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Hyponatraemia and hypokalaemia in adults with uncomplicated malaria in Thailand

Vipa Thanachartwet, MD*, Srivicha Krudsood, MD†, Noppadon Tangpukdee, PhD*, Weerapong Phumratanaprapin, MD*, Udomsak Silachamroon, MD*, Wattana Leowattana, MD*, Polrat Wilairatana, MD‡, Gary M Brittenham, MD‡, Sornchai Looareesuwan, MD, FRCP*, and Guy H Neild, MD, FRCP§

* Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithee Road, Ratchathevee, Bangkok 10400, Thailand † Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithee Road, Ratchathevee, Bangkok 10400, Thailand ‡ Department of Pediatrics and Medicine, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA § Institute of Urology and Nephrology, University College London, London, NW1 2BU, UK

SUMMARY

In a retrospective study of 1415 patients aged 15 and over, we determined the incidence of clinically important hyponatraemia and hypokalaemia in adults with uncomplicated malaria. On admission, serum concentrations of sodium (135–145 mmol/L) and potassium (3.5–5.0 mmol/L) were found outside these reference ranges in 81% of patients. Severe hypokalaemia ($K^+ < 3.0$ mmol/L) and severe hyponatraemia ($Na^+ < 125$ mmol/L) occurred in 4.4% and 0.6% of the patients, respectively. For hypokalaemia (43%) and hyponatraemia (37%), hypovolaemia, blood urea to creatinine ratio and high serum glucose (> 100 mg/dL) were all independent factors ($P < 0.001$). Other independent predictors for hypokalaemia were *Plasmodium vivax* infection, female gender; and for hyponatraemia, *P. falciparum* infection, male gender, concentrations of G-6-PD and serum bicarbonate.

Introduction

Clinical manifestations of uncomplicated malaria vary widely but are usually characterized by fever with rigour, headache and myalgia.¹ There is no published information regarding serum sodium and potassium abnormalities in uncomplicated malaria.

Hyponatraemia and hypernatraemia may cause drowsiness or confusion while there is an increased risk of arrhythmias for patients with hypokalaemia or hyperkalaemia. In general, symptoms requiring urgent correction of hypokalaemia begin as the potassium concentration falls to < 3.0 mmol/L and for hyponatraemia when the sodium concentration falls acutely < 125 mmol/L.^{2,3}

We have conducted a retrospective study of all adult patients admitted to the Hospital for Tropical Diseases, Bangkok, with uncomplicated malaria. The aims of this study were to determine the incidence of: (1) serum sodium and potassium out of the normal range and (2) severe hypokalaemia and hyponatraemia requiring urgent clinical correction.

Materials and methods

Study site and patients

The study was carried out at the Hospital for Tropical Diseases, Bangkok, Thailand. All adults ≥ 15 years of age admitted between January 2002 and August 2006 with a diagnosis of malaria, but without the World Health Organization's criteria for severe, complicated malaria, were considered for the study.

Methods

We reviewed all the medical records, investigations (Table 1) as well as chest X-rays and urinalysis. The diagnosis of malaria was confirmed by parasitaemia from blood smears in patients without any other detectable cause for their clinical illness, after a review of all the available data.

The following definitions were used: hyponatraemia and hypernatraemia, serum sodium levels of ≤ 134 and ≥ 146 mmol/L; hypokalaemia and hyperkalaemia, serum potassium levels of ≤ 3.4 mmol/L and ≥ 5.1 mmol/L, respectively. The normal blood urea nitrogen (BUN): creatinine (Cr) ratio is $<15:1$. High serum glucose level was a serum glucose > 100 mg/dL (5.6 mmol/L).

Clinical management

All patients were managed in malaria research wards. Patients were treated according to our hospital protocol for uncomplicated malaria based on local and national recommendations.¹

Statistical analysis

The variables for possible predictors of electrolyte disturbance that we examined are shown in Table 1.

All data were collected and analysed using SPSS for Windows release 11.0 (SPSS, Chicago, IL, USA). Proportions were compared by either the chi-squared or the Fisher's exact test as appropriate. Quantitative variables with normal distribution were expressed as mean and standard deviation (SD), and then compared between two groups using the Student's *t*-test. Quantitative variables with non-normal distribution were expressed as median and range, and compared using the Mann-Whitney U test. Binary logistic regression analysis was performed to determine the association of hyponatraemia and hypokalaemia with various risk factors taking confounding into account. Odds ratios and 95% confidence intervals were obtained. A *P* value of <0.05 was considered statistically significant.

Results

During the study period, a total of 1415 adults with uncomplicated malaria were admitted. The mean (SD) age was 26 (9.8) years; 65% were infected by *P. falciparum* and 35% by *P. vivax*. The majority of patients (60%) were clinically hypovolaemic at admission.

On admission, serum potassium was low in 43%, and six patients (0.4%) were hyperkalaemic. Of the patients with hypokalaemia 58% were infected by *P. falciparum* and 42% with *P. vivax*.

Hyponatraemia was present in 518 (37%), of whom 81% were infected by *P. falciparum* and 19% by *P. vivax*. The mean BUN to Cr ratio was 19 in patients with hyponatraemia (normal $<15:1$). Hypernatraemia was present in 18 patients (1.3%) and more common among those with *P. vivax* infection (Table 1).

Severe hypokalaemia and severe hyponatraemia were identified in 4.4% and 0.6% of patients, respectively. Both hyponatraemia and hypokalaemia were present in 244 (17%) patients.

Hypokalaemia was significantly associated with *P. vivax* infection ($P < 0.001$), female gender ($P < 0.001$), fever before admission ≤ 5 days ($P = 0.037$), hypovolaemia ($P = 0.001$), BUN:Cr ratio > 15 ($P = 0.030$), hyponatraemia ($P = 0.001$) and serum glucose > 100 mg/dL ($P < 0.001$).

Hyponatraemia was significantly associated with *P. falciparum* infection ($P < 0.001$), male gender ($P < 0.001$), hypovolaemia ($P < 0.001$), G-6-PD deficiency ($P = 0.009$), haemoglobin ≤ 11 g/dL ($P = 0.016$), BUN:Cr ratio > 15 ($P = 0.001$), serum glucose > 100 mg/dL ($P < 0.001$), serum ALT > 35 U/L ($P = 0.024$) and serum bicarbonate < 23 mmol/L ($P < 0.001$).

Discussion

In our study, 81% of patients with uncomplicated malaria had serum sodium and potassium disturbances. Both hyponatraemia and hypokalaemia were present in 17%.

Hypovolaemia

The majority of patients with uncomplicated malaria had clinical evidence of dehydration and hypovolaemia through failure to drink, increase insensible losses during high fever, diarrhoea and profuse vomiting. The mean BUN:Cr ratio was 19 in patients with hyponatraemia. The increased BUN was a result of a combination of decreased urea elimination, as a consequence of oliguria owing to volume depletion, and increased urea production from the hypercatabolic state.

Hypokalaemia

This was the most common disturbance. It was found in 43% of patients, and especially in women with *P. vivax* infection. Severe hypokalaemia was found in 4.4%. In contrast, in children hyperkalaemia is a more common electrolyte disturbance in severe malaria (up to 16%) whereas hypokalaemia was reported in only 7–11%.⁴ Similar data from adults with severe malaria is not available.

In our study, evidence of volume depletion was the predominant risk factor for hypokalaemia. In normal oliguric pre-renal failure hyperkalaemia is common owing to the low concentration of tubular Na⁺ for exchange with K⁺. Thus, the hypokalaemia we observed was unexpected. Regression analysis also showed that a fever of ≤ 5 days duration, and an increased serum glucose level, was associated with hypokalaemia. It is likely that hypokalaemia is multifactorial from a combination of intracellular translocation of potassium from extracellular fluid and urinary potassium loss.

Hyponatraemia

This occurred in 37%, the majority of whom were men, and the majority of patients with hyponatraemia were infected with *P. falciparum* (81%). Severe hyponatraemia was rare (0.6%). In severe malaria, hyponatraemia was more common and noted in 53–76%.^{5–7}

Hyponatraemia might result from an increased secretion of antidiuretic hormones.^{5,8} In our study, patients with G-6-PD deficiency or low haemoglobin level had a higher risk of hyponatraemia.

We conclude that the conspicuous laboratory findings in patients with uncomplicated malaria were hypokalaemia (43%) and hyponatraemia (37%). In a substantial minority, hypokalaemia and hyponatraemia was so severe as to be life-threatening and required urgent correction.

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Table 1

Baseline clinical and biochemical features

Characteristic	Sodium		Potassium	
	Na ≤ 134	Na ≥ 146	K ≤ 3.4	K ≥ 5.1
Number of patients (n [%])	518 (36.6)	18 (1.3)	603 (42.6)	6 (0.4)
Demographic				
Age (years), mean (SD)	26.2 (10.0)	25.1 (8.0)	26.2 (9.4)	22.6 (6.2)
Male (n [%])	378 (38.1)	15 (1.5)	379 (38.2)	6 (0.6)
Female (n [%])	140 (33.1)	3 (0.7)	224 (53.0)	0 (0)
Type of infection				
<i>P. falciparum</i> (n [%])	421 (45.9)	5 (0.5)	350 (38.1)	3 (0.3)
<i>P. vivax</i> (n [%])	97 (19.5)	13 (2.6)	253 (50.9)	3 (0.6)
Clinical				
Fever (days), mean (SD)	5.1 (3.8)	5.0 (1.8)	4.6 (3.6)	5.1 (2.4)
Hypovolaemia (n [%])	312 (36.6)	2 (0.2)	352 (41.3)	0 (0)
Hepatomegaly (n [%])	131 (48.7)	0 (0)	124 (46.1)	0 (0)
Laboratory data				
G-6-PD deficiency (n [%])	61 (37.0)	0 (0)	72 (43.6)	0 (0)
Hb (g/dL), mean (SD)	11.9 (2.3)	11.3 (3.1)	11.9 (2.1)	10.8 (2.6)
Glucose (mg/dL), mean (SD)	125.8 (33.3)	107.1 (17.9)	123.4 (31.9)	99.0 (8.8)
BUN (mg/dL), mean (SD)	18.2 (9.1)	12.6 (4.7)	15.7 (6.7)	15.7 (6.3)
Cr (mg/dL), mean (SD)	0.9 (0.3)	0.8 (0.1)	0.9 (0.3)	0.9 (0.2)
BUN/Cr ratio, mean (SD)	19.4 (6.2)	17.0 (8.4)	18.1 (5.8)	17.8 (4.6)
Na (mmol/L), mean (SD)	132.1 (2.7)	148 (1.9)	135.9 (4.1)	137.0 (3.7)
K (mmol/L), mean (SD)	3.6 (0.5)	3.7 (0.3)	3.2 (0.2)	5.6 (0.5)
HCO ₃ ⁻ (mmol/L), mean (SD)	22.8 (2.8)	26.5 (2.0)	23.4 (2.9)	24.0 (2.0)
Total bilirubin (mg/dL), mean (SD)	1.8 (1.5)	1.3 (1.2)	1.6 (1.3)	1.7 (0.9)
ALT (U/L), mean (SD)	40.8 (36.2)	25.8 (16.9)	38.7 (51.7)	26.1 (36.2)

SD, standard deviation; BUN, blood urea nitrogen; Cr, creatinine; ALT, alanine aminotransferase; Hb, haemoglobin; HCO₃⁻, bicarbonate; G-6-PD, glucose-6-phosphatase dehydrogenase