Intracranial hypertension in Africans with cerebral malaria

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Abstract
The causes of death and neurological sequelae in African children with cerebral malaria are obscure. Intracranial pressure (ICP) was monitored and cerebral perfusion pressure (CPP) calculated in 23 Kenyan children with cerebral malaria. Four children had severe intracranial hypertension (ICP >40 mm Hg, CPP <40 mm Hg); two died, one with an ICP of 158 mm Hg and signs of transtentorial herniation, the other one with an ICP of 42 mm Hg and cardiorespiratory arrest. The other two survived with severe neurological sequelae. Nine had intermediate intracranial hypertension (ICP >20 mm Hg, CPP <50 mm Hg) and 10 had mild intracranial hypertension (maximum ICP 10–20 mm Hg); all survived without severe sequelae. Mannitol controlled the ICP in children with the intermediate intracranial hypertension, but it did not prevent the development of intractable intracranial hypertension in children with severe intracranial hypertension. Intracranial hypertension is a feature of Kenyan children with cerebral malaria and severe intracranial hypertension is associated with a poor outcome.

Keywords: cerebral malaria; intracranial pressure.

Cerebral malaria is probably the most common paediatric encephalopathy in sub-Saharan Africa, accounting for many of the estimated 100 000 childhood deaths from falciparum malaria each year and producing neurological deficits in a further 40 000 children per year. The causes of poor outcome in these children are largely undetermined. Intracranial hypertension is an important determinant of poor outcome in other non-traumatic paediatric encephalopathies and aggressive treatment with agents such as mannitol is thought to improve the outcome in Reye's syndrome. Opening lumbar puncture pressures are raised in African children with cerebral malaria and we have documented clinical features compatible with transtentorial herniation in children who died, although the significance of these findings has been questioned. A relatively simple intervention, such as an osmotic agent may improve the outcome of a large number of children with cerebral malaria. Thus we monitored intracranial pressure (ICP) in children with severe cerebral malaria, to describe the pattern of intracranial hypertension and to determine the efficacy of mannitol in lowering ICP.

Patients and methods
This study was conducted at Kenya Medical Research Institute (KEMRI), Kilifi District Hospital, Kenya between May 1992 and August 1994. Ethical permission for the study was granted by the KEMRI/National Ethical Review Committee and written informed consent was obtained from the child's parents.

Children who fulfilled the World Health Organisation's criteria for cerebral malaria, that is patients who are unconscious (defined as the inability to localise pain), have asexual Plasmodium falciparum parasites detected in their blood, and other causes of an encephalopathy such as bacterial meningitis excluded, were assessed for ICP monitoring. Permission for monitoring was requested if the child was normoglycaemic, and had one of the following clinical signs at least an hour after the last seizure: (i) best motor response—sluggish flexion to a painful stimulus, (ii) decerebrate/posture, (iii) dilated and sluggish pupils, or (iv) absent oculocephalic reflexes. Children were not monitored if there was (i) a platelet count <40×10^9/l, (ii) evidence of spontaneous bleeding or (ii) severe metabolic acidosis (pH <7.1 with base excess <−10).

ICP was monitored with a fibresystem (model 110-4B, Camino Laboratories, San Diego, USA) inserted into the subarachnoid space. The wave form was verified on an HP-7834A monitor (Hewlett Packard, Andover, USA) and the opening ICP was noted. Mean arterial pressure (MAP) was measured with an intra-arterial line and cerebral perfusion pressure (CPP) was calculated from the MAP-ICP. The data were recorded at intervals of 15 minutes or less. The monitor was removed if the ICP was less than 20 mm Hg for longer than 12 hours, or if the child could localise pain. A lumbar puncture was performed shortly before the ICP monitor was removed to exclude bacterial meningitis. Computed tomography was performed in 15 children after the removal of the monitor.

GENERAL TREATMENT
Children were randomised to receive either intravenous quinine dihydrochloride (loading dose 20 mg/kg infused over four hours, followed by 10 mg/kg every eight hours) or intramuscular artemether (3.2 mg/kg intramuscularly, followed by 1.6 mg/kg daily), as
part of a multicentred clinical trial (results in preparation). Antimicrobials were adminis-
tered until a lumbar puncture was performed. Intravenous 0.18% normal saline/4% dex-
trose was infused at a rate of 3 ml/kg/hour after initial resuscitation. Seizures were treated
initially with intravenous diazepam (0.3 mg/kg) or intramuscular paraldehyde (0.1 ml/kg), and
were treated with intravenous phenytoin (15–20 mg/kg) or intramuscular phenobarbi-
tone (15–20 mg/kg). Blood transfusions (15–20 ml/kg) were given if the packed cell
volume was below 0.15 and the child had signs of respiratory distress. Hypoglycaemia (whole
blood glucose <2.2 mmol/l) was treated with 0.6 ml/kg of 50% dextrose.
Children were nursed supine, with the head flat and in the midline position. The stomach
contents were drained via a nasogastric tube. The children had six hourly neurological
evaluations, with depth of coma assessed by the paediatric modification of the Glasgow coma
scale, the Adelaide coma scale, until they recovered from coma (able to localise pain) or
died. None of the children was ventilated.

TREATMENT OF RAISED ICP
Mannitol (0.5–1.0 g/kg infused over 10–20
minutes) was administered if: (i) ICP was
above 20 mm Hg for longer than 20 minutes,
(ii) there were frequent spikes of ICP above 20
mm Hg with less than a five minute interval
between each, or (iii) CPP was less than 50 mm
Hg for longer than 20 minutes. Dopamine was
 infused (2.5–25 µg/kg/min) if mannitol did not
raise the CPP above 50 mm Hg.

DATA ANALYSIS
The ICP and CPP findings were classified as
follows: (a) severe intracranial hypertension: ICP above 40 mm Hg and CPP less than 40
mm Hg lasting longer than 15 minutes continuously, (b) intermediate intracranial
hypertension: ICP above 20 mm Hg and CPP less than 50 mm Hg lasting longer than 15
minutes continuously, (c) mild intracranial hypertension: maximum ICP 10–20 mm Hg
and minimum CPP above 50 mm Hg, and (d) normal intracranial pressure: maximum ICP
less than 10 mm Hg and minimum CPP above 50 mm Hg.

ICP waves were identified according to the
following criteria: (i) A waves, abrupt rise in
ICP to above 20 mm Hg with the ICP remain-
ing at this level for 5–20 minutes, before
returning to the baseline; (ii) B waves, sharp
peaked waves occurring at a frequency of 0.5 to
2 minutes; (iii) plateau-like waves, similar to
A waves, but with an ICP of 20–50 mm Hg at
the plateau and (iv) ‘tented waves’, increases in
ICP greater than 20 mm Hg, lasting 5–20
minutes.

Outcome
Neurological outcome was classified as no
sequelae (normal), mild/moderate sequelae
(hemiparesis, learning difficulties), severe se-
quelae (spastic quadriparesis, intractable epi-
lepsy and/or poor vision) or death. Poor out-
come refers to children who survived with
severe neurological sequelae or died and good
outcome to the remainder.

Statistical analysis
Comparisons of proportions were performed
with the two tailed Fisher's exact test, as the
expected frequencies in the cells were <5. Dif-
fences are regarded as significant if the prob-
ability of the test statistic is <5%.

Results
CHILDREN MONITORED
From 1 December 1991 to 1 August 1994, 40
children were identified for ICP monitoring on
the clinical criteria. Twenty three children had
ICP monitors inserted. Four children were
admitted during the absence of the personnel
trained to insert the ICP monitor and five were
not monitored because they were recruited for
another study which precluded adequate su-
 pervision of ICP monitoring. The others were
excluded because the parents refused consent
(n=1) or were not available to give consent
(n=2), or because of thrombocytopenia (n=2)
or severe metabolic acidosis (n=3).
The clinical and laboratory features of the
children who had ICP monitoring (arranged in
order of increasing severity of intracranial
hypertension) are shown in table 1. None of the
children had evidence of another central nervous
system infection (that is, no growth from
blood cultures; <5 leucocytes × 10⁹/l in
cerebrospinal fluid (CSF), and CSF glucose
greater than two thirds of the blood glucose).
There were no serious complications from ICP
monitoring; three of the 15 children who had
computed tomography had tomographic evi-
 dence of small amounts of blood in the
subarachnoid space and another child had a
superficial wound infection at the site of the
monitor.

ICP FINDINGS AND OUTCOME
All the children had intracranial hypertension
with a maximum ICP above 15 mm Hg (table
2). Four children had severe intracranial
hypertension and nine had intermediate intracra-
nial hypertension; in the other 10 children,
the ICP was raised but did not rise above 20
mm Hg for longer than 15 minutes. In two
children the ICP monitor drifted by −11 mm
Hg over 18 hours (number 10) and by 16 mm
Hg over 92 hours (number 21): although the
patterns of intracranial hypertension were
compatible with mild intracranial hypertension
and severe intracranial hypertension, respec-
tively, these data were not used for further anal-
ysis and not included in fig 1. There was no
difference between these groups in parasita-
emia, haemoglobin, or lactate.
Opening ICP did not predict maximum ICP
nor did opening CPP predict minimum CPP. A
maximum ICP above 40 mm Hg (p = 0.017,
Fisher’s exact test) and CPP below 40 mm Hg
(p = 0.009, Fisher’s exact test) were associated
with a poor outcome (fig 1). There was no
association between duration of coma or
duration of ICP waves and the pattern of in-
tracranial hypertension (table 1).
The children with severe intracranial hyper-
tension all did badly: two died and the other
Table 1  Clinical and laboratory features of children who had ICP monitoring

<table>
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<tr>
<th>Patient No</th>
<th>Age (months)</th>
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<th>During admission</th>
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<td>Brain stem deterioration‡ (hours after treatment)</td>
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* Patterns of intracranial hypertension defined in the text: MIH = mild, IIH = intermediate, SIH = severe.
† Adelaide coma scale: V = verbal, M = motor, E = eye opening.
‡ Brain stem signs: one or more of the following signs: pupillary dilation + sluggish response to light, absent corneal reflexes, mania or absent oculocephalic reflexes, decerebrate posturing.
§ Adverse outcomes: GTC = generalised tonic-clonic, PM = partial motor, S = status, PBG = partial becoming generalised.

** CNS = central nervous system.
not seen in the child who died of cardiorespiratory arrest (number 22). One child (number 20) had seven episodes of B waves, of which two were associated with the development of sluggish, dilated pupillary response to light, hypertonia, and hyperventilation. In the other children the B waves were not associated with clinical signs.

Infusion of mannitol was followed by a reduction in ICP in all instances. On eight occasions in the three children with quantitative data, mannitol did not reduce the ICP to below 20 mm Hg. In patient number 20, the time of the lowest ICP after the infusion was a median of 46 (range 10–99) minutes and on the occasions it fell below 20 mm Hg, the time it took to return to 20 mm Hg was a median of 73 (range 25–180) minutes. In patient number 23, from developing signs of the medullary stage of herniation (fig 2) or of the other child (number 22).

(2) Intermediate intracranial hypertension

The nine children with intermediate intracranial hypertension had a median opening ICP of 21 (range 14–32) mm Hg and median maximum ICP of 32 (range 22–56) mm Hg, at a median of 51 (range 12–63) hours after onset of treatment. Mannitol reduced the ICP in all cases, reaching a median of 10 mm Hg (range 4–17), but rising to above 20 mm Hg in 120 (range 50–180) minutes on nine occasions (table 2).

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Time from start of treatment to monitoring (hours)</th>
<th>Duration of monitoring (hours)</th>
<th>ICP Opening (mm Hg)</th>
<th>ICP Maximum (mm Hg)</th>
<th>Time spent &gt; 20 mm Hg (hours)</th>
<th>Time spent &gt; 40 mm Hg (hours)</th>
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</table>

Table 2: Intracranial monitoring in children with cerebral malaria

* Patterns of intracranial hypertension defined in the text: MIH = mild, IIH = intermediate, SIH = severe.
† Mannitol administered on an empirical basis.
‡ Excessive drift during ICP monitoring, hence unable to determine accurately.
returned to normal after the administration of mannitol (fig 3). Papilloedema developed in two children with severe intracranial hypertension: it was present on admission in one of the children who died (number 23) and it appeared after severe intracranial hypertension developed in the other child (number 20). There was an association between papilloedema and severe intracranial hypertension \( (p = 0.024, \text{Fisher's test}) \), but not between fundal haemorrhages and severity of intracranial hypertension. Twenty three episodes of decerebrate posturing occurred in five patients (numbers 7, 10, 11, 17, and 21). The ICP immediately before the onset of the posturing was a median of 23 mm Hg (range 11–28) and rose to a median of 28 (range 12–49) mm Hg during the posturing.

(3) ICP and seizures

Eighty one seizures were detected clinically in nine children during monitoring. Seizures were associated with transient increases of ICP often persisting after the clinical manifestations had ceased. The ICP rose by a median of +154\% (range +88 to +467\%) and CPP changed by −3\% (range −46 to +9\%) with generalised seizures. In partial seizures, the ICP rose by a median of 54\% (range +40 to +150\%) and the CPP fell by a median of −12 (range −30 to +36). In three children with intermediate intracranial hypertension and status epilepticus (numbers 11, 17, and 18), the ICP decreased to less than 20 mm Hg after the seizures were controlled.

ICP AND LABORATORY VARIABLES

There was no association between opening ICP, maximum ICP, or pattern of intracranial hypertension and blood tests on admission (parasitaemia, haemoglobin, carbon dioxide pressure, base excess, lactate, or glucose), CSF biochemistry (protein or lactate), which was sampled at the end of the ICP monitoring or choice of antimalarial.

Discussion

This study clearly shows that intracranial hypertension is a feature of cerebral malaria in African children and that severe intracranial hypertension is associated with a poor outcome. Critically high ICP developed in both children who died, one child had clinical signs of herniation, while the other had a cardiorespiratory arrest. Severe intracranial hypertension was also associated with severe neurological sequelae in two children. Although mannitol reduced ICP and appeared to control the ICP in children with intermediate intracranial hypertension, it neither prevented nor controlled severe intracranial hypertension.

There is a dilemma in the appropriateness of these high technical investigations in important health problems of countries with limited health resources. The justifications for the present study were (i) that despite the raised opening lumbar puncture pressures, these could not be used to predict maximum ICP\(^{27,5} \), (ii) there was good clinical evidence for hernia-
tion in children with cerebral malaria and therefore a relatively simple intervention, such as an osmotic agent may be beneficial, and (iii) we needed to ensure that the osmotic agent was effective in reducing ICP and determine the duration of action before proceeding to a randomised control trial.

Raised ICP causes death either by compressing the brain stem during transistorial herniation or by causing global ischaemia. Although we were unable to perform necropsy on the children who died, one was observed to have clinical features of the uncal and medullary stages of herniation which developed as the ICP rose to the critically high pressures. Further evidence that intracranial hypertension contributes to the death of children with cerebral malaria is provided by our original report, in which children died with signs suggestive of brain stem herniation and another study, in which three of the six children with cerebral malaria who were monitored with transcranial Doppler had sonographic evidence of progressive intracranial hypertension, associated with the signs of herniation during their agonal stages. Finally, frank herniation has been observed at necropsy in a Nigerian child with cerebral malaria and has been detected by magnetic resonance imaging in Thai adults. However, several other mechanisms, including metabolic acidosis, anaemia, and hypoglycaemia may interact to cause death and the exact role of intracranial hypertension as a cause of death awaits further studies of ICP monitoring and neuropathology.

Raised ICP produces brain damage by causing global ischaemia due to reduction in CPP or by compromising flow in the basal cerebral arteries during transtentorial herniation. In children with non-traumatic coma a CPP of 60 mm Hg is associated with a poor outcome.  In this study, two children with severe neurological sequelae both had severe intracranial hypertension. One child (number 20) had a minimum CPP of 32 mm Hg and had a watershed distribution of ischaemic damage on a later computed tomogram, while the other child (number 21) developed severe intracranial hypertension after he was admitted with severe hypotension and hypoglycaemia. Although another two children (numbers 9 and 11) also developed mild sequelae despite a minimum CPP of 60 and 46 mm Hg, both of these children had status epilepticus. The computed tomograms of children with cerebral malaria do not support the idea that sequelae are caused by herniation. Thus a low CPP appears to be associated with severe sequelae, although a causal relationship remains to be established.

The possible causes of intracranial hypertension in cerebral malaria are an increase in cerebral blood volume (CBV), cerebral oedema or acute hydrocephalus. An increase in CBV is most likely, since computed tomograms do not show any evidence of acute hydrocephalus or vasogenic oedema. Two children in this study had tomographic appearances compatible with cytotoxic oedema during recovery and were discharged with severe sequelae. Recent magnetic resonance imaging studies from Thailand also suggest that there is an increase in CBV. The CBV could be increased by the sequestration of parasitised erythrocytes in the cerebral venules (the histopathological hallmark of cerebral malaria) or an increase in cerebral blood flow (CBF). The sequestered mass of parasitised erythrocytes may represent a diffuse space occupying lesion increasing the space the vascular compartment occupies within the cranium. Furthermore it may also impede venous outflow. Sequestration may be particularly important in African children, since they have higher peripheral parasitaemias than do non-immune adults with cerebral malaria and thus by implication (although not proved, since the sequestered mass cannot be measured in vivo) a larger sequestered mass in a smaller volume cranium. In this study, the lack of association between the peripheral parasitaemia and the pattern of intracranial hypertension does not necessarily refute this suggestion, since the analysis was performed on only 23 patients and the peripheral parasitaemia is less likely to reflect the sequestered mass in treated patients.

Besides sequestration, an increase in CBV could be caused by an increase in CBF. In this study, cerebral or prolonged partial seizures raised the ICP, probably by increasing CBF, but also possibly by producing oedema. Anaemia increases the CBF by decreasing the viscosity and oxygen content of the blood. Tumour necrosis factor, which is raised in children with cerebral malaria, might also increase the CBF as it induces the release of nitric oxide, a potent vasodilator, and induces fever, which increases the cerebral metabolic rate. Lactic acidosis, a common feature of cerebral malaria, may be associated with an increase in CBF and luxury perfusion. The lack of association between the arterial carbon dioxide pressure and ICP suggests that vascular changes responsive to carbon dioxide are not the major determinants of raised ICP. Thus vascular factors are likely to be responsible for the raised ICP in most children with cerebral malaria, although cytotoxic oedema would contribute to severe intracranial hypertension.

In these children, ICP monitoring was unique, in that the children were of necessity not paralysed. Disappointingly there were few clinical correlates of raised ICP, pupillary dilation, particularly associated with a sluggish response to light, was the most reliable sign of a high ICP, although it was not specific and was not apparent during many of the episodes when the ICP was above 40 mm Hg. Furthermore, decerebrate posturing, often regarded as a sign of raised ICP, was present in two children when the baseline ICP was less than 20 mm Hg. As in other studies, we found that opening CSF pressures did not predict maximum ICP. These results clearly indicate that intracranial hypertension cannot be assessed by clinical examination, nor a single pressure measured at lumbar puncture.

The lack of clinical signs reflecting raised ICP makes the decision to institute ICP monitoring more difficult. Indications for monitoring ICP in
other encephalopathies are variable, reflecting the lack of any controlled studies which show the benefits of ICP monitoring. Most paediatric authorities would institute ICP monitoring if the child was unconscious with a summated Glasgow coma score less than 8. 4, 5 31 32 As yet, there are not enough data to provide reliable indications for ICP monitoring in cerebral malaria, although children with an Adelaide coma score of less than 6 and pupillary abnormalities are more likely to develop or have more severe intracranial hypertension than those without these signs.

The main rationale for our studies on intracranial hypertension is to develop empirical regimens for the management of cerebral malaria in peripheral settings. In Africa, potential treatments for intracranial hypertension are limited to nursing care, appropriate fluid regimens, osmotherapy, steroids, and other pharmaceutical agents. Corticosteroids are ineffective in diffuse encephalopathies and were found to be detrimental in adults with cerebral malaria, 33, 34 but have not been tested in African children. Osmotherapy has been used in children with cerebral malaria previously, but is not recommended by the World Health Organisation. 35 One osmotic agent, 30% urea in 10% invert sugar, appeared to improve the outcome in Liberian children. 36 Mannitol (1 g/kg eight hourly) was reported to improve the level of consciousness 37 and outcome 38 in Ghanian children. However, the significance of these reports are difficult to determine, as these studies lacked appropriate controls.

A major question to arise from our observation is whether osmotherapy contributed to the outcome in the group with intermediate intracranial hypertension. In 74% of the children the ICP was greater than 20 mm Hg for more than 15 minutes, a level which would be actively treated in most intensive care units. All these children except one (number 8) were given mannitol and 70% had a good outcome. However establishing cause and effect is difficult. Furthermore it is not possible to determine if severe intracranial hypertension is a consequence of untreated intermediate intracranial hypertension, or whether severe intracranial hypertension reflects the development of widespread cerebral damage secondary to other concurrent pathogenic processes. As yet there are not enough data to recommend an empirical regimen for control of ICP.

In conclusion, intracranial hypertension is a consistent feature of cerebral malaria in Kenyan children, but its precise role in this encephalopathy still remains to be defined. Further ICP monitoring is required to determine the incidence of severe intracranial hypertension and to identify the most effective regimens to reduce ICP. The role of intracranial hypertension in causing death needs to be substantiated by further detailed neuropathological studies in African children. The question of whether intracranial hypertension is a treatable cause of death and sequelae, or merely an epiphenomenon, can only be answered by large randomised trials of an effective intervention.

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References
Genetic immunisation

The Brown-Norway rat is prone to atopy; after intraperitoneal challenge with allergen it produces lots of IgE, develops eosinophilia, and shows early and late bronchospasm. Research workers in Taiwan (Ching-Hsiang Hsu and colleagues, *Nature Medicine* 1996;2:540-4) injected a plasmid DNA encoding a house dust mite allergen into the muscles of such mice. They showed that the muscle cells then produced the allergen for at least six months and that the rats produced IgG but not IgE specific antibodies. When later challenged with the allergen they produced only 20% of the allergen specific IgE produced by control rats similarly challenged and, unlike control rats, they did not develop bronchospasm or release large amounts of histamine into their lungs. This inhibition of response was specific to the house dust mite allergen, the rats responding as usual to a different allergen. Furthermore the response inhibition was transferred to immunologically naive rats by injecting them with CD8+ T cells from the experimental rats.

Intracellular and extracellular antigens are dealt with differently. Peptides from intracellular antigens are presented to CD8+ T cells by major histocompatibility complex class I molecules present on all cells whereas those from extracellular antigens are presented to CD4+ T cells by MHC class II molecules on specialised cells. This may explain why persuading somatic cells to produce an allergen might alter the immune response to that allergen.

There is much to be learned before this work can be translated to therapeutic use. There are fears of potential carcinogenesis because of interference with normal genes and it is not known how animals (or people) already sensitised to allergen would respond. It’s fascinating, though, isn’t it?

**ARCHIVIST**