FACTORS ASSOCIATED WITH CEREBRAL MALARIA

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Abstract. We conducted a retrospective unmatched case-control study using the medical records of patients admitted to the Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand to investigate factors associated with cerebral malaria. The records of 137 patients with severe *Plasmodium falciparum* without cerebral malaria and 35 patients with cerebral malaria hospitalized during 1997-2005 were reviewed and compared. Ten factors associated with cerebral malaria were identified: pulmonary edema [odds ratio (OR)= 13.8; 95% confidence interval (CI): 1.3-143.2], splenomegaly (OR=3.7; 95% CI: 1.3-44.7), fever (OR=3.3; 95% CI: 1.7-14.3), day 1 malarial density ≤249,999/ l (OR=1.6; 95% CI: 1.1-14.6), day 2 malarial density ≤249,999/ l (OR=3.4; 95% CI: 1.3-35.1), dyspnea (OR=1.4; 95% CI: 1.2-12.1), hepatomegaly (OR=1.8; 95% CI: 0.2-12.1), being a referred patient (OR=1.3; 95% CI: 1.0-2.2), a higher systolic blood pressure (OR=1.2; 95% CI: 1.0-2.1) and a higher body mass index (OR=1.6; 95% CI: 1.0-2.6). Pulmonary edema was the strongest factor associated with cerebral malaria in our study. Clinicians who treat patients with severe *Plasmodium falciparum* malaria should be aware these factors are associated with cerebral malaria.

Keywords: malaria, cerebral, severe, falciparum

INTRODUCTION

Cerebral malaria is an important complication in patients with severe falciparum malaria. Prodrome prior to developing cerebral malaria is usually several days in adults but may be as short as 6-12 hours in children; untreated cerebral malaria can be fatal within 24-72 hours (Idro *et al*, 2010). In the past, cerebral malaria was defined as unrousable coma in malaria patients (WHO, 2000), but the definition has changed to include impaired consciousness as well as unrousable coma (WHO, 2010). Although most cases of cerebral malaria occur in those with *P. falciparum* infection, other malaria species may also cause cerebral malaria (Idris *et al*, 2011; Singh *et al*, 2013). Factors associated with cerebral malaria have been studied (Achidi *et al*, 2012; Punsawad *et al*, 2013), but many of these factors require special laboratory tests not available at general hospitals in the tropics. The objective of this study was to determine factors associated with cerebral malaria among patients with falciparum malaria infection.

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METERIALS AND METHODS

Patients

One hundred seventy-two patients

aged ≥13 years old with severe falciparum malaria diagnosed by blood smear, admitted to the Hospital for Tropical Diseases (HTD), Mahidol University, Thailand, were included in the study. Severe malaria was defined as a malarial illness with at least one of the following complications (WHO, 2010): impaired consciousness or unrousable coma, prostration, failure to feed, ≥2 convulsions in 24 hours, adult respiratory distress syndrome (ARDS), shock, clinical jaundice or evidence of other vital organ dysfunction, hemoglobinuria, abnormal spontaneous bleeding, pulmonary edema (radiological evidence), hypoglycemia (blood glucose <40 mg/dl), metabolic acidosis (plasma bicarbonate <15 mmol/l), severe normocytic anemia (hemoglobin <5 g/dl or hematocrit <15%), hyperparasitemia (> 5% infected erythrocytes), renal impairment (serum creatinine >265 mol/l). Patients with mixed malarial infection were excluded from the study. Blood was drawn on the day of admission prior to treatment with antimalarial drugs at the HTD.

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

Treatment

All severe malaria patients were treated with intravenous artesunate 2.4 mg/kg per dose at 0, 12 and 24 hours after admission, then once daily until the patients could take oral medication. The treatment was then switched to oral artesunate 4 mg/kg/day for 3 days combined with oral mefloquine 25 mg/kg in 2 divided doses 12 hours apart. All the patients were admitted to the intensive care unit initially and hospitalized for a total of 28 days.

Other testing

On the day of admission, blood smears, liver function tests, plasma glucose, blood urea nitrogen, serum creatinine and electrolytes were obtained.

Statistical analysis

Quantitative parameters were compared by chi-square test. Quantitative parameters were compared using a Student's unpaired *t*-test where appropriate. Numerical values were given as means±standard deviation (SD). *P*-values <0.05 were considered significant.

RESULTS

Table 1 shows the demographic data for patients. Gender was associated with cerebral malaria (p=0.71). The ethnic groups were Mon (36.0%), Thai (29.7%), Karen (23.3%), Burmese (9.9%) and others (1.2%). Cerebral malaria was found among Thais (31.4 %), Burmese (23.5%), Mon (22.6%) and Karen (2.5%). Being Thai was significantly associated with cerebral malaria (p<0.01). The majority of patients presented to our hospital themselves (76.7%), or were referred by a tertiary care hospital (22.7%); the rest of the patients (0.6%) were referred by primary care hospitals. Of the patients who were self-referred 12.9% had cerebral malaria. Of the patients referred by tertiary care hospitals 46.2% had cerebral malaria. Being referred by a tertiary care hospital was significantly associated with cerebral malaria (p<0.01). Twenty-six point four percent of those referred from Kanchanaburi had cerebral malaria. Approximately 11% of the total number of patients who developed cerebral malaria were from Kanchanaburi Province; therefore, being referred from Kanchanaburi Province was significantly associated with cerebral malaria (p< 0.01).

Table 2 shows a comparison of symptoms between those with and without

Table 1
Demographic data of study patients in relation to cerebral malaria.

Parameters	Total subjects No.	With CM (n = 35)	Without CM (n = 137)	p-values
Age (mean)	172 (100%)	26.71±9.9	25.86±11.5	0.68
Gender				
Male	103 (59.9%)	20	83	0.71
Female	69 (40.1%)	15	54	
Ethnicity				
Thai	51 (29.7%)	16	35	<0.05
Mon	62 (36.0%)	14	48	
Burmese	17 (9.9%)	4	13	
Karen	40 (23.3%)	1	39	
Others	2 (1.2%)	0	2	
Occupation				
Farmer	18 (10.5%)	3	15	0.98
Student	17 (9.9%)	4	13	
Housewife	38 (22.1%)	8	30	
Daily laborer	72 (41.9%)	14	58	
Other	27 (15.7%)	6	21	
Referral source				
Self-referral	132 (76.7%)	17	115	<0.01
Tertiary level hospital	39 (22.7%)	18	21	
Primary level hospital	1 (0.6%)	0	1	
Likely province contracted malaria				
Kanchanaburi	72 (41.9%)	19	53	<0.01
Tak	55 (32.0%)	5	50	
Myanmar	4 (2.3%)	1	3	
Cambodia	3 (1.7%)	2	1	
Others	38 (22.1%)	8	30	

CM, cerebral malaria.

cerebral malaria. Fever (38ºC) was more common among cerebral malaria patients than non-cerebral malaria patients (80% *vs* 58.4%, p<0.05). Dyspnea was more common among cerebral malaria patients than non-cerebral malaria patients (28.6% *vs* 12.4%, p<0.05). Nausea and vomiting were less common among cerebral malaria patients than non-cerebral malaria patients (11.4% *vs* 69.3%, p<0.01). Seizures were found more commonly among cerebral malaria patients (1.7% *vs* 0%, p<0.01).

Hepatomegaly was more common among cerebral malaria than non-cerebral malaria patients (37.1% *vs* 19.7%, p<0.05). Splenomegaly was more common among cerebral malaria patients than non-cerebral malaria patients (17.1% *vs* 4.4%, p<0.05).

The mean temperature on admission was higher among cerebral malaria patients (38.5ºC *vs* 38.1ºC, p<0.05). The mean heart rate among cerebral malaria patients was higher than non-cerebral ma-

Table 2
Symptoms on admission in relation to cerebral malaria.

Symptoms	No. (%) (*n*=172)	With CM (*n*=35)	Without CM (*n*=137)	*p*-values
		No. (%)	No. (%)	
Fever >38ºC	108 (62.8)	28 (80.0)	80 (58.4)	<0.05
Cough	24 (14)	4 (11.4)	20 (14.6)	0.78
Dyspnea	27 (15.7)	10 (28.6)	17 (12.4)	<0.05
Diarrhea	27 (15.7)	4 (11.4)	23 (16.8)	0.43
Nausea/vomiting	99 (57.6)	4 (11.4)	95 (69.3)	<0.01
Alteration of consciousness	34 (19.8)	34 (97.1)	0	<0.01
Convulsions	3 (1.0)	3 (1.7)	0	<0.05

CM, cerebral malaria.

Table 3
Vital signs in relation to cerebral malaria.

Signs	With CM (*n*=35)	Without CM (*n*=137)	*p*-values
	Mean	Mean	
Temperature (ºC)	38.58	38.16	<0.05
Heart rate (beats/min)	108.37	102.12	<0.05
Respiratory rate (respirations/min)	27.51	26.41	0.27
Blood pressure			
Systolic (mmHg)	113.43	103.43	<0.01
Diastolic (mmHg)	62.57	61.47	0.64
Height (m)	1.61	1.59	0.15
Weight (kg)	54.97	50.75	<0.05
BMI	21.05	19.88	<0.05
Urine output (ml/day)	1,116.63	1,286.95	0.24

BMI, body mass index; CM, cerebral malaria.

laria patients (108 beats/min *vs* 102 beats/min, $p<0.05$). The mean systolic blood pressure in cerebral malaria patients was higher than non-cerebral malaria patients (113 mmHg *vs* 103 mmHg, $p<0.01$). More patients with cerebral malaria had a systolic blood pressure (SBP) >121 mmHg than patients with non-cerebral malaria (31.4% *vs* 18.9%, $p<0.01$). The mean body mass index (BMI) in cerebral malaria patients was 21.0 kg/m^2 and in non-cerebral malaria patients was 19.8 kg/m^2; this difference was significant ($p<0.05$) (Table 3 and Table 4).

Patients were categorized as having hyperparasitemia (≥250,000 parasites/ l) or non-hyperparasitemia (≤249,999 parasites/ l). On the day of admission

Table 4
Blood pressure groups in relation to cerebral malaria.

Signs	With CM (n=35)	Without CM (n=137)	p-values
	No.	No.	
Systolic BP (mmHg)			
<90	4	33	<0.01
91-100	5	45	
101-110	9	29	
111-120	6	21	
>121	11	26	
Diastolic BP (mmHg)			
<50	9	43	0.49
51-60	8	55	
61-70	8	38	
>71	10	36	

CM, cerebral malaria; BP, blood pressure.

Table 5
Adjusted odds ratio for factors associated with cerebral malaria.

Associated factors	Adjusted OR	95%CI	p-values
Pulmonary edema	13.8	1.3 - 143.2	<0.01
Splenomegaly	3.7	1.3 - 44.7	<0.01
Fever	3.3	1.7 - 14.3	<0.05
Malaria density (day 1)	1.6	1.1 - 14.6	<0.01
Malaria density (day 2)	3.4	1.3 - 35.1	<0.01
Hepatomegaly	1.8	1.2 - 12.1	<0.05
BMI	1.6	1.0 - 2.6	<0.05
Dyspnea	1.4	1.2 - 12.1	<0.05
Referral patients	1.3	1.0 - 2.2	<0.01
SBP	1.2	1.0 - 2.1	<0.01

BMI, body mass index; SBP, systolic blood pressure.
OR, odds ratio; CI, confidence interval; malaria density (day1), malaria density on day 1 < 249,999/ l; malaria density (day2), malaria density on day 2 < 249,999/ l.

fewer cerebral malaria patients had hyperparasitemia than non-cerebral patients (14.3% *vs* 61.3%, p<0.01). On the second day of hospitalization fewer cerebral malaria patients had hyperparasitemia than non-cerebral malaria patients (5.7% *vs* 32.1%, p<0.01). These unusual findings were also found with parasite clearance time (PCT) which was shorter in patients with cerebral malaria than in patients with non-cerebral malaria (47.0 hours *vs* 64.0 hours, p<0.01). The mean platelet count

was significant lower in cerebral malaria than non-cerebral malaria patients (53,971 / l *vs* 40,094 / l, $p<0.01$).

Analysis of factors associated with cerebral malaria

Adjusted odds ratios were calculated to identifying factors associated with cerebral malaria after controlling for other variables. The factors, odds ratios, 95% confidence intervals and *p*-values are shown in Table 5. Several of the variables were selected stepwise in the order of their statistical significance; as a result, previously associated variables were filtered throughout. All variables with a *p*-value <0.1 were included in the regression analysis. PCT was longer in non-cerebral malaria patients than cerebral malaria patients giving an odds ratio for association with cerebral malaria of <1.

Hyperparasitemia (OR=0.6, $p<0.01$) was significantly associated with non-cerebral malaria. Nausea and vomiting had the strongest association with cerebral malaria (OR=0.04, $p<0.01$). Although the mean weight of cerebral malaria patients was greater than non-cerebral malaria patients, the odds for cerebral malaria were <1. However, the weight of the patient might have affected the BMI. For every unit increase in BMI, the association with cerebral malaria increased 1.6 times.

The highest odds ratio among the clinical parameters was the presence of pulmonary edema (OR=13.8; 95%CI: 1.3-143.2, $p<0.01$). The laboratory parameter with a high odds ratio of being associated with cerebral malaria was a lower malaria parasite density (day 1: lower parasite density: OR=1.6; 95%CI: 1.1-14.6, $p<0.01$; day 2: OR=3.4; 95%CI: 1.3-35.1, $p<0.01$).

Dyspnea was 1.4 times more likely to be associated with cerebral malaria (OR=1.4; 95%CI: 1.2-12.1, $p<0.05$). The odds ratios show splenomegaly and hepatomegaly were significantly associated with cerebral malaria. Splenomegaly had a greater association with cerebral malaria than hepatomegaly (splenomegaly: OR=3.7; 95%CI: 1.3-44.7, $p<0.01$ and hepatomegaly: OR=1.8; 95%CI: 1.2-12.1, $p<0.05$).

The other two demographic factors associated with cerebral malaria were ethnicity and referral source. Karen, Burmese and Thai ethnic groups had a negative association with cerebral malaria (OR=0.5; 95%CI: 0.2-1.0, $p<0.01$). Patients referred from other tertiary level hospitals were more likely to have cerebral malaria than self-referrers (OR=1.3; 95%CI: 1.0-2.2, $p<0.01$).

DISCUSSION

The demographic parameters studied for their association with cerebral malaria were gender, ethnicity, occupation, referral source, likely province of contraction of malaria and history of malaria infection during the previous year. There was no gender association with cerebral malaria but males comprised the larger percentage of study subjects.

The Mon ethnic group comprised the largest percentage of study subjects (36%), followed by Thais (29.7%) and Karens (23.3%). Despite the fact the Mon ethnicity group was the largest, it was more likely to develop non-cerebral malaria ($p<0.05$). This implies the Mon ethnic group in this study had a lower factor associated with cerebral malaria than the Thai ethnic group. This could suggest immunity due to previous infections is more common in the Mon ethnic group or could suggest the genetic susceptibility of Thais to developing cerebral malaria. This needs further study. One study of the ge-

netic susceptibility of Thais toward developing cerebral malaria (Naka *et al*, 2009a) found the CTCTAA allele of interleukin 12 was associated with developing cerebral malaria (Naka *et al*, 2007, 2009a,b). Other studies of ethnic susceptibility for developing cerebral malaria are rare. Nacher *et al* (2001) studied severe malaria and socioeconomic risk factors and found Thais were more likely to develop cerebral malaria than other ethnic groups, such as Mon, Karen and Burmese; however, the focus of their study was on socioeconomic factors, not on genetic susceptibility.

A greater number of patients in our study referred from tertiary level hospitals had cerebral malaria than non-cerebral malaria. A probable explanation for this is sicker patients were more likely to be referred to our hospital.

Most of the patients in this study came from western Thailand. The majority came from Kanchanaburi Province (41.9%), followed by Tak Province (32.0%). Four patients came from Myanmar and 3 from Cambodia. Fifty-five percent of patients from Kanchanaburi Province in our study had cerebral malaria while 14.2% from Tak Province had cerebral malaria. This could be due to unstable malaria transmission in these provinces (White, 2009).

The Thai ethnic group was more likely to have cerebral malaria than other ethnic groups. Patients referred from tertiary level hospitals were more likely to have cerebral malaria than self-referred patients. Kanchanaburi Province has seasonal transmission of malaria (Childs *et al*, 2006) making it an unstable transmission area.

A fever >38.0°C, dyspnea, altered consciousness and convulsions were all significantly associated with cerebral malaria. One reason for a fever >38°C being associated with cerebral malaria could be the role of higher levels of TNF, which is also found in cerebral malaria (Kwaitkowski, 1990).

Hepatomegaly and splenomegaly were associated with cerebral malaria. The reasons for enlargement have been postulated by several authors (Nacher *et al*, 2000; White, 2009; Tangpukdee *et al*, 2010). The mean temperature in cerebral malaria patients was higher than in the non-cerebral malaria patients (38.5°C *vs* 38.1°C). Both body weight of subjects and BMI were significantly higher in cerebral malaria patients than non-cerebral malaria patients, consistent with a previous study of indicators for fatal malaria and predictors of severe malaria (Nacher *et al*, 2001).

Hypoparasitemia was associated with cerebral malaria in our study. We used WHO (2010) guidelines to define hyper- and hypoparasitemia. Tankpukdee *et al* (2012) suggested using a lower parasitemia index (0.5% *vs* 5% in our study) to define hyperparasitemia in areas of seasonal transmission. The discrepancy between disease severity and parasite index has been a point of interest for clinicians. One explanation for this is sequestration of parasitized red blood cells in the peripheral tissue vessels (Silamut and White, 1993; Silamut *et al*, 1999). On day 2, 5.7% of subjects with cerebral malaria had hyperparasitemia, suggesting hypoparasitemia is associated with cerebral malaria. Our findings are consistent with a similar study (Pongponratn *et al*, 2003) showing sequestration was more pronounced in brain tissue with 26.6 times more infected red blood cells in the brain than in the peripheral blood.

Parasite clearance time in our study

was shorter in cerebral malaria patients than in non-cerebral malaria patients (47.4 hrs *vs* 63.6 hrs). This supports the finding discussed above that peripheral parasitemia was more common in non-cerebral malaria patients.

Nausea and vomiting were more common in non-cerebral malaria patients in our study. There is little information about this factor in the literature but Tangpukdee *et al* (2010) found nausea and vomiting were more common in those who did not die from cerebral malaria.

Cerebral malaria is also associated with acute respiratory distress syndrome (ARDS) (Chaudhari *et al*, 2013). Possible causes for pulmonary edema and ARDS have been postulated to be: aspiration due to a decreased level of consciousness, sequestration of parasites in the pulmonary vasculature and acidosis (Olumese *et al*, 1995). An association between respiratory distress and cerebral malaria has been described in several reports (Mishra *et al*, 2007; Ranque *et al*, 2008; Tangpukdee *et al*, 2010).

Cerebral malaria is a predictor of mortality in severe malaria (Mishra *et al*, 2007). We attempted to determine the clinical, laboratory and demographic factors associated with cerebral malaria. One of the limitations of our study was there were no case fatalities so we were unable to assess indicators for mortality.

In conclusion, there were ten factors associated with cerebral malaria in this study: pulmonary edema, hepatomegaly, splenomegaly, fever >38ºC, malaria density ≤249,999/ l on days 1 and 2 of hospitalization, dyspnea, referral patients, a systolic blood pressure >121mmHg and a BMI ≥21 kg/m^2. Clinicians should be aware of the factors associated with cerebral malaria.

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