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Acidosis in severe childhood malaria

Sir,

In a recent paper on acidosis in childhood malaria in Kenya, English and co-workers conclude that 'elevated plasma lactate need not be an essential or major part of any metabolic acidosis in African children' (QJM 1997; 90: 263). From the viewpoint of basic biochemistry, this conclusion is no surprise. We were nevertheless pleased to see the question addressed, since the previous clinical malarial literature assumes that lactate and excess protons are automatically co-produced, and therefore has used hyperlactataemia and acidosis interchangeably. English and co-workers were correct to avoid the traditional malarial term 'lactic acidosis', which propagates a mistaken understanding of the underlying biochemistry. However, their assertion that raised lactate will cause metabolic acidosis once the body's buffering capacity is exceeded warrants some comment.

Despite the common assumption in the malarial literature to the contrary, no excess protons (H+) are formed by the conversion of glucose to lactate, and excess lactate production, alone, cannot cause acidosis. As reviewed from time to time,1-3 protons (H+) are formed on hydrolysis of ATP, which is independent of lactate formation. When this hydrolysis occurs aerobically protons are consumed within mitochondria, but under anaerobic conditions protons are not recycled during ATP regeneration and thus accumulate, reducing pH. Thus lactate formation and acidosis are independent processes, and acidosis occurs when the ratio of glycolytic to mitochondrial ATP hydrolysis increases above a certain threshold, irrespective of how much lactate is produced. Using this same reasoning, it has been recently noted that it is inaccurate to regard pH as a proxy for blood lactate in sick infants.4 This also applies to blood lactate as a marker for acidosis.

As reviewed by Mizock,5 if glucose metabolism is accelerated under aerobic conditions, such as by cytokine-mediated upregulation of the GLUT1 glucose transporter6 and phosphofructokinase activity,7 lactate formation can increase in the absence of a tendency to acidosis. Under an increasing influence of the inflammatory cytokines that are generated during malaria, sufficient nitric oxide may eventually be induced to cause a 'biochemical hypoxia' by inhibiting aconitase and cytochrome oxidase, and therefore oxidative metabolism.8 By causing ATP to be regenerated within the glycolytic pathway, this would precipitate metabolic acidosis, and thus compensatory respiratory distress in the absence of pulmonary oedema, as described in malarial children in Kenya.9 Since the metabolic acidosis in these children was accompanied by normal arterial pO2 values in 70 out of 73 individuals,9 malarial acidosis in Kenyan children is more likely to arise from cytokine-induced inhibition of oxidative metabolism than from hypoperfusion caused by vessels throughout the body being partially blocked by sequestered parasitised erythrocytes. Indeed, when blood flow has been measured in severe malaria (in brains of children with cerebral malaria, where vessel blockage might have been most anticipated from the classical literature) it was actually increased.10

Involvement of pro-inflammatory cytokines in this metabolic acidosis should not be discounted simply because the QJM paper did not find it was associated with levels of IL-6 or IL-10 in single plasma samples. The net effect of the pro- and anti-inflammatory cytokines is now appreciated to be very complex, involving a balance between rapidly-changing concentrations of soluble cytokine receptors, as well as the pro- and anti-inflammatory subsets of these mediators themselves. Moreover, the half-life of the inducible enzyme that generates nitric oxide is such that the cytokine responsible for its induction can have been absent for a day or so, yet nitric oxide is still being formed and cytochrome oxidase thereby inhibited.

As well as being likely in malaria, cytokine-induced acidosis can be deduced to be present in illnesses in which sequestering parasites are absent. For example, the Jarisch-Herxheimer reaction has now been confirmed experimentally to be mediated largely by excess production of tumour necrosis factor.11 The CO2 blow-off that occurs in this condition12 is therefore consistent with compensation for a metabolic acidosis caused by this cytokine inhibiting oxidative metabolism in these patients. Likewise,
chronic salicylate poisoning, which the Kilifi group has found to cause confusion with the metabolic acidosis seen in severe malaria, is proving to be associated with high levels of inflammatory cytokines. These mediators, noted by English and co-workers paper to be plausible contributors to the changes they observed, are proving to be more versatile and ubiquitous than previously thought.

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References


Sir,

We welcome the comments of Drs Clark, Jacobson and Rockett on our recent publication on acidosis in severe childhood malaria (QJM 1997; 90:263). One of the problems we wished to highlight in this publication is the potentially misleading tendency (that we are also guilty of!) of placing children in categories on the basis of some shared clinical features and assuming that these children manifest pathophysiological processes that are common in nature and degree.

While pooling data on reasonably sized groups of children allows this problem to be overcome to some extent, the heterogeneity should not be ignored. In the case of the cytokine analysis we performed, we were attempting to answer an apparently simple question. Amongst a large group of children, all of whom had severe disease by our early criteria, could we detect a difference in some simple markers of the systemic inflammatory response? Our failure to detect an association of high cytokine levels with either the syndrome with the highest mortality or with the outcome death itself, does not preclude a very important role of such mediators in pathogenesis. The limited numbers available for analysis (discussed in the original text) and the difficulty inherent in the question (most previously published comparisons in malaria are of severe disease vs. mild disease) make our negative result of limited value. A positive association within a cohort of severely ill children would, however, have been most interesting.

The same problem is inherent in discussing the pathophysiology of acidosis itself. We feel it is highly unlikely that only one explanation exists for its development in a child with severe malaria (as discussed in the original text). We have documented severe acidosis in the absence of a raised blood lactate, and a raised blood lactate in the absence of acidosis, and agree with Drs Clark, Jacobson and Rockett that it would therefore be hard to consider the terms synonymous. However, what should we make of the large number of children with both an


elevated blood lactate and an acidosis? Is the convenient term lactic acidosis always as misleading as Drs Clark, Jacobson and Rockett suggest?

Several points deserve attention. Calculations indeed suggest that the protons produced during glycolysis largely result from the hydrolysis of ATP also generated during glycolysis.\(^1\) If the rate of glycolysis is increased, and assuming that there is no accumulation of ATP and no further metabolism of lactate anions, then the concentration of protons and lactate anions would both rise. This non-steady-state situation would occur in anaerobically-respiring tissues, or might be secondary to the effect of cytokines. Cytokines would not alter the balance of release of lactate and protons per se, however, unless an increase in the net rate of hydrolysis of ATP also occurred. However, in the mouse model of malarial 'lactic acidosis' no change in cellular ATP levels is observed despite severe systemic acidosis.\(^2\) In contrast, in the case of fructose poisoning, a true lactic acidosis is thought to occur in the absence of inflammation or ischaemia.\(^3\) An accumulation of lactate can therefore be accompanied by an accumulation of protons (an acidosis) although this is not necessarily with the simple stoichiometry often described because, amongst other things, their respective rates of removal may vary considerably.\(^4\)

In general, it has been estimated that lactate production may have to rise 7-10-fold before acid-base homeostasis is disturbed.\(^3\)

The pathophysiology of a raised lactate may be similarly complex. An acidosis associated with a raised lactate can develop within minutes of severe exercise or a generalized seizure in a previously-well adult.\(^5\) In this situation, even if one accepted that the acidosis was entirely attributable to hydrolysis of ATP, it would be hard to consider the elevation in lactate resulting from anaerobic glycolysis to be an entirely independent process. In such a situation the blood lactate is at least an important marker of the pathophysiology. In experimental animals, a rise in blood lactate may also be produced within a matter of minutes by creating acute, isovolumetric anaemia,\(^6\) while acute hypovolaemia also results in an acute rise in blood lactate with an associated acidosis.\(^7\) In these situations, the rise in blood lactate is perhaps easiest to explain as an acute imbalance in oxygen supply and demand, with energy needs being met by an increase in anaerobic glycolysis. In such situations, the elevation in blood lactate is thus an appropriate marker of the pathophysiology, and the term lactic acidosis would appear to be a useful summary term with important implications for the clinical management.

The situation in 'septic' states is somewhat more complicated. We entirely agree that the cytokine cascade is pivotal in the development of many pathophysiological abnormalities, but is it operating in isolation to produce an elevation in blood lactate and/or acidosis? In the rat model 'sepsis' and hypoperfusion (ischaemia) appeared to be synergistic in causing tissue hypoxia, although it should be noted that even in this group neither hypotension nor systemic acidosis occurred, and lactate values were not particularly high (4 mmol/l).\(^8\) The authors of this work concluded that 'the presence of a metabolic acidosis...would be a helpful finding in suggesting that the increased lactate is due to anaerobic metabolism and cellular hypoxia'.\(^8\) They go on to say that the response of plasma lactate to measures which increase oxygen delivery would be useful in distinguishing the aetiology of the increased lactate.

Our finding that children with severe malaria, severe acidosis and an elevated blood lactate have normal arterial pO\(_2\) values\(^9\) tells us nothing about systemic perfusion. However, the rapid resolution of acidosis and associated fall in blood lactate that we have observed during blood transfusion (= an acute increase in oxygen delivery) in severe malaria does indicate a likely role for hypoperfusion in pathogenesis in these cases.\(^10\) Such a scenario would also be supported by evidence suggesting the presence of an 'oxygen debt' in severe malaria anaemia (English et al., this issue). Ignoring the debate over the precise role of lactate as an acid, therefore, it would seem reasonable to regard the elevation in lactate as a useful marker of anaerobic metabolism resulting in acidosis in some children with severe malaria. Hypoperfusion itself might result from severe anaemia and hypovolaemia alone without the need to invoke (or discount) the role of mechanical obstruction to flow resulting from sequestration.

However, we feel the potential synergy between such 'simple' physiological problems and the cytokine cascade possibly the most powerful pathogenic mechanism. In an individual contributions from ketoacids, impaired excretion of 'physiological' acids, altered renal tubular function (for which there may be some evidence)\(^11\) affecting bicarbonate handling or salicylate ingestion may also be important.

It is clear that the term 'lactic acidosis' implies a somewhat misleading oversimplification of the pathophysiology of acidosis in severe malaria. As a prompt to clinicians to treat the treatable, however, this term remains useful (as does the term 'cerebral malaria', which may be equally misleading). Disentangling the pathophysiology of acidosis further, in the hope that hypotheses may be substantiated and novel interventions developed should be a clear research priority given the high mortality with which it is associated in malaria and sepsis. Indeed, severe malaria may provide a useful model for investigating
the interaction of the various putative mechanisms involved.

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References

Buffer depletion and the reduction of capacity for work

Sir,

Myers and Ashley open a recent startling review1, entitled ‘Dangerous Curves’ with the words ‘the increase in blood lactate level that occurs in response to progressive exercise, and changes that are associated with it, have engendered a great deal of interest from coaches, athletes, clinicians and educators for most of this century. Few areas in the exercise sciences have generated as many scientific reports, editorials or debate.’ This takes me back to points Peter Nixon made in QJM two years ago.

Most of us are taught that the rise of blood lactate in progressive exercise is caused by a sudden increase of anaerobic metabolism, but Myers and Ashley provide the evidence that dissociates lactate production from anaerobiasis: the formation of lactate appears to depend upon several factors, including, but not limited to, the availability of oxygen.

They conclude that ‘lactate production and removal is a continuous process; it is a change in the rate of one or the other that determines the blood lactate level. Rather than a specific threshold, there is most likely a period of time during which lactate production begins to exceed the body’s capacity to remove it (through buffering or oxygenation in other fibres)’.

The authors regard it as important in clinical practice to document the point at which lactate begins to accumulate in the blood and cause an increase in hyperventilation, because the concomitant physiological changes, such as metabolic acidosis, impaired muscle contraction, hyperventilation and altered oxygen kinetics, reduce the capacity to perform work.

Nixon has put forward the hypothesis that this metabolic reduction of the capacity for work, together with its accompanying neuronal and autonomic changes, is the basis of chronic fatigue in many cases. The evidence of Myers and Ashley supports Nixon’s claim that exercise tolerance can be improved by training and other interventions.2,3 This is in accordance with my own findings over many years.4

The respiratory response to acidaemia demonstrated by capnography during rapidly incremental exercise appears to be a simple, non-invasive and inexpensive aid to diagnosis, and to the assessment of outcome of rehabilitation.2,3 It can be used in the clinic and the rehabilitation centre, and in the field where the resources of a mobile fully-equipped exercise laboratory are rarely available.

In my opinion, the particular value of this method is its providing a ready means for screening persons who might be regarded as psychiatric cases, malingerers, or the subjects of undiagnosable disease, when they lose ability to make and sustain effort, and present natural emotional and behavioural responses to that loss.
It is to be hoped that Dangerous Curves will encourage others to explore this field.

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References

Drop attacks in the elderly revisited

Sir,
In their recent comprehensive Editorial update (QJM 1997; 90:1–3) Dey and Kenny emphasize the frequency of haemodynamic factors, predominantly related to brain-stem ischaemia, as being responsible for this frequent disorder.

However, this pathogenic background is by no means invariably detectable, and other neuroanatomic sites have been postulated, in particular those involving a mechanism of failure of maintenance of normal activity at the neuromuscular junction of the quadriceps muscle. Some degree of inability to generate adequate tension at this site would then be held to be responsible for the sudden and unavoidable falls.

Based on this theoretical implication, possibly involving long-loop reflexes, I have reported a trial of the anti-cholinesterase pyridostigmine as a means of aiding appropriate responses and automatic reactions of the quadriceps muscle. In 4/6 elderly patients with typical histories of unexpected falls, cessation of the symptoms followed the administration of 60 mg of the medication twice daily, and continued to do so over a period of several years, with no adverse effects.

I believe that in those cases where overt clinical or laboratory evidence of a probable vascular vertebro-basilar or cardiac pathological basis is not discernible, a trial of this neuromuscular agent would be justifiable.

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References

Seizures in cerebral malaria

Sir,
We read with interest the article ‘Seizures and Status epilepticus in childhood cerebral malaria’ of Crawley et al., which presented the role of seizures in childhood cerebral malaria and their relation to morbidity and mortality very nicely. The role of seizures as a prognostic indicator in children and adults has also been described in other studies.

There are very few studies on the significance of seizures in adult cerebral malaria.

At the end of their article, the authors raised a vital question: ‘can anticonvulsant prophylaxis reduce
Correspondence

the incidence of status epilepticus complicating cerebral malaria? An ideal candidate drug would need to be cheap, safe, effective and preferably administered by the intramuscular route. Phenobarbitone fulfills these criteria, yet its role in seizures prophylaxis in cerebral malaria is unclear.

Their next idea was that 'if prophylactic phenobarbitone can reduce the incidence of status epilepticus complicating cerebral malaria, it is possible that this will also have an impact on the incidence of subsequent neurological sequelae. A definitive study of I.M. phenobarbitone would therefore seem to be an important next step'.

Recently, we studied the prophylactic role of single-dose i.m. phenobarbitone at the time of admission in preventing convulsions in adult cerebral malaria, and the results were as follows: 'The study was conducted on 185 patients (age 14–74 years) of strictly defined cerebral malaria from September to December 1994 at S.P. Medical College, attached P.B.M. Hospital, Bikaner (Rajasthan), India during an epidemic of malaria in this region. The patients were randomly allocated into two groups, Group I who received a single I.M. injection of phenobarbitone sodium (10 mg/kg, not more than 400 mg) and Group II those without phenobarbitone. Phenobarbitone significantly reduced (p<0.001) the incidence of subsequent convulsions from 23% in Group II to 2.9% in Group I without increasing adverse effects. Phenobarbitone also significantly reduced (p<0.001) the further occurrence of convulsions in patients who were having convulsions before admission. A single dose I.M. injection of phenobarbitone is a simple cheap and effective method for prevention of convulsions & convulsions related catastrophe in cerebral malaria'.

The details are given in Table 1.

Earlier, White et al.2 (1988) in a double-blind placebo controlled trial of a single dose of sodium phenobarbital 3–5 mg/kg given by i.m. injection on admission, demonstrated a significant reduction in the incidence of generalized convulsions in children, but the numbers were insufficient to test its effect on mortality.5 The authors had also discussed the possibility of better results with larger doses of phenobarbitone.

A number of factors have been thought to produce seizures in cerebral malaria, which include fever, hypoglycaemia, electrolyte imbalance, intra-cranial hypertension, brain oedema, etc. Recently, we could define a specific group of patients who were fulfilling all the criteria of WHO definition of cerebral malaria, but basically had only hypoglycaemia with falciparum malaria.7 Convulsion was one of the important features which was responsible for prolonged coma and could be easily corrected by simple administration of 25% glucose before starting specific anti-malarial therapy. Blood glucose was in the range of <2.2 mmol/l and they never required treatment with anti-convulsants in the further course of their illness. Hypoglycaemia may be an important factor in those children included in the study of Crawley et al.1 who became conscious within 6 h of admission. They received an anticonvulsant along with standard anti-malarial treatment with i.v. quinine, or i.m. artemether. Our patients also received 400 mg of phenobarbitone as a single i.m. injection, along with i.v. 25% glucose and quinine.6,7 In both these studies,1,7 one thing is common, that is administration of an anticonvulsant and simultaneously starting the treatment of cerebral malaria. In our opinion, a fraction of these patients are not cases of cerebral malaria but of falciparum malaria with hypoglycaemia as we discussed earlier.

In another study on 185 patients with adult cerebral malaria, Bajiya and Kochar8 recorded neurological sequelae in survivors after recovery from coma, 40 (21.62%) patients had convulsions at the

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<th>Incidence of convulsions and mortality in patients of adult cerebral malaria who received/did not receive phenobarbitone</th>
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<td>Group I (n=102) Who received phenobarbitone</td>
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<td>No. of patients</td>
<td>Death</td>
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<td>No history of convulsions before admissions</td>
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<td>History of convulsions before admissions</td>
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time of admission, 17 (42.5%) of them died, compared to 45 (31.03%) out of 145 patients without convulsions. Severe hypoglycaemia (blood glucose level <2.2 mmol/l) was present in eight patients; three of these had convulsions and all three died while five other patients had severe hypoglycaemia without convulsions, of whom one died, two had neurological sequelae (cerebellar ataxia) and the remaining two made a complete recovery.

All these studies on cerebral malaria had ample reflection of prognostic value of convulsions in terms of morbidity and mortality as recorded by Crawley et al. Further evidence on the specific issue of prophylactic phenobarbitone in preventing further convulsions in cerebral malaria is recorded in Kochar et al.6

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