Original articles

Electrolyte changes and renal functions in children with severe malaria

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Abstract

Background: Electrolyte disturbances and renal impairment have been reported in patients with severe malaria (SM). However, the contributing mechanisms are not well identified.

Objectives: The study aims to identify disturbances in electrolytes and renal functions in children with SM and their possible pathophysiology.

Methods: The study included fifty six children with SM identified according to WHO criteria of SM. Investigations included parasitemia; glucose; urea; creatinine; sodium; and potassium estimation. Plasma osmolality was calculated.

Results: Children with SM had higher frequency of hyponatremia and hypokalemia than children with uncomplicated malaria (UM). Hyperkalemia complicated 10.7% of cases of SM. Children with SM had lower creatinine and plasma osmolality than those with UM. Children presenting with more than one of the complications, showed higher plasma osmolality, urea levels and creatinine levels than those with UM.

Conclusions: Hyponatremia may reflect the syndrome of inappropriate ADH secretion. Hypokalemia is a frequent complication while hyperkalemia complicates some cases. Dehydration may play a role in renal impairment; thus fluid therapy is indicated in cases with evidence of dehydration.

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Introduction:

Electrolyte disturbances and renal impairment were reported in patients infected with malaria parasites and were associated with severity of the disease[1-3]. However, the contributing mechanisms are not well identified. Hyponatremia is a frequent presentation in children with severe malaria and it is a serious condition in other diseases that necessitates urgent treatment. The syndrome of inappropriate ADH secretion[3], renal impairment[4]. and dehydration are among the suggested mechanisms with controversial findings[1, 2]. On the other hand, potassium changes were also reported and were linked to acid- base balance status[5, 6].

This study investigated serum electrolytes and renal functions in children infected with malaria parasite to identify abnormalities and possible mechanisms.

Methods:

The study was a cross- sectional study, conducted at Wad Medani Pediatric Hospital. The collection of samples started in September 2007 and extended up to September 2008.The study included a cohort of fifty six children with severe malaria according to WHO criteria of SM. [7]Thirty one children with UM were included in the study for comparison. The age of both groups ranged from 2 to 12 years.

Exclusion criteria were as follows: patients who had antimalarial treatment before admission and those who were known to have renal disease; hepatic disease; and diabetes mellitus. Patients suffering from metabolic and developmental disorders; malnutrition; pneumonia; septicemia; meningitis; congenital heart diseases; HIV infection; and tuberculosis were also excluded.

The study was approved by the Institutional Ethical Committee of the University of Khartoum and informed written consent was obtained from children's parents.

History and physical examination: Both groups of patients underwent history taking and comprehensive physical examination by the researcher and hospital staff. A data collection form was completed for each patient including history and physical examination.

Malaria diagnosis and blood tests: A sample of 5 ml was taken from each patient on admission and before treatment was started and divided into 3 tubes: one containing EDTA was used for parasitemia estimation. The second tube was a plain tube which was used for urea, creatinine, sodium and potassium estimation. The third tube containing fluoride was used for random blood glucose (RBG) estimation.

The microscopic identification of the malaria parasite was the method of confirmation of infection with *plasmodium falciparum* used in the study to satisfy WHO criteria. Only positive cases were included. The thick blood film was used for parasite detection while thin film was used for identification of species and parasitemia estimation.

The thin blood film was fixed using absolute methyl alcohol, and then stock solution of Giemsa stain was diluted with distilled water. The distilled water was kept at pH 7.1-7.2 using phosphate buffer. Staining of films was done. Parasitemia estimated in thin films expressed as a percentage of infected RBCs from total RBCs[8].

Urea was measured by a UV enzymatic method using spectrophotometer[9]. Creatinine was measured by a colorimetric enzymatic method[10]. Sodium and potassium were measured in serum samples using a flame photometer[11]. RBG was measured by enzymatic colorimetric method[12].

Plasma osmolality was calculated using the following formula[13].

Plasma osmolality (mosm/l) = 2×sodium (mmol/l) + 0.055× urea (mg/dl) + 0.36 × glucose (mg/dl).

Statistical analysis: Statistical analysis was carried out with Statistical Package of Social Sciences (SPSS) for windows version 11.5. Normality of data distribution was checked using Kolmogrov-Smirnov test. Homogeneity of data was checked by the Levene's test for equality of variances. Data were presented as means and standard deviations and analyzed by student's *t* test. Correlations were compared using the χ^2 tests if the variables were qualitative. Pearson's correlation coefficient was used for quantitative variables and Spearman' rank correlation coefficient tests was used to correlate quantitive variable with qualitative variable. P values < 0.05 were considered as significant.

Results:

Clinical presentations: twenty three patients presented with repeated convulsions, thirteen patients presented with cerebral malaria and an equal number with severe anemia. Some patients presented with hemoglobinuria (n=2), hypoglycemia (n= 1) and some with more than one complication (n= 4).

Laboratory findings: Children with SM showed significantly lower mean creatinine level than those with UM (table-1).

The mean urea level in uncomplicated malaria was 22.78mg/dl while in severe malaria it was 25.14mg/dl. No significant difference was found between the two (P value=0.398). Significant difference was found with mixed presentations (UM=.22.78±6.14 versus 55.00±39.54 P value=0.000)

The mean creatinine level in uncomplicated malaria was 0.56mg/dl while in severe malaria it was 0.40mg/dl. A significant difference was found

between the two (P value=0.016) as well as with other severe malaria categories (Table 2)

The mean sodium level in uncomplicated malaria was 135mmol/l while in severe malaria 133mmol/l no significant difference was found between the two. However, a total of fifty children were found to be hyponatremic, most of them had severe malaria. Incidence of hyponatremia was more frequent in severe malaria than uncomplicated malaria (P value=0.005).

Plasma osmolality was lower in children with severe malaria than in those with UM with exclusion of mixed presentations (Table 3) and in some severe malaria categories (Table 4).

Although the mean potassium level in uncomplicated malaria showed no significant difference compared with severe malaria, hypokalemia was found to be significantly more frequent in severe malaria than uncomplicated malaria (P value=0.039) (Figure-1). Some children showed hyperkalemia and presented mostly with neurological manifestations in the form of cerebral malaria or repeated convulsions and one of them died.

About 30.4% of children with severe malaria were found to have hyperparasitemia while 19.4% of those with uncomplicated malaria had hyperparasitemia. The incidence of hyperparasitemia was significantly more in severe malaria than in uncomplicated malaria (P value=0.022). No significant correlation were found between the degree of parasitemia and potassium (P value=0.298) or sodium (P value=0.244).

Table1. Laboratory investigations of patients with uncomplicated malaria (UM) & severe malaria (SM)

Investigation	Kolmogrov-Smirnov test P value	UM (mean± SD)	SM (mean ±SD)	P value
Urea(mg/dl)	0.076	22.784±6.14	25.14±14.72	0.398
Creatinine(mg/dl)	0.063	0.561±0.22	0.40±0.32	0.016
Na+(mmol/l)	0.200	135.03±3.30	133.20±4.65	0.056
K+(mmol/l)	0.067	3.84±0.41	3.98±1.04	0.474
Random blood glucose(mg/dl)	0.367	108±39.14	89.27±39.06	0.035

Table2. Comparison of creatinine between UM& SM categories

UM	SM categories	Number	Mean ±SD	P value
0.56±0.22	Cerebral malaria	13	0.41±0.21	0.054
	Severe anemia	13	0.36±0.22	
	Repeated convulsions	23	0.36±0.15	
	Hypoglycemia	1	0.10	
	Hemoglobinuria	2	0.20±.00	
	Mixed presentations	4	0.90±.94	0.082

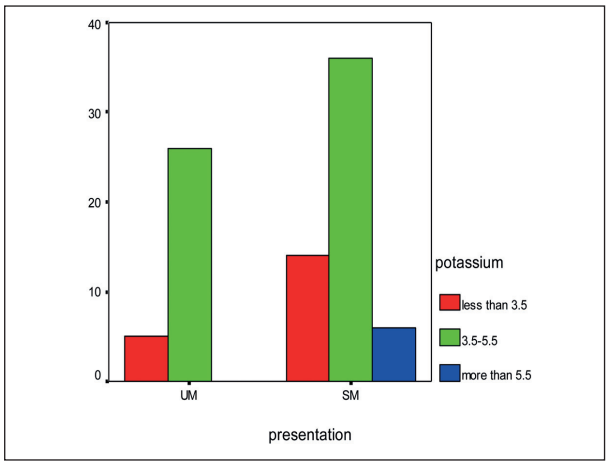
Table3. Comparison between osmolality in UM and SM cases (without mixed presentations)

UM	Number	Mean ±SD	P value
UM	31	6.9±284.2	0.007
SM	52	9.7±279.18	

Table 4. Comparison of plasma osmolality between UM& SM categories

UM	SM categories	Number	Mean ±SD	P value
284.± 6.9	Cerebral malaria	13	281.710.9±	0.36
	Severe anemia	13	276.88.7±	0.005
	Repeated convulsions	23	278.69.5±	0.016
	Hypoglycemia	1	286.96.9±	0.69
	Hemoglobinuria	2	280±.16.	0.43
	Mixed presentations	4	295.616.0±	0.251

Figure-1 Incidence of hypokalemia and hyperkalemia in UM & SM



Discussion

The present study reports children with severe malaria suffered from hyponatremia, hypokalemia and low creatinine level and low plasma osmolality. These could have well been due to inappropriate ADH secretion. No correlation was detected between the sodium level and degree of parasitemia.

Although the literature commonly reported sodium changes in malaria, the contributing mechanisms are not well identified. Possible mechanisms are: syndrome of inappropriate ADH secretion; renal impairment; and dehydration[1]; cerebral salt wasting[2]; renal losses[14]; and the "sick cell syndrome. [15] A study carried on Kenyan children detected hyponatremia in 53% of children with SM. Hyponatremia was not related to peripheral parasite density, dehydration and abnormal renal function. ADH was found to be inappropriate to the degree of dehydration. [3] However, some studies detected appropriate ADH secretion in patients with hyponatremia. [1, 2]

Renal impairment was reported as a cause of hyponatremia in malaria. [1, 4] Hyponatremia was associated with increased urinary sodium concentration in the presence of reduced creatinine clearance in these patients.[4] In this study, the mean plasma urea level in children with SM was normal and not significantly different from children with UM. The mean creatinine level was significantly low in children with SM most likely reflecting the diluted plasma as a result of inappropriate ADH secretion. This study did not show evidence of renal impairment thereby it is not the explanation of hyponatremia in the study cases.

In the present study the incidence of hypokalemia was more frequent in children with SM than in

those with UM. Hyperkalemia was detected in 10.7% of children with SM and most of them had neurological manifestations.

Alteration in potassium is associated with acidemia and alkalemia. A study carried in thirty eight Kenyan children with severe malaria and acidosis detected that at admission, serum potassium was normal in 31 (81.6%), low in 4 (11%) children and 3 (6.3%) children had hyperkalaemia. Plasma potassium decreased rapidly after correction of acidosis. Fractional excretion of potassium and the trans-tubular gradient of potassium were above normal range, indicating renal potassium loss and the study concluded that hypokalaemia was a common complication of severe malaria. However, it was often not apparent on admission. The plasma potassium decreased precipitously after correction of acidosis, and thus serial monitoring of serum potassium was suggested in patients with severe malaria complicated by acidosis. [5] Hyperkalemia was reported in malaria cases complicated by acidosis and was associated with increased mortality, generally soon after admission[6].

The present work showed that mean urea levels were nearly the same in SM and UM. Children with mixed presentation had significantly higher urea level than those with UM. They also had relatively higher creatinine, higher sodium and higher plasma osmolality in comparison with UM and other SM categories. They also had higher body temperature, higher incidence of tachycardia and tachypnea than UM and other SM categories. These findings suggest that dehydration might play a role in this subgroup of SM and that dehydration was an indicator of poor outcome in children with SM as this group of children had increased morbidity. Mild renal impairment was reported in children with malaria and dehydration was known as a contributing factor. [4, 1, 5] Maitland et al (2003) found that volume expansion in children with dehydration was associated with correction of the hemodynamic abnormalities and improvement of organ functions. [16] Therefore, volume resuscitation should be considered in severe malaria with evidence of dehydration.

Acute renal failure is seen mostly in *Plasmodium falciparum* infection, but *P vivax* and *P. malariae* can occasionally contribute to renal impairment. [17, 18] Malarial ARF is commonly encountered in non-immune adults and older children with *falciparum* malaria in areas of low endemicity. Several hypotheses including: mechanical obstruction by infected erythrocytes; immune- mediated glomerular and tubular pathology[19, 20]; fluid losses due to multiple mechanisms; and alterations in the renal microcirculation have been proposed[18, 21-23]. Renal impairment on admission carries a poor prognosis even though acute renal failure is rare in children[24, 25].

In this study creatinine was significantly lower in children with SM than in those with UM. This finding can be explained by the inappropriate ADH secretion which was reported to occur in SM[3].

Conclusions:

The findings of this study showed that electrolyte changes are common in malaria. Hyponatremia most probably reflects the syndrome of inappropriate ADH secretion (SIADH) . Potassium changes ranged from hypokalemia to hyperkalemia. Dehydration may play a role in renal impairment encountered during malaria infection.

It appears that fluid therapy is needed only in the subgroup of the infected children who showed evidence of dehydration. While those with hyponatremia may not need fluids therapy and close observation may be the only action needed.

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Authors' contribution:

Dr Nisreen had contributed to the design of the study, collection and analysis of the data, wrote the paper and approved the final version of the manuscript. Professor MY Sukkar had contributed

to the design of the study, analysis of the data, and critical revision of the paper and approved the final draft.

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