

Low plasma bicarbonate predicts poor outcome of cerebral malaria in Nigerian children

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Summary

Malaria remains a major cause of morbidity and mortality in many sub Saharan countries and cerebral malaria is widely recognised as one of its most fatal forms. We studied the predictive value of routine biochemical laboratory indices in predicting the outcome of cerebral malaria in 50 Nigerian children ages 9 months to 6 years with cerebral malaria at the University College Hospital, Ibadan, Nigeria. Of the 50 children studied, 43 (86%) made a full recovery, 5 (10%) developed neurological sequelae while 11 (22%) died. Biochemical derangements observed among the children included azotaemia (29%), elevated plasma creatinine (20%), metabolic acidosis (22%) and hyponatraemia (16%). Metabolic acidosis and elevated plasma creatinine on admission were significantly associated with a poor outcome ($p < 0.05$). Hyponatraemia and hypokalaemia were not significantly associated with outcome. On multivariate analysis, metabolic acidosis and elevated plasma creatinine on admission to hospital remained independent predictors of poor outcome after adjusting for other known risk factors. Patients with these findings require prompt referral for adequate treatment in centres equipped to manage such critically ill patients.

Keywords: *Cerebral malaria, Electrolyte imbalances, Acidosis, Children, Nigeria.*

Résumé

Le paludisme demeure une cause majeure de la morbidité et la mortalité dans la plu part de pays au sous Sahara et le Paludisme Cérébral est partout reconnu comme l'une de ses formes la plus grave. Nous avons étudié la valeur prophétique de l' indice biochimique laboratoire d'usage dans la prévision du résultat du paludisme cérébral chez 50 enfants nigériens âgés de 9 mois à 6 ans atteint du Paludisme Cérébral au collège Hospitalier Universitaire, Ibadan au Nigeria.

Entre 50 enfants étudié, 43 soit 86% se sont véritablement rétablies, 5 soit 10% sont atteints de la séquelle neurologique tandis que 11 soit 22% étaient morts. Aliénation mentale Biochimiques remarquées chez les enfants sont: azote mie 29%, plasma creatinine élevée 20%, acidose métabolique 22% et hyponatremie 16%. Acidose métabolique et plasma creatinine élevée ont été sensiblement associées avec un mauvais résultat ($P < 0,05$) pendant l'admission à l'hôpital. L "hyponatremie et l'hypokaliémie n'étaient pas sensiblement associées avec le résultat. A travers l'analyse multi-diversité, l'acidose métabolique et le plasma creatinine élevé avaient demeuré prédateurs indépendants de mauvais résultat après un ajustement par rapport à un autre facteur de risque connu pendant l'admission à l'hôpital.

Des patients avec ces résultats ont besoin d'être envoyé immédiatement aux centres équipés pour bien soigner les grands malades et afin d'avoir un traitement spécial.

Introduction

Malaria remains a major health problem of the tropics and sub-tropics, accounting for more than a million deaths annually worldwide.¹ It also accounts for up to 50% of hospital admissions in tropical Africa.² In Nigeria, malaria contributes significantly to

childhood morbidity and mortality.³⁻⁶ The emergence of chloroquine-resistant malaria in most endemic areas has further compounded this problem.⁷⁻⁹

Most of the deaths resulting from malaria are due to the severe and complicated forms of the disease. Cerebral malaria is the most lethal complication of malaria, accounting for 40-50% of malaria-related deaths and death may occur despite prompt and appropriate treatment.¹⁰ The causes of death in cerebral malaria are not completely understood. Various risk factors have been identified which include host, parasite and environmental factors. We have studied children with cerebral malaria at the University College Hospital, Ibadan, Nigeria, to define the routine biochemical findings on admission to hospital and to determine the prognostic significance (if any) of these parameters.

Patients and methods

The study was conducted in the Otunba Tunwase Children Emergency Ward of University College Hospital, Ibadan, Ibadan, over a one-year period. The protocol was approved by the Joint University College Hospital/University of Ibadan Ethical Committee. Children below 6 years of age presenting with cerebral malaria were enrolled into the study after informed consent had been obtained from the mother or principal caregiver of the child. Patients were considered to have cerebral malaria if they satisfied the World Health Organisation (WHO) research definition for cerebral malaria.¹⁰

The clinical history was obtained from the accompanying relative and complete physical examination was performed on all patients on admission. Coma was scored using the Blantyre coma scale.¹¹ Laboratory investigations included thick and thin capillary blood films. Blood films were stained by the Giesma technique for the identification and counting of malaria parasites.¹² Other investigations included analysis of cerebrospinal fluid by standard microbiological methods, packed cell volume and white blood cell count. The routine biochemical parameters estimated for each patient included plasma electrolytes (sodium, potassium, chloride, bicarbonate), urea, creatinine and glucose.

Patients were treated with either a standard loading dose regimen of intravenous quinine or intramuscular artemether.^{10,13,14} Patients who were hypoglycaemic were given an intravenous bolus of 50% dextrose (1-ml/kg) followed by nasogastric tube feeding. All patients were tube-fed with high protein pap until they were awake and could be fed by mouth in the usual way. Patients with packed cell volume $< 15\%$ (haemoglobin $< 5\text{g/dl}$) and who were symptomatic were transfused with HIV-negative packed red cells. Convulsions were aborted with intravenous diazepam (0.3-mg/kg). Metabolic acidosis was corrected with 8.4% sodium bicarbonate. Following commencement of treatment, physical examination and coma score were performed and recorded 4-hourly, but more frequently in severely ill patients, until full recovery or demise. Parasite counts were repeated 6 hourly until three successive negative blood films were obtained. Capillary blood glucose was monitored hourly for the first 6 hours of treatment and subsequently 4 hourly until levels stabilized. Packed cell volume was determined 12 hourly until stable. On discharge from hospital, patients were followed up weekly for at least four weeks.

Entry of the data on the case record forms was done using the

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Epi Info 6 software package and data analysis was done using the Statistical Package for the Social Sciences (SPSS). Means of continuous variables were compared using Student's t-test. Association between categorical variables was assessed using the chi-squared test or Fischer's exact test where appropriate. Multiple linear logistic regression analysis was used to determine the most sensitive predictors of a bad outcome.

Results

During the period of study, 50 patients with cerebral malaria as defined by WHO criteria were enrolled. They comprised 22 males and 28 females with a male: female ratio of 0.8:1. Their ages ranged from 9 months to 6 years with a mean of 3.0 (SD 1.3) years. The total duration of illness prior to hospital admission was

Table 1 Presenting clinical features in 50 children with cerebral malaria

Clinical feature	Number of cases	Percentage of total
Symptoms		
Fever	50	100
Generalized convulsion	41	82
Focal convulsion	3	6
Poor Feeding	40	80
Chloroquine Treatment	34	68
Restlessness	21	42
Vomiting	21	42
Irritability	15	30
Diarrhoea	4	8
Signs		
Spasticity	28	56
Hepatomegaly	26	52
Dilated Pupil	23	46
Papilloedema	13	26
Decerebrate posture	12	24
Absent conical reflex	9	18
Retinal haemorrhages	9	18
Splenomegaly	7	14
Flaccidity	5	10
Decorticate posture	2	4

Table 2 Laboratory indices (mean plasma concentration) in relation to outcome in 50 children with cerebral malaria

Parameter	Mean (SD)			t	P
	Full recovery n = 39	Sequelae n=5	Deaths n=11		
Potassium (mEq/l)	3.7 (0.7)	4.9 (1.6)	4.1(0/6)	4.677	0.026*
Bicarbonate (mEq/l)	20.3(3.3)	16.6(2.6)	17.4(3.0)	3.114	0.027*
Urea (mg/100ml)	47.7(23.7)	66.0 (48.1)	60.6(46.6)	1.129	0.570
Creatinine (mg/100ml)	0.47(0.2)	0.82(0.3)	0.76(0.3)	14.336	0.002*
Glucose (mg/100ml)	95.4 (45.5)	113.4 (39.6)	78.3(36.6)	1.836	0.399

*Significant association with outcome at p<0.05 for comparison of full recovery versus sequelae/death.

Table 3 Frequencies of biochemical derangements in relation to outcome

Parameter	Prevalence (%)	Frequency			P
		Full recovery n=39	Sequelae n=5	Deaths n=11	
Hyponatraemia	16	6	1	1	0.0495
Hypokalaemia	8	3	0	1	0.131
Hypochloraemia	10	3	2	0	0.518
Acidosis	22	3	3	5	0.002*
Azotaemia	29	18	3	8	0.453
Elevated creatinine	20	3	3	4	0.001*
Hypoglycaemia	8	2	0	2	0.380

*Significant association with outcome, p for chi-square or Fisher exact test for comparison of full recovery versus sequelae/death

short, with a mean of 2.0 (SD 1.2) days. The mean period from onset of coma to the time of admission was also short: mean 6.0

(SD 5.6) hours. The clinical features on admission are shown on Table 1. Forty-one patients had a Blantyre coma score of 0-2 and nine had a score of 3. Mean coma recovery time was 42.6 hours with 70% of the survivors having regained full consciousness by 48 hours of treatment. The mean parasite clearance time was 51.4 (SD 28.6) hours.

Of the 50 children studies, 34 (68%) made full recovery, 5(10%) developed neurological complications and 11(22%) died. The children with neurological sequelae included one child with spastic quadriplegia/aphasia, three children with motor deficits/regression of motor milestone and one child with hearing impairment/abnormal behaviour. At review one month after discharge from the hospital, all but one child with neurological sequelae had recovered fully. The affected child (the child with motor deficits) was still unable to walk after three months when he was lost to follow-up. Eleven children (22%) children died. Eight (73% of the deaths) of them died within 24 hours of admission.

To assess the relation between laboratory indices and outcome, the group of 34 children who made a full recovery were compared with the 16 children who had unsatisfactory outcome i.e. those who died or suffered neurological sequelae (Table 2). Mean plasma potassium and mean plasma creatinine were significantly lower among intact survivors compared to those with a bad outcome. In contrast, mean plasma bicarbonate was significantly lower among those with a bad outcome when compared with those who survived intact. Analysis of specific electrolyte derangements (such as hyponatraemia or hypokalaemia) in relation to outcome showed that metabolic acidosis and elevated plasma creatinine were significantly associated with a bad outcome (Table 3). A multiple linear logistic regression model was used to ascertain the relative contributions of different variables in predicting outcome. The laboratory indices that were significantly related to poor outcome were metabolic acidosis (odds ratio 4.5, p=0.043) and elevated plasma creatinine (odds ratio 10.5, p = 0.003).

Discussion

Malaria remains one of the greatest threats to child survival in

Africa, responsible for an estimated mortality of 12.5 per thousand in Nigeria.¹⁵ The most severe complications of malaria is cerebral malaria and its mortality rate approaches 50%.¹⁰ The average mortality rate due to cerebral malaria may be difficult to assess because some cases do not reach the attention of health facilities. A study in rural Gambia indicates that 92 per cent of malaria related deaths occurred at home without medical treatment.² The present study confirms the findings of other workers that the clinical course of cerebral malaria is rapid. Monyleux et al¹¹ found a mean duration of febrile illness of 49.9 hours and a mean duration of unconsciousness of 7.6 hours. The mean duration of febrile symptoms before hospital admission in the present study was 48 hours and the mean pre-admission duration of unconsciousness was 6 hours, showing rapid clinical course and pointing to the need for a high index of suspicion among child health care providers at all levels. In the present study, the mortality rate was 22 per cent and a further 10 per

cent of survivors developed neurological complications. Although it is the opinion of many authors that full recovery from cerebral malaria is almost inevitable in all patients surviving cerebral ma-

laria, neurological sequelae affecting up to 10 per cent has been reported.¹⁶⁻²⁰ The mortality rate of 22 per cent in this study is within the range previously reported in the literature, which is between 6 and 50 per cent. Compared with the previously reported mortality of 18 per cent in the same institution two years earlier, the present figure represents a slight but insignificant increase.

The need for assessment of severity of cerebral malaria in children using simple prognostic laboratory indices prompted this study. We have identified some routine biochemical indices associated with unfavourable outcome in this study. The presence of metabolic acidosis was observed to be associated with fatal outcome and low plasma bicarbonate best predicted an unsatisfactory outcome in this study. Plasma bicarbonate level below 15mmol/L exceeds the buffering capacity of the body and in such a situation metabolic acidosis could supervene. In a study of 141 Malawian children with *P. falciparum* infection,¹¹ acidemia was found to be the best predictor of fatal outcome. It results from increased lactic acid production by the parasites, hypoxic host tissue, intense muscular activity during convulsion, reduced hepatic clearance owing to impairment of gluconeogenesis. An acidic environment increases cytoadherence of erythrocytes to capillary and venular endothelium. Hypokalaemia showed also a significant association with outcome. Patients with poor outcome tended to have a raised plasma potassium level. There is paucity of literature on the status of potassium in cerebral malaria. However, in view of a possible haemolysis in severe malaria, it may be hypothesized that elevated potassium could arise from the haemolysis and this may contribute to the pathogenesis of cardiac arrest.

Results from this study confirm that mild hyponatraemia is a common electrolyte derangement in children with cerebral malaria.^{10,21,22} One in six children had this biochemical abnormality although it was not significantly associated with a poor outcome. The secretion of inappropriate antidiuretic hormone is thought by some authors to be responsible for hyponatraemia while others observed that the plasma level of this hormone is appropriate to serum osmolality among patients with cerebral malaria. Hypovolaemia in malaria results from fluid loss due to vomiting, diarrhoea, hyperventilation and reduced fluid intake. While elevated plasma urea concentration did not correlate with outcome in this study, plasma creatinine levels above 0.6mg/100ml of blood was significantly predictive of poor outcome. Unlike in Asian adults with cerebral malaria where renal impairment with attendant electrolyte disturbances is a common feature of severe malaria, this complication is reportedly uncommon in African children. The finding of raised plasma creatinine levels in up to 20% of subjects on this study, however, does not support earlier reports of uncommon renal dysfunction in children with cerebral malaria. It should be noted that in the present study, no child had clinical manifestations of renal dysfunction.

The incidence of hypoglycemia (8%) in this study was low compared with the 52% in the Gambian children with cerebral malaria. The reason for the low incidence may be the fact that virtually all the patients had been seen and treated in another hospital before referral to the University College Hospital. This prior treatment often involves the administration of glucose-containing intravenous fluids at these referral facilities. Thus, it is not possible to assess the true role of hypoglycaemia in relation to mortality in the present study.

In conclusion, we have studied the predictive value of routine biochemical laboratory indices in predicting the outcome of cerebral malaria in 50 Nigerian children ages 9 months to 6 years with cerebral malaria at the University College Hospital, Ibadan, Nigeria. Biochemical derangements observed among the children included azotaemia (29%), elevated plasma creatinine (20%), metabolic acidosis (22%) and hyponatraemia (16%). Metabolic acidosis and elevated plasma creatinine on admission were significantly

associated with a poor outcome ($p < 0.05$). It is recommended that patients with these findings be referred promptly for adequate treatment in centres equipped to manage such critically ill patients.

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