ACUTE RENAL FAILURE ASSOCIATED WITH MALARIA

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Background: Malaria has protean clinical manifestations and acute renal failure (ARF) is one of its serious complications and could be life threatening. This study was carried out to describe the clinical characteristics and factors associated with adverse out come in patients with malarial acute renal failure. **Materials and Methods**: Data of 46 Patients with ARF and smear positive malaria was analyzed further among all cases of ARF presented to us at Nephrology department of Jinnah Postgraduate Medical Centre, Karachi from January 2003 to December 2004. Results were expressed as mean, standard deviation and range. **Results:** Among 237 patients with ARF of diverse etiology, 46(19.4%) developed ARF due to falciparum malaria. The male to female ratio was 3.6:1. Oliguria was seen in 76.09% on admission, and 78.26% required dialysis. In addition to ARF, most of the patients had at least one other manifestation of severe malaria. 35(76.06%) patients recovered completely while 11(23.91%) died in early dialysis. Prolonged disease duration, severe ARF, cerebral malaria, hyperbilirubinaemia, and disseminated intravascular coagulopathy (DIC) were poor prognostic factors. **Conclusion**: Falciparum malaria associated with ARF is a life threatening condition, but early presentation and intervention with appropriate anti-malarial and dialysis therapy is associated with improved survival and recovery of renal function. Early dialysis treatment in patients with severe falcipaum malaria and signs of deteriorating renal function is recommended.

Key words: Acute renal failure, malaria, falciparum malaria, haemodialysis.

INTRODUCTION

Malaria remains a devastating global health problem. World-wide, estimated 300-500 million people contract malaria each year, resulting in 1.5 – 2.7 million deaths annually. Almost all complications and deaths from malaria are caused by plasmodium falciparum[1].

Recently there is a changing trend not only in the clinical manifestations but also the pattern of complications in malaria. Over a decade ago, cerebral malaria was the predominant manifestation of severe malaria, where as today the combination of jaundice and renal failure are more common[2].

Prevalence of ARF in malaria all over the world has been reported as 0.57% to 60%[3]. In Southeast Asia there is an upsurge in the overall incidence of malarial ARF and has been reported in between 13% to 17.8%[3].

ARF occurs commonly in plasmodium falciparum malaria, although its rare occurrence has been reported in plasmodium vivax malaria[4]. The disease is more common in adults in those areas of the tropics where transmission of malaria is low or unstable and where symptomatic disease occurs at all ages[5]. Established ARF is usually oliguric, but urine output may also be normal or even increased in the presence of increasing serum creatinine values[5].

Several factors; including various chemical mediators, catecholamine release, cytoadherence of parasitized erythrocytes, dehydration, intravascular haemolysis, intravascular coagulation, sepsis hyprebilirubinaemia and hyperparasitaemia have been implicated in the pathogenesis of ARF in malaria[6]. Acute tubular necrosis is the principal pathologic mechanism in malaria induced ARF[6].

Malarial ARF is emerging as an important problem in tropical countries and carries a high mortality, especially when the disease is not diagnosed early, the referral to health centre having dialysis facility is late or when dialysis facility is not available. This study was conducted with the objectives to highlight the occurrence of acute renal failure in patients with established diagnosis of malaria in our country and to describe the clinical characteristics, laboratory parameters and predictors of mortality in these patients, the majority of whom required dialysis.

PATIENTS AND METHODS

This cross-sectional comparative hospital based study took place in nephrology department of Jinnah postgraduate medical centre, Karachi, Pakistan over a two year period, between January 2003 to December 2004. This centre is one of the main hospitals in Karachi and it serves as a tertiary referral centre, predominantly for urban population. Approximately, 1,500 adult patients are admitted annually to its 30-bed nephrology ward, which deals with all kinds of renal diseases.

The study includes the patients who were referred to us with the diagnosis of ARF, on biochemical investigations and/or oliguria, and admitted directly thorough accidents and emergency department in our unit, as well as those who were already diagnosed and had received partial or

complete treatment with antimalarials, before shifted from other medical units for the management of ARF. Interestingly, referral diagnosis did not include malaria as a cause of ARF in majority of patients. Those patients suffering from ARF due to malaria were selected for further study on the basis of following inclusion criteria:

i. Adult patients with ARF and peripheral smear positive for malarial parasite
ii. Normal sized kidneys on ultrasonography.
iii. Absence of any other disease or condition leading to ARF or affecting the outcome of malarial ARF.

Patients who had haemolysis along with glucose-6-phosphate dehydrogenase deficiency were excluded from the study.

The definition of malarial ARF was a serum creatinine concentration > 3mg/dl (>265µmol/L) and/or 24-hour urine output < 400 ml, despite rehydration, in patients who had documented malaria, i.e. asexual forms of malarial parasite on their peripheral blood smear[5].

We describe systemic complications by using the World Health Organization (WHO) criteria[5].

Details of history and clinical assessment were noted in all the patients on a questionnaire to analyze the factors associated with adverse out come.

Thick and thin smears were prepared, stained with Giemsa and examined under the microscope for the diagnosis and type of malarial parasite.

All patients underwent a set of investigations including blood sugar, electrocardiogram and chest radiopraph.

Haematological assay including haemoglobin , total and differential leukocyte count and platelet count, was performed on a coulter machine. Renal profile included complete urine examination, blood urea, serum creatinine, and serum electrolytes. Twenty four hours urinary proteins and endogenous creatinine clearance were done whenever needed. Liver function tests including serum transaminases, serum bilirubin, and prothrombin time were performed in all patients.

Lactate dehydrogenase and reticulocyte count were required if haemolysis was suspected to be the cause of severe anaemia. Partial activated thromboplastin time and D-dimer were analyzed based on clinical suspicion of coagulopathy.

Blood tests for the makers of hepatitis B and C were done in patients who were clinically jaundiced or underwent haemodialysis. Arterial blood gases, ultrasonography of abdomen, cerebrospinal fluid examination, and blood cultures were done when indicated.

All patients received anti-malarial drug therapy. Quinine and atremether were the first line of drugs in this study. Quinine was given intravenously as recommended[5]. The usual dose was continued for two days and then adjusted accordingly.

Initially, conservative management was tried (in patients who were dehydrated, or oliguric and had serum creatinine<5mg/dl on admission.). In these patients fluid replacement, correction of electrolyte and acid-base imbalance, high-dose furosemide, and low dose dopamine infusion, was considered accordingly before the need of dialysis.

Renal replacement therapy in the form of haemodialysis was performed using the standard criteria for indications of dialysis[5] which were, anuria (24-hour urine out put <50ml), fluid overload, advanced uraemia, acidosis, serum creatinine concentration rising rapidly by >2.5mg/dl/day and hyperkalemia.

Urethral catheters were inserted in all patients, and an accurate record was kept of fluid balance. Subclavian, internal jugular or femoral veins were used as vascular access for double lumen catheters. Heparin free haemodialysis was performed in cases with deranged coagulation profile; otherwise 500-1000 units heparin was used. The frequency and duration of dialysis were adjusted according to the clinical or biochemical parameters. Most of the cases required haemodialysis thrice a week.

All patients were followed in hospital with respect to severity of ARF, prognostic factors and final out come till death or recovery of renal function. The factors responsible for adverse out come were noted in individual patients.

To assess the factors adversely affecting the outcome, patients were divided into those who survived and those who expired during the course of their illness. Data was analyzed using the SPSS version 11. The comparison of difference in the means was calculated by student's t-test and the difference in proportions was compared by chi-square test of proportions. P-value of <0.05 was taken as significant for all statistical analysis.

RESULTS

A total of 237 patients with ARF were admitted during the two year period from January 2003 to December 2004. Out of these, 46(19.4%) had malarial ARF. Among the malarial species, as demonstrated on blood film, plasmodium falciparum was responsible for all cases of malarial ARF.

There were 36(78.26%) males and 10(21.74%) females who ranged in age from 16-65years (mean ± SD age=32±12.61) (Tables1&3). Most of the patients were in the second and third decades of their life. The presenting clinical features

and associated complications are shown in (Table1). Fever was the leading symptom. 43(93.48%) patients were febrile at the time of admission while the remaining 03(6.52%) had a history of fever in the preceding one week. Oliguria (76.09%), jaundice (71.73%), hepatomegaly (67.39%), and impaired consciousness (63.04%), were the most common presenting abnormalities. Although impaired consciousness was present in 29 patients, only 09 fulfill the WHO criteria for cerebral malaria. Most of the patients had at least one other manifestation of severe malaria other than ARF. Thrombocytopenia (89.13%), hyponatraemia (28.26%), cerebral malaria (19.57%), acidosis (19.57%), sepsis (15.21%), and DIC (13.04%) were associated complications in malarial ARF (Table 1)

Table 1: Main characteristic of the 46 study patients with malarial acute renal failure

Variables	Cases	%
Male	36	78.26
Female	10	21.74
Fever	43	93.48
Oliguria or anuria	35	76.09
Jaundice	33	71.73
Impaired consciousness	29	63.04
Anaemia	26	56.52
Hepatomegaly	31	67.39
Splenomegaly	24	52.17
Thrombocytopenia	41	89.13
Hyponatraemia	13	28.26
Acidosis	09	19.57
Cerebral malaria	09	19.57
Sepsis	07	15.21
Disseminated intravascular coagulopathy (DIC)	06	13.04
Conservative treatment	10	21.74
Haemodialysis	36	78.26
Expired	11	23.91

The mean duration of illness was 6.02±2.60 (range 3-15) days. Moderate reduction in hemoglobin was common. Hyperbilirubinaemia was noted in majority of cases. The mean bilirubin level was 11.22±9.34mg/dl (range 0.57-37 mg/dl). This was predominantly of the conjugated variety. Serum transaminases were not significantly raised, in comparison with serum bilirubin. Serum alanine aminotransferase (ALT) <128 IU/L and serum aspartate aminotransferase (AST) <321IU/L was noted in all patients. The mean levels of urea and creatinine on admission were 282.5±83.92 mg/dl and 7.304±3.16mg/dl respectively. Positive correlation was found between duration of illness and impairment of renal function. Significant hypoglycemia was not seen. Only 03(6.52%) had blood sugar <40mg/dl. Compared with patients with short duration of illness (<7days), those with prolonged duration (>7days) were more likely to have higher degree of derangement of urea and creatinine,(p=0.001). Only 02(4.34%) of our patients showed serum potassium >5mEq/L. One had 5.3mEq/L and other 5.5mEq/L. Urine examination showed presence of granular cast in 19(41.30%), proteinuria (++) in 13(28.26%), and microscopic haematuria in 10 (21.74%) patients.

Over all, haemodialysis treatment was performed in 36(78.26%) of the patients. The remaining 10(21.74%) patients were treated conservatively. Among 36 patients requiring the haemodialysis 32(88.89%) were oliguric and 04(11.11%) non-oliguric. Compared with non-oliguric subjects, the oliguric patients had higher need of dialysis. (p=0.001).

The average number of dialysis sessions required per patient was 06, with a minimum of 03 to a maximum of 15. The oliguric patients also needed more haemodialysis sessions than the non-oliguric patients (mean SD=7±4.6 versus 2.2±1.2 haemodialysis treatment, respectively), (p=004). 10(21.74%) patients were treated conservatively, whose biochemical abnormalities were not severe enough to require dialysis. In this group the mean value of serum creatinine on presentation was 4.57±1.11 mg/dl (range 3.2-7) as compared with the mean value of 8.064±3.124mg/dl(range4-16mg/dl), in those who required dialysis(p=0.001). In survivors, the course of illness lasted 2-28 days depending upon the severity of ARF. The time taken for serum creatinine level to return to with in the normal range was 13.71±6.40 days in the oliguric patients and 8.45±4.70 days in non-oliguric (p=0.021).

11(23.91%) of total 46 patients succumbed to the disease while 35(76.09%) had complete recovery. Tables 2&3 compare the parameters between patients who survived and those who expired. Death occurred at a mean time of 1.27±0.47 days (range 1-2 days) after admission. All deaths were in dialysis group. Serum creatinine (mean±SD) value was significantly higher in them (10.53±3.00 mg/dl) compared to those who survived (6.29±2.48) (p=0.001).

Table 2: Predictors of mortality in malarial ARF.

Indicator	Survived group (n=35)	Expired group (n=11)	p-value
Age	31.86±13.5	32.45±9.5	0.893
Duration of illness (in days)	5.06±1.71	9.09±2.63	0.001
Haemoglobin (g/dl)	9.08±2.0	8.48±3.07	0.453
White blood cell count (×10³/L).	7.24±2.81	12.1±4.30	0.001
Platelet count (×10³/L).	46.0±22.1	109.8±223.1	0.001
Serum creatinine (mg/dl)	6.29±2.48	10.53±3.00	0.001
Blood urea (mg/dl)	259.5±59.22	355.6±109.7	0.001
Serum sodium (mEq/L)	133.89±9.23	127.91±11.15	0.082
Serum potassium (mEq/L)	4.13±0.50	4.29±0.80	0.423
Serum bicarbonate (mEq/L)	21.49±3.16	15.18±6.57	0.001
Serum total bilirubin (mg/dl)	8.39±7.53	19.42±10.35	0.001
Serum alanine aminotrasferase(U/L)	40.37±14.54	58.09±26.36	0.006
Prothrombin time (in seconds)	13.74±1.50	20.0±4.29	0.001
Score on Glasgow coma scale	12.63±2.37	10.0±2.28	0.002

Table 3: Associated complications as predictors of mortality in malarial acute renal failure

Parameter	No of cases	Survived group n=35(76.09%)	Expired group n=11(23.91%)	p-value
Oliguria on admission	35	24 (68.57)	11(31.43)	0.03
Jaundice	33	24(72.73)	09(27.27)	0.03
Impaired consciousness	29	20(68.96)	09(31.04)	0.011
Anaemia	26	19(73.08)	07(26.92)	0.058
Cerebral malaria	09	03(33.33)	06(66.67)	0.001
Hyponatraemia	13	09(69.23)	04(30.77)	0.026
Acidosis	09	02(22.22)	07(77.78)	0.001
DIC.	06	01(16.67)	05(83.33)	0.001

09 of the patients who died were jaundiced and 06 of them had cerebral malaria. Presence of jaundice was not predicted as a marker of mortality. Instead it was the severity of hyprebilirubinaemia which appeared as a risk factor associated with adverse out come (table3) P=0.001. Patients who were oliguric on admission had a significantly higher mortality P=0.03. Compared with those with out cerebral malaria patients with cerebral malaria were more likely to die (p=0.001). When impaired consciousness alone was taken as a marker of mortality in malarial ARF, it could not prove itself as a predictor of mortality. Acidosis in combination with ARF increased the risk of dying. (P=0.001).

Multiple complications of falciparum malaria were responsible for death in individual patient. Pronged duration of illness, oliguria on admission, hyprebilirubinaemia, cerebral malaria, DIC, and acidosis were the main causes of mortality in our patients (table 2&3)

DISCUSSION

Although only a small proportion of patients with malaria develop severe manifestations, these patients require the most urgent and intensive care. Acute renal failure is a serious complication of falciparum malaria that is especially common among adults in Southeast Asia and carries a high mortality[7].The contribution of malaria to the number of cases of ARF in any particular setting depends to a large extent on the local prevalence of malaria and on the pattern of referral to specialized centre[8].In our study ARF due to malaria was seen in 19.4% of the cases which is comparable to results of other studies conducted in India and Ethiopia[3,9].

There were more males than females in the study patients. This male predominance is difficult to explain but is supported from other studies[3, 4, 8]. A genuine sex difference in susceptibility to renal dysfunction in patients with falciparum malaria is possible. Among the plasmodium species, only falciparum was seen in our all case of malarial ARF. This finding is documented in majority of the studies[10] but is different from some other studies in which, plasmodium vivax also has been noted as a cause of ARF[3,4]

ARF in falciparum malaria is usually oliguric and hypercatabolic and oliguric phase lasts for a few days to several weeks. Blood urea increases more rapidly than serum creatinine concentration[11]. Despite this consideration, blood urea levels do not reflect the performance of the kidneys as compared to serum creatinine. This is because urea production is

also altered by dehydration, food intake, and tissue catabolism[5,12] .In this study we observed oliguric ARF, in majority of our patients. This finding reflected that more patients with malarial ARF were referred to our dialysis facility unit, when their urine out put was decreased and they became oliguric .High incidence of oliguric renal failure in falciparum malaria has been reported previously[4,8,12].

Jaundice is a common feature in malarial ARF. This association with malarial ARF is well described and may contribute to the reduction of glomerular filtration rate or development of ATN[13]. This finding was noted in 71.73% of our patients. Hyperbilirubinaemia was predominantly conjugated. In malarial ARF, conjugated hyperbilirubinaemia in high incidence is a well documented observation[8].

Often in a patient of falciprum malaria with cerebral symptoms and renal failure, cerebral malaria is diagnosed but the renal aspect of the disease is over looked. The administration of excessive parenteral fluid to such a patient during the period of unrecognized impaired renal function can easily lead to pulmonary oedema and acute water intoxication[14]. Cerebral symptoms were observed in 63.04% of our cases. The severity of these symptoms ranged from impaired consciousness to coma. We used score on Glasgow coma scale(GCS) to assess the severity of these symptoms. High proportion of impaired consciousness in patients with malarial ARF is documented in the past studies[4,15.] To our surprise, significant hyperkalemia was not seen in the present study. Only two patients showed hyperkalemia which was mild and did not require the treatment. The reason for this is not clear. However, this finding is supported from the study conducted in India in which out of 24 patients with malarial ARF, none showed serum potassium >5mEq/L[3].

Anti-malarial therapy was the main stay of treatment of malaria associated with ARF along with the symptomatic and dialysis support. Although peritoneal dialysis has been used in the treatment of malarial ARF, its effectiveness in severe cases is limited because of peritoneal dysfunction and low clearance due to the impaired microcirculation[12]. For this reason haemodialysis appears to be beneficial for ARF associated with malaria, particularly when started earlier in the course of illness[12].

We used only haemodialysis technique in our patients who required dialysis. The need for dialysis was seen in 78.26% of cases and most of them were oliguric. Greater proportion of patients requiring the haemodialysis in malarial ARF has been documented in the past studies[3,4,8,12] .In non-oliguric patients dialysis was also needed for additional removal of waste products since the remaining renal function could not cope with hyper-catabolic state. But the number of such patients was small and we could not compare the difference in number of dialysis sessions required for the oliguric and non-oliguric. The recovery of renal function was quick in survivors especially those who were non-oliguric on admission and had less severe renal dysfunction. The baseline serum creatinine was significantly low after three sessions of haemodialysis. In malarial ARF prognosis depends on the severity of the condition, associated extra-renal complications, and early institution of anti-malarial therapy along with dialysis support.

Availability of renal replacement therapy for malarial ARF has been shown to improve the outcome. In a study performed in Vietnam, mortality in patients with malarial ARF was 75% with out dialysis and 26% when dialysis was available. More over, the authors stated that more effective dialysis or diafiltration might further reduce the mortality rate[16].

In our study, mortality was 23.91% which is in agreement with other studies conducted in areas with similar pattern of malaria transmission and where dialysis support was available[3,4,8,17]. Majority (54.5%) deaths in the study patients occurred in first 24 hours after admission, even when dialysis was started. Prolong duration of illness, before reaching the dialysis facility unit and severity of ARF probably explained the early deaths in our patients. Nearly similar, observation is documented in the study conducted in Thailand, in which 58.3% patients died during the first 24 hours after admission[12]. The severity of hyprebilirubinaemia significantly predicted the adverse out come in present study. It is documented that total bilirubin level >20mg/dl is often associated with severe renal failure and adverse out come[18]. Peripheral neutrophil leucocytosis has been observed in severe falciparum malaria, even in the absence of detectable bacterial infection. It is associated with poor pronosis[5,19]. Thrombocytopenia is a common feature in falciparum and vivax malaria, whether mild or severe, but profound thrombocytopenia is more common in severe falciparum malaria[20]. Significant leucocytosis and severe thrombocytopenia was seen in fatal cases in this series. But due to the presence of high proportion of DIC in expired group, these both were not considered as independent predictors of mortality in our patients.

In present study prolonged duration of illness, oliguria, higher concentration of bilirubin, Severity of ARF (higher urea and creatinine with acidosis), cerebral malaria and DIC were associated with poor prognosis. Most of these findings, as a predictor of mortality in malarial ARF and in complicated falciparum malaria, are consistent with other studies[3,8,10,17,21].

Protean manifestations of falciparum malaria especially the presence of jaundice delayed the diagnosis. If dialysis was started at an early stage of the disease perhaps the mortality would have been reduced further.

CONCLUSION

It is concluded that falciparum malaria in adults is one of the causes of acute renal failure in this population. In the patients presenting with fever, jaundice and acute renal failure, there should be a high index of suspicion for malaria even in the face of negative blood film. Early and prompt diagnosis along with anti-malarial therapy, are the main measures likely to reduce the malarial ARF in this setting. Haemodialysis is an effective treatment for malarial ARF. Early referral of malarial ARF patients to dialysis facility unit and early institution of haemodialysis in complicated falciparum malaria may further reduce mortality and enhance recovery function.

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