PULMONARY EDEMA IN CEREBRAL MALARIA PATIENTS IN THAILAND

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Abstract. Pulmonary edema is a serious complication of falciparum malaria that usually occurs in association with cerebral malaria, acute renal failure, high parasitemias, or delayed antimalarial treatment. From 1993 to 1996, 120 adult patients admitted to the intensive care unit of the Bangkok Hospital for Tropical Diseases were enrolled in a prospective study to assess the combination of artesunate and mefloquine for the treatment of cerebral malaria. Twenty-five patients (21%) presented with pulmonary edema and a majority developed complications in other organs as well, especially acute renal failure. In most patients (19 of 25), pulmonary edema was noted on the first day of admission and was associated with higher parasitemias and levels of acidemia, than in patients without pulmonary edema. Ten of the 25 patients diagnosed with pulmonary edema developed signs consistent with adult respiratory distress syndrome (ARDS). The mean central venous pressure when pulmonary edema was diagnosed was markedly lower in ARDS than in non-ARDS patients, supporting the argument that fluid imbalance is not essential for malaria-induced lung injury. Seven of 10 patients with ARDS died, 5 within 24 hours of admission, but there were no deaths in the 15 pulmonary edema patients without ARDS. Early diagnosis and prompt treatment remain important principles to reduce the morbidity and mortality associated with complicated falciparum malaria. This report emphasizes that ARDS, when concurrently occurs, is a poor prognostic clinical indicator in cerebral malaria.

INTRODUCTION

Pulmonary complications in falciparum malaria, estimated to occur in 3 to 10% of cases, range from mild respiratory distress to pulmonary edema (PE). (Brooks *et al,* 1968; Feldman and Singer, 1987; Molyneux, 1995; White, 1996a). There are 2 forms of pulmonary edma (PE) : severe pulmonary edema (adult respiratory distress syndrome; ARDS) and non-severe pulmonary edema (non-ARDS) (Brooks *et al,* 1968). Indeed, benign pulmonary lesions such as pleural effusions or interstitial edema often go unrecognized as part of the clinical and radiological spectrum of malaria (James, 1985). Several mechanisms of lung injury may be involved, but disturbances in the pulmonary microcirculation are thought to be key events (Brooks *et al,* 1968; Tatke and Malik, 1990). Autopsy specimens show pulmonary vessels lined with both leukocytes and parasitized red blood cells (RBC), in contrast to brain capillaries from cerebral malaria (CM) patients which contain primarily sequestered parasitized RBCs (MacPherson *et al,* 1985; Tatke and Malik, 1990).

PE is usually associated with cerebral malaria (CM), high parasitemias, acute renal failure (ARF), or delayed diagnosis or treatment, and has been circumstantially linked to some treatments (Feldman and Singer, 1987). PE is considered an especially dangerous complication because it may develop abruptly, develop rapidly and occur in the absence of cardiac decompensation or fluid overload. Intensive care is usually required for optimal management, especially for ARDS, but the response to therapy is variable (James, 1985; Punyagupta *et al,* 1974). Some reports describe the development of PE several days after treatment for CM, especially with quinine is used, the drug of choice for

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CM in many regions (Feldman and Singer, 1987). In Southeast Asia, particularly Thailand and Vietnam, there is a growing trend to use rapidly acting artemisinin derivatives such as artesunate in complicated falciparum malaria patients (Hien, 1994; Hien *et al,* 1996; Hien and White, 1993; Wilairatana and Looareesuwan, 1995; Wilairatana *et al,* 1997).

Here we describe a subset of CM patients with concurrent PE with and without ARDS and their outcomes. All were treated with intravenous (IV) artesunate, and then mefloquine.

PATIENTS AND METHODS

Patients

All one hundred and twenty adult patients with CM admitted to the intensive care unit (ICU) of the Hospital for Tropical Diseases, Bangkok, Thailand between 1993 and 1996 were enrolled in a prospective treatment study. CM was diagnosed in any patient with unarousable coma, without evidence for other forms of encephalopathy, and whose peripheral blood smear contained asexual falciparum malaria parasites (Warrell *et al,* 1990). Upon admission, all patients were immediately treated with intravenous (IV) artesunate 120 mg, then 60 mg every 12 hours (total dose 600 mg). Twelve hours after the last dose of artesunate, mefloquine 750 mg was administered orally or per nasogastric tube, then 500 mg 6 hours later (total dose 1,250 mg). Vital signs were recorded hourly until resolution of fever, and then daily. Quantitative parasite counts were determined every 6 hours until parasite clearance.

Pulmonary monitoring

To monitor for pulmonary involvement, chest radiographs were obtained in all patients upon admission, repeated and then daily in patients with pulmonary signs until normal. All films were read by one radiologist who was unaware of the patient's diagnosis or condition. PE was diagnosed by progressive respiratory distress and suggestive radiographs (Molyneux, 1995). ARDS was diagnosed in any patient with diffuse pulmonary infiltrates and hypoxemia resistant to supplemental oxygen (PaO_2 < 60 mm Hg with FiO_2 > 60%) (Ashbaugh *et al,* 1967; Ingram, 1994; James, 1985). Central venous pressure (CVP) was monitored in all patients with PE by a central venous catheter.

All patients were intubated to provide mechanical ventilation, maintain airway patency, and prevent aspiration. Positive-end expiratory pressure (PEEP) ventilation was used for ARDS cases only. Patients with PE were nursed upright and given oxygen. Central venous pressures (CVP) were measured every 4 to 6 hours. In patients with CVP greater than 5 cm H_2O, loop diuretics or dialysis were used to reduce CVP to the lowest level compatible with an adequate cardiac output, usually between 1 and 5 cm H_2O.

Data analysis

CM patients were classified into PE and non-PE groups. PE patients were then sub-divided into ARDS and non-ARDS groups. Continuous variables were compared between the 2 groups using the independent samples Student's *t*-test. Proportions were compared using Fisher's exact test. A two-sided p-value of 0.05 was considered statistically significant.

RESULTS

A comparison of CM patients with and without PE is shown in Table 1. All were direct admissions to the ICU. Twenty-five of 120 (21%) developed PE. Patients with PE had higher parasitemias and levels of acidemia (defined as arterial pH <7.25) at the time of diagnosis than non-PE patients. Concurrent complications (other than CM or PE) were common. There were no significant differences among in patient ages or Acute Physiology and Chronic Health Evaluation System (APACHE II) (Seneff and Knaus, 1990) scores between the 2 groups. Seven of 25 (28%) patients with PE died, all with ARDS.

A comparison of PE patients with and without ARDS is shown in Table 2. PE was noted in the majority of patients (19 of 25) on the first day of admission; others developed PE on days 2 or 3 after admission. Seven of 10 patients with ARDS died, versus none in non-ARDS group. Surviving ARDS patients (n = 3) required longer periods of weaning from mechanical ventilation than non-ARDS pa-

Table 1

Comparison of cerebral malaria patients (n = 120), with and without pulmonary edema.

	Pulmonary edema	
	Yes (n = 25)	No (n = 95
Male : female	17 : 8	78 : 17
Age (years)	31.1 ± 11.3	28.1 ± 11.9
(range)	(15-51)	(16-71)
APACHE II score	23.9 ± 3.6	20.3 ± 3.1
(range)	(17-28)	(17-30)
Parasitemia * (per (μl) (geometric mean)	215,179	87,740
(range)	(60-870,400)	(200-246,900)
Concurrent complications **(No. and %)		
acute renal failure	20 (80%)	62 (65%)
severe acidosis*	17 (68%)	13 (14%)
jaundice	20 (80%)	68 (72%)
hyperpyrexia	2 (8%)	2 (2%)
shock	5 (20%)	7 (7%)
severe anemia	10 (40%)	18 (19%)
Deaths (%)	7 (28%)	7 (7%)

Values are expressed as mean ± SD (range) unless otherwise indicated.

* Significant difference between patients with and without pulmonary edema ($p < 0.05$).

** Concurrent complications include acute renal failure (defined as oliguria with serum creatinine >3 mg/dl), acidemia (defined as arterial pH <7.25), jaundice (with total serum bilirubin > 3 mg/dl), hyperpyrexia (with a rectal temperature > 40°C), shock (hypotension with systolic blood pressure <70 mmHg and cold, clammy skin), and severe anemia (with hematocrit <15%).

tients and had normalization of their chest films than non-ARDS patients (n = 15). On the day PE was diagnosed, most ARDS patients had CVPs less than 5 cm H_2O whereas non-ARDS patients generally had higher CVPs.

In 5 PE patients (2 ARDS, 3 non-ARDS) of this study, over-hydration was indicated by CVPs of 7 to 10 cm H_2O; these patients developed PE on the second or third days after treatment began. The first patient developed PE (no ARDS) 2 days after admission with a CVP < 5 cm H_2O. The second patient with deep coma and severe metabolic acidosis and shock aspirated before endotrachial intubation and died 1 hour after ICU admission. The left three patients with PE also developed bacterial pneumonia and were placed on mechanical ventilators for more than 5 days.

DISCUSSION

PE may be related to an imbalance of Starling forces (increased pulmonary capillary pressure or decreased plasma oncotic pressure) or altered alveolar-capillary membrane permeability (ARDS) (Ingram, 1994). Fully developed PE is typically characterized by wet rales and rhonchi on physical examination and by chest radiographs showing diffuse lung haziness. Conditions characterized by increased interstitial fluid that are primarily related to disruption of the alveolar-capillary membrane, not hemodynamic imbalance, may lead to ARDS.

ARDS, a descriptive term applied to acute, diffuse infiltrative lung lesions with severe arterial hypoxemia, is invariably associated with increased

Table 2

Comparison of pulmonary edema (PE) patients with and without ARDS.

	ARDS (n = 10)	non-ARDS (n = 15)
Patients with PE (No. and %)		
on day 1	8 (80%)	11 (73%)
after day 1	2 (20%)	4 (27%)
Parasitemia (per μl) (geometric mean)	231,840	184,600
(range)	(100-870,400)	(250-242,510)
CVP (cm H_2O) on day PE diagnosed	3.9 ± 1.1	7.3 ± 2.1
(range)	(2-7)	(3-10)
Deaths* (No. and %)	7 (70%)	0 (0%)
Days intubated**	7.1 ± 1.1	3.3 ± 1.5
(range)	(5-10)	(1-5)
Day chest film cleared**	10.1 ± 2.5	5.1 ± 1.0
(range)	(7-14)	(3-7)

Values are expressed as mean ± SD (range), unless otherwise indicated.

* Within 24 hours of admission.

** Survivors.

fluid in the lungs and is therefore considered a form of PE (Ingram, 1994). Patients become cyanotic, dyspneic and tachypneic and rales are heard in both lung fields. Chest radiographs show diffuse, bilateral interstitial and alveolar infiltrates. Increasing the inspired oxygen concentration does not correct the hypoxemia and mechanical ventilation is necessary.

In falciparum malaria, PE is a potentially serious complication that is not well understood and is probably under-recognized (Brooks *et al,* 1968; Punyagupta *et al,* 1974; Tatke and Malik, 1990). Clinically, the distinction between PE due to volume overload and PE associated with ARDS is important (Molyneux, 1995). Early reports proposed fluid imbalance as a primary cause of PE; indeed, hemodynamic management in severe malaria patients is a "fine line" (White, 1996b). However, as invasive monitoring technics became available, it became evident that at least a proportion of PE cases are unrelated to fluid imbalance or cardiac factors, indicating that malaria may injure lung tissue in a process akin to ARDS (James, 1985; Martell *et al,* 1979; Warrell *et al,* 1990; White, 1996a).

In this report, we summarize the clinical characteristics of a subset of CM patients with concurrent PE. As part of a treatment protocol for CM, all received parenteral artesunate, followed by mefloquine. Consistent with previous descriptions, PE patients had higher parasitemias and levels of acidosis (Feldman and Singer, 1987; Molyneux, 1995). A high rate of acute renal failure was noted, but this was common in non-PE patients as well. As in previous report from Thailand (Punyagupta *et al,* 1974), most patients had signs of PE before therapy was initiated (on day 1 of ICU admission). Other reports emphasize that PE may also develop after treatment has started (Feldman and Singer, 1987; Warrell *et al,* 1990). Ten patients were diagnosed with an ARDS-like syndrome, 7 of whom died. The high proportion of deaths in the ARDS patients raised the overall mortality rate in PE patients to 28%, versus just 7% in the non-PE patients. Interestingly, there were no deaths in PE patients without ARDS. However, APCHE II scores were significantly higher

At diagnosis, the mean CVP in patients with ARDS was considerably lower than in PE patients without ARDS, supporting the argument that severe lung injury may occur without hemodynamic imbalance. In the setting of complicated malaria,

death may be multi-factorial. Nonetheless, our observations suggest, not unexpectedly, that ARDS is an especially poor prognostic sign. PE alone (without ARDS-like signs) appears to be less dangerous and when mechanical ventilation and intensive care monitoring is available, mortality rates may drop (Feldman and Singer, 1987; James, 1985; Martell *et al,* 1979).

Several mechanisms may contribute to lung injury in falciparum malaria: (i) impaired perfusion and tissue hypoxia in the pulmonary microcirculation; (ii) abnormal autonomic effects on the lung resulting from reduced blood flow in the central nervous system; (iii) immunologic injury to alveolar-capillary structures; and (iv) morphologic changes in the membranes of infected erythrocytes, leading to sequestration of parasitized erythrocytes in vascular beds and pulmonary capillary damage (Feldman and Singer, 1987).

That PE may develop several days after implementation of antimalarial therapy has led some to question a link (Feldman and Singer, 1987). Other contributors for "delayed" PE include unawareness that severe malaria may be associated with prolonged altered capillary permeability (and vulnerability to fluid overload) and that CVP should be adjusted to between 0 and 5 cm of H_2O (Warrell *et al,* 1990). Adjustment of the CVP to between 10 and 12 cm H_2O (the "high normal" value) may contribute to hemodynamic PE by causing fluid imbalance. In this regard, a rapidly acting agent like artesunate that resolves malaria complications sooner and allows patients to begin oral therapy, might potentially reduce the risk or progression of PE from IV fluid overload.

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