Brain swelling and ischaemia in Kenyans with cerebral malaria

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Abstract

Computed tomography was performed on 14 unconscious Kenyan children recovering from cerebral malaria (seven of whom had another scan 12–120 days later) to elucidate the cause of intracranial hypertension and neurological sequelae. Brain swelling, defined as a loss of cerebrospinal fluid spaces, was documented in six children, while a further two had conspicuously small ventricles only. There was severe intracranial hypertension in the two children with definite brain swelling in whom intracranial pressure was monitored. There was no evidence of acute hydrocephalus or vasogenic oedema. Four children with brain swelling also had widespread low density areas suggestive of ischaemic damage. The patterns of damage were not uniform but were consistent with a critical reduction in cerebral perfusion pressure (which was documented in the two in whom this was monitored), hypoglycaemia, or status epilepticus. All four had serious neurological sequelae. These data suggest that brain injury in cerebral malaria may be due in part to secondary systemic and intracranial factors as well as to the direct effect of intravascular sequestration.

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Cerebral malaria is the most important paediatric encephalopathy in Africa, accounting for a large proportion of the estimated 0·5–2 million childhood deaths each year from falciparum malaria in this region.[1] The mortality of children admitted to African hospitals with malaria is 10–40%[2] and a further 9–11% are discharged from hospital with neurological sequelae including motor disorders (hemiparesis and quadriparesis), blindness, epilepsy, and aphasia.[3 4] The pathological basis of these handicaps is not clear.[4] Widespread blockage of small vessels by parasitised erythrocytes has been proposed as a mechanism for ischaemia,[5] but hypoglycaemia, seizures, and anaemia, which are all clinical features of cerebral malaria, might also contribute to brain damage.[6] Occlusion of basal cerebral arteries has been shown in some children who developed hemiparesis.[7] In other encephalopathies, intracranial hypertension is associated with poor neurological outcome, either by precipitating transtentorial herniation or by reducing cerebral perfusion pressure (CPP=mean arterial pressure (MAP)−intracranial pressure (ICP)) below the threshold for ischaemia.[8] Increased ICP has been documented in African children with cerebral malaria[9 10]; possible mechanisms include an increase in blood volume, cerebral oedema, and acute hydrocephalus. Cerebral oedema has been described at necropsy in children[11] and detected by computed tomography in a few adults with cerebral malaria.[12 13] Tomographic findings in adults may not reflect the situation in African children, however, as intracranial hypertension is not thought to play an important part in the pathophysiology of cerebral malaria in adults.[6] The role of cerebral oedema in the pathogenesis of coma and neurological sequelae remains controversial. Fourteen unconscious Kenyan children with cerebral malaria were investigated using computed tomography to investigate the cause of increased ICP and neurological sequelae.

Patients and methods

Fourteen children who fulfilled the World Health Organisation's criteria for cerebral malaria[2] were studied. Parasite counts were performed on admission and blood glucose was measured at least every six hours and at any clinical deterioration using Dextrostix (Bayer Diagnostics), confirmed with an Analox GM6 microstat analyser (London). The children were treated with parenteral antimalarial drugs, either quinine dihydrochloride (20 mg/kg as a loading dose followed by 10 mg/kg every eight hours) or artemether (3·2 mg/kg intramuscularly and 1·6 mg/kg daily) until they could drink, when they were given a single dose of sulphadoxine/pyrimethamine (Fansidar). Antimicrobial drugs were given from the time of admission until a lumbar puncture was performed to exclude meningitis. Initial hypoglycaemia and dehydration were corrected and thereafter the children were given 0·18% normal saline and 4% dextrose at a rate of 3 ml/kg/hour while unconscious. The level of consciousness was assessed at least every six hours by one of the clinical investigators using the Adelaide coma scale.[14]

The ICP was monitored with a fibreoptic system (Camino Laboratories, USA)[15] if the children had signs of brain stem compromise (decorticate or decerebrate posturing, impaired oculocephalic reflexes, or dilated and sluggish pupils) or if they had no response to painful stimulation other than non-specific extension. The ICP and MAP were recorded every 15 minutes during the monitoring period. Mannitol (0·25 g/kg or 0·5 g/kg

Table 1 Grading of diffuse brain swelling on computed tomography

N	Normal scan
1	Narrowing of sulci and fissures. Small ventricles compared with early recovery scans
2	Loss of sulci and fissures. Small ventricles and narrow basal cisterns compared with early recovery scans
3	Complete loss of sulci, fissures, and supratentorial basal cisterns

intravenously over 20 minutes) was administered if the ICP was greater than 20 mm Hg for 20 minutes or increased above 40 mm Hg. Severe intracranial hypertension was defined as a maximum ICP >60 mm Hg and a minimum CPP <40 mm Hg, intermediate intracranial hypertension as maximum ICP 20–60 mm Hg and minimum CPP <50 mm Hg, and mild intracranial hypertension as maximum ICP 10–20 mm Hg. The children were scanned while they were still unconscious (not yet able to localise pain) but neurologically stable. Scans were performed at least 36 hours after admission as the children had to be transferred to other hospitals for computed tomography. Most children were scanned with a Siemens Somatogram DR, but three scans were performed with a Shimadzu SCT-3000TE (both scans of patient 11 and the follow up scan of patient 14). Contrast iopamidol (300 mg/kg) was given in four patients, three during the scan in the acute phase of illness (acute scan) and one on a follow up scan. The scans were examined by an experienced neuroradiologist (BK). Brain swelling was assessed by examining the size of the following cerebrospinal fluid spaces: (a) the cerebral sulci; (b) the perimesencephalic and chiasmatic cisterns; and (c) the ventricular system. Table 1 shows the grading scale used.[16] The Evans ratio (width of the frontal horns divided by the internal skull diameter) was used to compare the ventricular size on the scans obtained during the acute phase with those obtained on recovery.[16] The Evans ratio was not calculated in children who did not have follow up scans as small ventricles are seen in scans which are interpretated as normal.

Comparisons of proportions was performed using Fisher's exact test.

Results

Table 2 presents the clinical features. The admission parasitaemia ranged from 1200 to 1 108 800 parasites/mm^3. On admission the summated Adelaide coma score varied from 6 to 9. There was a deterioration in coma score in 12 children after admission. Two children showed signs of brain stem compromise on admission and a further six children deteriorated with abnormal brain stem signs (compatible with transtentorial herniation) 6–60 hours later. All except one had seizures either on presentation or during admission.

The children were scanned three to nine (median five) days after the onset of the illness. Six children had clear evidence of diffuse brain swelling while still unconscious, as defined by a loss of sulci (n=6), loss of spaces around the cisterns (n=2), and resolution of the swelling without atrophy on the follow up scans (n=2) (fig 1). In addition, of the eight children whose scans were reported as normal, two had small ventricles. The Evans ratio increased in the three children (patients 2, 9, and 10) in whom two measurements were made from 0·27, 0·25, and 0·26 on the initial scans to 0·30, 0·28, and 0·27 respectively on the follow up scans. Tissue density was not increased in any of the children with diffuse brain swelling. None of the children had features of vasogenic oedema or midline shift on computed tomography.

Four children (all with diffuse brain swelling) had low tissue density and a loss of grey/white matter differentiation affecting the cerebral hemispheres (fig 2), compatible with a diffuse ischaemic or hypoglycaemic insult. All were unconscious for more than 120 hours. In two children there was also low tissue density in the basal ganglia. The pattern of brain

Table 2 Clinical features of 14 children with cerebral malaria

Patient No	Age (years)	Sex	AMS on admission*	Seizures†	Status‡	Deterioration in coma score (hours after admission)	Duration of coma (hours)	ICP pattern§	Hypoglycaemic episodes¶	Outcome
1	2	M	3	GT and R UC	1	None	38	NP	NA+1	Normal
2	7	M	3	GTC	4	22	87	MIH	0	Mild left dystonic hemiparesis and learning difficulties
3	2·5	F	3	R and L UC	1	None	42	NP	A	Normal
4	1·5	F	3	R and L UC	1	4	48	MIH	0	Normal
5	3	M	3	LUC	0	10	78	NP	A+1	Normal
6	3	F	3	GTC	0	18	120	MIH	A	Transient mild right hemiparesis
7	3·8	F	3	GT	1	27	108	NP	0	Normal
8	3	M	3	GTC and UC	0	36 and 48	106	NP	A+1	Normal
9	4·5	M	4	R UC	0	12	42	MIH	0	Normal
10	4	M	3	GTC and UC	0	12 and 39	114	IIH	A	Normal
11	2·5	F	3	GTC and L UC	0	20	>192	SIH		Asymmetrical dystonic/spastic motor disorder with recovery of vision and speech over four months
12	4·5	M	1	GTC and UC	2	6	>192	NP	0	Blind, no language, normal gait
13	2	M	3	GTC and L UC	0	6	>192	SIH	0	Blind, no language, spastic quadriparesis, and epilepsy
14	2	F	2	L UC	1	12	>192	NP	A	Vegetative state, with mixed pyramidal/extrapyramidal motor disorder

*AMS=Adelaide motor score: 4, localising pain; 3, flexing to pain; 2, extending to pain; and 1, no response to pain.
†Seizures: G=generalised; U=unilateral; T=tonic; C=clonic; L=left; R=right.
‡Status: time (hours) with one seizure lasting >30 minutes or more than three consecutive seizures.
§Intracranial pressure (ICP) monitoring: mild intracranial hypertension=maximum ICP 10–20 mm Hg; intermediate intracranial hypertension=maximum ICP 20–60 mm Hg and minimum cerebral perfusion pressure (CPP) <50 mm Hg; severe intracranial hypertension=maximum ICP >60 mm Hg and minimum CPP <40 mm Hg. NP=not performed; MIH=mild intracranial hypertension; IIH=intermediate intracranial hypertension; SIH=severe intracranial hypertension.
¶Hypoglycaemia <2·2 mmol/l. A=admission; NA=not on admission.

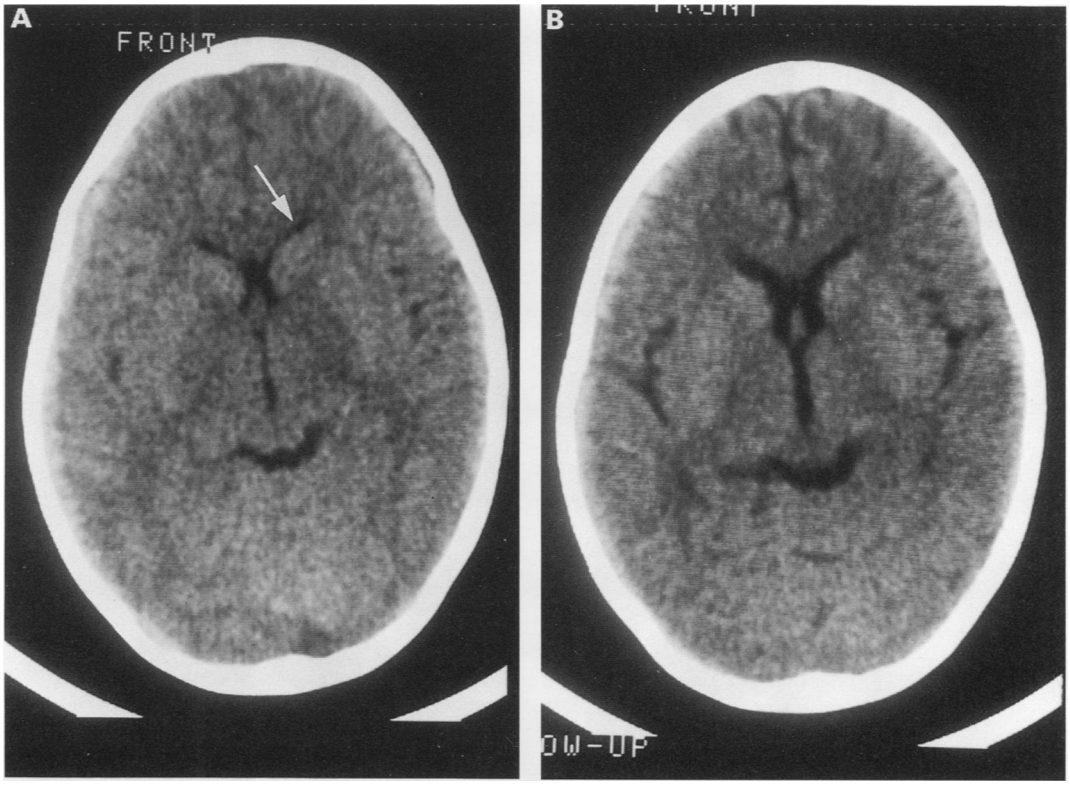

Figure 1 Patient 10. (A) Acute scan: diffuse brain swelling with loss of sulci and compression of ventricles (arrow). (B) Convalescent scan: resolution of brain swelling, with increase in the sulci and ventricles but without atrophy.

damage was different in each patient. One child (patient 11) had a typical superficial watershed distribution on the initial scan with low density in the basal ganglia, and subsequently developed an intracerebral haemorrhagic lesion in the watershed area between the left middle and posterior cerebral arteries, which enhanced with intravenous contrast (fig 3). Another child (patient 12) had a maximum watershed distribution with sparing of small areas in the anterior cerebral artery and posterior cerebral artery territories only. The third child (patient 13) had diffuse low density tissue in the cerebral hemispheres, but the basal ganglia and posterior fossa were spared; he went on to develop cerebral atrophy and evidence of infarction in the right frontal and parietal regions (fig 2). The other child (patient 14) had scattered irregular areas of hypodensity throughout the cerebral hemispheres and basal ganglia compatible with microvascular obstruction (fig 4). None of the children had any evidence of thalamic or posterior fossa abnormality. Generalised hypodensity on the acute scans reliably predicted prolonged coma, followed by significant neurological sequelae associated with cerebral atrophy on the convalescent scans.

There was no association between the finding of low density on computed tomography and hypoglycaemia (blood glucose <2·2 mmol/l) either on admission or during the stay

Table 3 Computed tomography findings in 14 children with cerebral malaria

	Acute scan			*Convalescent scan*		
Patient No	*Time since onset of coma (days)*	*Time since admission (hours)*	*Appearances on computed tomography*	*Grade* of diffuse brain swelling*	*Time since initial scan (days)*	*Appearances on computed tomography*
1	4	48	Normal	N	NP†	–
2	4	84	Normal	N	120	Mild cerebral atrophy
3	1·5	48	Normal	N	NP	–
4	4	48	Normal	N	NP	–
5	6	70	Normal	N	NP	–
6	6	44	Normal	N	NP	–
7	3	36	Normal with small ventricles	N	NP	–
8	4·2	71	Normal with small ventricles	N	NP	–
9	3·4	40	Swollen brain	1	12	Normal
10	4	72	Swollen brain	1	24	Normal
11	5	120	Generalised hypodensity of hemispheres and basal ganglia but sparing posterior fossa. Watershed distribution	3	11	Generalised infarction of hemispheres and basal ganglia with enhancement of watershed area between left posterior and middle cerebral arteries
12	4	72	Ischaemia of hemispheres not affecting basal ganglia or posterior fossa. Maximum watershed distribution	1	49	Cerebral atrophy with infarction of posterior temporal and parietal regions
13	6	148	Ischaemia of hemispheres not affecting basal ganglia or posterior fossa. Not watershed distribution	1	70	Cerebral atrophy with infarction of right anterior and posterior regions (with occipital sparing) and left parietal regions
14	5	76	Ischaemia of hemispheres and basal ganglia. Scattered hypodense areas. Not watershed distribution	2	31	Cerebral atrophy without any focal infarcts

*Criteria for grading in table 1.
†NP=Follow up computed tomography not performed.

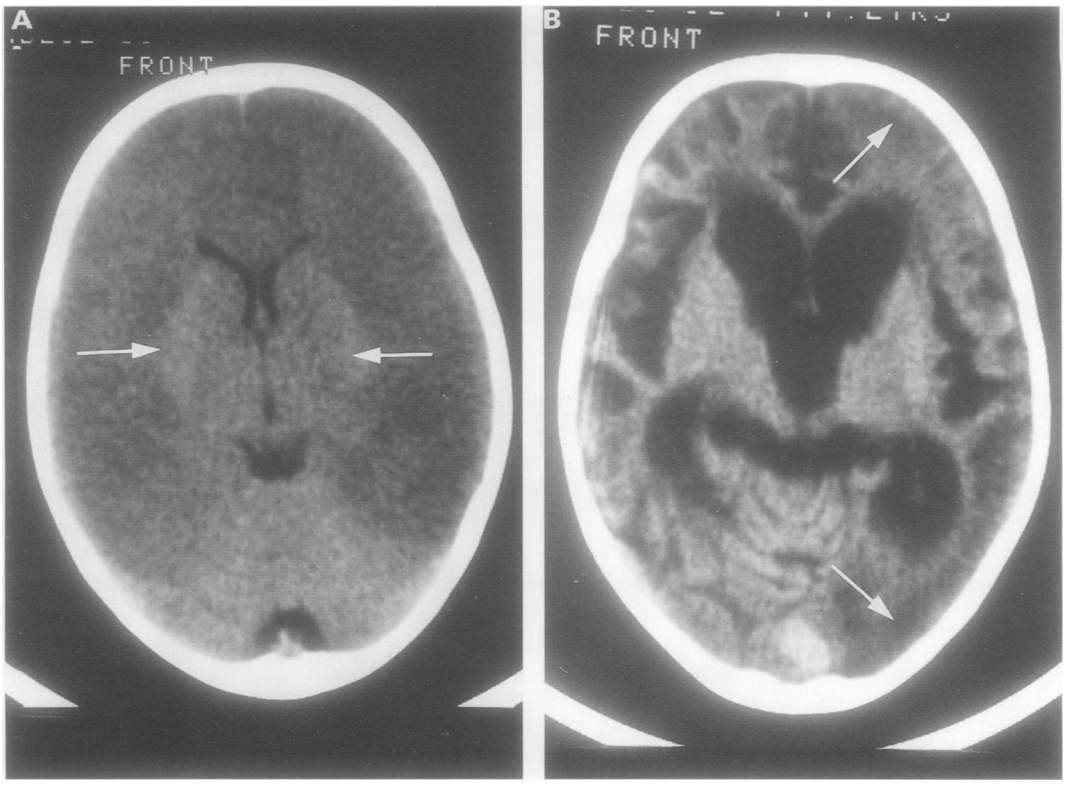

Figure 2 Patient 13. (A) Acute scan: brain swelling with diffuse hypodensity sparing the basal ganglia (arrows). (B) Convalescent scan: cerebral atrophy with infarction (arrows) of right frontal and parietal regions.

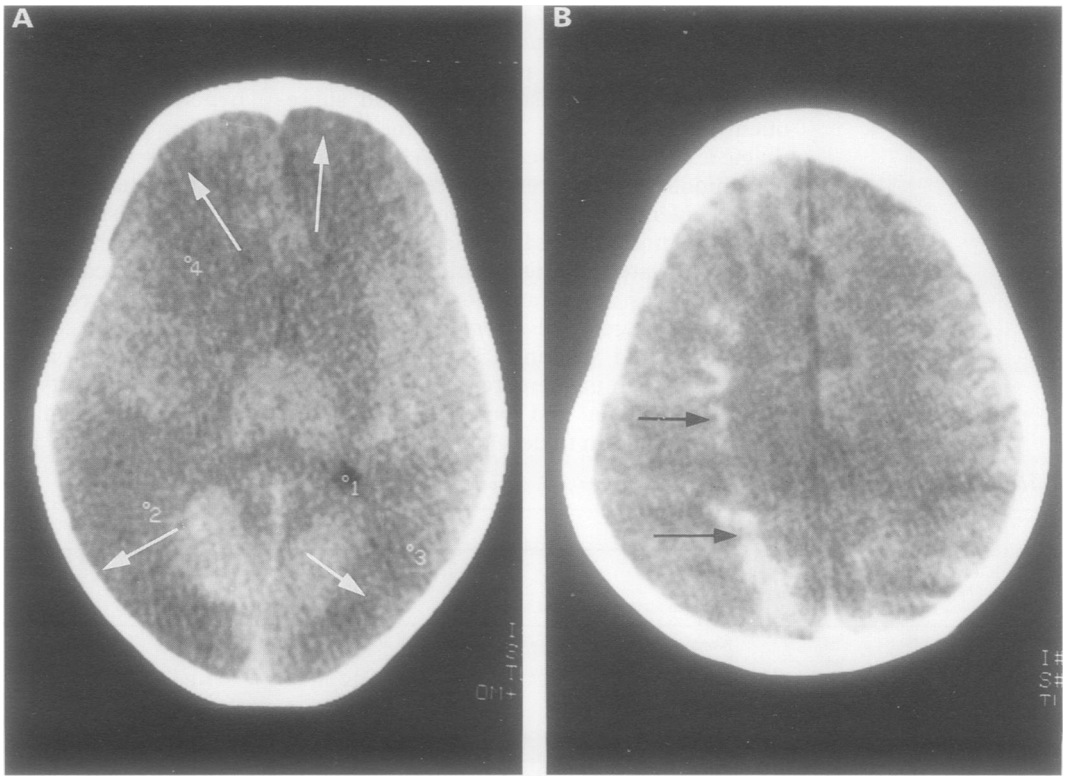

Figure 3 Patient 11. (A) Acute scan: diffuse brain swelling with extensive hypodensity of the superficial watershed areas (arrows) and the basal ganglia. (B) Convalescent scan: contrast scan showing enhancement of the border zone (arrows) between the left middle and posterior cerebral artery areas.

in hospital (Fisher's exact test one tail p=0·58) or status epilepticus (three or more seizures each hour, or a seizure lasting more than 30 minutes) (Fisher's exact test one tail p=0·59). There was no relation between the parasitaemia on admission and the presence of brain swelling or hypodensity on computed tomography.

The ICP was monitored in seven children (three others fulfilled the criteria but were not monitored, either for technical reasons (two children) or because the platelet count was $<40\times10^9$/l (one child)). Four had mild intracranial hypertension of whom one had diffuse brain swelling without evidence of brain damage and three had normal scans, one had intermediate intracranial hypertension and diffuse brain swelling without brain damage,

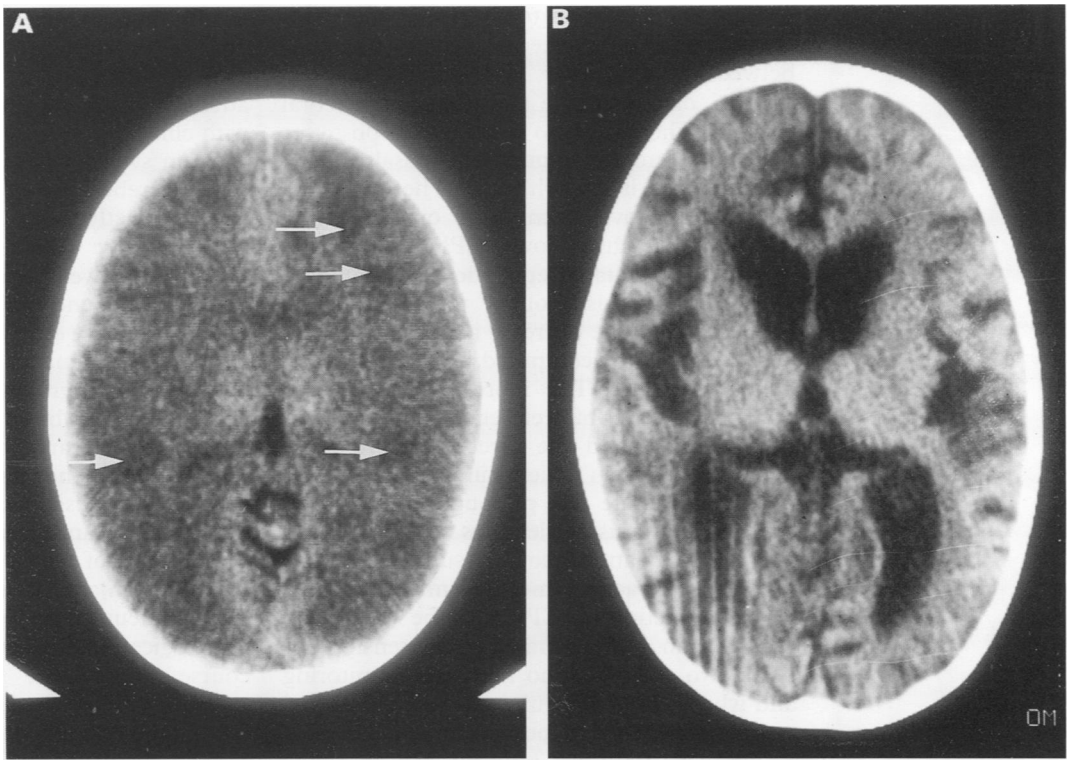

Figure 4 Patient 14. (A) Acute scan: diffuse brain swelling with scattered areas of hypodensity (arrows) throughout including the basal ganglia. (B) Convalescent scan: cerebral atrophy.

and two had severe intracranial hypertension with minimum CPP <40 mm Hg and had diffuse brain swelling with widespread hypodensity. Detailed analysis of the ICP data is in preparation.

Discussion

This is the first report describing computed tomography findings in African children with cerebral malaria. Computed tomography performed during the recovery phase in 14 children showed a wide range of appearances, some of which have not been documented previously in adults. Eight scans were normal, though two of these had ventricles which were noticeably small, but within the normal range. Six children had diffuse brain swelling; only two of these had no evidence of brain damage. Their follow up scans showed complete resolution of the swelling and they recovered without sequelae. In the other four children diffuse brain swelling was associated with widespread areas of low density on the initial scan, and all these children had severe cerebral atrophy and infarction on their follow up scans associated with significant neurological sequelae.

Diffuse brain swelling is characterised in computed tomography by small ventricles, the absence of sulci, and compression of the perimesencephalic and chiasmatic cisterns with resolution on follow up scan.[17 18] In head injury, diffuse brain swelling occurs more commonly in children than adults[19] and has been associated with a greater tomographic density in the white matter, reflecting an increase in blood volume.[17] The swelling may resolve quickly,[17] and thus we cannot exclude the possibility that we did not detect this in some of the normal scans, as these were performed while the child was recovering consciousness. The degree of brain swelling correlated with ICP in a study of children with non-traumatic coma; however, the appearances on computed tomography could not be used to predict the ICP as some children with normal scans developed increased ICP and children with focal abnormalities in the basal ganglia or cerebral hemispheres had a loss of cerebrospinal fluid space without a generalised increase in ICP.[16] In the children with cerebral malaria the most severe swelling occurred in those with the highest ICP, whether or not there were also low density areas. In the four children with the most severe swelling the tomographic densities were decreased, probably from an accumulation of intracellular fluid secondary to impaired cellular metabolism (cytotoxic oedema) and interstitial fluid after the breakdown of the blood-brain barrier (vasogenic oedema).[20] Acute hydrocephalus was not seen in any of the children and thus is unlikely to be the cause of increased ICP in children with cerebral malaria.

In the two children with diffuse brain swelling without low density areas, the tomographic densities in the white matter were normal and there was no enhancement with the administration of contrast medium. Thus there is no evidence for an increase in blood volume or for vasogenic oedema, but these possibilities cannot be excluded as computed tomography may not detect mild increases in cerebral blood volume or oedema. Furthermore, if these disorders coexist, the changes in tomographic density will tend to cancel the two out.

In this series all the children with severe neurological sequelae had evidence of brain

damage on computed tomography which was either diffuse or affected the boundary zones between the anterior and middle cerebral arteries, or the middle and posterior cerebral arteries. There was no evidence of posterior fossa abnormality, though the basal ganglia were affected in two children. These patterns of damage have been seen on computed tomography after low CPP,[21] hypoglycaemia,[22] and status epilepticus.[23] Boundary zone ischaemia is thought to arise from a sudden precipitate decrease in CPP,[24] but has also been seen by computed tomography after hypoglycaemia.[22] The more diffuse changes affecting in order of preference the cortex, the basal ganglia, and the cerebellum are more likely to be seen in patients in whom there has been a moderate but prolonged decrease in CPP[24] or status epilepticus.[25] In cerebral malaria such patterns could result from several possibly interacting mechanisms. Firstly, a global reduction in CPP may be caused by hypotension or intracranial hypertension, or both; two children who had ICP monitoring and who developed neurological sequelae had severe intracranial hypertension and in both children the CPP was reduced into the range associated with poor outcome in other encephalopathies.[8] Because of the timing of ICP monitoring and computed tomography, however, it is not clear whether intracranial hypertension has a primary role or is itself a secondary response to cellular damage caused by other mechanisms. Status epilepticus and hypoglycaemia are common features of cerebral malaria and although the mechanisms of damage may be different from low CPP,[25 26] both may produce additive neuropathological changes when the CPP is reduced. It is also possible that there is a synergistic interaction between decreased CPP and the sequestration of parasite infected cells. Sequestration may lead to reduced peripheral perfusion and as infected cell cytoadherence is enhanced by low shear stress,[27] a decrease in CPP from any cause may promote sequestration in areas of low flow. A further potential mechanism for brain damage in cerebral malaria would be transtentorial herniation secondary to intracranial hypertension. Although children who die of cerebral malaria often show progressive neurological deterioration consistent with herniation,[9] the distribution of damage observed in this study of survivors is different, without the expected prominent involvement of structures in the territory of the posterior cerebral artery. However, this possibility could not be excluded in those with very diffuse hypodensity on computed tomography. It is likely that in cerebral malaria herniation is a cause of death rather than of sequelae.

The features seen on computed tomography in these children contrast with those in adults with cerebral malaria and provide further evidence of the differences in the pathophysiology between these two groups. In non-immune adults brain swelling is associated with cerebral oedema and in a study of 10 patients cerebral oedema was only detected during the agonal phases in two adults.[12] Cerebral oedema has since been reported in an adult who survived.[13] Focal areas of altered tomographic density have been seen in adults,[12 13] but this feature was not associated with clinical signs or neurological sequelae.

Brain swelling is a feature of children with severe cerebral malaria and it is likely to contribute directly to the intracranial hypertension seen in these children. Although the most severe brain swelling was associated with cytotoxic oedema and brain damage, two children with definite swelling recovered without any neurological sequelae. These features seen on computed tomography suggest that secondary events such as brain swelling, hypotension, hypoglycaemia, and status epilepticus may be important in the pathogenesis of cerebral malaria and its sequelae. Further understanding of brain damage in children with cerebral malaria and of the importance of intracranial hypertension requires clarification from detailed neuropathological studies and neuroradiological studies undertaken earlier in the course of the illness.

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Evening primrose oil

It would be right and proper if evening primrose oil were 'a good thing' simply because the name has such implications of beauty. As you know, there has been considerable debate and conflicting data on its use in eczema. Recently published data from Leicester (J Berth-Jones and R A C Graham-Brown, *Lancet* 1993; **341:** 1557–60) add to the 'con' side of the argument.

It is postulated that the effect of evening primrose oil is dependent on its content of n6 series essential fatty acids (EFAs) which might effect the metabolism of the mediators of inflammation such as prostaglandins and leukotrienes. Fish oil, which provides n3 series EFAs, has also been suggested as a treatment for eczema. The Leicester workers performed a double blind trial in which patients received one of three possibilities: evening primrose oil alone, evening primrose oil with fish oil, or placebo. There were 41 patients in each group and half were children of 12 years and under.

The treatment was given for 16 weeks and the results assessed using clinical severity scores, patient diary scores, and use of topical steroid. No improvement was demonstrated with either of the active treatments. The patients' diary scores tended to be better on placebo but there were no significant differences between the three groups at 16 weeks. There was no demonstrable difference in response between children and adults.

These authors point to methodological problems with previous studies which have shown a beneficial effect of evening primrose oil, though they do not claim to be able to explain away all such results. No doubt the debate will continue.

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