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Acidosis in severe childhood malaria

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Summary

Data were prospectively collected on 306 Kenyan children, including blood gases in 258 (75%). Severe malaria caused a predominantly high-anion-gap metabolic acidosis in at least 43% of children. Children with coma and respiratory distress (CM + RD) had greater evidence of renal dysfunction, lower mean pH and higher mean plasma osmolality than those with respiratory distress (RD) or coma (CM) as isolated findings (mean urea 10.7 vs. 6.0 vs. 4.3 mmol/l; mean creatinine 97 vs. 74 vs. 58 µmol/l; mean osmolality 301 vs. 288 vs. 283 mosmol/l; and mean pH 7.16 vs. 7.29 vs. 7.39, respectively, $p < 0.001$ for each comparison of CM + RD vs. RD or CM). In addition, children with CM + RD had a higher mean blood lactate (6.7 vs. 3.3 mmol/l, $p < 0.001$), a lower mean haemoglobin (5.5 vs. 7.0 g/dl, $p = 0.002$) and a lower mean age (26.4 vs. 41.9 months, $p < 0.001$) than children with CM and accounted for 15/24 (63%) of all deaths. These and previous data implicate hypovolaemia and renal impairment in the pathogenesis of metabolic acidosis in severe childhood malaria. In children who are acidotic, anaemia is strongly associated with lactic acidaemia and may therefore contribute to its pathogenesis. These data also imply that coma in acidotic children (CM + RD) and those with an isolated encephalopathy (CM) may result from quite different pathophysiological mechanisms.

Introduction

Cerebral malaria, to most clinicians and even laymen, is perhaps the most infamous of tropical diseases. Efforts have recently been made to establish a simple, consensus definition of cerebral malaria in African children,[1,2] the principal group affected by the disease. The use of simple clinical criteria has allowed large studies of the biochemical, immunological and genetic features of children with severe malaria to be performed. The results of these studies have fuelled debate over the pathogenesis of cerebral malaria, which remains controversial, hypotheses representing a range of views from simple mechanical obstruction of blood flow in the cerebral microvasculature to a primary metabolic encephalopathy.[3,4] The clinical prominence of central nervous system dysfunction, the apparent lack of other major organ damage[2,5] and the use of simple criteria to diagnose coma in situations with very limited facilities have encouraged the assumption that cerebral malaria is an homogenous clinical syndrome.

Recent studies have, however, indicated that metabolic acidosis or a raised blood lactate on admission are features of major prognostic importance in cerebral and non-cerebral malaria.[5–9] Although dehydration is likely to contribute to the development of acidosis in some children,[10] the roles of seizures, anaemia, renal impairment and raised levels of cytokines in the pathophysiology of acidosis and/or a raised blood lactate remain confused.[6,7,10] We have examined the nature and prevalence of acidosis in a prospectively recruited, sequential sample of children with severe malaria in an attempt to answer some of these questions.

Methods

Clinical staff of the Kenya Medical Research Institute (KEMRI) provided 24-h medical cover for all paediat-

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ric admissions to Kilifi District Hospital on the Kenyan coast over a 15-month period from July 1993 to September 1994. All children with a positive blood film for *P. falciparum* and one or more of the following clinical syndromes indicative of severe malaria were admitted to the research ward for this prospective study: (i) coma, defined as a summated Blantyre coma score[2] of <3 at least 30 min after the last seizure, at least 6 h after treatment with diazepam and after treatment of hypoglycaemia if appropriate; (ii) prostration, the inability to sit unaided in older children or breast feed in those less than 1 year, (this included children with summated Blantyre coma scores 3–5 who could localize a painful stimulus); (iii) hyperparasitaemia, $\geqslant 20\%$ red cells parasitized on a peripheral blood film; (iv) respiratory distress, the presence of deep breathing, indrawing or nasal flaring in the absence of crackles, bronchial breathing or chest X-ray changes indicating acute respiratory infection. The clinical category to which a patient was assigned was determined before the results of laboratory investigations, including blood gases, were known. A child who was prostrated and had respiratory distress was included in the respiratory distress group only for all analyses. Falciparum parasitaemia accompanied by severe anaemia (Hb $\leqslant 5$ g/dl), or convulsions, even multiple, followed by a short post-ictal phase (<30 min) were not by themselves taken to indicate severe malaria. In the case of severe anaemia, this meant that even children with very low haemoglobins and parasitaemia were excluded from the study unless there was evidence of respiratory distress or another feature of severe malaria (they may nevertheless have received transfusion). This was felt to be justified since we have previously reported that the risk of death in this large group is low.[5]

Detailed historical and examination proformas were completed for all patients admitted with severe malaria. Baseline investigations performed on site included: full blood count (Coulter), thick and thin blood films Giemsa-stained and counted for asexual forms of *P. falciparum* (per 100 Wbc or 500 Rbc), blood culture, venous blood gas (CIBA Corning Diagnostics), venous glucose and lactate (Analox Instruments), urea and creatinine (Beckman Instruments), electrolytes using ion selective electrodes (CIBA Corning Diagnostics) and plasma osmolality (Osmostat). In children in whom sample volumes were sufficient plasma was immediately separated by centrifugation from blood collected into lithium heparin bottles and frozen at $-70\,^{\circ}C$ before transport on dry ice to The Netherlands. Chloride was then measured using an ion-selective electrode (Boehringer Mannheim/Hitachi 747) and interleukin 6 (IL-6) and interleukin 10 (IL-10), elevated levels of which have been associated with severe disease,[11,12] were measured by ELISA.[13,14] The anion gap was calculated using the formula (sodium) $-$ (chloride + bicarbonate)[15] and the non-lactate anion gap using (sodium) $-$ (chloride + bicarbonate + lactate), all measurements being in mmol/l. Chest X-rays were performed if co-existent pneumonia was suspected, and lumbar puncture was done for all children presenting in coma, to exclude meningitis.

Some children in coma were treated with either intravenous quinine or intramuscular artemether followed by pyrimethamine/sulphadoxine (Fansidar) as part of a randomized, controlled trial.[16] All other children were treated with parenteral quinine in the same dose as given in the trial, followed by pyrimethamine/sulphadoxine. Transfusion was given for severe anaemia (Hb $\leqslant 5$ g/dl) accompanied by either respiratory distress or hyperparasitaemia ($\geqslant 20\%$ peripheral parasitaemia). All children unable to take sufficient fluids orally were given a minimum of 75 ml/kg/day of intravenous 0.18% saline in dextrose with additional 0.9% saline given to children who were clinically dehydrated (reduced skin turgor, poor capillary filling). Further supportive treatment has been described in full elsewhere.[10] The study was performed as part of an ongoing programme investigating the pathophysiology of severe malaria approved by Kenyan, national scientific and ethical committees.

Statistical analysis

Data were double-entered and verified using dBase IV prior to analysis with SPSS. Data which were not normally distributed were log-transformed prior to analysis. Analysis of variance, Pearson's χ^2 or Fisher's Exact Test were used as appropriate to examine the differences between groups. Since a large number of comparisons were performed and no adjustment was made for this in the analysis, traditional levels of significance ($p<0.05$) may not be applicable and a cautious interpretation of the data is probably warranted, with $p<0.01$ likely to denote statistical significance. Stepwise linear regression, with a probability of F of $p=0.05$ used for entry of variables and $p=0.1$ for removal of variables, was used to evaluate associations with metabolic acidosis (represented by the base excess).

Results

There were 423 children with *P. falciparum* parasitaemia who met the previously-defined clinical criteria of severe malaria on admission between July 1993 and September 1994. However, 10 children admitted in critical condition died before completing the

admission procedure, and one child died from an unknown cause 3 days after being discharged well from the research ward. These children were excluded from the analysis. A further 70 children were excluded when more historical information or the results of investigations indicated the presence of a second, significant pathology including: lobar pneumonia on chest X-ray, meningitis, septicaemia, congenital heart or renal disease, salicylate toxicity, preceding developmental delay or epilepsy. Thus 342 children remained eligible for the study, of these key data (including a blood lactate) were available in 306 children (89%). Results represent analysis of data from these 306 children (48% males) who had a mean age of 31 months (interquartile range 13 to 41 months) and from whom blood gas data were available in 258 (84%).

Outcome

Twenty-four children died (8%) and 22 (7%) were discharged with gross clinical neurological sequelae (hemi- or quadriplegia, blindness, recurrent seizures or loss of previously-acquired motor skills). The admission clinical findings of children studied, outcome and the overall prevalence and character of acidosis are shown in Table 1. Deaths were much more frequent amongst children with both coma and respiratory distress (CM + RD, 41%) than amongst children presenting with the other clinical syndromes of severe malaria: hyperparasitaemia/prostration (H/PR, 0%), respiratory distress alone (RD, 6%) or coma alone (CM, 8%) ($p < 0.0001$ for each comparison). Two of the four children who died having been admitted conscious, but with respiratory distress, deteriorated and were comatose for several hours prior to death. For the purposes of analysis, these children were considered part of the respiratory distress group. The other two had sudden cardiorespiratory arrests. All four had severe metabolic acidosis (BE $\leqslant -19.5$) and hyperlactataemia (lactate > 12.5 mmol/l).

Major differences in the means of admission laboratory values were apparent between children who died and those who survived without sequelae. Thus children who died had a lower mean pH (7.11 vs. 7.36, $p < 0.001$), a higher mean osmolality (296 vs. 283 mosmol/l, $p < 0.001$), urea (7.6 vs. 5.2 mmol/l, $p = 0.02$) and creatinine (80 vs. 62 µmol/l, $p = 0.009$) and a higher geometric mean lactate (8.2 vs. 4.2 mmol/l, $p < 0.001$) than normal survivors. No significant differences in geometric mean IL-6 or IL-10 levels, which were closely correlated with one another ($r = 0.52$, $p < 0.001$), were observed between children who died and normal survivors, although the number of results available for analysis from children who died was small ($n = 18$ and 13, respectively).

Children surviving with sequelae were less acidotic than those who died (mean pH 7.30 vs. 7.11, $p < 0.001$), had a lower geometric mean blood lactate (3.9 vs. 8.2 mmol/l, $p < 0.001$) and a higher mean haemoglobin (7.4 vs. 5.4 g/dl, $p = 0.02$). No significant differences were apparent between deaths and sequelae for mean age, glucose, osmolality, urea

Table 1 Admission diagnosis, outcome and acid-base status of children studied

Acid-base status	H/PR	RD	CM	RD + CM	Total
Normal (pH 7.301–7.500, pCO_2 4.0–6.7 kPa)	36 (2, 0)	1 (0, 0)	20 (4, 0)	0 (0, 0)	57 (6, 0)
Compensated respiratory alkalosis (pH 7.401–7.500, $pCO_2 < 4.0$ kPa)	29 (0, 0)	12 (1, 0)	10 (2, 0)	2 (0, 0)	53 (3, 0)
Compensated metabolic acidosis (pH 7.301–7.400, $pCO_2 < 4.0$ kPa)	17 (0, 0)	21 (0, 1)	13 (2, 2)	7 (0, 3)	58 (2, 6)
Partly compensated metabolic acidosis (pH < 7.300, $pCO_2 < 4.0$ kPa)	7 (1, 0)	23 (1, 3)	0 (0, 0)	25 (5, 11)	55 (7, 14)
Uncompensated metabolic acidosis (pH < 7.300, pCO_2 4.0–6.7 kPa)	10 (0, 0)	1 (0, 0)	6 (0, 0)	2 (1, 1)	19 (1, 1)
Acute ventilatory failure (pH < 7.300, $pCO_2 > 6.7$ kPa)	3 (1, 0)	0 (0, 0)	3 (0, 0)	0 (0, 0)	6 (1, 0)
Uncompensated respiratory alkalosis (pH > 7.500, $pCO_2 < 4.0$ kPa)	5 (0, 0)	2 (0, 0)	3 (0, 1)	0 (0, 0)	10 (0, 1)
Undetermined	33 (2, 0)	4 (0, 0)	10 (0, 2)	1 (0, 0)	48 (2, 2)
Totals	140 (6, 0)	64 (2, 4)	65 (8, 5)	37 (6, 15)	

Numbers in parentheses indicate (neurological sequelae, deaths).

or creatinine. Means for osmolality, urea and creatinine were however greater in those with sequelae than in normal survivors (291 vs. 284 mosmol/l, $p=0.03$; 7.1 vs. 5.2 mmol/l, $p=0.05$; and 91 vs. 62 μmol/l, $p<0.001$, respectively). Children with seizures on or less than 1 h before admission fared no worse than other children. Similarly the type of seizures reported on presentation (either partial or generalized) gave no indication of likely outcome. However, amongst survivors, children with documented status epilepticus during admission (clinical seizure activity > 30 min duration) were more likely to be discharged with sequelae (9/22, 41% vs. 20/260, 8%; $p<0.0001$). In fact of those children not admitted in coma who nonetheless developed sequelae, 6/8 had an episode of status epilepticus either before or during admission.

Clinical syndromes in severe malaria

The differences in laboratory values between deaths and survivors appear simply to reflect differences between the major clinical groups (Table 2) since 15/24 of the deaths occurred in the CM + RD group. Most striking are the differences between children admitted with CM and those with CM + RD. In fact children with CM have a biochemical profile almost identical to that found in children with H/PR (none of whom died). Respiratory distress is clearly related to the presence of metabolic acidosis, but the acidosis is more profound and there is greater evidence of renal impairment in children whose respiratory distress is complicated by coma (RD vs. CM + RD, Table 2). Children with respiratory distress are also those most at risk of hypoglycaemia (blood glucose < 2.2 mmol/l). Thus 15/37 (41%) of those with CM + RD were hypoglycaemic on admission, a much higher proportion than amongst those with H/PR (11/140, 8%; $p<0.001$) or CM (8/65, 12%; $p=0.002$) but similar to that in children with RD (18/64, 28%).

High osmolalities occur in CM + RD in association with raised lactates and biochemical indices of reduced renal function. Although plasma sodiums are a little higher in this group, they mostly remain in the normal range, and are thus rarely the major contributor to an abnormally elevated osmolality. The geometric mean plasma levels of the cytokines IL-6 and IL-10 were similar across the clinical groups. However those with H/PR (none of whom died) had higher levels of IL-10 than children with life-threatening forms of disease, this difference reaching statistical significance in comparison with children having RD or CM ($p=0.008$ and $p<0.001$, respectively), while children with RD had lower levels of IL-6 than children with CM + RD (Table 2). The difference in mean age of children presenting with the major life-threatening syndromes reflects a marked change in pattern of admissions with age (Figure 1). In particular, it appears to be rare for falciparum malaria to result in coma as an isolated abnormality in the very young or for respiratory distress to occur alone in older children.

Acidosis and hyperlactataemia

In 132 children, the presence of a metabolic acidosis was demonstrated using venous blood gas data, which provide a good approximation of the corresponding arterial values[17] for which the definition used was intended[18] (Table 1). In 105 (80%) of these children, chloride values were available, and a high-anion-gap acidosis (anion gap > 11[15]) was present in all but six children. After subtraction of blood lactate, the anion gap remained above 11 in 82/105 (78%) of children. Using a stepwise linear regression model applied to all children in whom a blood gas was taken ($n=258$), and with base excess as the dependent variable, four features were found to be associated with acidosis ($R^2=0.64$): blood lactate (B, the slope $=-1.1$, $p<0.0001$), creatinine ($B=-0.08$, $p<0.0001$), age in months ($B=0.06$, $p<0.0001$) and urea ($B=-0.21$, $p=0.02$). The duration of illness, glucose, $\log_{10}$ parasitaemia, sodium and haemoglobin were non-contributory in the presence of the other variables. Fitting the model excluding both urea and age only reduced R^2 to 0.60.

In those with an uncompensated acidosis, the mean pH was actually higher than in those who had partly compensated (pH 7.213 vs. 7.153, $p=0.05$). This reflects the much less pronounced metabolic acidosis in children with an uncompensated metabolic acidosis (mean base excess values −10.0 vs. −20.6, $p<0.001$) and probably explains their lower mortality (Table 1), a finding consistent with observations in Malawi.[6] Amongst children with a metabolic acidosis ($n=132$) 84% had a lactate > 2.2 mmol/l, and in 64% it was > 5.0 mmol/l. The latter, in the presence of a reduced plasma bicarbonate (i.e. a metabolic acidosis) and low arterial pH, has been considered indicative of true lactic acidosis.[19] However, 10/57 (17%) of those with normal acid-base balance also had a blood lactate > 5 mmol/l. Higher lactates in the group of children with a normal blood gas were not associated with recent seizures (on or ⩽1 h before admission) but were associated with a lower haemoglobin (regression coefficient, $R=-0.28$, $p=0.005$; Figure 2). This association was much weaker than that found in children with a metabolic acidosis (regression coefficient, $R=-1.17$, $p<0.0001$; Figure 2) in whom statistically significant, but very weak correlations between blood lactate levels and liver size, urea,

Table 2 Admission data (means) for children with prostration/hyperparasitaemia (H/PR), respiratory distress (RD), coma alone (CM) and both coma and respiratory distress (CM + RD)

	H/PR ($n=140$)	RD ($n=64$)	CM ($n=65$)	RD + CM ($n=37$)	H/PR vs. RD	HPR vs. CM	H/PR vs. CM + RD	RD vs. CM	RD vs. RD + CM	CM vs. RD + CM
Age (months)	33.1 (29.4, 36.8)	18.6 (14.8, 22.4)	41.9 (35.7, 48.0)	26.4 (18.7, 34.0)	<0.001	0.007	NS	<0.001	NS	<0.001
History of illness (days)	3.5 (3.2, 3.7)	5.5 (4.1, 6.9)	3.5 (2.9, 4.1)	4.0 (3.0, 4.9)	<0.001	NS	NS	<0.001	0.02	NS
Hb (g/dl)	7.1 (6.7, 7.6)	4.5 (3.9, 5.0)	7.0 (6.5, 7.6)	5.5 (4.7, 6.3)	<0.001	NS	<0.001	<0.001	0.04	0.002
Wbc count* ($\times 10^6$ µl)	12.9 (11.8, 14.0)	21.9 (18.2, 26.3)	13.0 (11.3, 14.8)	26.6 (21.0, 33.6)	<0.001	NS	<0.001	<0.001	NS	<0.001
Glucose (mmol/l)	5.5 (5.0, 5.9)	4.0 (3.3, 4.7)	5.0 (4.4, 5.5)	4.0 (2.8, 5.2)	<0.001	NS	0.009	0.04	NS	NS
Sodium (mmol/l)	133 (132, 134)	135 (133, 136)	135 (134, 136)	137 (134, 139)	0.01	0.01	<0.001	NS	NS	NS
Creatinine (µmol/l)	56 (52, 60)	74 (65, 82)	58 (51, 65)	97 (80, 114)	<0.001	NS	<0.001	0.004	<0.001	<0.001
Urea (mmol/l)	4.4 (3.9, 5.0)	6.0 (5.1, 7.0)	4.3 (3.6, 5.0)	10.7 (7.9, 12.7)	0.009	NS	<0.001	0.02	<0.001	<0.001
Osmolality (mosmol/l)	280[1] (278, 282)	288[1] (284, 291)	283[1] (280, 286)	301[1] (293, 309)	0.001	NS	<0.001	0.05	<0.001	<0.001
Lactate* (mmol/l)	3.6 (3.3, 4.0)	7.4 (6.2, 8.9)	3.3 (2.8, 3.9)	6.7 (4.9, 9.0)	<0.001	NS	<0.001	<0.001	NS	<0.001
pH	7.38[2] (7.36, 7.40)	7.29[2] (7.26, 7.33)	7.39[2] (7.36, 7.41)	7.16[2] (7.09, 7.24)	<0.001	NS	<0.001	0.001	<0.001	<0.001
Base excess	−5.7[2] (−4.5, −6.7)	−16.0[2] (−14.5, −17.6)	−4.5[2] (−3.2, −5.9)	−19.5[2] (−16.9, −22.2)	<0.001	NS	<0.001	<0.001	0.003	<0.001
Parasitaemia (/µl)	102825 (70080, 150868)	70974 (436419, 108517)	48473 (27745, 85664)	48484 (22829, 102943)	NS	0.02	NS	NS	NS	NS
IL-6* (pg/ml)	67.5 (50.9, 89.6)[3]	40.2 (28.2, 57.5)[3]	68.5 (43.1, 108.7)[3]	108.6 (50.0, 245.6)[3]	0.05	NS	NS	NS	0.008	NS
IL-10* (pg/ml)	818 (605, 1108)[4]	375 (250, 563)[4]	294 (204, 425)[4]	457 (177, 1181)[4]	0.003	<0.001	NS	NS	NS	NS

Parentheses indicate 95%CIs.

* Geometric mean.

[1] $n=109$, 60, 59 and 31 for groups H/PR, RD, CM and CM + RD, respectively (total 259).

[2] $n=107$, 60, 55 and 36 for groups H/PR, RD, CM and CM + RD, respectively (total 258).

[3] $n=99$, 55, 57 and 25 for groups H/PR, RD, CM and CM + RD, respectively (total 236).

[4] $n=60$, 33, 36 and 14 for groups H/PR, RD, CM and CM + RD, respectively (total 143).

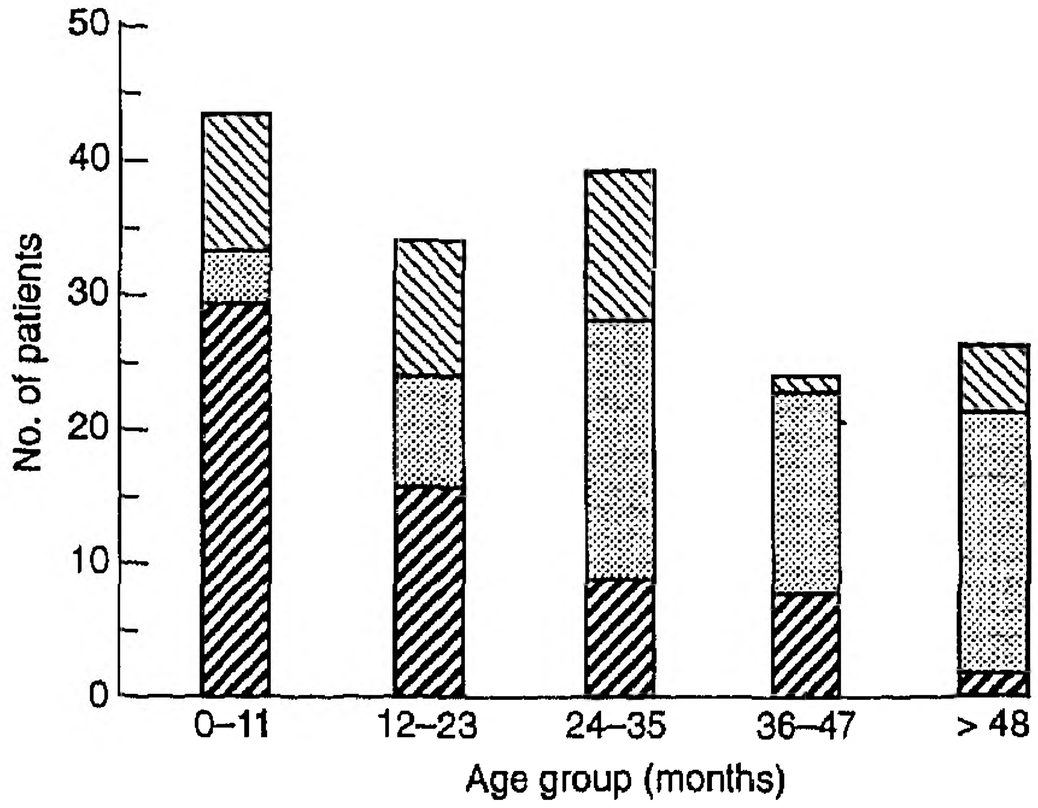

Figure 1. Age at presentation with coma alone, coma plus respiratory distress and respiratory distress alone in Kilifi, Kenya. ▨, Respiratory distress; ▧, Coma + respiratory distress; ▩, Coma alone.

creatinine, and age were also observed ($p < 0.05$, $r > -0.3$, < 0.3).

Discussion

The results of this study have several clear and striking implications. Perhaps most importantly it is obvious that coma resulting from falciparum malaria in African children may occur in association with two biochemically quite distinct syndromes which occur at different ages. It is also apparent that the presence of an elevated plasma lactate need not be an essential nor a major component of any metabolic acidosis in African children. The variation with age in the presentation of acidosis (Figure 1) may have major implications for investigations into the pathophysiology, immunology and epidemiology of severe malaria.

Acidosis

Falciparum malaria in Kenyan children causes a high-anion-gap acidosis. An elevation in plasma lactate frequently contributes to, but very rarely entirely accounts for this high anion gap. Raised ureas and creatinines indicate that impaired renal function, for which there is also evidence amongst Gambian, Nigerian and Papua New Guinean children,[9,20,21] is likely to result in reduced acid excretion. Although numerically small, rises in plasma creatinine poorly reflect the degree of reduction in glomerular filtration rate documented in children with severe malaria.[21,22] Hypovolaemia is a major contributor to this renal impairment[22] and may itself often be secondary to simple dehydration,[10] consistent with the observed hyperosmolality. A further contribution is likely from ketoacids which are detectable in the urine on dipstick testing of more than 50% of children with severe malaria (M. English, *in press*). *It is also possible, although we excluded* children with probable toxicity, that salicylate ingestion may contribute to the development of acidosis in some children.[23]

The pathogenesis of a raised blood lactate in severe malaria is almost certainly multifactorial. It need not cause acidosis until the body's buffering capacity is exceeded,[24] but at this stage any further increase in lactate production may have a major effect on acid-base balance. An increase in lactate production may result from recent seizure activity[25] in some children, but this is not supported as a general mechanism by our data. While high levels of TNF are associated with high blood lactates in childhood malaria,[7] the relationship between TNF,[6] IL-6 and IL-10 and the presence of acidosis remains unclear. Lactate production by the parasite[26] is also considered to be quantitatively of only minor impor-

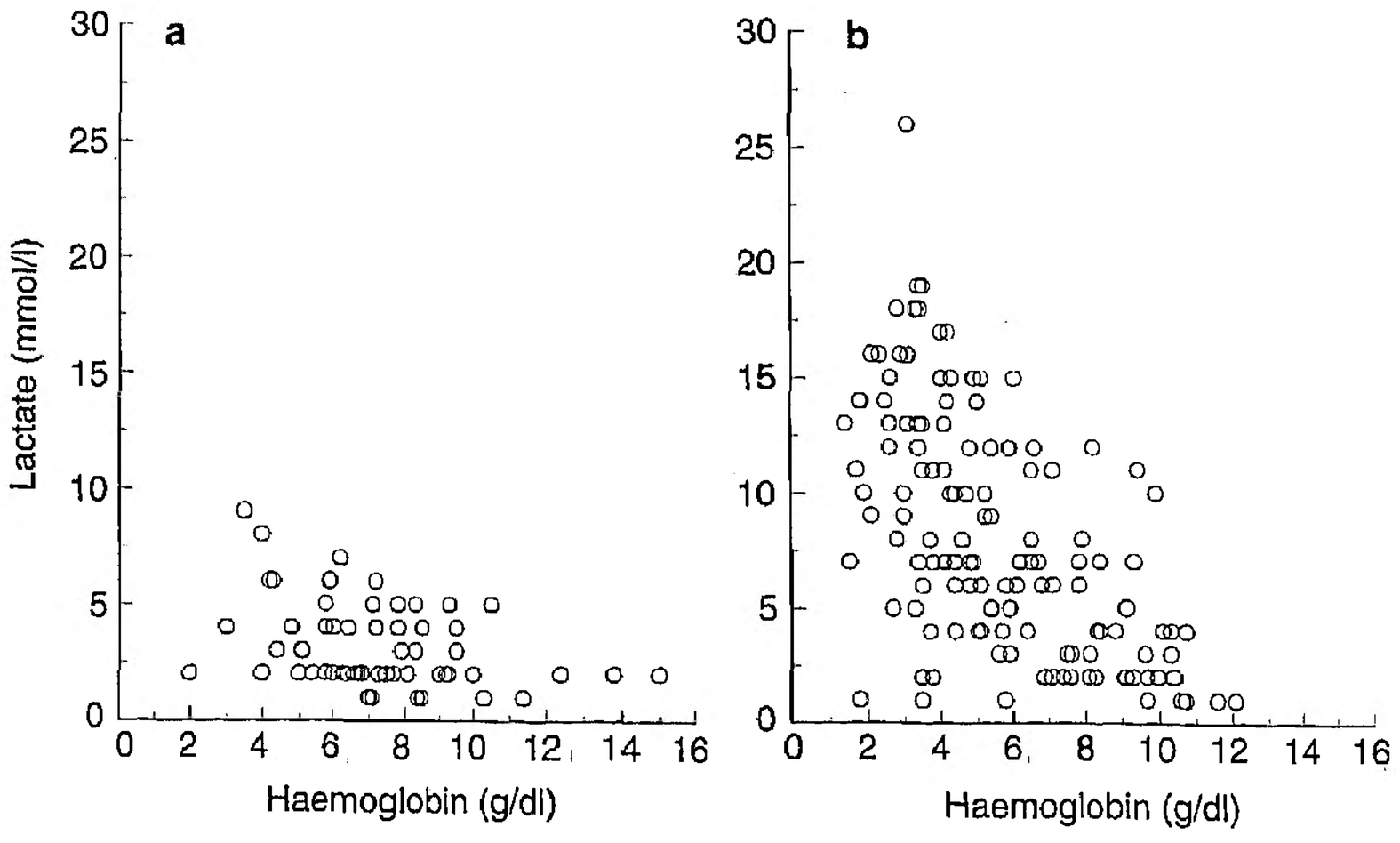

Figure 2. Scatter plot of blood lactate vs. haemoglobin in children with severe malaria. (**a**) In children with normal acid-base balance; (**b**) In children with a metabolic acidosis.

tance,[7] and the lack of association between peripheral parasitaemia and blood lactate supports this conclusion. Anaerobic respiration in poorly perfused host tissues, as occurs in severe sepsis,[27] may however be an important mechanism, and would be in keeping with our observations that lactic acidosis in some critically ill children with malaria and severe anaemia resolves rapidly during aggressive resuscitation.[22] The stronger relationship noted between blood lactate and anaemia in acidotic children (Figure 2) may reflect greater tissue oxygen supply dependency and/or that additional mechanisms altering the balance between tissue oxygen supply and demand are operating in acidotic children. Possible mechanisms include depletion of 2,3 diphospho-glycerate in chronic acidosis,[28] an increase in tissue oxygen requirement in more severely ill children or a reduction in peripheral blood flow in hypovolaemic children. The absence of these factors in children with severe anaemia alone (who were excluded from this study) may account for the paradoxical finding that they do not have a particularly high risk of death despite haemoglobins frequently as low as those described here.[5] Alternatively, severe anaemia in the absence of additional features of disease severity may represent an entirely different pathophysiological process.

Coma and the syndromes of severe malaria

Coma, the inability to make age-appropriate responses to simple stimuli, is a clinical and not a pathological diagnosis. Failure to make a response may reflect dysfunction anywhere along the pathway from sensation to motion. Children in this study with coma alone differed markedly from children with coma and respiratory distress in terms of many laboratory variables, except for their degree of peripheral parasitaemia and levels of the cytokines IL-6 and IL-10. Although higher levels of these cytokines do not appear to be associated with poor outcome, or the syndrome with the highest case fatality rate, levels were similar to those previously reported for IL-6[11] but a little lower than those reported for IL-10[10] in severe malaria. Therefore, while there is evidence that the inflammatory response is greater in severe malaria than mild malaria,[11,12,29,30] we were unable to demonstrate specific pathophysiological associations within the context of severe disease for the cytokines IL-6 and IL-10.

Neurological impairment is a common complication of severe systemic illness[31] or shock. It would therefore appear dangerous to assume that intracerebral events are the same in the clinically and biochemically distinct groups CM and CM+RD. Studies which consider all children meeting a simple definition of coma, irrespective of additional findings, to have 'cerebral malaria' may therefore provide misleading or conflicting results. The over-representation of children with major systemic disturbance amongst deaths indicates that researchers should also be wary of assuming that findings amongst those who die are relevant to all of those admitted in coma.

For clinicians dealing with severe childhood malaria, often in far from ideal circumstances, we believe some simple points deserve emphasis. Two clinical syndromes, coma and respiratory distress, identify most Kenyan children at high risk of death.[5] However, the key sign in respiratory distress, deep breathing,[8] is subject to considerable interobserver variability,[32] possibly explaining the apparent failure of respiratory distress to identify acidotic children in Papua New Guinea.[9] Training in the recognition of deep or Kussmaul's breathing might therefore aid in the identification of children who should be considered a high priority for investigation, observation and intervention. In particular, in addition to the administration of effective anti-malarial drugs correction of hypoglycaemia, anaemia and hypovolaemia should be urgently treated in these acidotic children. While very few children meet the current WHO criteria for shock in childhood malaria,[1] this term would appear to be apt for the group with neurological disturbance, renal impairment, acidosis, a raised blood lactate, moderate or severe anaemia and a mortality of more than 40% (i.e. those with CM+RD). Redefining shock in childhood malaria to include this group might encourage clinicians to make their immediate, appropriate resuscitation a priority and help to reduce now the unacceptably high mortality from 'cerebral' malaria while more specific anti-disease interventions are awaited.

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