SCHIZONTEMIA AS AN INDICATOR OF SEVERE MALARIA

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Abstract. We conducted this study to determine if the finding of schizontemia could be used as an indicator of severe falciparum malaria. We enrolled 250 patients with severe falciparum malaria and 250 patients with umcomplicated falciparum malaria into the study. Severe falciparum malaria was defined following World Health Organization criteria (2010). Of the 250 patients with severe falciparum malaria, 99 (39.6%) had schizontemia on admission. Of the 250 patients with uncomplicated falciparum malaria, 0 (0%) had schizontemia ($p<0.05$). Schizontemia was also found to be significantly correlated with parasite density, severe malaria, impaired consciousness, pulmonary edema, hypoglycemia, jaundice and hemoglobinuria ($p<0.05$). Schizontemia may be considered as an indicator of severe malaria.

Keywords: falciparum, malaria, schizont, severe

INTRODUCTION

Plasmodium falciparum malaria can cause severe malaria. Hyperparasitemia is associated with severe malaria (WHO, 2010); however, some patients with low parasitemia may have severe disease. Red blood cells infected with *P. falciparum* (in the form of schizonts) can cytoadhere to capillary endothelium via knobs on the red cell membrane, resulting in sluggish blood flow and hypoxia in severe malaria (White and Ho, 1992; Mackintosh *et al*, 2004). These knobs are not found in newly infected red blood cells (asexual non-schizonts). The objective of this study was to determine whether schizontemia may be an indicator of severe malaria.

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MATERIALS AND METHODS

Study subjects

Five hundred adult patients aged ≥18 years with falciparum infection, proven by blood smear, admitted to the Hospital for Tropical Diseases, Mahidol University, Thailand were studied. The subjects were divided in 2 groups: 250 subjects with uncomplicated malaria and 250 subjects with severe malaria. WHO criteria (2010) were used to determine if the study subjects were severe or not. Criteria for severe infection were a malaria infection with at least one of the following complications: prostration, impaired consciousness, respiratory distress (acidotic breathing), multiple convulsions (more than 2 within 24 hours), pulmonary edema, abnormal bleeding (from the gums, nose or gastrointestinal tract, and/or laboratory evidence of disseminated intravascular coagulation), hemoglobinuria, severe anemia (hemoglobin < 5 g/dl), hypoglycemia

Table 1
Clinical presentations on admission of study subjects.

Clinical manifestations on admission	UM (*N*=250) *n* (%)	SM (*N*=250) *n* (%)	*p*-value
History of malaria in the past 1 year	100 (40.0)	93 (37.2)	0.520
Chills	197 (78.8)	215 (86.0)	0.035
Abdominal pain	50 (20.0)	70 (28.0)	0.036
Diarrhea	15 (6.0)	45 (18.0)	<0.001
Anorexia	176 (70.4)	208 (83.2)	<0.001
Nausea	146 (58.4)	193 (77.2)	<0.001
Vomiting	112 (44.8)	164 (65.6)	<0.001
Weakness	220 (88.0)	236 (94.4)	0.012
Headache	227 (90.8)	236 (94.4)	0.124
Dizziness	157 (62.8)	190 (76.0)	0.001
Myalgia	201 (80.4)	224 (89.6)	0.004
Dehydration	42 (16.8)	76 (30.4)	<0.001
Hepatomegaly	54 (21.6)	99 (39.6)	<0.001
Splenomegaly	13 (5.2)	30 (12.0)	0.007

UM, uncomplicated malaria; SM, severe malaria.

(plasma glucose <40 mg/dl), acidemia (arterial pH <7.35 or plasma bicarbonate concentration <15 mmol/l), renal impairment (urine output < 400 ml in 24 hours, failing to improve after rehydration or serum creatinine > 3 mg/dl), hyperparasitemia (>5%), and jaundice (icteric sclera on initial presentation). Patients with mixed malarial infection, a history of underlying hepatobiliary tract disease, a history of alcohol, medicine, or herb consumption one month prior to admission were excluded from the study. The blood tests were drawn on admission prior to receiving antimalarial drug therapy.

Treatment

All the severe malaria patients were treated with intravenous artesunate 2.4 mg/kg at 0, 12 and 24 hours after admission and then continued once daily until they could take oral medication; then, the treatment was switched to artesunate 4 mg/kg/day for 3 days combined with mefloquine 25 mg/kg taken in 2 doses 12 hours apart. Uncomplicated malaria patients were treated with artemisinin combination therapy. All patients with severe malaria were admitted to the intensive care unit. All the subjects were kept in the hospital for 28 days for monitoring and laboratory testing.

Laboratory testing

On admission malaria blood films, liver function tests, plasma glucose levels, blood urea nitrogen, serum creatinine and electrolyte levels were all determined.

Statistical analysis

Qualitative parameters were compared with the chi-square test. Quantitative parameters were compared using the Student's unpaired *t*-test where appropriate. Numerical values were given as mean ± standard deviation (SD). A *p*-value <0.05 was considered statistically significant.

Ethics statement

This study was approved by the Ethics Committee of the Faculty of Tropical

Table 2
Baseline characteristics of study subjects.

Characteristics	UM (*N*=250)	SM (*N*=250)	*p*-values
Gender			
Male /Female, number (%)	191(76.4) /59(23.6)	181(72.4) /69(27.6)	0.305
Age (years), mean (SD)	25.6 (8.6)	25.7 (8.8)	0.833
Body Mass Index (kg/m^2), mean (SD)	20.5 (3.9)	20.3 (2.4)	0.400
Geometric mean parasite count (/ l) (min-max)	5,406.0 (16-183,200)	143,483.6 (54-1,271,160)	<0.001
Mean (SD) duration of fever before admission (days)	4.6 (3.9)	4.8 (2.8)	0.629
Hematology profiles, mean (SD)			
Red blood cell count (10^6/ l)	4.4 (0.9)	4.7 (0.9)	0.003
White blood cell count (x10^3/ l)	5.9 (1.9)	6.7 (7.4)	0.118
Platelets count (x10^3/ l)	121.1 (83.8)	49.6 (37.3)	<0.001
Presenting schizontemia, number (%)	0	99 (39.6)	NA
Blood chemistry profiles, mean (SD)			
Glucose (mg/dl)	118.0 (39.6)	128.8 (37.6)	0.002
Blood urea nitrogen (mg/dl)	14.7 (7.0)	25.2 (14.0)	<0.001
Creatinine (mg/dl)	0.8 (0.2)	1.1 (0.5)	<0.001
Total bilirubin (mg/dl)	1.2 (0.6)	3.8 (3.0)	<0.001
Direct bilirubin (mg/dl)	0.4 (0.2)	1.7 (1.5)	<0.001
Total protein (g/dl)	6.9 (0.9)	6.5 (0.7)	<0.001
Albumin (g/dl)	3.6 (0.5)	3.4 (0.5)	<0.001
Aspartate aminotransferase (U/l)	43.2 (39.3)	67.4 (64.0)	<0.001
Alanine aminotransferase (U/l)	43.2 (41.0)	54.7 (52.3)	0.007
Alkaline phosphatase (U/l)	97.3 (50.8)	106.4 (46.0)	0.037
Gamma glutamyl transpeptidase (U/l)	44.1 (35.2)	84.6 (58.8)	<0.001
Sodium (mmol/l)	134.0 (3.7)	131.1 (4.5)	<0.001
Potassium (mmol/l)	3.5 (0.7)	3.6 (0.7)	0.441
Bicarbonate (mmol/l)	24.4 (3.1)	21.3 (3.3)	<0.001

UM, uncomplicated malaria; SM, severe malaria; NA, not applicable.

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RESULTS

Chills, abdominal pain, diarrhea, anorexia, nausea, vomiting, weakness, dizziness, myalgia, dehydration, hepatomegaly and splenomegaly were found significantly more often in patients with severe malaria than in patients with uncomplicated malaria (p<0.05) (Table 1).

Schizontemia was found in 99 severe malaria patients (39.6%) and was not found in any uncomplicated malaria patient (0%). Parasite count, glucose level, blood urea nitrogen, creatinine, total bilirubin, direct bilirubin, transaminases and gammaglutamyl transpeptidase levels were significantly greater in severe malaria patients than in uncomplicated malaria patients (p<0.05) (Table 2). Platelet counts, total protein, albumin, sodium, and bicarbonate levels were significantly lower in severe malaria patients than in

Table 3
Association between presence of schizontemia and manisfestrations of severe malaria.

Severe manifestations	% without schizontemia (*N*=401)	% with schizontemia (*N*=99)	*p*-value
Impaired consciousness	1.0	9.1	<0.01
Pulmonary edema	1.0	5.1	<0.01
Hypoglycemia	0	1.0	NA
Jaundice	18.5	50.5	<0.01
Hemoglobinuria	4.7	29.3	<0.01

uncomplicated malaria patients ($p<0.05$). The presence of schizontemia was significantly correlated with asexual parasite density ($r=0.123$, $p<0.05$) and was significantly associated with severe malaria, impaired consciousness, pulmonary edema, jaundice and hemoglobinuria ($p<0.05$) (Table 3).

DISCUSSION

Peripheral parasite counts do not always correlate well with parasite burden in falciparum malaria. A schizont is the mature stage of malaria in red blood cells. Schizont cytoadhere to capillaries in acute malaria infections causing mechanical obstruction of microvessels. Tangpukdee *et al* (2007) found schizontemia in 0.3% of uncomplicated falciparum malaria patients and 11.5% of uncomplicated malaria patients who subsequently developed severe malaria; schizontemia was associated with prognosis in their study. The presence of schizontemia is thought to be a marker of a high sequestered parasite burden and severe falciparum malaria (White and Ho, 1992). In non-immune patients schizontemia is an early marker for severe malaria (van Wolfswinkel *et al*, 2012). In the present study, schizontemia was found only in severe malaria patients. Schizontemia may be an additional laboratory indicator of severe malaria and may be a prognostic marker in falciparum malaria infection.

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REFERENCES

Mackintosh CL, Beeson JG, Marsh K. Clinical features and pathogenesis of severe malaria. *Trends Parasitol* 2004; 20: 597-603.

Tangpukdee N, Krudsood S, Thanachartwet V, *et al*. Predictive score of uncomplicated falciparum malaria patients turning to severe malaria. *Korean J Parasitol* 2007; 45: 273-82.

van Wolfswinkel ME, de Mendonca Melo M, Vliegenthart-Jongbloed K, Koelewijn R, van Hellemond JJ, van Genderen PJ. The prognostic value of schizontemia in imported *Plasmodium falciparum* malaria. *Malar J* 2012; 11: 301.

White NJ, Ho M. The pathophysiology of malaria. *Adv Parasitol* 1992; 31: 83-173.

WHO guidelines for the treatment of malaria. 2nd ed. Geneva: WHO, 2010.