

FACTORS ASSOCIATED WITH ACUTE RENAL FAILURE IN SEVERE FALCIPARUM MALARIA PATIENTS

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Abstract. Acute renal failure (ARF) is a common cause of morbidity and mortality in severe malaria infection. We evaluated factors associated with acute renal failure in severe malaria by comparing patients with severe malaria with and without ARF admitted to the Hospital for Tropical Diseases, Bangkok, Thailand. Nine hundred fifteen severe malaria patients were included in the study, of whom 195 had ARF and 720 did not have ARF. We found jaundice, anemia, hypoalbuminemia, hyponatremia, hyperkalemia, acidosis, leukocytosis, elevated transaminases (SGOT and SGPT) and cerebral malaria, were significantly associated with ARF among patients with severe malaria ($p < 0.05$). Patients who have ARF and any of these clinical or laboratory manifestations of severe malaria should be monitored and managed properly, since early detection and treatment may reduce morbidity and mortality.

Key words: severe falciparum malaria, acute renal failure, associated factor, Thailand

INTRODUCTION

Malaria is a major public health problem in many parts of the world. Acute renal failure (ARF) is a significant contributor to the morbidity and mortality associated with severe malaria infection (Karnik, *et al*, 1998; Lombardi *et al*, 1998). ARF resulting from falciparum malaria infection is becoming increasingly common. The incidence of ARF in falciparum malaria has been reported as 0.37-60% (Sheety and Reba, 1967; Sitprija, 1988). We describe our experiences with ARF due to falciparum

malaria over a 10-year period during 1991-2003 at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. ARF management in this hospital includes hemodialysis in most patients, except for those who are HIV-positive, for whom peritoneal dialysis is performed. The objectives of this study were 1) to evaluate patients with ARF due to falciparum malaria, 2) compare their clinical and laboratory findings with other severe falciparum malaria patients who did not develop ARF, and 3) determine ARF-associated factors in falciparum malaria.

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MATERIALS AND METHODS

The inclusion criteria in this study

were all patients with severe *P. falciparum* malaria defined by WHO criteria (2006) with a microscopically confirmed diagnosis admitted to the ICU of the Hospital for Tropical Diseases between 1991 and 2003. Cases included males and females aged ≥ 15 years. Exclusion criteria were patients without malaria or mixed malaria infection, pregnant or lactating women, known cases of chronic renal failure, patients with known concurrent significant illnesses, and patients treated with antimalarial drugs outside the hospital during one month prior to admission. The information obtained from the records included demographic, clinical and laboratory data, and the presence of complications either on admission or during the hospital stay and the outcome of each case.

ARF was defined as a sudden increase in serum creatinine level to >3 mg/dl (>265 $\mu\text{mol/l}$) and/or a urine output of <400 ml/24 hours, despite rehydration, in adult patients documented as having falciparum malaria by the finding of asexual forms of *P. falciparum* on peripheral blood smear. Jaundice was defined as icteric sclera with a total bilirubin level >3 mg/dl (50 $\mu\text{mol/l}$). Severe hypoglycemia was defined as a serum glucose level <40 mg/dl (2.2 mmol/l). The definition of oliguria was a urine output <400 ml/24 hours. Hyperparasitemia was defined as $>250,000$ parasites/ μl of blood (or $>5\%$ of erythrocytes parasitized). Severe anemia was defined as a hematocrit $<15\%$ or a hemoglobin <5 g/dl.

Treatment

Of the 915 patients with severe malaria (195 patients with ARF and 720 without ARF) included in the study, antimalarial drug information was available in 807 patients; 724 (89.7%) were treated with artemisinin derivatives (artesunate, arteether or artemether) and 83 (10.3%)

were treated with quinine. Two hundred sixty-eight patients (33%) received mefloquine after artemisinin derivatives.

Of the 195 patients with ARF, 175 (90%) were treated with artemisinin derivatives and 20 (10%) with quinine. Forty-nine patients (25%) received mefloquine after artemisinin derivative treatment. Eight patients were treated with a combination of an artemisinin derivative and quinine.

The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Thailand.

Statistical analysis

Quantitative and qualitative data were expressed as mean with standard deviation (SD) and number of observations with percentage (%), respectively. All *p*-values reported were from 2-tailed testing, and statistical significance was set at <0.05 . Descriptive statistics were used to summarize baseline values and demographic data. The chi-square or Fisher's exact tests were used to compare proportions where appropriate, and the Student's *t*-test was used to analyze continuous data.

RESULTS

One hundred ninety-five (21%) of the 915 severe falciparum malaria patients included in the study were diagnosed with ARF; of whom 24 (12.3%) did not undergo hemodialysis and 171 (87.7%) did undergo hemodialysis at least once. Most of the patients were infected with malaria for the first or second time.

The ages of those with severe malaria (both with and without ARF) ranged from 15-74 years (mean 27.7 ± 11.43 years). The age range for those with severe malaria with ARF was 15-71 years (mean 30.5 ± 12.5 years). The mean age of those with ARF

was not significantly different from those in the total group. Out of 915 patients with severe malaria, 223 were female (24%) and 692 were male (76%). Out of 195 patients with ARF, 42 (21.5%) were female and 153 (78.5%) were male. The overall total male-to-female ratio in all studied patients (both with and without ARF) was 3:1 and the ratio was 3.7:1 in the ARF group; this difference was not significant.

In our study of 915 patients with severe malaria, 35 died (3.8% total mortality rate). The mortality rate of those with ARF was 6.2% (12/195) and of those without ARF was 3.2% (23/720). This difference in mortality was not significant ($p>0.05$). Of the patients with ARF who died ($n=12$), 1 patient (8.3%) underwent hemodialysis while 11 patients (91.7%) did not undergo hemodialysis.

Out of the 195 ARF patients, 54 (28%) had a normal serum glucose level (70-110 mg/dl) upon admission to our hospital, 36 (18.5%) had a low glucose level (<70 mg/dl) and 104 (53%) had an elevated level (>110 mg/dl). Out of the 915 patients included in the study (both with and without ARF), 364 (40.8%) had normal serum glucose levels. Using WHO criteria to define severe malaria by hypoglycemia (serum glucose <40 mg/dl; 2.2 mmol/l) (WHO, 2006), only 3 patients (1.5%) in the ARF group had hypoglycemia and 9 patients (1.0%) in the total group had hypoglycemia; this difference was not significant. Most of the severe malaria patients treated at our hospital were referred from other hospitals and private clinics, and were given intravenous fluid containing dextrose before or during transportation to our hospital resulting in fewer than expected hypoglycemic patients and many had hyperglycemia. Patients with glucose levels less than 70 mg/dl were treated with

intravenous dextrose before they reached the severe hypoglycemic levels described by the WHO (2006) as defining severe malaria.

Regarding low albumin, defined as an albumin <3.5 mg/dl, 308 of 720 patients (43%) in the group without ARF had hypoalbuminemia, whereas 135 of 195 patients with ARF (79%) had hypoalbuminemia. There was a significant association between hypoalbuminemia and ARF ($p<0.001$).

Regarding serum electrolytes, of the 888 patients for whom serum sodium records were available, 694 did not have ARF, and 194 did. Out of the 694 patients without ARF, 257 (37%) had a normal serum sodium level (defined as a sodium level 135-148 mmol/l), 62.5% had a low serum sodium level and <1% had a high serum sodium level. Out of those with ARF, 30 (15%) had a normal serum sodium level, 162 (84%) had a low serum sodium level and 2 (1%) had a high serum sodium level. Out of the 887 patients with serum potassium records, 193 had ARF and 694 did not have ARF. In the patients without ARF, 471 (68%) had a normal serum potassium level, defined as a serum potassium 3.5-5.3 mmol/l; 212 (30%) had a low serum potassium level and 11 (2%) had a high serum potassium level. Out of those with ARF, 124 (64%) had a normal serum potassium level, 52 (27%) had a low serum potassium level and 17 (9%) had a high serum potassium level.

A serum bicarbonate level was determined in 551 patients, of whom 383 (70%) had no ARF and 168 (30%) had ARF. Out of the 383 patients without ARF, 121 (31.6%) had a normal serum bicarbonate level, defined as a serum bicarbonate level of 22-33 mmol/l, whereas 260 (67.9%) had a low serum bicarbonate level and 2 (0.5%)

had a high serum bicarbonate level. Out of the 168 patients with ARF, 19 (11%) had a normal serum bicarbonate level, 148 (88%) had a low serum bicarbonate level and 1 (<1%) had a high serum bicarbonate level. There was a significant association between low serum bicarbonate level (metabolic acidosis) and ARF ($p<0.001$).

A serum total bilirubin level was available for all 915 patients. Out of the 720 patients without ARF, 360 (50%) had a normal serum total bilirubin level, defined as a serum total bilirubin level of 0.5-3.0 mg%, and 360 (50%) had jaundice with high serum total bilirubin level (greater than 3.0 mg/dl). Out of the 195 patients with ARF, 23 (12%) had a normal serum total bilirubin level and 172 (88%) had jaundice with a high serum total bilirubin level. There was a significant association between ARF and jaundice with a high serum total bilirubin level ($p<0.001$).

The transaminases, serum glutamic pyruvic transaminase (SGOT; AST- aspartate aminotransferase) and serum glutamic oxaloacetic transaminase (SGPT; ALT- alanine aminotransferase), were determined for all 915 patients. Out of the 720 patients without ARF, 138 (19%) had a normal SGOT level, defined as 7-40 U/l, whereas 582 (81%) had a high SGOT level. Out of the 195 patients with ARF, 7 (4%) had a normal SGOT level and 188 (96%) had a high SGOT level. There was a significant association between a high SGOT level and ARF ($p<0.001$). Out of the 720 patients without ARF, 379 (53%) had a normal SGPT level, defined as 7-40 U/l, whereas 341 (47%) had a high SGPT level. Out of the 195 patients with ARF, 46 (24%) had a normal SGPT level and 149 (76%) had a high SGPT level. There was a significant association between a high SGPT level and ARF ($p<0.001$).

Hemoglobin was determined for all 915 patients. Out of the 720 patients without ARF, 532 (74%) had a normal hemoglobin level and 188 (26%) had a low hemoglobin level, defined as a hemoglobin <10 g/dl. Out of the 195 patients with ARF, 115 (59%) had a normal hemoglobin level and 80 (41%) had a low level. No patients had severe anemia with a hemoglobin <5 g/dl. There was a significant association between anemia (low hemoglobin level) and ARF ($p<0.001$).

White blood cell counts were determined for all 915 patients. Out of the 720 patients without ARF, 564 (78.3%) had a normal white blood cell count, 96 (13.3%) had a high white blood cell count (>10,000/ μ l) and 60 (8.4%) had a low white blood cell count (< 4,000/ μ l). Out of the 195 patients with ARF, 97 (50%) had a normal white blood cell count, 94 (48%) had a high white blood cell count, and 4 (2%) had a low white blood cell count. There was a significant association between a high white blood cell count and ARF ($p<0.001$).

The presence of cerebral malaria was assessed in all 915 patients. Out of the 720 patients without ARF, 73 (10%) were diagnosed with having cerebral malaria and 647 (90%) as not having cerebral malaria. Out of the 195 patients with ARF, 77 (39%) were diagnosed with having cerebral malaria and 118 (61%) as not having cerebral malaria. There was a significant association between cerebral malaria and ARF ($p<0.001$).

DISCUSSION

ARF is a major cause of morbidity and mortality in severe malaria infection (Karnik *et al*, 1998; Lombardi *et al*, 1998). The mortality rate of those with ARF was higher than those without ARF in this

study, 6.2% and 3.2%, respectively, but this difference did not reach significance. The mortality rate of those with ARF who did not have hemodialysis was significantly higher than those who did have hemodialysis. The main reasons for not having dialysis in patients with ARF were shock or the patient died before dialysis could be carried out. This underlines the importance of early diagnosis and appropriate treatment of severe malaria and its complications.

In our study, the male-to-female ratios in the groups with and without ARF were not significantly different (3.7:1 in the ARF group and 4:1 in the non-ARF group). These ratios were similar to a study from India (Panda *et al*, 2003) with a male-to-female ratio of 3:1 in those with ARF.

Our study found jaundice, anemia, hypoalbuminemia, hyponatremia, hyperkalemia, acidosis, leukocytosis, elevated SGOT and SGPT, and cerebral malaria, were all significantly associated ($p < 0.05$) with ARF in severe malaria. Other studies have looked at risk factors for severe malaria or mortality in malaria infection (Westerlund *et al*, 2000; Panda *et al*, 2003). Westerlund *et al* (2000) found the APACHE score was not helpful in predicting individual outcomes; hemodialysis was found to reduce the risk of dying. Panda *et al* (2003) found the risk factors for severe malaria were elevated bilirubin, ARDS, DIC, shock and delayed treatment. Sitprija (1988) found hypovolemia, hyperparasitemia and jaundice were risk factors for ARF, but hyperparasitemia was not a risk factor for higher mortality. Sharma *et al* (1999) also found jaundice was a risk factor for ARF in malaria. Wilairatana *et al* (1999) evaluated outcomes in severe malaria and ARF and found patients with cerebral malaria and jaundice had a higher risk of death.

In the setting where peritoneal dialysis was used for treatment of ARF in severe malaria (Trang *et al*, 1992; Panda *et al*, 2003), mortality rates were approximately twice those of patients treated with hemodialysis (18-20% vs 9.7%, respectively) (Wilairatana *et al*, 1999). Hemofiltration was also found to be superior to peritoneal dialysis in malaria patients with ARF (Phu *et al*, 2002).

The usefulness of hemodialysis in the treatment of malarial ARF was highlighted in a study from Yemen in which peritoneal dialysis was used to treat ARF in severe malaria instead of hemodialysis; the mortality rate in a group of 64 children was 43.8% ($n=28$) (Sheiban, 1999). Even with hemodialysis, the mortality rate is still high, as is seen in a study from India by Prakash *et al* (1996) in which they studied 26 patients with ARF due to severe malaria; dialysis was carried out in 15 of those patients, with a mortality rate of 30.8%. A study of 2,200 malaria patients from India by Panda *et al* (2003) found ARF in 75%, volume depletion in 65.3%, hyperparasitemia in 30.8%, intravascular hemolysis in 30.8%, cholestatic jaundice in 23%, and hypotension in 19.2%, respectively. In another study from India (Mishra *et al*, 2007), the mortality rate in patients having severe malaria with ARF was higher than in patients having severe malaria without ARF (13.9% vs 39.5%). Although peritoneal dialysis was conducted in the patients with ARF, the outcomes were not good, possibly due to severity of the malarial disease or because peritoneal dialysis might be less effective in removing some waste products from circulation than hemodialysis or hemofiltration (Daugirdas, 2002).

Naqui *et al* (2003) found 79.8% of severe malaria patients needed "renal replacement therapy"; the mortality rate in that study was 25.8%. The risk factors for

poor outcomes were higher age, oliguria, central nervous system involvement, and presence of DIC.

In conclusion, ARF is a major cause of morbidity and mortality in severe malaria infection. We found a number of factors associated with ARF in severe malaria infection: jaundice, anemia, hypoalbuminemia, leukocytosis, elevated SGOT and SGPT levels and cerebral malaria. Although no causal relationship may be deduced from this study, physicians should monitor and correctly manage these factors in patients with severe malaria, because of their association with ARF. Early diagnosis with prompt and correct management, including dialysis in ARF, may reduce morbidity and mortality in malarial ARF.

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REFERENCES

- Daugirdas JT. Peritoneal dialysis in acute renal failure-why the bad outcome? *N Engl J Med* 2002; 347: 933-5.
- Karnik AM, Bashir R, Khan FA, Carvounis CP. Renal involvement in systemic inflammatory reaction syndrome. *Renal Failure* 1998; 20: 103-16.
- Lombardi R, Zampedri L, Rodriguez I, et al. Prognosis in acute renal failure of septic origin: A multivariate analysis. *Renal Failure* 1998; 20: 725-32.
- Naqui R, Ahmed E, Akhtar E, Naqui A, Rizvi A. Outcomes in severe acute renal failure associated with malaria. *Nephrol Dial Transplant* 2003; 18: 1820-3.
- Mishra SK, Dieta K, Mohanty S, Sudhansu SP. Influence of acute renal failure in patients with cerebral malaria-a hospital based study from India. *Trop Doc* 2007; 378: 103-4.
- Panda SK, Das MC, Meher LK, Rathod PK. Risk factors for acute renal failure in severe falciparum malaria. *Indian J Nephrol* 2003; 13: 55-8.
- Phu NH, Hien TT, Mai NTH, et al. Hemofiltration and peritoneal dialysis in infection associated acute renal failure in Vietnam. *N Engl J Med* 2002; 347: 895-902.
- Prakash J, Gupta A, Jumar O, et al. Acute renal failure in falciparum malaria-increasing prevalence in some areas of India - a need for awareness. *Nephrol Dial Transplant* 1996; 11: 2414-6.
- Sharma AP, Sural S, Gupta A. Acute renal failure in high risk patients: Pathogenetic mechanisms in septicemia and malaria. *Indian J Nephrol* 1999; 9: 147-53.
- Sheety TW, Reba RC. Complications of falciparum malaria and their treatment. *Ann Intern Med* 1967; 66: 807-9.
- Sheiban AK. Prognosis of malaria associated severe acute renal failure in children. *Renal Failure* 1999; 21: 63-6.
- Sitprija V. Falciparum malaria. *Kidney Int* 1988; 34: 867-77.
- Trang TT, Phu NH, Vinh H, et al. Acute renal failure in patients with severe falciparum malaria. *Clin Infect Dis* 1992; 15: 874-8.
- Westerlund EK, Wilairatana P, Looareesuwan S, et al. Predicting mortality in patients with malarial acute renal failure. *Nephrology* 2000; 5: 109-13.
- WHO. Guidelines for the treatment of malaria. Geneva: WHO, 2006.
- Wilairatana P, Westerlund EK, Aursudkij B, et al. Treatment of malarial acute renal failure by hemodialysis. *Am J Trop Med Hyg* 1999; 60: 223-37.