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 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.

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Cerebral malaria is probably the most common paediatric encephalopathy in sub-Saharan Africa, accounting for many of the estimated 1 000 000 childhood deaths from falciparum malaria each year[1 2] and producing neurological deficits in a further 40 000 children per year.[3] 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[4–9] and aggressive treatment with agents such as mannitol is thought to improve the outcome in Reye's syndrome.[8] Opening lumbar puncture pressures are raised in African children with cerebral malaria[10–12] and we have documented clinical features compatible with transtentorial herniation in children who died,[10] although the significance of these findings has been questioned.[13 14] 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,[15] 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/decorticate posturing, (iii) dilated and sluggish pupils, or (iv) absent oculocephalic reflexes. Children were not monitored if there was (i) a platelet count $<40 \times 10^9$/l, (ii) evidence of spontaneous bleeding or (ii) severe metabolic acidosis (pH <7.1 with base excess <–10).

ICP was monitored with a fibreoptic system (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 administered until a lumbar puncture was performed.[10]

Intravenous 0.18% normal saline/4% dextrose 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 if they persisted, with intravenous phenytoin (15–20 mg/kg) or intramuscular phenobarbitone (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 50 mm Hg with the ICP remaining at this level for 5–20 minutes, before returning to the baseline[16 17]; (ii) B waves, sharp peaked waves occurring at a frequency of 0.5 to 2 minutes[16 17]; (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.[18]

Outcome

Neurological outcome was classified as no sequelae (normal), mild/moderate sequelae (hemiparesis, learning difficulties), severe sequelae (spastic quadriparesis, intractable epilepsy and/or poor vision) or death.[19] Poor outcome 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. Differences are regarded as significant if the probability 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 supervision 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 $\times$ 10^6/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 evidence 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 intracranial 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, respectively, these data were not used for further analysis and not included in fig 1. There was no difference between these groups in parasitaemia, 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 history or duration of coma and the pattern of intracranial hypertension (table 1).

The children with severe intracranial hypertension all did badly: two died and the other

Table 1 Clinical and laboratory features of children who had ICP monitoring

Patient No	Age (months)	Pattern of intracranial hypertension*	Duration of coma before ICP monitoring (hours)	On admission							During admission			On discharge (CNS sequelae**)
				Adelaide coma scale (V,M,E)†	Brain stem signs‡	Parasite count (per μl)	Haemoglobin (g/l)	Lactate (mmol/l)	Episodes of hypoglycaemia	Clinically detected seizures¶	Brain stem deterioration‡ (hours after treatment)	Computed tomography‖	Duration of coma (hours)	
1	24	MIH	5	2, 3, 2	No	3090	34	9.7	None	PM × 5	No	N	12	None
2	21	MIH	19	2, 3, 4	No	49 742	49	6.2	None	None	No	N	39	None
3	71	MIH	40	2, 4, 2	No	3848	60	5.8	None	S-GTC	36	—	77	None
4	35	MIH	47	1, 3, 1	Yes	242 880	69	9.6	None	None	18	N	68	None
5	77	MIH	44	2, 3, 4	No	80 340	83	2.7	None	GTC × 1	19	—	49	None
6	26	MIH	10	2, 3, 2	No	800 000	49	9.1	None	PM × 6, PBG × 1	No	—	37	None
7	26	MIH	4	2, 3, 2	No	12 402	33	11.2	None	PM × 11, PBG × 5	No	N	56	None
8	69	MIH	6	2, 3, 2	Yes	3196	81	2.6	None	GTC × 3	No	N	41	None
9	17	MIH	44	2, 3, 1	Yes	1377	83	2.0	None	None	7	N	96	Mild
10	19	MIH	17	2, 3, 2	No	36 580	43	—	None	S-PM	11	N	48	None
11	81	IIH	24	2, 3, 2	Yes	1200	110	1.1	None	S-GTC	19, 36	N	87	Mild
12	51	IIH	15	2, 3, 4	No	45 144	86	2.2	None	None	6	N	36	None
13	36	IIH	6	2, 3, 2	No	739 200	52	2.2	None	None	No	—	32	None
14	23	IIH	42	3, 4, 4	No	10 535	31	11.1	None	PM × 10, PBG × 5	10	—	90	None
15	40	IIH	53	2, 3, 2	No	3060	83	1.4	None	PM × 2	26	—	96	None
16	53	IIH	16	2, 4, 3	No	9200	50	5.1	None	PM × 4	No	BS	36	None
17	84	IIH	16	2, 3, 2	No	15 200	81	0.9	None	S-GTC	No	N	18	None
18	24	IIH	25	2, 3, 3	Yes	4293	48	3.9	None	PBG × 2	No	N	44	None
19	42	IIH	75	2, 3, 2	No	1 108 800	111	1.9	A§ + 1	GTC × 2	12, 40	BS	120	None
20	24	SIH	13	2, 3, 2	No	92 520	60	8.2	NA§ + 1	GTC × 4	6, 24	BS + H	> 140	Severe
21	30	SIH	25	1, 3, 1	Yes	37 269	132	3.4	A§ + 4	PM × 1	15	BS + H	> 140	Severe
22	35	SIH	12	2, 2, 2	Yes	842	99	5.4	A§ + 1	None	9	—	—	Died
23	36	SIH	16	1, 1, 1	Yes	310 200	54	8.9	None	None	18, 23, 24	—	—	Died

* 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, minial or absent oculocephalic reflexes, decerebrate posturing.
¶ Seizures: GTC = generalised tonic-clonic, PM = partial motor, S = status, PBG = partial becoming generalised.
‖ Computed tomography appearances: BS = brain swelling as defined by loss of sulci and fissures, with small ventricles and narrow basal cisterns; H = generalised hypodensity, N = normal.
** CNS = central nervous system.
§ A = on admission, NA = not on admission.

two had severe neurological sequelae. The children with severe sequelae had severe visual impairment, cognitive problems, and spastic quadriparesis. One child (number 20) was discharged in a vegetative state and died four months later with a respiratory illness, while the other child (number 21) showed little improvement after a year. Two children who presented with status epilepticus had mild or moderate sequelae; one with intermediate intracranial hypertension (number 11) recovered with learning difficulties, while another with mild intracranial hypertension (number 9) was discharged with a right sided hemiparesis, sensory inattention, and visual field defect. All the other children had a good outcome.

PATTERNS OF INTRACRANIAL HYPERTENSION

(1) Severe intracranial hypertension

Four children developed severe intracranial hypertension, two of whom died. One child who died (number 23) was admitted with opisthotonic posturing and papilloedema. The opening ICP and CPP were 25 mm Hg and 55 mm Hg. During the first 11 hours of monitoring, three doses of mannitol were given and the ICP was maintained below 30 mm Hg, with the CPP above 55 mm Hg (fig 2). Thereafter the ICP rose inexorably, despite two additional doses of mannitol, to an agonal peak of 153 mm Hg (CPP, 2 mm Hg). During this period, the child developed clinical evidence of transtentorial herniation; initially he had features of the uncal syndrome[10] and then progressed to the medullary syndrome shortly before his death. The other child who died (number 22) had an opening ICP of 28 mm Hg and CPP of 75 mm Hg. The first dose of mannitol only reduced the ICP from 30 to 24 mm Hg (CPP remained unchanged at 50 mm Hg), during which child developed ataxic respiration. Thereafter the CPP fell despite dopamine infusion. The second dose of mannitol was administered 15 minutes before the child had a terminal cardiorespiratory arrest.

The other two children with severe intracranial hypertension (numbers 20 and 21) had similar patterns of intracranial hypertension: they had an opening ICP of 13 mm Hg and 9 mm Hg, respectively, and an initial period of 10–12 hours during which the ICP was less than 20 mm Hg, after which they developed intractable intracranial hypertension. In one child (number 20) the maximum ICP and minimum CPP were recorded at 33 hours and 97 hours after the onset of monitoring. The other child (number 21) was admitted with hypoglycaemia and hypotension but the maximum ICP and minimum CPP could not be determined accurately. The monitor was removed from these children when they became neurologically stable.

Pressure waves (B and 'tented' waves) were detected in three of the children with severe intracranial hypertension, but were

Table 2 Intracranial monitoring in children with cerebral malaria

Patient No	Time from start of treatment to monitoring (hours)	Duration of monitoring (hours)	ICP				ICP waves	CPP					Pattern of intracranial hypertension*
			Opening (mm Hg)	Maximum (mm Hg)	Time spent > 20 mm Hg	Time spent > 40 mm Hg		Opening (mm Hg)	Minimum (mm Hg)	Time spent < 50 mm Hg	Time spent < 40 mm Hg	No of mannitol infusions	
1	3	10	10	16	0	0	None	54	54	0	0	0	MIH
2	2	20.5	15	19	0	0	None	(50)	55	0	0	0	MIH
3	32	22	16	17	0	0	None	64	64	0	0	0	MIH
4	23	9	10	17	0	0	None	48	40	6	0	0	MIH
5	28	31	6	20	< 0.1	0	None	84	51	0	0	0	MIH
6	18	20	11	23	0.2	0	None	58	51	0	0	2†	MIH
7	6	39	20	35	0.1	0	None	40	40	1	0	0	MIH
8	10	30	14	54	0.4	0.1	None	72	43	0.1	0	0	MIH
9	8	22	7	24	< 0.1	0	None	70	60	0	0	0	MIH
10	16	18	14	?	?	0	None	75	?	?	?	0	MIH
11	15	18	14	26	0.2	0	None	(61)	46	0.6	0	1	MIH
12	4.5	18	14	22	0.5	0	None	(46)	36	10	3	1	IIH
13	9	18	21	30	0.75	0	None	54	42	0.1	0	3	IIH
14	42	50	21	31	2.0	0	None	49	45	0.1	0	1	IIH
15	29	66	15	56	3.65	0.1	None	69	31	0.1	0	3	IIH
16	16	23	20	43	1.5	0.1	None	72	43	0.7	0	1	IIH
17	1.5	20.5	23	56	6.8	0.3	None	57	45	0.5	0	1	IIH
18	8	36	32	32	14.5	0	None	43	35	17.8	0.7	2	IIH
19	49	32	28	49	21.9	0.9	None	51	34	3.6	0.3	6	IIH
20	13	122	13	95	63.2	13.9	B, T	60	32	23.9	1.4	26	SIH
21	22	92.5	9	> 60	> 30	?	B, T	42	< 30	> 6	?	8	SIH
22	7	4	28	42	4.0	0.75	None	50	18	1.75	1.25	2	SIH
23	10	16.5	25	158	7.3	4.5	B	55	2	3.3	3	5	SIH

* 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.

not seen in the child who died of a 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 the 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 97 (range 11–179) minutes. In the children who died, mannitol caused only a transient reduction in ICP and did not prevent one child (number 23) from developing signs of the medullary stage of herniation (fig 2) or the other child (number 22) dying.

(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).

(3) Mild intracranial hypertension

In the 10 children with mild intracranial hypertension the median opening ICP was 14 (range 10–16) mm Hg and the median maximum ICP 19.5 (range 16–54) mm Hg. The children were monitored for a median of 22 (range 9–39) hours. One child was given mannitol on an empirical basis.

RELATIONSHIP OF ICP TO CLINICAL SIGNS

(1) Clinical signs predicting pattern of intracranial hypertension

A sluggish or absent pupillary response, detected before monitoring, was associated with the development of intermediate or severe intracranial hypertension ($p = 0.003$, Fisher's test), while other signs (such as absent or extensor motor response, pupillary dilatation, decerebrate posturing, or absent oculocephalic reflexes) were not. In the group of 14 children in whom all the components of the Adelaide coma scale were tested every six hours, a worst summated score before monitoring of less than 6 was associated with the development of severe intracranial hypertension ($p = 0.038$, Fisher's test).

(2) Clinical signs during monitoring

The most reliable signs of ICP spikes were dilated pupils, which responded sluggishly to light. In one child (number 19), the left pupil dilated and reacted sluggishly to light when the ICP rose above 40 mm Hg, became smaller and reacted more briskly after the spike, and

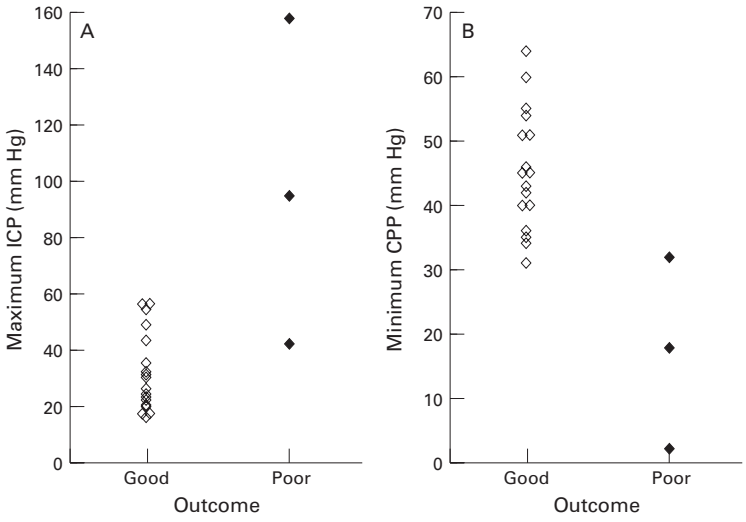

Figure 1 Relationship between (A) maximum ICP and (B) minimum CPP and outcome. The measurements of children without accurate quantitative data (numbers 10 and 21) are not shown.

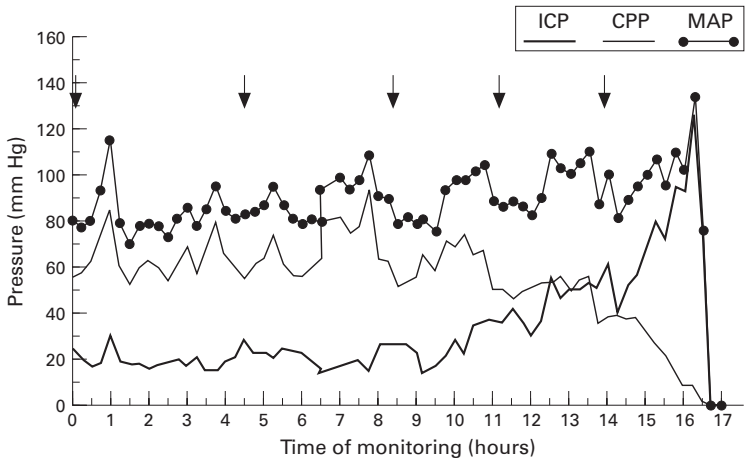

Figure 2 ICP record in the child (number 23) who died during monitoring. Mannitol was infused (arrows) on five occasions.

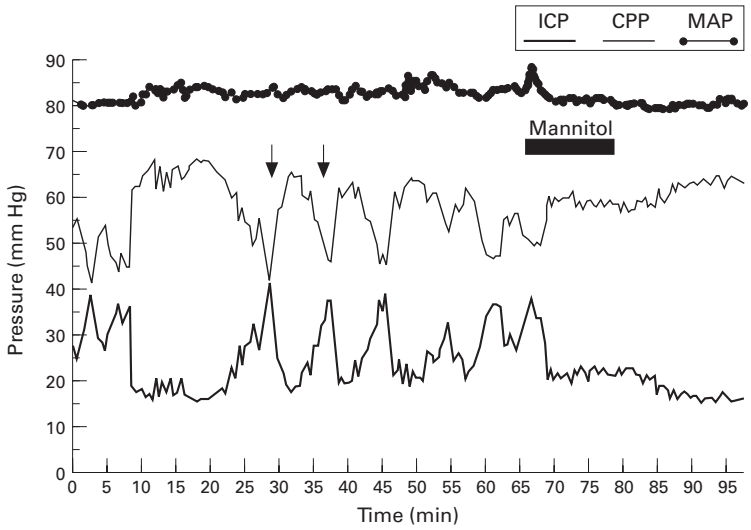

Figure 3 ICP record of a child with intermediate intracranial hypertension (number 19), showing 'tented' waves associated with sluggish dilated pupils (arrows), which disappeared with the infusion of mannitol (black rectangle).

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 ($p = 0.024$, 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,[5 9] (ii) there was good clinical evidence for hernia-

tion in children with cerebral malaria[10] 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 transtentorial 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[10] 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.[20] Finally, frank herniation has been observed at necropsy in a Nigerian child with cerebral malaria[21] and has been detected by magnetic resonance imaging in Thai adults.[14] 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 less than 40 mm Hg is associated with a poor outcome.[5 8 22] 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.[23] 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,[10] since computed tomograms do not show any evidence of acute hydrocephalus or vasogenic oedema.[23] 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.[14] 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[15] 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 generalised or prolonged partial seizures raised the ICP, probably by increasing CBF,[24] but also possibly by producing oedema. Anaemia increases the CBF by decreasing the viscosity and oxygen content of the blood.[25] Tumour necrosis factor, which is raised in children with cerebral malaria,[26 27] 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,[28] may be associated with an increase in CBF and luxury perfusion.[29] 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 edema 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 dilatation, 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,[30] was present in two children when the baseline ICP was less than 20 mm Hg. As in other studies,[5 9] 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 9 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.[15] One osmotic agent, 30% urea in 10% invert sugar, appeared to improve the outcome in Liberian children.[35] Mannitol (1 g/kg eight hourly) was reported to improve the level of consciousness[36] and outcome[37] 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 all 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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Genetic immunisation

The Brown-Norway rat is prone to atopy; after intraperitoneal challenge with allergen it produces lots if 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