Cerebral malaria versus bacterial meningitis in children with impaired consciousness

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Summary

Cerebral malaria (CM) and acute bacterial meningitis (ABM) are the two common causes of impaired consciousness in children presenting to hospital in sub-Saharan Africa. Since the clinical features of the two diseases may be very similar, treatment is often guided by the initial laboratory findings. However, no detailed studies have examined the extent to which the laboratory findings in these two diseases may overlap. We reviewed data from 555 children with impaired consciousness admitted to Kilifi District Hospital, Kenya. Strictly defined groups were established based on the malaria slide, cerebrospinal fluid (CSF) leucocyte count and the results of blood and CSF culture and CSF bacterial antigen testing. Our data suggests significant overlap in the initial CSF findings between CM and ABM. The absolute minimum proportions of children with impaired consciousness and malaria parasitaemia who also had definite bacterial meningitis were 4% of all children and 14% of children under 1 year of age. The estimated maximum proportion of all children with impaired consciousness and malaria parasitaemia in whom the diagnosis was dual or unclear was at least 13%. The finding of malaria parasites in the blood of an unconscious child in sub-Saharan Africa is not sufficient to establish a diagnosis of cerebral malaria, and acute bacterial meningitis must be actively excluded in all cases.

Introduction

Impairment of consciousness associated with a febrile illness is a common presentation of severely ill children in the tropics. Cerebral malaria (CM) and acute bacterial meningitis (ABM) are the two commonest causes, and they both have a high mortality and a significant risk of neurological sequelae in survivors.³ CM has been defined as a clinical syndrome of Plasmodium falciparum infection (asexual parasites on a peripheral blood film) with unrousable coma not attributable to another cause.⁴ Absolute definition of ABM requires the culture of pathogenic bacteria from the CSF, though other findings such as a raised CSF white cell count or the detection of bacterial antigens are strongly suggestive.³ From a practical point of view, problems may arise when laboratory facilities are limited, as is often the case in African hospitals. However even when such facilities are available, differentiation may not be clear-cut. Low-density parasitaemia is a common coincidental finding in malaria endemic areas and CSF cultures are often negative even if other features strongly suggest ABM. One approach has been to base the diagnosis on the CSF leukocyte count,³ but this begs the question as to whether the CSF findings in CM and ABM overlap.

We report here a retrospective analysis of data from 555 Kenyan children consecutively admitted to hospital with non-traumatic impaired consciousness. Our goals were to describe the spectrum of disease definable by history, examination and routine laboratory investigations and to examine the implications of these findings for the management of children.
presenting with impairment of consciousness in malaria endemic areas.

Methods

Location

The study was conducted at Kilifi District Hospital, Kilifi, Kenya. The hospital serves a predominantly rural population in a malaria endemic area on the Kenyan Coast. The pattern of malaria transmission and clinical spectrum of admissions to the paediatric unit have been described previously.6–8

Patients

Prospectively collected clinical and laboratory data on all children over 1 month of age, admitted with non-traumatic impairment of consciousness between January 1994 and August 1996, were reviewed. Impaired consciousness was defined as a Blantyre score9 of <5 in children aged 8 months or over, or a Blantyre score of <4 in children under 8 months. During the period reviewed, 555 children meeting the study criteria were admitted.

Clinical management

All children with impairment of consciousness were admitted to the 6-bed high-dependency ward adjacent to the 35-bed paediatric ward. Detailed history and clinical examination proformas were completed as part of ongoing studies into the pathophysiology of severe malaria. Malaria parasitaemia, hypoglycaemia, seizures, hypovolaemia, severe anaemia and respiratory distress were managed according to principles described elsewhere.10 Until the CSF results were known, children with P. falciparum parasites on peripheral blood smear who were unable to localize a painful stimulus were treated with broad spectrum antibiotics as well as antimalarial drugs. The lumbar puncture (LP) was delayed until the child was neurologically stable.11 If a child died before the LP was performed then a post-mortem LP was done as soon as possible after death with the permission of the child’s guardian.

Laboratory methods

Baseline investigations included venous glucose (Analox Instruments), full blood count (Coulter), venous blood gas analysis (CIBA Corning) blood cultures and thick and thin blood films Giemsa stained and examined for asexual forms of P. falciparum. Blood was cultured on brain-heart infusion broth. Growth of coagulase negative staphylococci, bacillus or candida species in a single culture bottle were considered contaminants. Cerebrospinal fluid glucose (Analox Instruments) and protein (Sulphasalicylic acid method) were determined and a Gram stain and manual cell count were performed. All CSF samples were cultured on blood agar and chocolate plates. When there was sufficient, remaining CSF was stored at −70 °C. Stored CSF samples with a leucocyte count of over 10 cells/µl were tested in September 1997 by latex agglutination for the presence of antigens of Haemophilus influenzae and Streptococcus pneumoniae (Murex Diagnostics).

Analysis

Children were grouped according to the results of the malaria slide, CSF leucocyte count and microbiological findings. Two polar reference groups were established: ‘Cerebral’ malaria (group 1) was defined by impaired consciousness in the presence of circulating asexual malarial parasites and the absence of growth on CSF or blood cultures and a CSF leucocyte count of 10 cells/µl or less. Acute bacterial meningitis (group 5) was defined as the absence of malaria parasitaemia plus the presence of a CSF leucocyte count >10 cells/µl plus either a positive CSF culture or a positive blood culture or positive CSF bacterial antigen detection. We have used the term ‘cerebral’ in inverted commas because there are differences in our operative definition from that given by the WHO in order to make our series comparable with other recent series.1,9

Data were double-entered using Dbase IV and analysed using Epi Info (version 6.0) and SPSS (version 5.0). Proportions were compared with the χ² test with the Yates correction. The parasite density, CSF leucocyte count and CSF protein were log-transformed prior to analysis. The means of normally distributed, continuous variables were compared using Students t test.

Results

Between January 1994 and August 1996, 555 children (51% female) were admitted with non-traumatic impairment of consciousness. The overall mortality was 23.4%. One hundred and thirty children (23.0%) presented in deep coma (Blantyre coma score <2). Their mortality was 30.8%, compared to 15.8% in those with a Blantyre coma score of 2 or more.

A CSF leucocyte count was available for 450 children. Groups identified by malaria slide, CSF leucocyte count and culture results of these children are presented in Table 1. The clinical and laboratory findings of these groups are presented in Table 1.

A CSF leucocyte count was not available for 105 children. Sixty-eight were malaria parasite slide (MPS) positive (mortality 26%) and 37 were MPS-negative
Distinguishing malaria from meningitis

Figure 1. Construction of diagnostic groups in 555 African children with non-traumatic impairment of consciousness. Mortality is given in parenthesis for each group.

(mortality 38%). In 17 children, an LP had been performed but the samples obtained were unsuitable for cell counting. The 88 children not having had an LP fell into three groups: those who recovered consciousness quickly, those in whom there was a clear alternate diagnosis and those that died within a very short period after admission. Thus, 20 children had a metabolic disturbance such as hypoglycaemia or metabolic acidosis that resolved within 6 h of admission. Thirteen children were admitted during a prolonged post-ictal state and recovered full consciousness within 6 h of admission. Twenty-three children were considered to have a clear diagnosis other than CM or ABM, not resolving within 6 h. Of these, eight had a primary diagnosis of severe gastro-enteritis, five were diagnosed with severe lower respiratory tract infection, two with severe anaemia (MPS negative), two with renal failure and one each due to aspirin poisoning, chlorpromazine overdose, diabetic ketoacidosis, tetanus, hepatic failure and advanced Burkitt’s lymphoma. Of remaining cases not having had an LP, 17/32 died within a very short period following admission. All children with no CSF leucocyte count available were excluded from further analysis.

Group 1: ‘cerebral’ malaria

Two hundred and ninety-seven children met the definition of CM. Blood cultures were negative in 210 and contaminated in a further 36. Fifty-one children had not had blood cultures done. The mortality and mean age did not differ between those who had a blood culture and those who did not. One cannot absolutely exclude the possibility that in a proportion of these ‘cerebral’ malaria cases the parasitaemia was in fact coincidental and impairment of consciousness was caused by another agent. However, the marked seasonal pattern of admissions in this group (data not shown), the normal CSF white cell count and the absence of other findings suggest that in the majority of cases, malaria was the cause of the encephalopathy. Seventy-two children in group 1 presented in deep coma (24.2%). This proportion was similar to both the overall proportion of children in deep coma and to that of all other groups.

Group 2: ‘cerebral’ malaria plus sepsis/ meningitis

Eighteen children with impaired consciousness, a malaria parasitaemia and normal CSF white cell count had a pathogenic organism identified from blood or CSF culture. Sixteen children in group 2 had positive blood cultures as follows: *Staphylococcus aureus*; Group A *Streptococcus; Pseudomonas aeruginosa; Streptococcus pneumoniae* and *Salmonella* (non-typhi) in two patients each; *Haemophilus influenzae; Enterobacter cloacae*;
Table 1  Comparison of clinical variables and laboratory parameters in 450 African children with impaired consciousness by diagnostic group

<table>
<thead>
<tr>
<th></th>
<th>1 (CM)</th>
<th>2 (n=18)</th>
<th>3 (n=30)</th>
<th>4 (n=14)</th>
<th>5 (ABM)</th>
<th>6 (n=16)</th>
<th>7 (n=18)</th>
<th>8 (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>11.1</td>
<td>22.2</td>
<td>30.0</td>
<td>42.9</td>
<td>17.2</td>
<td>18.8</td>
<td>33.3</td>
<td>32.1</td>
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<tr>
<td>Age (months)</td>
<td>35.1</td>
<td>36.4</td>
<td>36.4</td>
<td>21.1</td>
<td>23.7</td>
<td>16.1</td>
<td>39.7</td>
<td>38.6</td>
</tr>
<tr>
<td>Deep coma (%)</td>
<td>24.2</td>
<td>22.2</td>
<td>23.3</td>
<td>28.6</td>
<td>20.7</td>
<td>18.8</td>
<td>27.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Respiratory distress (%)</td>
<td>26.3</td>
<td>44.4</td>
<td>26.7</td>
<td>21.4</td>
<td>6.9</td>
<td>0.0</td>
<td>11.1</td>
<td>21.4</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>6.9</td>
<td>6.4</td>
<td>6.9</td>
<td>6.6</td>
<td>7.8</td>
<td>8.3</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>WBC (× 10^9/l)*</td>
<td>15.6</td>
<td>16.2</td>
<td>16.0</td>
<td>13.7</td>
<td>18.1</td>
<td>17.8</td>
<td>14.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Parasitaemia (per µl)*</td>
<td>37 584</td>
<td>60 674</td>
<td>31 477</td>
<td>13 964</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>pH**</td>
<td>7.31</td>
<td>7.34</td>
<td>7.31</td>
<td>7.18</td>
<td>7.25</td>
<td>7.36</td>
<td>7.28</td>
<td>7.26</td>
</tr>
<tr>
<td>Base excess**</td>
<td>−10.2</td>
<td>−10.7</td>
<td>−8.2</td>
<td>−19.4</td>
<td>−10.9</td>
<td>−3.5</td>
<td>−13.2</td>
<td>−11.0</td>
</tr>
<tr>
<td>CSF WBC (per µl)*</td>
<td>2</td>
<td>3</td>
<td>27</td>
<td>290</td>
<td>679</td>
<td>166</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CSF protein (g/l)*</td>
<td>0.19</td>
<td>0.30</td>
<td>0.32</td>
<td>1.86</td>
<td>1.56</td>
<td>1.45</td>
<td>0.19</td>
<td>0.17</td>
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<tr>
<td>CSF glucose (mmol/l)</td>
<td>3.4</td>
<td>3.5</td>
<td>3.8</td>
<td>2.1</td>
<td>0.5</td>
<td>2.7</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>5.1</td>
<td>4.7</td>
<td>5.0</td>
<td>4.5</td>
<td>6.8</td>
<td>5.7</td>
<td>5.6</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*Log mean. **Venous blood gas determination was performed on 313 children. p values are in comparison to group 1 (CM). CM, ‘cerebral’ malaria; ABM, acute bacterial meningitis.
Escherichia coli; viridans Streptococci and a Gram-negative rod (not further identified) in one patient each. One further patient grew both Staphylococcus aureus and Group A Streptococcus on blood culture. A group D Streptococcus and Klebsiella pneumoniae were grown from CSF in one patient each.

**Group 3: malaria with CSF leucocytosis of uncertain cause**

Thirty children with impaired consciousness and a peripheral parasitaemia had an abnormally high CSF white cell count but no convincing evidence of bacterial meningitis. Blood culture was negative in 22 children, contaminated in four and not done in four. In 15 children, antigen detection was negative and no sample was available for antigen testing in another 15. The log mean CSF leucocyte count of children in group 3 was 27, only one child having a CSF leucocyte count of >100 cells/µl. The mean age of children in group 3 was similar to that of group 1.

**Group 4: acute bacterial meningitis in children with malaria**

Fourteen children had an abnormally high CSF white cell count in association with either positive blood cultures or positive CSF culture or positive CSF antigen detection. The following organisms were cultured from CSF: Streptococcus pneumoniae in five, Haemophilus influenzae in two, and Salmonella (non-typhi) in one patient. Shigella dysenteriae and Escherichia coli were grown from blood culture from one child each. Haemophilus influenzae was identified by retrospective antigen detection on the CSF of four patients, all of whom survived. The mean age of children in group 4 was similar to that of the pure ABM group (group 5).

**Group 5: acute bacterial meningitis**

Twenty-nine aparasitaemic children were considered to have definite ABM. The following organisms were cultured from both CSF and blood: Haemophilus influenzae in seven, Streptococcus pneumoniae in seven, Salmonella (non-typhi) in two and Group A Streptococcus in one patient. Haemophilus influenzae and Streptococcus pneumoniae were cultured from CSF but not blood in five patients each, these two organisms were cultured from blood but not CSF in one patient each. This group of children was on average approximately 1 year younger than those with CM; they were also less anaemic and had a lower incidence of respiratory distress.

**Group 6: CSF leucocytosis of uncertain cause**

In group 6, blood cultures were negative in 13, contaminated in one and were not done in two patients. The LP was performed later on children in group 6 than group 5 (1.0 vs. 0.4 days, \( p = 0.06 \)). The characteristics of this group were otherwise similar to the ABM group. It seems likely that this group was a mixture of some children with partially-treated ABM and others with viral meningitis.

**Group 7: encephalopathy of known cause**

Eighteen children were MPS-negative, had a CSF leucocyte count of <10 cells/µl and had an identified cause for their encephalopathy. Streptococcus pneumoniae was cultured from the CSF of one child and a Salmonella species (non-typhi) was cultured from the blood of another. Encephalopathy associated with hepatic failure, sepsis and severe gastro-enteritis each accounted for two patients. Each of the following conditions occurred in one child: sickle-cell crisis; diazepam overdose; deterioration in chronic hydrocephalus; prolonged post-ictal state in a known epileptic and severe anaemia (MPS-negative).

**Group 8: encephalopathy of unknown cause**

Twenty-eight children were MPS-negative, had a CSF leucocyte count of <10 cells/µl, and had no clearly identified cause for their impaired consciousness. All had negative CSF culture, 19 had negative blood cultures, two had a contaminated blood culture and seven had no blood culture performed.

**Discussion**

Impaired consciousness, associated with a febrile illness or convulsions, is a common presentation of severely ill children to African hospitals. This study highlights a number of problems when attempting to differentiate CM from ABM on the results of initial investigations. Firstly, some children with meningitis may have a coincidental malaria parasitaemia. On the Kenyan coast, as in other areas, a large proportion of the community have a low-density background parasitaemia, even during low transmission periods. Secondly, there is the possibility that CM itself can cause an elevated CSF leucocyte count. This circumstance is usually excluded by arbitrary definition rather than because of the natural history of the condition. Thirdly, meningitis may present with a normal CSF leucocyte count, as was the case with three children in this study. Fourthly, there may be cases of a genuinely dual diagnosis, and these
may occur more frequently than expected by chance alone.

Only one previous study has directly addressed the issue of differentiating CM and ABM in African children with impairment of consciousness in which it was concluded that the CSF leucocyte count alone distinguished ABM from CM. However, the groups studied did not accord with widely accepted clinical definitions, for example 45% (41/94) of the CM cases had a negative slide and in 37% (10/27) of meningitis cases, no organism was identified in the CSF. Importantly, the CSF leucocyte count was used by clinicians to distinguish CM from ABM when reaching a final diagnosis, making it impossible to perform an analysis of its use as an independent discriminator.

Our data suggest that in a significant number of children admitted with impairment of consciousness, the diagnosis is unclear or dual. The absolute minimum proportion of children with a P. falciparum parasitaemia and impairment of consciousness who had coexisting meningitis i.e. those in whom an organism was identified from CSF, was 4% (14/359). The proportion in whom the diagnosis was unclear was at least 13% (46/359), i.e. those children with a CSF leucocyte count of >10 cells/µl and/or an organism detected in the CSF. There are several reasons to believe that the maximum proportions are even higher. Firstly, the mortality amongst those not having had an LP is high and it seems likely that these children would have fallen into the higher mortality diagnostic groups (2, 3 and 4). Secondly, the use of broad-spectrum antibiotics prior to or during the admission may have masked the identification of bacterial pathogens in the CSF or blood.

Thirdly, it was only possible to do antigen testing for Haemophilus influenzae and Streptococcus pneumoniae when sufficient CSF had been stored. Only those with a CSF leucocyte count of >10 cells/µl were tested. In total, only 25 CSF samples were antigen tested from MPS-positive children.

Children in group 2 were MPS-positive and also had an organism isolated from blood or CSF. Seventy-five percent of children in this group had a parasitaemia of >25 000 per µl, suggesting that in the majority of cases there was dual pathology with malarial disease complicated by bacterial infection, rather than simply a low-density, asymptomatic parasitaemia. Two of the children in group 2 had positive CSF culture despite a CSF leucocyte count of <10 cells/µl. These, together with one case in group 7, represent 7% of positive CSF cultures in this series, and illustrate the point that the finding of a normal CSF leucocyte count cannot be taken to rule out ABM.

Children in group 3 were MPS-positive and had a CSF leucocytosis without any organism being identified. CSF leucocytosis is not a generally reported feature of childhood CM, indeed it is excluded by the most commonly used definition. Molyneux et al. studied 131 children with CM, and found a CSF leucocyte count of <5/µl in all cases, however, it was not clear whether other children had been excluded on the basis of a raised CSF white cell count. Multiple or prolonged seizures are common in cerebral malaria and a moderate CSF leucocytosis (up to 100 cells/µl) has been reported in 2 to 5% of adults following status epilepticus. However, Portnoy et al. found no difference in the CSF leucocyte count in 107 children with seizures and 266 without in the absence of other evidence of central nervous system disease. The proportions of children in group 3 with a history of seizures prior to admission (73%) or witnessed status epilepticus whilst on the research ward (7%), were similar to those of group 1 (76% and 9%, respectively). It seems unlikely that seizures account for the raised CSF leucocyte count in the majority of children in this group. It is possible that some children in group 3 have an alternate diagnosis, such as viral meningitis or encephalitis, or either a coincidental parasitaemia, or a genuine dual pathology. Alternatively, it may be that cerebral malaria may in some circumstances lead to a moderate CSF leucocytosis. In either case, it is important that the finding of a moderately raised CSF white cell count, even in the presence of full antimeningitic cover as in this series, is associated with a markedly higher mortality than CM alone (30.0% vs. 11.1%, p<0.01).

Children in group 4 were parasitaemic and had microbiologically-proven meningitis. The log mean P. falciparum density was not significantly different from the pure malaria group (group 1). These children had a more severe metabolic disturbance and much higher mortality than either CM or ABM alone. It therefore seems likely that in the majority of these children both the malaria parasites and the bacteria played a role in pathogenesis.

Of the children with asexual P. falciparum parasitaemia under 1 year old in this study, 14% (9/64) had identifiable bacteria in their CSF. Of MPS-negative children under 1 year, 37% (14/38) had bacteria isolated from their CSF. The real proportions with meningitis are likely to be higher than this for the reasons discussed above. Thus, children under 1 year with impaired consciousness are at particularly high risk of having bacterial meningitis whether or not they have malaria parasites seen on a blood film.

Children in group 8 had no cause found for their encephalopathy. This group represents 31% (28/91) of the MPS-negative children in this series and has a high mortality (32%). Children in this group have a similar age profile to the CM group and tended to be older than those in the groups of confirmed or suspected meningitis. It is possible that some of these
children may have had ‘slide negative’ cerebral malaria, i.e. that parasites were sequestered in the cerebral vasculature. However this seems an unlikely explanation for more than a few cases for several reasons. Firstly, the cases are distributed evenly through the year, whilst cases in group 1 showed a very marked seasonal variation corresponding to the two rainy seasons occurring in Kilifi each year (data not shown), though numbers are small for this comparison. Secondly, the mean haemoglobin is significantly higher than in group 1 (8.8 vs. 6.9, \( p < 0.01 \)). Further studies are needed to identify the cause of impaired consciousness in these children.

In conclusion, we have studied a large group of Kenyan children with impairment of consciousness. As expected, malaria was the commonest cause of non-traumatic impaired consciousness with 297/450 children satisfying the criteria for ‘cerebral’ malaria and having no evidence of other coexisting infections. However there were a further 46 children (13% of those with asexual malaria parasitaemia) who had findings compatible with the possibility of coexisting meningitis. Some of these children had definite bacterial meningitis, some had a pathogenic bacteria grown from blood culture and an abnormal CSF white cell count, whilst others had only an abnormally elevated CSF leucocyte count. It seems likely that in some of the latter cases the CSF abnormalities may have been part of the spectrum of severe malaria, without coexisting bacterial infection. However, in all groups, mortality was markedly higher than that of pure ‘cerebral’ malaria. Children under 1 year of age with impairment of consciousness are at particularly high risk of having bacterial meningitis, whatever the findings on blood film examination.

References


