia. Hypotension, oliguria and jaundice were associated with poor prognosis.66% mortality was noticed in patients having thrombocytopenia with ARF. Multi organ system dysfunction (more than or equal to 3 systems) resulted in 100% mortality. CONCLUSIONS: 70% of patients with ARF in P. falciparum malaria required dialysis. The risk factors determining the prognosis were high serum bilirubin, hyperkalemia, shock, impaired consciousness, oliguria, anaemia ARDS, DIC and delay in the initiation of treatment. Timely offering renal replacement therapy is an important measure to decrease mortality in developing countries.

Keywords: Acute Renal Failure, P. falciparum malaria, renal replacement therapy

INTRODUCTION

Malaria is a major public health problem in tropical developing world. State-wide distribution of malaria cases reveals an incidence of 17.3% in Madhya Pradesh, 14.5% in Maharashtra and 13% in Orissa. Almost the entire population of India (95.9%) is now deemed to be under malaria risk. Almost parallel to this, an upsurge in the incidence of ARF in malaria has been reported in India and varies from 13% to 17.8%. Malaria is caused by protozoan parasites of the genus Plasmodium, namely, P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi. Patients with P. falciparum infection are prone to develop severe malaria in 30% of cases, which results in case fatality rate of 20% 4. In Southeast Asia, acute renal failure (ARF) is one of the most common complications in adults with falciparum malaria5-6. Malaria is endemic throughout South and South-East Asia, South America and Africa. It accounts for 1,000,000–3,000,000 deaths per year in those areas.7 So the incidence of ARF in patients with severe malaria varies widely ranging from 15% to 48%-14 which resulted in a high fatality rate of over 70% in untreated patients.15

ARF in falciparum malaria is multifactorial. Ischemic acute tubular necrosis (ATN) is by far the most common pathology resulting from hypovolemia, peripheral pooling of blood and blockage of microcirculation by parasitized red blood cells and non-specific effects of infection. Massive intravascular hemolysis
itself is uncommon and confined to patients with G6PD deficiency or those receiving a combination of treatments. The latter can cause an immune complex mediated glomerular disease, leading to nephrotic syndrome. Infection with P. falciparum produces only acute manifestations, ranging from asymptomatic urinary sediment abnormalities, mild proteinuria, and mild electrolyte disturbances to acute renal failure (ARF) requiring dialysis support. Renal carries a high mortality, especially in late referrals or if renal replacement therapy is not available. The mainstay of treatment in malarial ARF revolves around appropriate antimalarial therapy, fluid replacement, renal replacement therapy, supportive therapy, and avoidance of nephrotoxic drugs. The availability of renal replacement therapy (RRT) and appropriate antimalarial chemotherapy has been shown to reduce case fatality rate as well as enhance the recovery of renal function.

The term ARF is now replaced with Acute kidney injury (AKI) which was classified as the risk, injury, failure, loss, and end-stage renal failure criteria (RIFLE criteria) proposed by the Acute Dialysis Quality Initiative (ADQI) Group. The aims of our study were to find out the incidence of ARF in cases of P. falciparum malaria and to study the role of Renal replacement therapy in patients of ARF due to P. falciparum malaria. We also observed the various clinical presentations of P. falciparum malaria with acute renal failure. We also find out various prognostic factors and mortality rates in patient of ARF with P. falciparum malaria.

MATERIALS AND METHODS
Study Design. This study was approved by the Ethical Committee of Government medical college Surat. A prospective study of cases of plasmodium Falciparum malaria has been carried out between August 2005 to October 2006 in New Civil Hospital, Surat, Gujarat. All the cases of P. Falciparum positive on peripheral smear examination were included in this study. ARF in P. falciparum malaria was diagnosed following WHO 2006 criteria. ARF (Serum creatinine >3 mg/dl with or without urine output <400 ml per 24 hours despite rehydration).

Inclusion criteria were (1) aged 18 years or above, (2) Presence of asexual stage of plasmodium falciparum on peripheral blood smear examination. Exclusion criteria were (1) patients with previous history of chronic kidney disease or (2) patients with mixed infection. Patients with diseases other than malaria which involved liver and kidney simultaneously e.g., leptospirosis, septicaemia, hepatorenal syndrome, vasculitis, etc. were excluded.

WHO definition of severe P. falciparum malaria - Presence of one or more clinical features in presence of asexual parasitemia defines severe malaria, these clinical features are cerebral malaria, severe haemolytic anaemia, renal failure, pulmonary oedema, hypoglycaemia, circulatory collapse, spontaneous bleeding or disseminated intravascular coagulopathy, acidosis, convulsions and malarial haemoglobinuric.

WHO definition of ARF in P. falciparum malaria - Serum creatinine >3 mg/dl with or without urine output <400 ml in 24 hours despite rehydration is considered as ARF.

Oliguria – Urine output < 400 ml in 24 hours.

Anuria - Urine output less than 50 ml per day.

Multiorgan system failure: Simultaneous dysfunction of 2 or more organs in acutely ill patients such that their homeostasis cannot be maintained without intervention. Patients’ data comprising demographic, clinical features, laboratory data, urine output and outcomes including death and requirement for Renal replacement therapy were reviewed. All the patients were subjected to complete haemogram, peripheral smear for malarial parasite, routine examination of urine, G6PD, RBS, renal and liver function tests, Serum electrolytes, arterial blood gas, DIC profile, ultrasonography (USG) of abdomen, blood cultures, serum leptospirosis.
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antibody, urine for leptospira, ECG, Chest, X-ray, HIV, HBsAg and HCV.

Artemisinin based combination was the main stay of treatment which includes ACT-AL. Co-formulated tablet of artemether (80 mg) - lumefantrine (480 mg) twice daily for 3 days or Artesunate 4 mg/kg body weight daily for 3 days Plus Sulfadoxine (25 mg/kg body weight) – Pyrimethamine (1.25 mg/kg body weight) on first day followed by Primaquine 0.75 mg/kg on second day. Quinine was used as second line or in cases of severe malaria as first line. Quinine dose was not modified if serum creatinine (Scr) was < 3 mg%. When Scr exceeded 3 mg%; usual dose was continued for two days and then reduced as per creatinine clearance.

Renal replacement therapy (Dialysis) was given when indicated. Early dialysis was considered in the presence of severe acidosis and/or fluid overload. Clinical indications of Renal replacement therapy are uremic symptoms and symptomatic volume overload e.g. pulmonary edema, congestive heart failure. The laboratory indications of RRT are severe metabolic acidosis (HCO3 <15 mEq/l), Hypermkalemia (k+ >6.5 mEq/l) and S.creatinine >6 mg/dl.

RESULTS

In present study, we came across 100 cases of P. falciparum malaria in our study period. The incidence of ARF in P. falciparum malaria was 10%(10 cases). All the mentioned results below were observed in patients having both Acute renal failure and P. falciparum malaria. Male to female ratio was 4:1 and 50% of the patients were in age group 45-54 years. Mean age was 38.3 yrs. The average duration of fever was less than or equal to 7 days in 80% of the patients. All the patients presented with high grade fever, 60% had decreased urine output, 70% had jaundice, 80% had headache, 70% had vomiting, 20% had altered sensorium, 60% had cough, 20% had breathlessness, 20% had systolic hypotension, 40% had hepatosplenomegaly and 40% had bleeding manifestations. Hence fever, headache and vomiting were common presentations.

Clinical presentations of ARF in P. falciparum malaria are oliguria (<400 ml), anuria, electrolyte imbalance, increased s.creatinine level (>=3mg/dl), jaundice and anemia.

Out of 10 patients of ARF, 60% had proteinuria, 40% had microscopic haematuria, 30% had pyuria, 20% had hyaline cast and 60% had granular cast in urine for routine examination. 60% were having oliguric renal failure and 40% were non oliguric.

The present study showed 30% mortality in patients of ARF in P. falciparum malaria. Mortality was more in higher age groups. Mortality in oliguric renal failure was 50% where as in non oliguric group, it was nil. 6 patients out of 10 patients of ARF were oliguric out of which 5 were put on renal replacement therapy. Only 4 patients had non oliguric renal failure, out of which 50% required dialysis. Those oliguric patients who undergone dialysis, survival was better as compared to those who did not undergo dialysis. A rapid rising creatinine level is the most sensitive indicator of the need for dialysis. Hemofiltration is more effective and is associated with improved outcome.

Table 1 Table showing relation between urine output, dialysis and mortality

<table>
<thead>
<tr>
<th>Urine output in first 24 hours in ml</th>
<th>Total No of patients</th>
<th>No of expired patients</th>
<th>Mortality</th>
<th>Total No of patients</th>
<th>No of expired patients</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=400</td>
<td>5</td>
<td>2</td>
<td>40%</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>&gt;400</td>
<td>2</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 2 Table showing relation of urine output, hemodialysis and jaundice with mortality

<table>
<thead>
<tr>
<th>Patients with Jaundice</th>
<th>Total No of Patients</th>
<th>No of expired patients</th>
<th>Mortality</th>
<th>Total No of Patients</th>
<th>No of expired patients</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliguria=400 ml/d</td>
<td>4</td>
<td>2</td>
<td>50%</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Non Oliguria &gt;400 ml/d</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
20% patient had ARDS associated with oliguric renal failure in P.falciparum malaria and all those patients died inspite of renal replacement therapy and invasive ventilator support.Jaundice(>3 mg/dl) was present in 70% cases of P.falciparum with ARF. Mortality was high in patients with jaundice as compared to those without jaundice. All patients of grade IV parasitemia were associated with jaundice and 100% mortality.

30% of the patients of ARF with P.falciparum had thrombocytopenia. Renal replacement therapy has definitive role in decreasing mortality when patients have thrombocytopenia with oliguric ARF in P.falciparum malaria. 20% of the patients presented with hyperkalemia. Oliguric, hyperkalemic patients has higher mortality than oliguric normokalemic.

Table: 3 Table showing associated complications in patients of ARF with falciparum malaria

<table>
<thead>
<tr>
<th>Complication</th>
<th>No of Patients(n=10)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>7(70%)</td>
</tr>
<tr>
<td>Cerebral Malaria</td>
<td>3(30%)</td>
</tr>
<tr>
<td>Severe Anaemia (&lt;5 mg/dl)</td>
<td>2(20%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1(10%)</td>
</tr>
<tr>
<td>ARDS</td>
<td>2(20%)</td>
</tr>
</tbody>
</table>

Table: 4 Table showing relation of multiorgan system involvement and mortality

<table>
<thead>
<tr>
<th>No of system involved beside ARF</th>
<th>Total No of patients (%)</th>
<th>No of patients expired</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only ARF</td>
<td>2(20%)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>ARF+1 organ system dysfunction</td>
<td>3(30%)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>ARF+2 organ system dysfunction</td>
<td>2(20%)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>ARF+3 organ system dysfunction</td>
<td>1(10%)</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>ARF+4 organ system dysfunction</td>
<td>1(10%)</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>ARF+5 organ system dysfunction</td>
<td>1(10%)</td>
<td>1</td>
<td>100%</td>
</tr>
</tbody>
</table>

Mortality increases as patient acquires additional organ failure.

DISCUSSION

P. falciparum infection is the most common cause of ARF in patients with severe malaria. We have observed the incidence of ARF in P.falciparum malaria of 10% which is similar to Mehta et al9.

The duration of fever in our study was equal to or less than 7 days which is similar to the study of S.K Panda et al23 in which it was 5-7 days. High grade fever was the commonest clinical presentation as similar to other studies24,25,26. Decreased Urine output was present in 60% of patients as similar to 68% in study of Rubina Naqvi et al25. Jaundice was found in 70% cases of ARF in P.falciparum malaria. In our study, protienuria was present in 60% of the cases which is very close to the figures of study Prakash J. et al10.

It appears that several factors contribute to ARF in falciparum malaria which includes parasitized erythrocytes inducing microvascular obstruction and/or causing hemolysis. Apart from parasites glycosylphosphatidylinositol which is a receptor on monocytes covalently bound to the surface antigens of falciparum malaria parasites. The monocytes are then stimulated to release the tumor necrosis factor, which in turn enhances synthesis of various cytokine cascades and mediators. These mediators also cause changes in blood volume status, vasodilation, and increase vascular permeability resulting in hypovolemia which contributes to ischemic renal failure. Both conjugated and unconjugated bilirubin and bile acid as well have been shown to be involved in the pathogenesis of acute renal failure in falciparum malaria27,28,29.

Microscopy of stained thick and thin blood smears remains the gold standard for confirmation of diagnosis of malaria30. The sensitivity of microscopy is high (>99%). It is possible to detect malarial parasites at low densities. It also helps to quantify the parasite load. It is possible to distinguish the various species of malaria parasite and their different stages.

Factor predisposing ARF in P. falciparum malaria are dehydration, Severe haemolysis, Jaundice, Impaired
ARF is observed, as a rule, only in patients with heavy parasitaemia, or intravascular haemolysis with or without glucose-6-phosphate dehydrogenase Deficiency31. In our study 30% of the patients of ARF with P.falciparum had ++++ parasitemia and all of them died. In a study Prakash J et al32, ++++ parasitemia was present in 30.8% of the patients. In our study 70% patients had jaundice, out of them 42% patients expired which is comparable to Rubina Naqvi et al25, in which 58% had jaundice and out of which mortality was 56%. Almost all patients with jaundice had conjugated hyperbilirubinaemia with cholestasis. This association with malarial ARF is well described and may contribute to the reduction of GFR or development of ATN 16.

In our study 60% patients were oliguric and out of them 50% had mortality showing a great correlation between oliguria and mortality Thrombocytopenia was observed in 30% of the cases and associated with 66.6% mortality as compared to J. Prakash et al33 in which 12.7% had thrombocytopenia. The prognosis of ARF is favourable in patients who have early and frequent dialysis. In our study 70% of ARF patients needed dialysis and mortality was 28.5%. Similar to that, in one study 60% of patients with malarial ARF require Renal replacement therapy 17, 34. In a study Rubina Naqvi et al, 82% oliguric patients required dialysis. 25. In a study S.K Panda et al 23, 75% patients were dialysed and mortality was 20%.

The complications noticed in patients of ARF with P. Falciparum malaria were Jaundice, cerebral malaria, severe anemia, hypoglycemia and ARDS. Our study is comparable to Maheshwari A et al35, Mathieu Nacher et al 36, DK kochar et al13 and Shakya K et al. 24. Mortality increases as the number of complication increases. In our study when ARF was associated with 3 or more organ dysfunction mortality was 100%. Cerbral malaria, jaundice and ARDS were the commonest associations. Our study is similar to that of MK. Mohapatra et al 37.

In developing countries, limited medical resources at primary health care centers and late referrals compound outcomes. This is reflected in the need for immediate dialysis at presentation of 70% of patients referred to our center; slightly higher than in other reports, which showed a need of dialysis in only 60% of patients with malarial ARF 17, 34.

Very high mortality is reported in presence of multiple organ failure. Mortality can be reduced to 10% if early and frequent dialysis is instituted 38.

The prevention of malarial infection and early diagnosis are the only measures likely to decrease malarial ARF in developing countries. Early referral to centers equipped to provide renal replacement therapy, if necessary, along with antimalarial therapy and support, could further reduce mortality and enhance recovery of renal function 25.

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