Afr. J. Med. med. Sci. (1997) 26, 9-11

Clinical study of cerebral malaria in African children

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Summary

Of 51 consecutive children with cerebral malaria, fever, convulsions, and drowsiness were the commonest presenting symptoms. Decerebrate and decorticate postures and absent cornea reflex were the commonest brain stem signs. Opening lumbar cerebrospinal (CSF) pressure was raised in all but one of 24 children in whom it was reliably measured [mean 15.2 $\pm$ 5.7 mmHg, range 6-24]. Hyponatraemia occurred in 17 (33%). Acute renal failure was not uncommon; the combination of hypercreatininaemia (plasma creatinine > 100 μmol/L) and hyperkalaemia (plasma potassium > 6.0 μmol/L) was fatal in 5 out of 7 patients in whom it occurred. Disturbances of acid-base status were present in all 40 children in whom it was assessed on admission. Mortality rate was 16% (8 patients). Neurological deficits occurred in 7 (14%) of the survivors and included cortical blindness [3], aphasia [3], hypertonia [3], hearing loss [2], and dystonia [1]. In addition to the present measures aimed at reducing morbidity and morality in children with cerebral malaria, efforts should be directed at rapid assessment of renal function and prompt correction of such dysfunction if found.

Résumé

De 51 enfants souffrant du paludisme cerébral, la fievre, les convultions, et la sommolence ont été les symptomes les plus communs. Les postures decérebrés et décortique, l'absence de reflex de la cornee ont été les signes de déficience du cervaux. L'ouverture de la pression cerebrospinal lombaire (CFS) a été mesuré (moyenne 15.24 $\pm$ 5.7 mmHg, ecart type 6.24) L'hypernatraemie, a été constaté chez 17 patients (33%). L'insufisance renal aigüe, a elle aussi été observée chez certains patients, la combinaişon de l'hypercreatininaemie (taux de la creatine du plasma 100 μmol/L), et de l'hyperkalaemie (taux de potassium du plasma 6.0 μmol/L) a été observée. Les perturbations des statuss acid-base ont été presentés chez tous les 40 enfants hospitalisés pour cause de paludisme cerebrale. Le taux de mortalité a été de 16% (8 patients). Les deficiences neuroloques ont été observé chez 7(14%) des survivants, parmis ces deficiences: l'aveuglage, dû à la laision de la corticoide [3]; l'aphasie [3]; l'hypertonie [3]; la perte de l'audition [2]; et la dystonie [1]. En plus des presente mesures destinées 'a reduire la morbidité et la mortalité chez les enfants souffrant de paludisme cerebrale, des éfforts devraient être mis sur l'evaluation rapide de la fonction renale, et la correction rapide de cette mauvaise fonction, si jamais elle est observée.

Introduction

Malaria is a major cause of childhood morbidity and mortality in Africa; its most lethal complication, cerebral malaria, may be an important cause of neurological deficits in African children [1,2,3]. Because of increasing morbidity and mortality despite effective antimalarial therapy, there is a need for further clinical and laboratory studies in African children with cerebral malaria. The present report describes a prospective hospital based study of clinical features of and laboratory findings in cerebral malaria in 51 consecutive African children and highlights the poor outcome in patients with impaired renal function and cerebral malaria.

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Patients and methods

The study was conducted between March and December 1992 at the Kilifi District Hospital, Kenya. The diagnosis of cerebral malaria was based on the World Health Organisation definition [4]. At presentation, a detailed history and thorough clinical examination was done. A thick and thin blood film was taken for parasitaemia quantification and blood was obtained for culture, full blood count, electrolytes, urea, creatinine, glucose, and arterial blood gases parameters. Urine was obtained for analysis and culture. In some patients, assessment of renal function was also done and these are reported elsewhere. Clinical assessment was done 6 hourly until the patient recovered consciousness or died, and thereafter daily until discharge in those who recovered consciousness. The level of consciousness was assessed according to modified Glasgow coma scale [5,6].

Parasitaemia quantification was done 6 hourly until 2 consecutive thick and thin peripheral blood films showed no patent parasitaemia. Arterial blood gases, blood glucose, electrolytes, urea, and creatinine were repeated when necessary. A lumbar puncture was done, usually on the second day of admission when the patient was stable, and the opening cerebrospinal fluid pressure measured using a paediatric cerebro-spinal fluid namometre and /or a non-displacement transducer (Gaeltech, Isles of Skye, Scotland).

All patients were treated with a loading dose of 20 mg/kg of body weight quinine (in saline) intravenously over 4 h followed by 10 mg/kg of body weight 12 hourly until parasitaemia had cleared completely. Thereafter, a sulfadoxine-pyrimethamine combination was given according to body weight and administered orally or parenterally. Fits were controlled with appropriate anticonvulsants, usually parenteral paraldehyde, diazepam, phenobarbitone or phenytoin, and pyrexia by tepid sponging and administration of paracetamol rectally. Blood sugar was monitored 1-2 hourly using dextrosix (Ames Co, England) and hypoglycaemia promptly corrected by intravenous administration of glucose. Anaemia was corrected by blood transfusion. A repeat detailed clinical examination was performed at discharge and 2 weeks later. Where essential, statistical analyses were by student's *t* test or by Mann-Whitney's U test.

Results

Of the 51 children (33 males, 18 females), 2 were aged less than one year and 8 were over 5 years. The mean age of the group was 40.2 $\pm$ 14.6 months. The presenting clinical features are summarized in Table 1. The duration of coma before presentation was 6-48 h (median, 11 h).

The number of fits before presentation ranged from 0-8 (median, 3). In four patients, multiple fits occurred, and the exact number could not be ascertained. Partial, partial becoming generalized, tonic, and generalized tonic-clonic fits occurred in 7, 4, 2, and 32 patients, respectively. The laboratory parameters at presentation are summarized in Table 2. Hyponatraemia was the commonest electrolyte abnormality at presentation occurring in 17 (33%) of the patients. The combination of hyperkalaemia (plasma potassium > 6.0 μmol/L) and hypercreatininaemia (plasma creatinine > 100

μmol/L) was fatal in 5 out of 7 patients in whom it occurred and was associated with prolonged coma in another patient. Acute tubular necrosis occurred in four out of 19 patients in whom renal function was assessed. This sub-group is reported in detail elsewhere. Table 2 summarizes the acid-base status as determined by arterial pCO_2 and pH values on admission. Acidaemia (defined as arterial pH < 7.300) was present in 8 of 40 subjects. Twenty-five, 7 and 8 out of 40 patients in whom acid-base status was assessed prior to admission, had compensated respiratory alkalosis, partially compensated metabolic acidosis and compensated metabolic acidosis, respectively. Normal acid-base status and acute ventilatory failure were not seen in any child at admission.

Blood and cerebrospinal fluid culture yielded no growth in all patients. Cerebrospinal fluid white cell count was less than 3 in all patients except in three patients in whom the count was 8. Opening lumbar cerebrospinal fluid pressure was raised in all but one out of 24 in whom it was measured (Fig. 1). Mean opening lumbar cerebrospinal fluid pressure was 15.2 ± 5.7 mmHg (range 6-24). One of the patients in whom the lumbar cerespinal fluid was measured died. In this patient, opening pressure was 9.0 mmHg. The patient also had a combination of hypercreatininaemia (creatinine of 120 μmol/L) and hyperkalaemia (potassium of 7.2 μmol/L), suggesting acute renal dysfunction.

Table 1: Presenting features in 51 children with cerebral malaria

Presenting symptoms	
Age (months ± SD) /M:F	40.2±14.6 /33:18
fever	51
convulsions	45
vomiting	27
diarrhoea	13
irritability	31
drowsiness	39
cough	24
poor feeding	39
Duration of illness (days)	
1-2	8
3-4	36
>4	7
Examination	
Response to pain	
localizing	0
flexion	38
extension	12
none	1
Absent cornea reflex	33
Posture	
normal	27
decorticate	16+
decerebrate	7+
opisthotonic	1
Blantrye coma scale	
0	17
1	16
2	18
3	0
Retinal haemorrhage	13
Papilloedema	1

+ 3 patients with normal posture became decorticate or decerebrate within 48-72 hours of admission.

Parasitaemia generally cleared within 72-96 h after commencement of therapy; recovery from coma occurred within 6-24 h (median 18 h) after commencement of treatment. In 19 children in whom renal function was assessed, coma recovery time was significantly longer, and plasma creatinine significantly higher in patients with reduced endogenous creatinine clearance < 65 ml/min 1.73m² (131.8 ± 60.8 [SEM] vs 19.9 ± 6.97 [SEM] h, $t = 2.5$, $P = 0.02$ and 93.7 ± 10.8 [SEM] vs 56.3 ± 6.77 [SEM] μmol/L, $t = 3.1$, $P = 0.007$, respectively). A biphasic illness comprising recovery from coma (within 36 h of admission) followed 12 h later by repeated convulsions and subsequent prolonged coma (about 96 h), occurred in one patient. Acute renal failure also occurred in this patient. Eight (16%) of the children died and in five of these, there was a combination of hypercreatininaemia and hyperkalemia suggesting acute renal impairment. Prompt correction of hypoglycaemia reduced the mortality associated with this syndrome. Neurological sequelae were present at discharge or follow up in 7 patients and comprised cortical blindness [3], aphasia [3], hypertonia [3] hearing loss [2], and dystonia [1]. Psychosis and abnormal behaviour in one child at discharge resolved at 2 weeks of follow up.

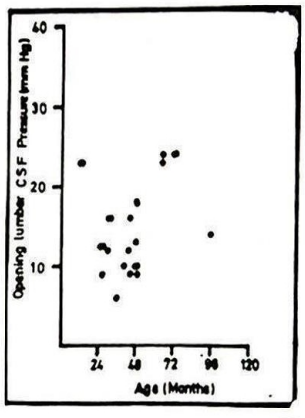

Fig. 1: Lumbar cerebrospinal fluid pressure in 24 children with cerebra malaria

Table 2: Parasitological, haematological and biochemical parameters and acid-base status in children with cerebral malaria

Parasitaemia %	
< 1	13
1-5	7
5.1-20	21
>20	10
White blood cell count x 10^9/L	
3-11	23
12-15	26
>15	25
Red blood cell count x 10^9/L	
< 2	8
2-4	38
>4	5
Sodium (μmol/L)	
<130	17
130-145	34
>145	7
Potassium (μmol/L)	
<2.5	1
2.5-6.0	43
>6.0	7
Creatinine (μmol/L)	
<80	38
81-99	2
>100	11
Blood sugar <2.2 mmol/L	13
Acid-base status *	
pH < 7.300; PCo_2 < 30 mmHg	8
pH 7.301-7.400; PCo_2 < 30 mmHg	7
pH 7.41-7.50; PCo_2 < 30 mmHg	25
Other	0

*Done in 40 subjects only on admission

Discussion

The predominance of fever, convulsions, drowsiness, and anorexia in the children is in keeping with the known common

but non-specific symptoms of cerebral malaria in children [7]. Less common presentation included diarrhoea, cough, and rapid breathing. Convulsions are a common finding in children with malaria and may be difficult to ascribe to a specific cause; it may be due to hyperpyrexia, hypoglycaemia, or cerebral malaria *per se*. In the series of children studied, irrespective of cause, generalized tonic-clonic fit was the most and tonic fit the least common. These responded adequately to anticonvulsant therapy. Neurologic signs in the children comprised brain stem disturbances, including dysconjugate gaze, hypertonicity, and abnormal postures including opisthotonos. Retinal haemorrhage also occurred. However, it was impossible to clearly delineate what proportion of these signs were due to cerebral malarial *per se* or hypoglycaemia, as hypoglycaemia was vigorously sought and promptly corrected in all children. Presumably in a large proportion of the children, decorticate and decerebrate posturing was not due to hypoglycaemia.

The commonest electrolyte abnormality was hyponatraemia, which occurred in 33% of the children. Hyponatraemia is a well known feature of severe malaria in adults [8] and has been attributed to salt and volume depletion, reset of the osmoreceptor, and the syndrome of inappropriate antidiuretic hormone secretion [SIADH] [8]. However, other causes of sodium loss have not been excluded and cerebral and renal salt wasting remain distinct possibilities.

It is generally assumed that renal failure is uncommon in Africa children with malaria or cerebral malaria, although children with raised serum creatinine tend to have worse prognosis than children without [6]. However, a recent study has shown that renal dysfunction in the form of reduced endogenous creatinine clearance may occur in nearly 50% of children with uncomplicated malaria [9]; renal function returning to normal after complete clearance of parasitaemia. It would appear that renal dysfunction including acute renal failure is not uncommon in the children studied and appeared to have poor prognostic outcome. Moreover, the characteristic biphasic clinical course of recovery of consciousness followed by recurrent convulsions and coma occurred in the one patient who also had acute renal failure. The contribution, if any, of renal impairment to the production of this syndrome needs to be urgently clarified.

Opening CSF pressure was elevated in virtually all children in whom it was measured. However, it was impossible to assess its prognostic significance as only one of the 24 children in whom it was reliably measured, died. A similar pattern of raised intracranial pressure has been recorded in both children [10,11] and adults [12]. It is possible that raised intracranial pressure may contribute to the fatal outcome in children with cerebral malaria [10].

Neurological deficits occurred in 14% of the patients. The occurrence or otherwise of neurological deficits in survivors of cerebral malaria has been a subject of considerable debate [13,14]. Recent reports however, have confirmed that neurological sequelae may be present in up to 17% of children who recover from cerebral malaria [1,3,6]. An interesting finding was the occurrence of a self-limiting psychosis characterized by auditory and visual hallucinations and abnormal behaviour in an 8-year-old male survivor. The psychosis was clearly attributable to cerebral malaria as drugs likely to cause psychotic symptoms were not given to this child during the illness. Moreover, there was no personal or family history of psychosis in the patient. A striking feature of the present series was that mortality was low (16%) and in a considerable proportion of these (63%), there was an associated acute renal failure. While this low mortality is encouraging, further measures to reduce morbidity and mortality in addition to the present valuable measures should aim at rapidly assessing renal function and prompt correction of such dysfunction if present.

Acknowledgements

This study was conducted while the investigator was in receipt of a WHO Research Training Grant. The invaluable assistance of members of the medical and nursing staff of Kenya Medical Research Institute (KEMRI), Kilifi Coastal Unit, Kilifi, Kenya during the period of the study is gratefully acknowledged.

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