INTRACRANIAL HYPERTENSION IN KENYAN CHILDREN WITH CEREBRAL MALARIA

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For the women in my life

ABSTRACT

Cerebral malaria is a common encephalopathy in African children, but the cause of death and neurological sequelae are unknown. This dissertation examines the hypothesis that raised intracranial pressure (ICP) is a determinant of poor outcome in Kenyan children with cerebral malaria.

The opening cerebrospinal fluid pressure was raised in all 26 children in whom it was measured on admission and 92% of 35 children in whom it was measured after admission. Brain stem signs, particularly an abnormal respiratory pattern, absent pupillary responses and a lack of spontaneous eye movement were associated with a death. In 33 children who died with cerebral malaria, at least 18-42% had clinical features of transtentorial herniation, according to the criteria used.

Intracranial pressure monitoring was performed in 18 children with severe CM, of whom 14 had computerised tomography (CT) and in 10 the basal cranial arteries were monitored with transcranial Doppler (TCD) sonography. Three children with severe intracranial hypertension (maximum ICP > 60 mmHg and minimum cerebral perfusion pressure (CPP) < 40 mmHg) had a poor outcome despite aggressive therapy with mannitol. One child with a maximum ICP of 151 mmHg died with the signs of uncal and medullary stages of herniation. In the other 2 children, middle cerebral artery velocity and vascular resistance monitored with TCD sonography changed with ICP and CPP. Both of these children had diffuse brain swelling associated with generalised hypodensity on their acute CT scans. These

children survived with cerebral atrophy on their convalescent scans and severe neurological deficits.

In the 8 children with intermediate intracranial hypertension (maximum ICP 20-60 mmHg and CPP < 50 mmHg) mannitol was effective in controlling the intracranial hypertension. TCD was not reliable in detecting changes in ICP or CPP. Two of these children had acute brain swelling, but the tomographic density was normal and the swelling had resolved when the repeat scans were performed 12-24 days later. All the children with intermediate intracranial hypertension survived without major neurological sequelae. In the remaining 7 children who had ICP monitoring, the maximum ICP was <20 mmHg and mannitol was not administered. None of the CT scans showed brain swelling and the children survived without severe sequelae.

In a further 9 children with severe malaria (6 with CM) the agonal stages were monitored with TCD. Three children with CM had sonographic features of progressive intracranial hypertension associated with signs of herniation, whilst the other children (including 3 with CM) did not have these sonographic features, although one had evidence of brainstem compromise before dying.

Thus raised ICP is a feature of CM in Kenyan children. Severe intracranial hypertension is associated with a poor outcome and could be responsible for at least a third of the children dying from CM. Mannitol reduces the ICP, but does not prevent nor control severe intracranial hypertension.

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DECLARATION

I, Charles Richard James Carruthers Newton, hereby declare that the work on which this thesis is based, is my original work (except where acknowledgements indicate otherwise) and neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

In particular, I designed the studies and wrote the protocols presented in this thesis. I performed most of the lumbar puncture measurements. I designed the forms on which the clinical data were recorded (although these were subsequently modified with the help of my colleagues in Kilifi) and performed many of the clinical examinations on which the findings are based I conducted the interobserver study. I was primarily responsible for the institution of the intracranial pressure monitoring and inserted the monitor in thirteen children (Dr J Crawley insert the monitor in the other five children). I performed almost all the transcranial Doppler examinations reported here and I interpretated the CT scans, before conferring with my colleagues.

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Signed

Dr CRJC Newton

August 8th 1994

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ABBREVIATIONS

ABM	Acute Bacterial Meningitis
ACA	Anterior Cerebral Artery
BA	Basilar Artery
BBB	Blood Brain Barrier
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CM	Cerebral Malaria
CNS	Central Nervous System
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fliud
CSFP	Cerebrospinal Fliud Pressure
CT	Computerised Tomography
EEG	Electroencephalogram
ICA	Internal Carotid Artery
ICP	Intracranial Pressure
IgG	Immunoglobin G
IgM	Immunoglobin M
IH	Intracranial Hypertension
IIH	Intermediate Intracranial Hypertension
IL-1	Interleukin-1 alpha
IL-6	Interleukin-6
IM	Intramuscular
IV	Intravenously
JVP	Jugular Venous Pressure
KEMRI	Kenya Medical Research Institute

LP	Lumbar Puncture
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MIH	Mild Intracranial Hypertension
MRI	Magnetic Resonance Imaging
NCM	Non-Cerebral Malaria
NO	Nitric Oxide
NPRBC	Non Parasitised Red Blood Cells
NR	Not recorded
OFR	Oxygen Free Radicals
PCA	Posterior Cerebral Artery
PI	Pulsatility Index
PRBC	Parasitised Red Blood Cells
RBC	Red Blood Cells
RICP	Raised Intracranial Pressure
SIH	Severe Intracranial Hypertension
TNF	Tumor Necrosis Factor
UR	Unrecordable
WHO	World Health Organisation

1 INTRODUCTION

Cerebral malaria (CM) is a life threatening complication of *Plasmodium falciparum* infection and is one of the major causes of death in African children. Most studies of the pathophysiology of CM have been conducted in non-immune adults and there is growing evidence that these findings are not directly applicable to African children living in endemic areas [261]. In particular the causes of death and neurological sequelae (which are more common in African children), have not been determined [226].

This thesis examines the role of raised intracranial pressure (RICP) as a cause of poor outcome in children with CM. This chapter provides background information on falciparum malaria and describes the clinical manifestations of CM before setting up the hypothesis that RICP is an important determinant of death and neurological sequelae in children with CM. Thereafter I review the pertinent literature on RICP, firstly I establish that RICP is an important determinant of outcome in other paediatric encephalopathies and then discuss the pathophysiology of RICP. Finally I review the pathogenesis of CM, including the pathophysiology, before outlining the central questions of this thesis.

I. FALCIPARUM MALARIA

Epidemiology

P. falciparum is the most lethal of the four parasites that cause malaria in humans, and accounts for practically all the mortality. Over 80% of the falciparum malaria in the world occurs in subsaharan Africa [43,202], where children bear the brunt of the disease.

The lack of data makes it difficult to establish the number of children affected and dying from CM in Africa. However the magnitude of the problem can be gauged from the following figures. The World Health Organisation (WHO) estimated that there were 269.8 million children in Africa during the mid 1980s, of whom 250 million lived in the malarious areas of West, Central and East Africa [327]. Based upon these figures, the estimates of the total number of children with falciparum malaria in Africa is estimated to be in the range of 35 - 190 million [8,327], with between 0.5 and 1 million children dying from falciparum malaria every year in subsaharan Africa [50,113].

The major life threatening complications of falciparum malaria in African children are CM, acidosis, hypoglycaemia and severe anaemia. It is impossible to calculate the overall incidence of CM, since the proportion of patients with this complication varies considerably throughout the continent. Some idea can be gained from studies in Brazzaville, Congo conducted during 1988 and 1989, where the annual incidence rates of CM were estimated at 240, 61, and 13 per 100 000, with mortality rates of

58, 5 and 1 per 100 000, for the 0-4, 5-9 and 10-14 year age groups respectively [55]. Malaria accounts for 5-59% of the paediatric admissions to hospital in many parts of Africa [43,86,145,337] and the majority of admissions in endemic areas [1,111] with the reported mortality rate of CM varying between 10-57% [65,293,354]. Thus CM contributes significantly to the mortality of children in subsaharan Africa and is arguably the most lethal non-traumatic encephalopathy on this continent.

MALARIA PARASITES

Malaria is caused by protozoal parasites (order Coccidiida, family Plasmodiidae). Although Plasmodiidae infect a large number of vertebrates from reptiles to humans, only 4 species of *Plasmodium* infect humans; *P. falciparum*, *P.ovale*, *P.vivax* are peculiar to man, while *P.malariae* also naturally infects African apes. Several simian species can also infect humans, but rarely cause disease.

Life cycle

Human malaria is initiated by a female Anopheles mosquito injecting saliva containing sporozoites into the blood stream during feeding (fig 1.1). The sporozoites circulate for up to 1 hour in the blood before entering the hepatocytes or being removed by phagocytes. In the liver they undergo pre-erythrocyte schizogony with asexual multiplication, culminating in the rupture of the changed hepatocyte (now called an exo-erythrocytic schizont) and the release of thousands of merozoites into the blood stream. *Plasmodium ovale and P.vivax* can differentiate into hypnozoites which lie dormant within the liver and produce

relapses up to many years later. This does not occur with *P. falciparum* or *P. malariae*.

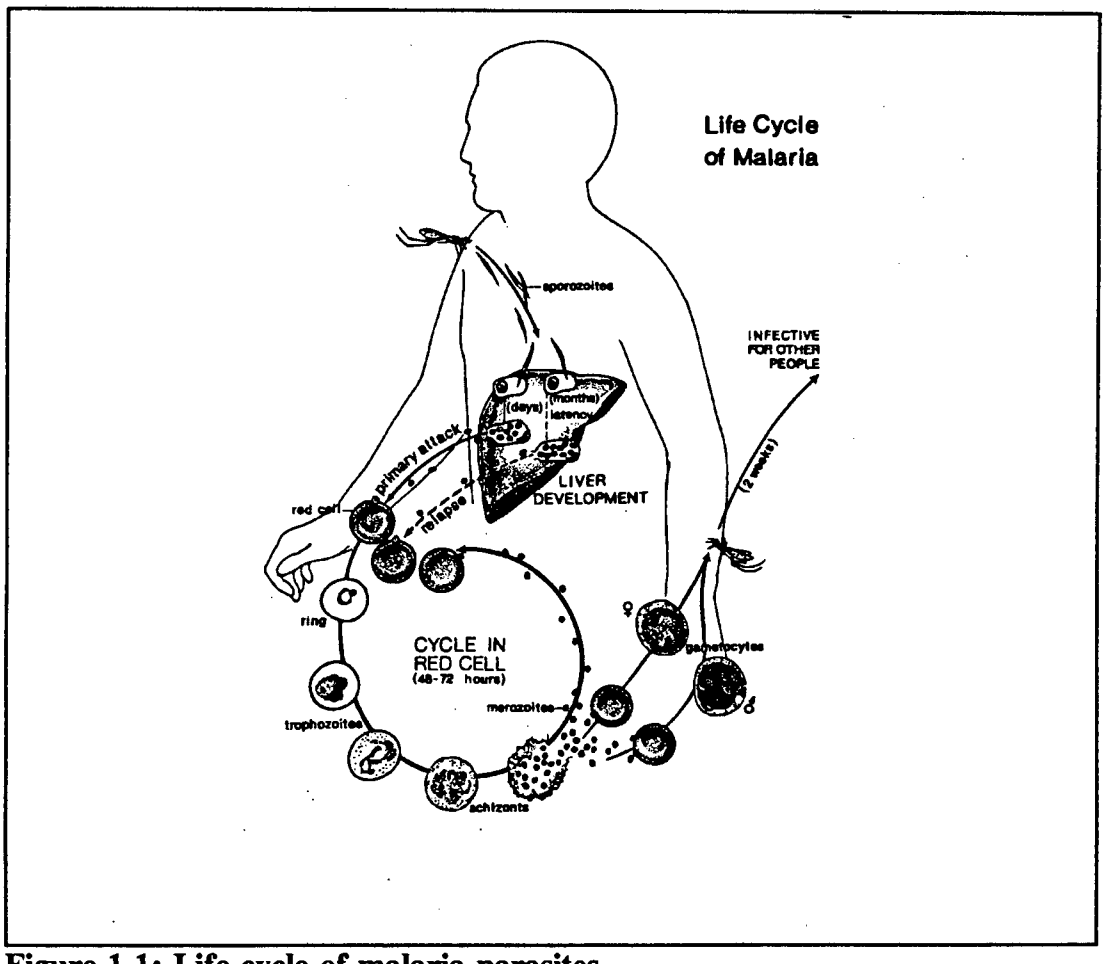


Figure 1.1: Life cycle of malaria parasites

The sub-microscopic merozoites (about 1μm) invade the red blood cells (RBC) where they undergo a second stage of asexual multiplication (erythrocytic schizogony). After the erythrocyte invasion, the merozoites grow in size, undergoing morphological changes. The parasite's biconcave disc structure produces a ring form or trophozoite. During the next 12-24 hours, the trophozoite grows and the parasite produces pigment (haemozoin, which contains haematin) from the

catabolism of the RBC's haemoglobin. Thereafter the nucleus divides, until the parasite reaches maturity, with the formation of a species specific number of merozoites (table 1.1), and then the cell ruptures releasing the merozoites into the blood. This cycle is repeated until increasing parasitaemia is inhibited by immunity, chemotherapy or the death of the host. After several cycles of erythrocytic schizogony, some of the merozoites differentiate into sexual forms, the gametocytes. These forms are ingested by the female Anopheles mosquito. Within the mosquito's stomach, the male gametocyte produces flagella which aids motility in the fertilisation of a single female gametocyte to form a zygote. The zygote penetrates the stomach wall as an ookinete, undergoes repeated asexual multiplication as an oocyst on the outer surface of the stomach wall, before rupturing to release about a thousand spindle shaped sporozoites into the body cavity. The sporozoites make their way through the body cavity to the salivary glands, at which point the mosquito becomes infective.

Parasite virulence

The erythrocytic stages of the parasites are responsible for disease, since the liver stages and gametocytes are asymptomatic. The cause of *P.falciparum*'s virulence in comparison to the other human plasmodia is unknown, but a number of features may contribute. *P.falciparum* is phylogenetically closer to the malaria parasites of birds than to other human parasites and its recent emergence from an avian progenitor may explain its lethal effects in humans [357]. The differences in *P.falciparum's* life cycle may also contribute to its virulence [50] (table 1.1). In comparison with other human parasites it has a shorter pre-erythrocytic stage (5-7

days), pre-patent period (interval between infection and the appearance of parasites in the RBC), incubation period (interval between infection and onset of symptoms). It also produces more merozoites from liver schizonts and after erythrocytic schizogony. In comparison to the other parasites, *P. falciparum* can invade red cells of any age and since more than one merozoite can infect a single RBC, multiple infections are common in falciparum malaria. All of these factors culminate in a parasitaemia (20-500 000 per µl) which is a log order higher than infections with the other parasites (table 1.1) [50].

Table 1.1: Characteristics of the 4 species of human plasmodia

	P.falciparum	*P.vivax*	*P.ovale*	*P.malariae*
Pre-erythrocytic period (days)	5-7	7-8	9	14-16
Prepatent period (days)	9-10	11-13	10-14	15-16
Incubation period (days)	12	15	17	28
Merozoites released by liver schizont	30 000	10 000	15 000	15 000
Erythrocytic cycle (hours)	48	48	50	72
Merozoites released by RBC	16 (8-24)	12-18	8-10	8
Parasitaemia				
Average	20000-500 000	20 000	9 000	6 000
Maximum	2 000 000	50 000	30 000	20 000

P. falciparum is unique amongst the species infecting humans in that late trophozoites and schizonts are removed from the peripheral circulation, as they are hidden (sequestered) in the microcirculation of the vital organs. Thus the late stages

not only evade clearance by the spleen but may also obstruct the blood flow and may interfere with the metabolism of the surrounding parenchymal cells. Sequestration is thought to cause the severe complications of falciparum malaria such as cerebral involvement, which are not found in the other types of human malaria [361].

Parasite metabolism

Parasites increase the permeability of the red cell membranes, allowing essential nutrients to enter the cell from the plasma. The host cell's haemoglobin is the major source of amino acids, although the parasite can take up free amino-acids from the plasma and synthesise other amino-acids [313].

P. falciparum lacks the enzymes for the citric acid cycle and thus cannot utilise oxygen, therefore anaerobic glycolysis is the main pathway for energy production. *P.falciparum* infected cells consume about 26 times more glucose and produce 18 times more lactate than non-parasitised red cells (NPRBC) [141]. The glucose utilisation and lactate production are stage dependent, with the later stages, particularly the schizonts, the most metabolically active [141].

Malarial parasites synthesise pyrimidines *de novo*, but must obtain the purines for nucleic acid from the plasma and host RBC. Fatty acids and cholesterol are obtained from the host cell. Para-amino benzoic acid is essential for growth. Since the parasites are dependant on the *de novo* synthesis of the folate co-factors, ther are suscepitible to dehydofolate synthesase inhibitors [313].

CLINICAL FEATURES OF FALCIPARUM MALARIA

Although *P.falciparum* elicits a strong immunological response involving both the humoral and cell-mediated systems, immunity to this protozoa is only acquired by constant exposure over a number of years [50]. In areas of high transmission, children bear the brunt of the morbidity and nearly all the mortality [43,202]. By the end of the first decade, most inhabitants will have acquired immunity and no longer be at risk of death, provided they maintain constant exposure [210]. Thus adults living in endemic areas may have mild symptoms *eg* headache, arthralgia and fever, but will rarely develop severe malaria. Non-immune adults do develop life threatening complications, although the clinical picture is different from that seen in African children (*vide infra*).

One of the interesting features of clinical studies of malaria in endemic areas, is the lack of a relationship between the peripheral parasitaemia and the number of clinical attacks or deaths from malaria (fig 1.2). In endemic areas mortality occurs almost exclusively in children under the age of ten years. Clinical infections persist into adulthood, although the symptoms become less severe. The density of parasites decreases with age, but older children and young adults still harbour considerable loads of parasites without an apparent ill effect. Furthermore a significant number of children in endemic areas with a peripheral parasitaemia are asymptomatic and the annual peak in the prevalence of parasitaemia does not coincide with peak prevalence of clinical attacks or deaths from malaria [202] (fig 1.2). The poor

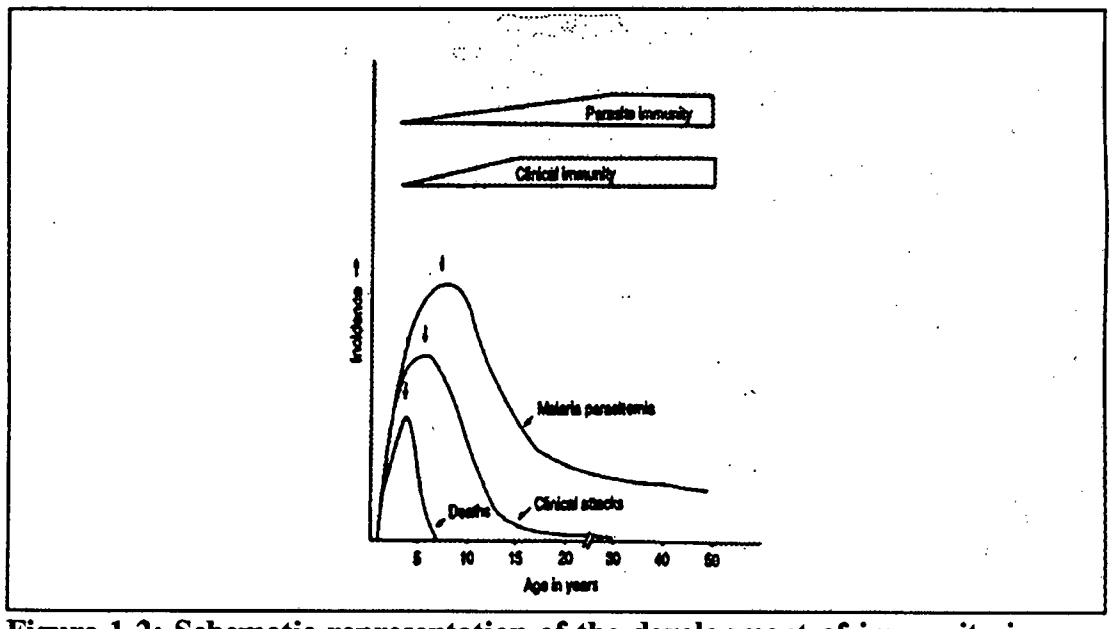


Figure 1.2: Schematic representation of the development of immunity in a hyperendemic area (From B. Greenwood)

relationship between the acquisition of clinical immunity and parasite immunity is not understood.

The low incidence of falciparum malaria in children less than 6 months old in endemic areas has been attributed to the persistence of maternal antibodies in the infant, the lack of substrates for parasite growth such as para-amino benzoic acid in breast milk, factors that prevent growth within the erythrocytes eg foetal haemoglobin [255] and the possibility that mothers may protect the infants from vectors [202]. During the later part of infancy and early childhood, the incidence of severe malaria rapidly rises. This increase is not simply due to the disappearance of the protective factors coupled with the lack of immunity (because of limited previous exposure), for no difference was found in malarial antibody levels between Gambian children with severe malaria and controls [70]. Furthermore the

pattern of complications of falciparum malaria changes with age. Thus children with severe malarial anaemia are considerably younger than those presenting with CM [202] (fig 1.3). This suggests that some host factor(s), as yet unidentified, are responsible for the development of the cerebral complications.

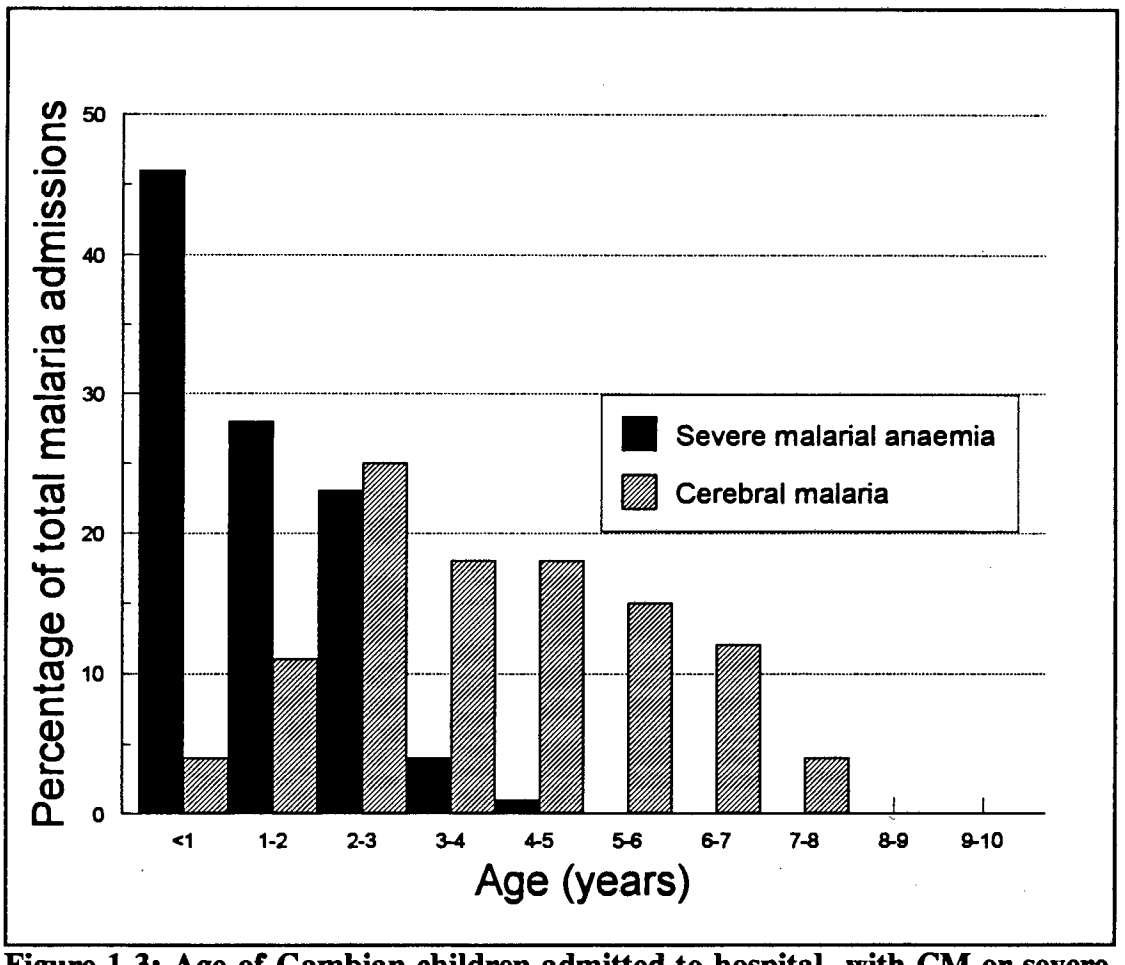


Figure 1.3: Age of Gambian children admitted to hospital, with CM or severe anaemia [202]

CLINICAL FEATURES OF CEREBRAL MALARIA

Definition of cerebral malaria

Cerebral malaria is a clinical term which implies a perturbation of the central nervous system (CNS) associated with a malaria infection. The definition of CM is not consistent throughout the literature, because direct CNS involvement by *P.falciparum* is difficult to define and there are no pathognomonic pathological features that differentiate CM from non-cerebral malaria (*vide infra*). Central nervous system manifestations such as seizures, drowsiness and flaccidity can be induced by the systemic effects of the infection *eg* fever or hyponatraemia [137]. Thus it is unlikely that CNS signs are caused by a single intracranial pathophysiological process, so impairment of consciousness may be associated with cerebral factors such as seizures, abnormal metabolism *eg* hypoglycaemia or may appear without any evident cause. It was not until Warrell and colleagues proposed a strict definition based upon the Glasgow coma scale for use in adults, that most studies of CM became comparable [353]. This definition was slightly modified by the WHO, but is now used by most researchers [354].

WHO definition of cerebral malaria Warrell et al [354]

A patient who:

1. is unable to localise a painful stimulus (such as pressure on the sternum) at least 1 hour after the last seizure.
2. has asexual parasites detectable in the peripheral blood

and in whom

3. other causes of an encephalopathy eg meningitis, encephalitis or hypoglycaemia have been excluded.

Inability to localise pain was chosen as a depth of coma that excludes the systemic effects of infection and is a sign that can be elicited easily. Lesser degrees of CNS dysfunction may also be caused by falciparum involvement of the brain and as such should be treated as severe malaria with parenteral antimalarials. The patient needs to be reassessed at least 1 hour after a seizure, since post-ictal coma is not acceptable for the definition of CM. Warrell *et al* originally stipulated that the period should be 6 hours, but this was shortened to 1 hour since it is thought that children regain consciousness from febrile seizures within 30 minutes and children may recover more quickly from CM than adults (Warrell personal communication).

Asexual parasitaemia is a prerequisite since the liver stages are undetectable and gametocytes do not cause symptoms. However this definition does not include the well documented cases of blood slide negative CM [88,104,349] *ie* patients who have profound CNS disturbance, but in whom asexual parasites are not detectable in the peripheral blood because the late stages are sequestered in the deep tissues. In these cases the diagnosis may be confirmed only when there is a good response to antimalarials or finding sequestered parasites in the brain at post mortem.
The exclusion of other causes is determined by the facilities available. In most African hospitals, this largely entails the exclusion of CNS infections (by obtaining a clear cerebrospinal fluid (CSF)) and hypoglycaemia (by either performing a blood glucose estimation or observing the clinical response to glucose administration). Thus other causes of encephalopathy *eg* encephalitis without a pleocytosis or Reye's syndrome cannot be confidently excluded, although a good response to antimalarial therapy would support the diagnosis of CM.

Coma scores

A summated Glasgow coma score less than eight (table 1.2) has been proposed as part of the definition of CM, instead of the inability to localise pain [178]. This criteria is not applicable to children, since children do not have the same range of summated scores [238] and has not been generally accepted. Molyneux and Taylor developed a score, the Blantyre coma score (BCS) for the assessment of young Malawian children with CM [226]. This scale is based upon the Glasgow coma scale (Table 1.2), but measures different responses and appears to assess the overall degree of compromise due to malaria, rather than the neurological complications (Newton *et al* in preparation). However it is used by many researchers who define CM as a summated score of 2 or less: a total which is mostly derived from a motor and verbal score of 1 each and thus is equivalent to the strict WHO definition. Other researchers include children with scores of 4 or less to define CM; however this is would not exclude systemic effects and is not directly comparable to the strict WHO definition.

The WHO criteria and the BCS have 2 major limitations when applied to children living in endemic areas:

i) a lack of a direct relationship between the peripheral parasitaemia and clinical illness. Since a considerable proportion (up to 100%) of children living in endemic areas are infected with P. falciparum, but are asymptomatic; children admitted with other encephalopathies that also require other causes to be excluded eg Reye's syndrome, may have a concomitant peripheral parasitaemia and thus be diagnosed as CM.

Table 1.2: Blantyre and Glasgow Coma Scales

Response	Blantyre Coma Scale [226]	Glasgow Coma Scale [335]
Verbal	2. Appropriate cry 1. Inappropriate cry or moan 0. No cry	5. Able to give name and age 4. Recognisable and relevant words 3. Incomprehensible but complex vocalisation 2. Cry or grunt 1. No response
Motor	2. Localises pain 1. Withdrawal from pain 0. Non-specific or no response to pain	6. Obeys commands 5. Localises pain 4. Withdrawal from pain 3. Flexes to pain 2. Extends to pain 1. No response
Eye	1. Directed eye movements 0. Not directed	4. Spontaneous eye opening 3. Opens eyes to voice 2. Opens eyes to pain 1. No eye opening

ii) the definition does not account for the fact that very young children may not have acquired the ability to localise pain and thus may not satisfy the formal definition, but might nonetheless be suffering from the same pathological entity. Thus the definition of CM should be restricted to children over 8 months, until more appropriate criteria are found for younger children (Newton *et al* in preparation).

Despite these reservations, the WHO criteria offer a pragmatic definition that can be used for research in children older than 8 months. Coma scores may be useful in categorising the severity of CM, but are inappropriate for the diagnosis of CM.

Clinical presentation of cerebral malaria

The clinical picture of African children presenting with CM in endemic areas is different from non-immune adults and children (table 1.3). African children usually present in coma with a 2-3 day history of fever [68,135,200,226,278], and a temperature often above 39.0°C on admission. Fifty to eighty percent of children have a history of convulsions [68,135,200,226,301] one of which often precipitates coma [88,354,362]. Brain stem signs, including dysconjugate and conjugate eye movements (which may be seizures) and decerebrate posturing occur in about one third of children [98,226,301]. Retinal haemorrhages are present in 6-28% of African children during admission [150,226,239] and less than 2% have papilloedema [150,226]. They are associated with a high mortality in adults [190], but in children they do not appear to have prognostic significance [150]. In both groups they resolve without long term visual defects [27,150].

Laboratory features of cerebral malaria

The parasite count in African children with CM varies considerably, from a barely detectable parasitaemia to over 1 million parasites per microlitre (μl). The median parasitaemia is in the order of 10^5 per μl, considerably higher than non-immune adults (table 1.3). In African children, high parasitaemia is associated with deep coma, hypoglycaemia [226] and a poorer outcome [226]. Furthermore, the presence of late stages and synchronous infections are associated with death in Gambian children [318]. Children are often anaemic [135,200,226], hypoglycaemic [333] and may have a lactic acidosis (*vide infra*).

Table 1.3: Clinical features of cerebral malaria in children and adults

	African Children [37,42,226]	Vietnamese children *	Non-immune adults[228,260 ,353,367]
Immunity	Growing up in an endemic area	Non-immune	Non-immune
Age in years (range)	median 3 (0.5-8)	median 7 (1-14)	mean 23 (6-70)
History of fever (days)	2 (0-7)	6 (1-10)	10 (6-70)
History of convulsions	82%	52%	40%
Brain stem signs	34%	21%	?
Retinal haemorrhages	6%	12%	15%
Parasitaemia (natural log)	5.2	3.9	4.2
Hypoglycaemia (glucose < 2.2 mmol/l)	23%	19%	11%
Severe anaemia (Hb < 50 g/l)	46%	65%	34%
Lactic acidosis	42%	?	?
Other complications:	All very rare		
Urinary tract infection			
Septicaemia		?	24%
Pneumonia		?	9%
Pulmonary oedema		?	7%
Spontaneous bleeding		35%	7%
Renal failure		9%	10%
Duration of coma (median in hours)	18	48	48
Sequelae	9-11%	6%	< 5%
Death	15%	26%	17-20%

* The data on Vietnamese children was kindly supplied by Dr Delia Bethell, Wellcome Trust Research Unit, Ho Chi Minh City, Vietnam.

? Incidence could not be reliablely ascertained from the literature.

The total nucleated cell count in the blood is raised, particularly in those children with a poor prognosis, although most of the nucleated cells are reticulocytes [240]. Unconjugated bilirubinaemia, mainly caused by intravascular haemolysis, is the major cause of the raised total bilirubin [226]. Some liver enzymes are consistently elevated (5' nucleotidase), whilst others eg alanine transaminase are mildly raised in those with jaundice. Most children have normal renal function, although slightly elevated urea and creatinine are associated with mild dehydration. Children with grossly elevated creatinine levels have a worse prognosis [226], but these children rarely die with acute renal failure [42].

The reported CSF findings are determined by the fact that a clear CSF is one of the prerequisites of the diagnosis of CM. CSF lactate is raised (*vide infra*) and protein concentrations are usually normal, but the results of other biochemical tests have not been reported in children.

Clinical progress

With appropriate antimalarial therapy, 50-90% of African children recover consciousness by 18 hrs [226]. Over 50% of children develop convulsions after admission. Some children have recurrent episodes of hypoglycaemia despite the administration of 5% dextrose [226]. The cause of death in most children is not defined [226], although some children clearly die from the common complications (table 1.3).

Most children who survive appear to make a full recovery, but about 10% (up to 21%) [295] develop neurological sequelae, [42]. The most common sequelae in African children are hemiparesis [42,226,250] and cortical blindness [42,173,248], though aphasia [42], epilepsy [37,42] ataxia [42] and other motor disorders also occur. Some sequelae, particularly blindness and hemiparesis resolve [37]; severe quadriparesis usually persists.

CAUSE OF DEATH AND NEUROLOGICAL SEQUELAE

Mechanism of death in cerebral malaria

The cause of death or neurological sequelae in African children with CM is largely unexplained [226,361]. Non-immune adults with CM usually die from a combination of pulmonary oedema, acute renal failure and/or superadded sepsis with metabolic acidosis and circulatory failure (table 1.3) [356, 361]. These complications, except metabolic acidosis are rarely seen in African children [354].

In the 1940s, shock was suggested as the cause of death in children with malaria [280], but this has not been confirmed by other investigators. Some children undoubtedly die from intractable hypoglycaemia, severe anaemia and metabolic acidosis [333,361] or from aspiration during a seizure. However most children die suddenly in the acute phase without adequate explanation [226,361]. Spontaneous respiratory arrest also occurs in adults, but nervous system dysfunction does not appear to contribute directly to death (N White personal communication).

Mechanism of neurological sequelae

Neurological sequelae following CM are much more common in African children than non-immune adults (table 1.3). The development of sequelae is associated with protracted seizures [37,42], prolonged coma [37,42,295] and anaemia in some studies [42], but not in others [37]. In about half of the children with hemiparesis following CM, stenosis or occlusion of the basal cerebral arteries were demonstrated by angiography [66,76,250], but abnormalities were not detected in the other children. Blindness is associated with intact pupillary responses and normal fundi [42]. It may follow seizures [249] and although it can occur in isolation following CM, it is usually associated with evidence of more diffuse damage [173]. The cause of the other sequelae is obscure.

The pattern of neurological sequelae in adults is different from children and the risk is not confined to CM, but is often associated with laboratory evidence of severe disease. In the few adults who develop sequelae the pattern is different with isolated cranial nerve lesions, mononeuritis multiplex, polyneuropathy, extrapyramidal tremor and other cerebellar signs [362]. Some adults have transient psychosis or delirium during recovery, whilst others develop focal epilepsy sometimes associated with transient tomographic opacities in the brain [191].

Intracranial hypertension as a determinant of poor outcome in CM

Raised intracranial pressure (RICP) is thought to be an important determinant of death and neurological sequelae in head injury and non-traumatic encephalopathies, particularly those associated with abnormal brain stem signs [288]. The role of

RICP in CM has been largely discounted by observations in non-immune adults. However the differences in the clinical picture suggest that the observations on the adults cannot be extrapolated to African children. This thesis examines the hypothesis that RICP is an important determinant of death and severe neurological sequelae in African children.

II. INTRACRANIAL PRESSURE

DEFINITION AND MEASUREMENT

Raised intracranial pressure (RICP) can cause a poor outcome by two mechanisms; herniation of brain tissue or reduction of cerebral blood flow (CBF). Herniation occurs if pressure differentials are created within the cranium, causing the brain tissue to move along the paths of least resistance, usually caudally, ultimately compressing the vital centres within the brain stem and thus cause death. RICP also reduces CBF by decreasing the cerebral perfusion pressure (CPP), since:

$$CPP = MAP - ICP \quad \text{equation 1.1}$$

where MAP is the mean arterial pressure and ICP is the intracranial pressure. Prolonged reduction of CBF causes ischaemia of brain tissue, resulting in the development of neurological sequelae or, if extensive, death.

Nomenclature

Intracranial pressure refers to pressure measured within the cranial cavity and should be qualified by the site at which it is measured [229]. For the purposes of this thesis it is defined as the pressure measured by a monitor in the supratentorial region. Lumbar cerebrospinal fluid pressure (CSFP) is measured at lumbar puncture (LP). RICP is defined as any pressure above the upper limit of normal for age (*vide infra*). For the purposes of this thesis intracranial hypertension (IH) is defined as a maximum ICP above 15 mmHg [222]. Although the SI units for pressure are kilo Pascals (KPa), pressures in this thesis will described in millimetres of mercury (mmHg) since this unit is still in clinical use.

Measurement of ICP

ICP was first measured by Quincke with a fluid manometer attached to an LP needle [270]. Since then other techniques have been used, each with its own and advantages and difficulties (Table 1.4).

a) CSF pressure

The most commonly used method of measuring ICP is at LP with a fluid manometer. This method removes CSF from the cranio-spinal axis to measure the pressure, thus altering pressure dynamics within the craniospinal space. More recently, non-displacement transducers which attach to the LP needle have been developed, thus giving more accurate measurements of CSFP [222]. The pressure measured at the LP will only reflect ICP if there is a free subarachnoid communication between the cranium and the lumbar region [175,324].

b) Intracranial pressure

The most accurate methods of measuring ICP require penetration of the protective coverings of the brain, but then the pressure can be measured in the extradural or subdural space, brain parenchyma or ventricles (table 1.4). Intraventricular measurements are considered to reflect brain tissue pressure more accurately than the other methods [2] for in the absence of a blockage to CSF flow, the pressure is distributed evenly throughout the ventricular system. This method allows the measurement of intracranial compliance and the treatment of RICP by removal of fluid. However the penetration of the brain tissue and increased risk of infection are potentially serious disadvantages and have restricted the use of this technique. ICP is transmitted evenly throughout the supratentorial compartment in monkeys [176] and man (in the absence of unilateral intracranial bleeds) [328,375], thus other intracranial methods reflect brain tissue pressure under most circumstances.

Measurement of the ICP in the epidural and subarachnoid spaces is more likely to be damped at high pressures than intraventricular measurements, although the recent development of fiberoptic systems has alleviated this problem.

Fontanometry is a non-invasive measurement of ICP by a transducer applied to the skin overlying open fontanelles. Although it can be used in infants (children < 1 year old), it's use is limited to neonates, since the skin overlying the fontanelle is pliable and able to transmit the ICP. The technique detects fluctuations in ICP, but quantification of ICP is inaccurate [146,286] and thus it has not gained wide acceptance.

Table 1.4: Methods for monitoring ICP

Method	Advantages	Disadvantages
Lumbar puncture	Brain & dura in the cranium not penetrated	May precipitate herniation Can only be used for short term monitoring
Epidural	Brain & dura not penetrated Low infection rate	Invasive, requires a burr hole. Cannot drain CSF Must be carefully placed for accurate functioning
Subarachnoid	Brain not penetrated Low infection rate	Invasive with penetration of skull & dura Cannot drain CSF External transducer required Unreliable with severe brain swelling
Intraventicular	Accurate and reliable Allows - CSF drainage - compliance tests - analysis of ICP waves	Invasive with brain penetration Difficult to site in swollen brains with small ventricles Highest infection rate
Parenchymal (fiberoptic)	Easily inserted in any age group Wave forms and ICP responses similar to intraventricular Good correlation with intraventricular measurements Low infection rate Can be placed subarachnoid or intraventricular	Invasive with minimal brain penetration Cannot drain CSF Cannot re-zero once inserted
Fontanometry	Non-invasive	ICP measurement not accurate Pulse pressure recordings not accurate Requires an open fontanelle

Normal range of ICP

In adults and children with rigid skulls, systemic venous pressures transmitted through the sagittal sinus appear to set the tonic pressure within the head, to which are added pressures from arterial input, CSF flow and brain tissue pressure [80,229]. ICP normally fluctuates with arterial pulsation by about 0.15 mmHg and with respiration by 0.15 to 0.37 mmHg. Mean arterial and intracranial pressure should be calculated from the area under the curve, but for clinical purposes an estimate of mean pressure is:

Mean pressure = diastolic pressure + 1/3 (pulse pressure) . . equ 1.2

However as the pulse rate rises the arterial pressure tracing becomes more sinusoidal and the actual mean increases towards diastolic pressure + 1/2(pulse pressure). Likewise if there is a marked respiratory component the mean ICP is derived from "diastolic" + 1/2(pulse pressure) [217].

Normal ranges are difficult to determine in children, but are thought to be considerably lower than in adults. Significant increases can be produced by coughing, crying or other causes of an increase in venous pressure. The normal range increases with age, the mean upper normal limit in neonates is 3.5 mmHg, in infants 5.8 mmHg, children 6.4 mmHg and adults 15.3 mmHg [223]. These ranges, however, are based upon a small group of children, many of whom had CNS symptoms and had the LPs to exclude CNS disease (Table 1.5). In children some authorities consider pressures greater than 10 mmHg to be abnormal and unequivocal intracranial hypertension to occur when ICP is persistently over 15 mmHg in children [222], whilst others retain the adult criteria.

Table 1.5: Normal opening CSFP measured in children

Reference	Age	Indication for LP	CSFP range (mmHg)
Sidbury 1920 [315]	Infants	Raw data not presented, indication for LP not defined	2-5
Levinson 1928 [184]	Infants & children	Meningism without meningitis	3 - 6
Quinke 1891 [270]	Children	2 children with headaches and CNS symptoms	2.9 - 4.4
Lups et al 1954 [196]	Children	Raw data not presented, indication for LP not defined	2.9 - 7.4

RAISED INTRACRANIAL PRESSURE

Role of RICP in paediatric encephalopathies

Since the initial studies of ICP monitoring and its' safety was established in adults [194], ICP has been monitored in a variety of encephalopathies in children. Most of the data has accumulated in head trauma [14,31,69,194,206,229], but RICP is a feature of many non-traumatic encephalopathies as well [103,157,222,329]. Since the pathophysiology of head trauma, which involves the effects of intracranial bleeds and diffuse axonal injury, is likely to be very different from the pathophysiology of CM, the following discussion concentrates on the data from non-traumatic encephalopathies.

The role of RICP in non-traumatic encephalopathies is difficult to establish from reported studies because:

a) the observations were on either statistically small groups of children or larger groups with heterogeneous diagnoses [103,157,329].
b) many of the children studied had multiple organ failures which may have determined outcome.
c) the classification of outcome was not similar.
d) the data presented is variable. Most studies present either the maximum ICP and/or minimum CPP; but few studies present mean ICP, mean CPP or periods spent below certain critical levels of CPP.
e) the studies lack radiological evidence that the children with sequelae had patterns of damage compatible with low CPP.

f) lack of post mortem evidence that the children who died had features of herniation or brain damage compatible with RICP or low CPP.

Despite the above limitations, the differences in methods and indications for monitoring, and the treatment of ICP between these paediatric series, a general association between high ICP and low CPP with poor outcome (severe neurological sequelae and death) has emerged. The following conclusions can be drawn:

a) Opening ICP does not predict maximum ICP [102,157,329]. In one study children who died with CNS infections had significantly higher opening ICP than those who survived, but this was not true for those with ischaemia [102]. Opening ICP was less than 20 mmHg in 37-79% of children who subsequently developed ICP >20 mmHg [102,157,329].

b) The incidence of RICP varied. The percentage of children with non-traumatic coma who had an ICP >20 mmHg detected by monitoring varied from 47-66% [102,157,222,329]. In comparison, 53-80% children with head injury had pressures greater than 20 mmHg [157,222].

c) A critical maximum ICP is not easily identified. A child with an ICP greater than 80 mmHg survived [58], but in another series those children with maximum ICP greater than 50 mmHg all had severe neurological sequelae [214]. In a further series, the maximum ICP during the first 12 hrs or the entire period of monitoring was not correlated with outcome, although children with an ICP >55 mmHg had a poor outcome [329].

d) The data on mean ICP is conflicting. Two studies reported no significant association between mean ICP and outcome [157,222] while another found the mean ICP to be significantly higher in those who died [214].

e) A minimum CPP <40 mmHg was associated with a poor outcome, especially death, in almost all series. In one study a minimum CPP of 30 mmHg was a good discriminator between death and survival, with values <30 mmHg always associated with death and higher values with survival [102]. In another series lowest CPP in those with a poor outcome was significantly lower than in those with a good outcome (37.2 + 16.6 vs 56.9+10.6 mmHg, $p<0.001$) and a poor outcome was associated with minimum CPP <40 mmHg, although 7 out of 30 children who had a minimum CPP above 40 mmHg also had a poor outcome [329]. Five of these children had identifiable complications such as cardiac arrest or multisystem failure, highlighting the importance of systemic perturbations in determining outcome [329]. In other studies, a CPP below 50 mmHg was associated with poor outcome [222], a minimum CPP was significantly lower in the poor outcome group and all children who had a minimum CPP <34 mmHg did badly [157].

f) Mean CPP was also associated with outcome. In a retrospective series reviewed, a mean CPP of less than 70 mmHg averaged over the whole monitoring period was associated with poor outcome except in those children who were surgically decompressed [157].

RICP in Reye's Syndrome

Reye's syndrome is an acute non-inflammatory encephalopathy, characterised by cerebral oedema and fatty infiltration of the liver and to a lesser extent other organs. It commonly occurs after a viral illness, usually chickenpox or influenza, and often associated with the use of aspirin in these illnesses [222]. Children usually present with a history of fever and vomiting developing as the symptoms of an upper respiratory tract infection abate. The illness may improve spontaneously at this stage, or the child may deteriorate with impairment of consciousness, seizures and hypoglycaemia.

Intracranial hypertension is thought to play an important role in the outcome of Reye's syndrome, since aggressive treatment of RICP and mechanical ventilation reduced the mortality of children with severe disease from 60% to 12% [312]. An ICP above 10 mmHg has been documented in 70-100% of children with Reye's syndrome, the incidence of RICP depended upon the stage at which monitoring was started [58,206], as a normal ICP was frequently recorded during the early stages of the encephalopathy [33,140].

Various clinical staging systems have been proposed; most are based upon a rostrocaudal progression of brain stem signs, highlighting the importance of these features in those who die. Stage III of Lovejoy's classification [193] is a child who is unable to localise pain (table 1.6), the depth of coma is comparable to children fulfilling the WHO definition of CM.

Table 1.6; Lovejoy's classification of Reye's syndrome [193]

Stage	Signs	Laboratory findings	Electroencephalographic findings
I	Vomiting, lethargy & sleepiness	Liver dysfunction	Rhythmic slowing with dominant theta waves & rare delta waves
II	Disorientation, delirium, agitation, hyperventilation, hyperreflexia, localises pain	Liver dysfunction	Dysrhythmic slowing with dominant theta & rare delta waves
III	Coma, hyperventilation, decorticate rigidity, preservation of the pupillary & oculocephalic reflexes	Liver dysfunction	Same as stage II
IV	Deep coma, decerebrate rigidity, loss of oculocephalic reflexes, dilated fixed pupils, dysconjugate response to the oculocephalic reflexes	Minimal liver dysfunction	Disorganised monorhythmic or polyrhythmic delta waves of low voltage with burst suppression or brief isoelectric intervals. Isoelectric
V	Seizures, loss of deep tendon reflexes, flaccidity, respiratory arrest	No liver dysfunction	Isoelectric

Table 1.7: Comparison between Reye's syndrome & CM in African children

	Reye's syndrome	Cerebral Malaria
Age: median (range) in years	11 (1-19)	3 (0.5-8)
M:F ratio	1:3.2	1:1
Prodromal illness	In 76-100%	2-3 days of fever
Fever on admission	?	>99 %
Vomiting	95%	55 %
Seizures	50-72%	50%
Brainstem signs	38%	34%
Papilloedema	Rare	Rare
Hypoglycaemia	5-25%	23%
Metabolic acidosis	100%	42%
Severe anaemia	0%	46%
Sequelae	10-15%	11%
Death*	43-62%	15%

* prior to ICP monitoring

Reye's syndrome has many clinical and biochemical features in common with CM (table 1.7), but the two main distinguishing features in Reye's syndrome are hepatic involvement (fatty infiltration) and cerebral oedema.

Opening ICP and CPP do not predict maximum ICP [205] or minimum CPP [140] respectively. Seizures are associated with an increase in ICP [33] and spontaneous pressure waves have been observed [33,44]. There is no association between outcome and opening ICP [140] or maximum ICP [58,140]. Indeed an ICP between 51 and 69 mmHg for more than 15 minutes has been recorded in children with full neurological recovery [205]. However there is a strong relationship between a low minimum CPP and poor outcome in the series in which this parameter was calculated. In Northern Ireland all the children with a minimum CPP <40 mmHg had a poor outcome. The 2 children with minimum CPP >40 mmHg who had a poor outcome had maximum ICP <20 mmHg, and their clinical courses were complicated by severe hypoglycaemia and profound pulmonary complications [140].

ICP in CNS infections

Many studies reporting ICP measurements in CNS infections do not differentiate between encephalitis ABM. The differences in the pathophysiology may influence the significance of the ICP findings. For example in ABM, the highest pressures are recorded during the early part of the disease [273], whilst in encephalitis, the maximum ICP usually occurs later [25].

Acute bacterial meningitis

Opening lumbar CSFP was raised in 94% of children with ABM, with higher pressures found on admission than on subsequent days [223]. There was no correlation between the single CSFP measurements and outcome, although in a study of ICP monitoring the mean opening ICP was lower in the children who died [273].

Although ICP monitoring in ABM has been reported in many series, only 3 have sufficient numbers for conclusions to be drawn. Maximum ICP was not a good predictor of outcome [103,222,273], although the few children with an ICP >65 mmHg all died. All the children with a minimum CPP <30 mmHg died, but the same children who survived with severe neurological sequelae had CPP >40 mmHg [103,273].

Encephalitis

The ICP recorded during encephalitis is generally lower than in ABM, with only 30-55% of children with maximum ICP greater than 20 mmHg [103,118,153,222,273]. There is little association between maximum ICP and outcome, with pressures as high as 75 mmHg being recorded in children who survived without sequelae [103]. Likewise there is little correlation between minimum CPP and poor outcome in most series [103,222,273], although there was an association in one study [118]. thus RICP does not appear to be a major determinant of outcome in the encephalopathy.

PATHOPHYSIOLOGY OF RICP

A. Pressure/volume relationship

Monro-Kellie Doctrine

In 1783 Alexander Monro proposed that as the cranium is a rigid closed cavity, the volume of blood within it, must be constant for stable pressure relationships to exist. The concept that blood volume determined ICP, as brain tissue is incompressible, was confirmed by the experimental work of George Kellie, published in 1824. However it was Burrows (1846) who established that a third component, the CSF, also played a role in ICP dynamics. He modified the Monro-Kellie doctrine to propose that if there is an increase in the volume of one intracranial component, then the volumes of one of the other components must decrease for the ICP to remain constant. Thus if the components cannot be compressed any further, ICP will rise. Although this doctrine does not take into account the dissipation of pressure through expansion of the skull in infants with unfused sutures it has formed the basis of the understanding of the pressure relationships in older children and adults.

Pressure/volume curve

The relationship between ICP and intracranial volume has been extensively studied in experimental models, by increasing ICP with an expanding balloon [179] or infusing CSF [187]. Since the CSF infusion model is most likely to reflect the changes that occur in a diffuse encephalopathy, I shall use this model to illustrate

Lofgren et al [187] created a model of diffusely raised ICP, by infusing CSF into the cisterna magna of dogs at a constant rate of 0.25ml/sec after the ICP had been reset to the venous pressure of -10mmHg by withdrawal of CSF (fig 1.4). The pressure-volume relationship was best quantified by the elastance *ie* the change in pressure divided by change in volume (E=dP/dV). During the initial part of the infusion the pressure rose little and the elastance was 1.3 mmHg/ml. As the infusion continued, the gradient increased steeply with an easily identifiable breakpoint (see fig 1.4), E = 25.2 mmHg/ml. When the ICP rose towards the diastolic blood pressure, the curve flattened with an increase in the amplitude of the CSF pulsations. Increased rates of infusion produced steeper curves.

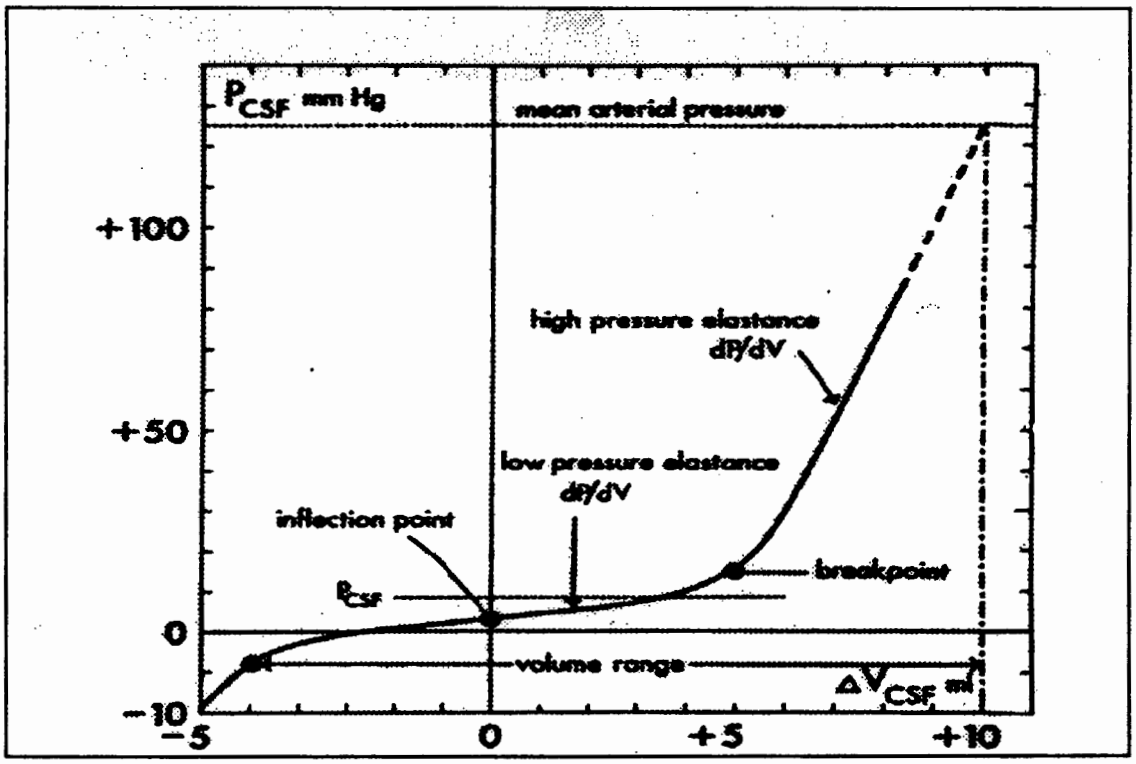


Figure 1.4: The CSF pressure-volume curve as derived by infusion of CSF into the supratentorial space of dogs [187]

The compensation that occurs during the initial increase in the volume of an intracranial compartment is produced by several mechanisms:

a) slight distensibility of the dura, chiefly in the lumbosacral region (this accounted for 70% of the initial compensation in the above model [188]),
b) decrease in CSF volume, initially from an increase in CSF absorption and then a decrease in production;
c) collapse of the cerebral veins and dural sinuses decreasing the intracranial blood volume
d) compressibility of the brain, which is very limited.

The recruitment of these mechanisms depends upon the cause of RICP, the stage of compensation and whether or not there is continuity between the intracranial and lumbar subdural spaces.

Pressure Volume Index

Miller and Leech were able to quantify the elasticity of the intracranial system by measuring the response of ICP to the addition or withdrawal of 1ml of CSF (volume/pressure response (VPR)) [179]. However, since compliance (C=dV/dP) and elasticity change with ICP, Marmarou subsequently suggested the Pressure Volume Index (PVI) as a measure of the intracranial compliance. This is the gradient of the linear relation of V plotted against log P (PVI=dV/dlogP) *ie* the volume of CSF that produces a 10 fold increase or decrease in ICP [309]. In normal children up to the age of 14 years the PVI varies with the estimated neural axis volume, ranging from 8 ml in infancy to 25ml in adults [309]. This demonstrates the reduced buffering capacity for rises in ICP in children. The PVI

has been used clinically to estimate buffering capacity in children with head injuries [205] and metabolic encephalopathies [116]; but since an intraventricular catheter is required to measure it, this index has not been used extensively for the management of intracranial hypertension.

B. Cerebral haemodynamics during RICP

Normal cerebral blood flow

The brain receives about 20% of the cardiac output under normal conditions, but blood flow to the brain is preferentially maintained if cardiac output is low [89]. The total cerebral blood flow (CBF) is determined by the activity of the brain, for in most circumstances CBF and metabolism are tightly coupled. In sedated children, the CBF is about 100 ml/100g/min [152], whilst under anaesthetic the mean is 69 ml/100g/min [296], and in children unconscious following head injury it ranges from 25 ml/100g/min to over 90 ml/100g/min [230]. CBF is higher in gray matter than white matter and there are further regional differences which may change with functional activation.

The major physical determinants of CBF are the pressure differences across the vascular bed and the diameter of the arterioles, the main resistance vessels. The pressure difference is the arterial pressure minus the cortical venous pressure. Since the cortical venous pressure is just lower than ICP and usually follows ICP [100], the cerebral perfusion pressure (CPP) can be defined as:

$$CPP = MAP - ICP \quad \text{equation 1.3}$$

In most vessels the relationship between flow and perfusion pressure can be understood from the application of Laplace's law:

$$CBF = \frac{\pi * r^4 * CPP}{8 * \eta * l} \quad \text{equation 1.4}$$

where r = arteriolar radius, η=viscosity of blood and l=length of vascular bed. However, this equation does not describe the relationship between CBF and CPP in the normal brain since the cerebral vessels are able of maintaining CBF by changing arterial diameter (autoregulation). The change in vessel diameter influences the cerebrovascular resistance (CVR) which can be defined as:

$$CVR = \frac{CBF}{CPP} \quad \text{equation 1.5}$$

Autoregulation

CBF remains relatively constant over a range of CPP (autoregulation), although the upper and lower limits of CPP at which autoregulation no longer occurs are not fixed points, but are determined by a variety of factors such as sympathetic nerve activity, $PaCO_2$, pharmacological agents and the renin-angiotensin system [89]. These limits have not been determined in normal children, but in adults CBF remains constant between arterial blood pressures of 60 to 140 mmHg. Autoregulation may become impaired in encephalopathies, in which case CBF will be directly dependent upon the CPP according to equation 1.4.

The CPP may be reduced by an elevation of ICP or cortical venous pressure, or a reduction in MAP. The effects of changes in these parameters are different. In dogs, the lower limit of autoregulation was higher when CPP was reduced by hypotension than with an increase in ICP or jugular venous pressure (JVP) [219]. In contrast, another study found that autoregulation was impaired when the CPP dropped to 40 mmHg with an increase in ICP or a decrease in MAP, although autoregulation started to fail at a CPP of 50 mmHg when the JVP was increased [211]. Perhaps more importantly, the latter study found that autoregulation was impaired when the CPP was reduced to 50 with an increase in the JVP but only became impaired when the CPP reached 30 mmHg by hypotension or intracranial hypertension.

Mechanisms of autoregulation

Three main mechanisms have been postulated to explain autoregulation [89,285]:

a) The myogenic hypothesis suggests that the smooth muscle of the cerebral vessels is responsive to changes in the transmural pressure; with the arteries and arterioles constricting to increases and dilating to decreases in transmural pressure. This hypothesis is supported by the rapidity of the vessel response to changes in the transmural pressure, but not by the observation that the autoregulation of CBF occurs regardless of changes in transmural pressure at low CPP [211].

b) The release of vasoactive substances, including nitric oxide (NO), in response to decreases in CBF is the basis of the metabolic theory. Although CO_2, hydrogen ions, oxygen, potassium, calcium and adenosine may mediate the changes of CBF with CPP, a principle mediator has not been identified; although there is growing

evidence that oxygen and NO are involved in the mechanism [89].

c) Lastly the neurogenic control of autoregulation has been extensively investigated, albeit inconclusively. The stimulation of sympathetic nerves causes a shift of the limits of autoregulation to higher CPP, although there is little influence on resting CBF [89]. Stimulation of the parasympathetic ganglia cause vasodilation, but denervation or neurotoxins do not ablate vessel responses to blood pressure changes, but make the response slower [89]. Neurogenic mechanisms do not appear to be responsible for autoregulation, but may have a modulating role.

CBF, CBV and ICP

Progressive IH not only causes cerebral vasodilation, but also provokes an increase in MAP (Cushing response) to maintain perfusion pressure [74]. In an experimental model of a diffuse increase in ICP with the infusion of fluid into the cisterna magna of monkeys, initially CBF remained constant despite an increase in CBV [115]. Further increases in ICP, reducing the CPP to below the autoregulatory range, decreased the CBF, although CBV remained constant. In other experimental models, which had methodological problems [118,144], similar changes were seen. In all these models a transient reactive hyperaemia occurred after ICP had been reduced, with a marked increase in CBV, though a less pronounced increase in CBF.

Carbon dioxide (CO_2) reactivity

Normal cerebral vessels are very sensitive to changes in the arterial pCO_2 ($PaCO_2$) and the vascular reactivity to CO_2 has been used as a test of vessel integrity.

Normal cerebral vessels are very sensitive to changes in the arterial pCO_2 ($PaCO_2$) and the vascular reactivity to CO_2 has been used as a test of vessel integrity. Hypocapnia causes vasoconstriction, which is maximal at $PaCO_2$ of 3.3-4.0 kPa (25-30 mmHg), with a 30-50% reduction in CBF [89]. The response to hypercapnia is greater, with a 200% increase in CBF at $PaCO_2$ of over 13.3 kPa (100 mmHg) from normocapnic values.

The CO_2 reactivity appears to be mediated by changes in extracellular pH surrounding the smooth muscle cells in the arterioles. Carbon dioxide diffuses easily across the blood brain barrier (BBB), and lowers the pH by reacting with water to form bicarbonate and hydrogen ions. An increase in the concentration of hydrogen ions appears to cause the relaxation of the smooth muscle, although the mechanism is unclear. Nitric oxide is likely to be the mediator of hypercapnia [133]. Systemic acidosis *per se* does not cause vasodilation of the cerebral vessels [121].

The CO_2 reactivity is modified by a variety of factors and is progressively attenuated by a gradual reduction in blood pressure [285]. Prolonged hyperventilation (for more than a few hours) diminishes the vasoconstrictive response, probably because there are adaptive changes in the bicarbonate concentration of the brain's extracellular fluid. Carbonic anhydrase inhibitors increase the reactivity of the cerebral circulation to hypercapnia, whilst indomethacin diminishes the hypercapnic increase in CBF. In hypoglycaemia, CBF does not decrease with hypocapnia, but the EEG becomes flat despite a lack of

change in the cerebral oxygen consumption [316].

Impaired cerebrovascular response to changes in pCO_2 has been documented in a number of encephalopathies, including head injury [89], subarachnoid haemorrhage [303] and acute bacterial meningitis [256]. In children with non-traumatic coma, poor outcome was associated with a negative minimum CO_2 reactivity gradient, measured with transcranial Doppler (TCD) sonography [157]. The loss of CO_2 reactivity diminishes the coupling between metabolic demand and CBF and restricts the use of hyperventilation in the management of IH.

Metabolism

The brain, with limited glycogen stores derives almost all its energy from aerobic glycolysis and is dependent upon a continuous supply of oxygen and glucose. Although the brain may utilise ketones, glycerol and lactate under adverse conditions *eg* starvation, the relatively slow transport of these compounds across the BBB limits their utilisation [100]. Thus the brain is particularly vulnerable to hypoxia or conditions that impair substrate supply.

Since the brain is almost entirely dependent upon glucose and oxygen for normal function, cerebral metabolism may be described by cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral metabolic rate of glucose (CMR_{gluc}), where:

$$CMRO_2 = CBF * [\text{cerebral A-V } O_2 \text{ content differnce}) \ldots . \text{equation } 1.6$$

(A-V = aterio-venous difference)

$$CMR_{gluc} = CBF * (A\text{-}V\ glucose\ content)\ ..\ equation\ 1.7$$

If CBF falls, $CMRO_2$ may remain constant if the oxygen extraction ratio(OER) increases where:

$$OER = \frac{Cerebral\ (A\text{-}V)\ -O_2\ content\ difference}{arterial\ O_2\ content} \ldots equ\ 1.8$$

Luxury perfusion

Cerebral blood flow is usually coupled with cerebral metabolism. However in some encephalopathies, such as head injury [230] and meningitis [256] there is an increase in the cerebral venous oxygen saturation, suggesting 'luxury perfusion' [177]. Global CBF values are usually raised, but may be normal since there may be areas of high flow adjacent to those with low flow. In some encephalopathies eg head injury, luxury perfusion is thought to raise the ICP by increasing the CBV. Although luxury perfusion is associated with lactic acidosis [177], the causes of this phenomenon are unclear.

INTRACRANIAL PRESSURE WAVES

The presence of ICP waves is thought to indicate lack of compliance of the intracranial contents. Lundberg described 3 types of waves in his original monograph on ICP monitoring [194]: A-, B- and C-waves.

A-waves or plateau waves

Plateau waves are increases in ICP up to 50-100 mmHg, which then remain at that

level for 5-20 minutes. They occur exclusively in the presence of intracranial hypertension. They appear as the patient deteriorates clinically, with the magnitude, duration and frequency of the waves often increasing, although they may disappear as the patient lapsed into "irreversible unconsciousness" [194]. These waves are often accompanied by a variety of symptoms and signs (table 1.8).

Table 1.8: Signs recorded during A-waves [194]

System	Sign
General	restlessness agitation disorganised motor activity disorders of wakefulness and responsiveness
Eye signs	miosis, mydriasis, aniscoria IV nerve palsy no spontaneous movement pupillary areflexia
Tone	rigidity, espiecally of the neck, arms and legs opisthotonus
Abnormal movements	tonic flexion or extension of the limbs 'Parkinson' type tremor clonic movements extensor plantars
Cardiovascular abnormalities	bradycardia rise in systolic blood pressure periodic variation of pulse frequency
Respiratory abnormalities	involuntary hyperpnoea irregular breathing periodic breathing apnoea
Miscellaneous	sweating shivering hiccup

Causes of A-waves

A-waves are thought to be caused by cerebral vasodilation and are associated with increases in CBV in the cerebral hemispheres [126,283], although a decrease in CBF has also been documented [126]. However the haemodynamic changes do not necessarily appear in the brain stem probably explaining normal conscious levels and the lack of a Cushing response in many patients [126].

Rosner has proposed that plateau waves are generated by a drop in MAP precipitating a vasodilatory cascade [290]. When CPP is reduced below a critical level (70mmHg in adults), the rate of vasodilation in response to a fall in CPP increases logarithmically. Thus a fall in MAP will lead to a decrease in CPP, causing an exaggerated vasodilatory response, which increases CBV and thus ICP. If there is no Cushing response to the rise in ICP, a further reduction in CPP will occur and a vicious cycle will develop. The generation of the pressure wave is dependent upon a delay in the autoregulatory response, with the ICP increasing until there is maximal vasodilation. The waves are thought to be aborted by sympathoadrenal discharges [290]. More recently plateau waves have been shown to be associated with impaired CSF flow and absorption [124] and appear to increase the ICP at which signs compatible with herniation appear [125].

B-waves

These are rhythmic increases in ICP up to 50 mmHg occurring at a frequency of 0.5-2 per minute and are much more common than plateau waves. Unlike A-waves, they can arise from a normal baseline ICP. If they are regular and persist for long

periods, they indicate reduced intracranial compliance and should be regarded as a sign of cerebral dysfunction [194]. Few B-waves are accompanied by symptoms and signs. In unconscious patients the waves are sometimes related to periodic breathing, the peaks of the waves coinciding with the periods of hyperpnoea. They are thought to be caused by rhythmical changes in cerebral vasomotor tone inducing changes in CBV [21] and CBF [236].

C-waves

These waves occur at a frequency of 4-8 per minute; the same frequency as the spontaneous variations of blood pressure (the Traube-Hering-Meyer waves) which are associated with RICP. C-waves are often not detected because of their fast frequency, but at a high ICP, they are accentuated and more conspicuous. Their clinical significance is undetermined, but their appearance in association with RICP probably implies dysfunction of the centres controlling vasomotor tone [194].

CAUSES OF RAISED ICP

As predicted by the Monroe-Kellie doctrine, RICP develops when there is an increase in intracranial blood, CSF or brain volume without a compensatory decrease in the other components. The causes of RICP in children are shown in table 1.9. Unfused sutures in children influence the ICP, since the pressure can be dissipated by expansion of the cranium. Alternatively premature closure of the sutures makes the child prone to the development of intracranial hypertension.

Table 1.9: Causes of RICP in children

Cause	Mechanism
Brain swelling	Cerebral congestion: increase in blood volume Cerebral oedema - vasogenic - hydrostatic - osmotic - cytotoxic
Space occupying lesion	Tumour Abscess Cyst Blood clot
Hydrocephalus	Excess production of CSF Obstruction of CSF pathways Failure of absorption of CSF
Cranio-cerebral	Reduction in expansibility of the skull

Cerebral congestion

In cerebral congestion, the increase in CBV occurs predominately in the venous circulation since the arterial blood volume is tightly controlled in a brain that has intact autoregulation. Since over seventy percent of the CBV is in the venous side, a substantial increase in CBV may occur without changes being detected in CBF.

Cerebral oedema

Cerebral oedema has been classified into four categories (summarised in table 1.10), based upon the pathogenesis. Although in most encephalopathies oedema is caused by more than mechanism, this classification is useful in that dictates appropriate therapy. Cytotoxic oedema, the swelling of cells caused by the influx of fluid from the interstitial spaces may be caused either by the disturbance of cellular energy metabolism or impairment of other aspects of metabolism.

Table 1.10: Types of cerebral oedema

	Vasogenic	Cytotoxic	Osmotic	Hydrostatic
Pathogenesis	breakdown of the BBB	disturbed cellular metabolism	osmotic gradient	hydrostatic gradient
Oedma fluid				
composition	plasma exudate	water, sodium	water, sodium	water, sodium
cellular	extracellular	intracellular	extracellular	both
localisation	white and gray matter	both	both	white matter
Causes	focal lesions ABM head injury	hypoxia poisons	water intoxication	hydrocephalus hypertension
Computerised tomography appearences	loss of gray/white differentiation, white matter pseudopodia & enhancement with contrast	hypodensity of white and gray matter	generalised hypodensity	hypodensity of white matter
Therapeutic effects:				
steriods	beneficial in brain tumour and abscess	no effect	no effect	no effect
osmotherapy	reduces volume in normal tissue, but may aggravate fluid accumulation in abnormal areas	no effect	no effect	no effect

CONSEQUENCES OF RICP

RICP can affect outcome by two mechanisms; by displacement of brain tissue (herniation) and/or by producing ischaemia.

Post mortem findings in RICP

Flattening of the gyri, lateral displacement of midline structures, downward displacement of the hypothalamus, supracallosal and tonsillar herniation are the commonly accepted pathological features of supratentorial RICP [218]. Necrosis of the parahippocampal gyri, and to a lesser extent the cingulate gyrus and medial occipital cortex are associated with RICP measured ante-mortem [10]. However the

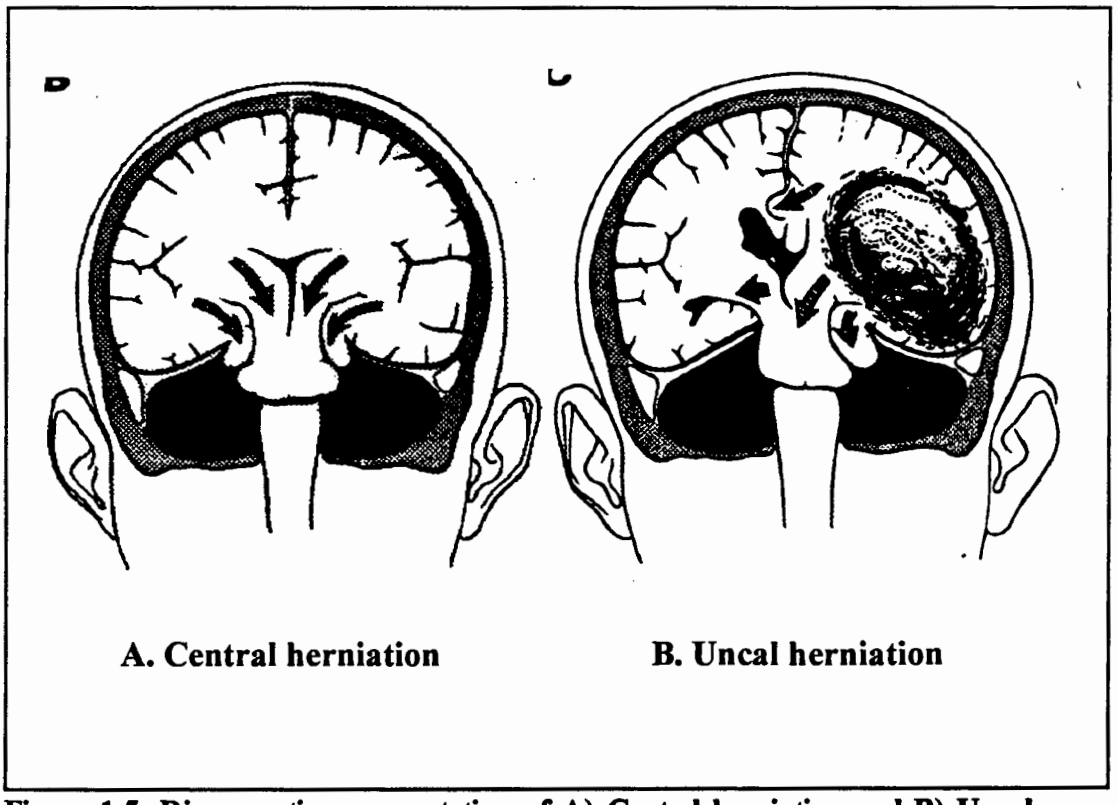


Figure 1.5: Diagramatic representation of A) Central herniation and B) Uncal herniation [264]

necrosis may be microscopic and thus easily missed. Furthermore these hippocampal changes are not necessarily implicated as the cause of death in these patients [10].

Most studies have been performed on patients dying from space occupying lesions. The features of a diffuse increase in supratentorial ICP are not so clearly defined. Minor degrees of caudal displacement are less easy to identify than the lateral shifts, particularly when the deterioration has been very rapid [218]. Diffuse brain swelling may lead to small symmetrical ventricles, without a lateral shift of the midline structures. Although bilateral tentorial herniae may occur (figure 1.5), it is the caudal displacement of the diencephalon and brain stem that are thought to be responsible for death [218]. When both parahippocampal gyri herniate through the incisura, producing circular or ring hernia, the clinical manifestations are bilateral ptosis, loss of upward gaze [143] and finally loss of pupillary response to light. The features of fully established central transtentorial herniation are displacement of the mamilliary bodies downwards and backwards and compression of the pituitary stalk. Infarction of the mamilliary bodies, anterior lobe of the pituitary and the areas supplied by the anterior choroidal, posterior cerebral and superior cerebellar arteries occurs. The neurons become elongated and distorted [218]. Haemorrhage and infarction in the tegmentum of the midbrain and pons are often terminal events [218]. The propensity of patients to develop herniation depends upon the cause of the pressure gradient, the rapidity at which it develops and the size of the tentorial incisura in relation to the brain stem [263].

The effects of a reduction in CPP are determined by the magnitude of the reduction and the rate at which it is reduced. Most of the reports have described the pathological changes following hypotension. Briefly, sudden drops in CPP are associated with infarction in the areas between the major vascular territories ie the borderzone areas, whilst a gradual prolonged reduction in CPP produces a diffuse loss of neurones [9].

Clinical signs of RICP

RICP *per se* is not necessarily associated with symptoms and signs. People with benign intracranial hypertension may be completely asymptomatic despite ICP of 50-80 mmHg [224]. Furthermore acute elevations of ICP to 600 mmH_2O by an infusion of fluid through an LP needle produced headaches in only 25% of conscious adults [292]. The symptoms of RICP in children (table 1.11) are not specific [28] and are common in children with any infectious illness.

Table 1.11: Symptoms and signs of RICP in children (Bell & McCormick) [28]

Symptoms	Signs
Headache, manifesting as irritability and anorexia in infants and toddlers	Papilloedema
Nausea and vomiting	Sixth nerve palsy
Diplopia	Decreased awareness
Lethargy and drowsiness	Bulging fontanelle (infants)
Transient obscuration	Palpable suture spread
None	None

Some signs are more specific, but occur infrequently in children with RICP, partly because of the ability of the open sutures to compensate until the ICP is very high. Papilloedema is one of the most reliable sign of RICP, but it is relatively uncommon in children with acute increases in ICP, as it may take 24 - 48 hours for the earliest features to develop and a week for it to become fully evident [28]

Clinical signs of brain herniation

Movement of brain tissue from areas of high ICP to those of lower pressure is the most serious consequence of RICP. There are 3 patterns of supratentorial herniation (central, uncal and cingulate) (figure 1.5) and 2 of subtentorial herniation (upward or downward displacement). In supratentorial lesions, particularly in diffuse encephalopathies, central herniation occurs most commonly [264], although uncal herniation can also develop.

Most of the clinical data on herniation is derived from adults with space occupying lesions. Plum and Posner's influential descriptions of the central herniation syndrome (table 1.12) were based entirely upon supratentorial space occupying lesions; only 2 of 48 had bilateral lesions [264]. They emphasised that the clinical signs of herniation were more apparent in patients with slowly developing lesions. They described clinical signs of central herniation in patients dying from encephalitis or toxic encephalopathies, who had transtentorial herniation at post mortem. They also described coma, respiratory abnormalities, anisocoria, decorticate and decerebrate rigidity in patients with diffuse encephalopathies, who did not have any evidence of herniation. Plum and Posner emphasised that

Table 1.12: Signs of central and uncal herniation as described by Plum & Posner [264]

Stages	Respiratory pattern	Pupillary size & reaction	Oculocephalic & oculovestibular responses	Motor responses
Central syndrome of rostro-caudal deterioration				
Diencephalic	eupneic with deep yawns or sighs Cheyne-Stokes	small pupils limited range of contraction	full conjugate	localises painful stimulus bilateral Babinski paratonic resistance
Late Diencephalic	Cheyne-Stokes	small pupils limited range of contraction	full conjugate, but easier to obtain (absent nystagmus)	motionless decorticate rigidity
Midbrain /upper pons	sustained regular hyperventilation rarely Cheyne-Stokes	midposition, often irregular no response to light	impaired, may be dysconjugate	usually motionless decerebrate rigidity
Lower pons /upper medullary	eupneic, often shallow and rapid ataxic	midposition no response to light	no response	motionless & flaccid no response to painful stimulus bilateral Babinski or occasional flexor response of lower limbs when feet stroked
Medullary	slows, becomes irregular in rate &depth deep sighs or gasps respiratory arrest	dilated pupils no response to light	no response	motionless & flaccid no response
Uncal herniation and lateral brainstem compression				
Early IIIrd nerve	eupneic	unilateral dilated pupil with sluggish response to light	present dysconjugate	localises pain contralateral (to eye signs) extensor plantar
Late IIIrd nerve	sustained regular hyperventilation rarely Cheyne-Stokes	unilateral dilated pupil with no response to light	no movement of one eye	decorticate or decerebrate response

preservation of pupillary light reflexes in the presence of the other clinical features of herniation, suggests metabolic coma and that the signs of patients with metabolic brain disease do not necessarily progress through the orderly rostro-caudal deterioration described in the central herniation syndrome [264].

Little has been reported on the correlation between clinical features and post mortem findings in children. Children may be more susceptible to develop some of the clinical features suggestive, but not diagnostic of herniation *eg* decerebrate posturing [285] and thus these signs may not have the same significance as in adults. In a child dying from hepatic encephalopathy a raised opening CSFP and clinical signs of the central herniation (including decerebrate posturing) were associated with striking bilateral uncal herniation, with herniation of the left temporal lobe and cerebellum at post mortem [186].

The studies of herniation in paediatric encephalopathies are usally retrospective and depend on the clinical definition of herniation, without emphasising the importance of the rostro-caudal deterioration. Horwitz *et al* documented uncal herniation at post mortem in one child with ABM who had clinical signs compatible with rostrocaudal progression, but did not perform autopsies on the other 2 children who died with these signs, nor did they report the postmortem findings of 7 children who died without clinical features of herniation [130]. In a more recent study of children with ABM, post mortem evidence of herniation (which was not defined) was found in 6 of 7 children who had autopsies [277]. Five of these children had an impaired conscious level, 4 had fixed or dilated pupils, 3 had abnormal

respiration (hyperventilation, irregular breathing pattern including Cheyne-Stokes, apnoea or respiratory arrest), 5 were ventilated and two had abnormal posture (decorticate, decerebrate or complete flaccidity) in addition to all of the above signs. The child without frank herniation at post mortem also had depressed consciousness, fixed or dilated pupils and abnormal respiration requiring ventilation. In another paediatric study of diabetic ketoacidosis, only one child who died within 24 hours of depression of consciousness, anisocoria and loss of pupillary light reflex was reported to have post mortem evidence of uncal and tonsillar herniation [122]. Thus the brain stem signs described by Plum and Posner are associated with herniation at post mortem, although the specificity is undetermined, particularly in children.

CONTROL OF RICP

Removal of the cause of the RICP is an important intervention the control of ICP and needs to be achieved as soon as possible. However during the initial management of an unconscious child, the diagnosis may not be clear and the outcome may be determined by an immediate reduction of RICP and improvement of CPP. Possible modalities for the management of RICP are outlined in table 1.13.

B. Steroids

Corticosteroids have been shown to reduce cerebral oedema around tumours, but the efficacy in other causes of oedema has not been established. Their mechanism of action is unknown, but inhibition of CSF production, an increase in CSF absorption and improvment in the BBB integrity are thought to be important [100].

C. Hyperventilation

A reduction in CBV following hypocapnic vasoconstriction of the cerebral vessels induced by hyperventilation causes a reduction in ICP. Although there are concerns that cerebral ischaemia might develop with severe hypocapnia, this has not been documented in humans, since the cerebral oxygen extraction ratio increases or the CBF does not decrease further. In prolonged hyperventilation the vasoconstriction may not persist, as the vessels adapt to the hypocapnia [100].

D. Drainage of CSF

CSF drainage is an effective measure for reducing ICP, particularly in treating ICP spikes, and can be used to maintain ICP at a predetermined level with continuous drainage. It is particularly useful when the other methods have loss their efficacy with prolonged use. This intervention requires the insertion of an intraventricular cannula, which is associated with risks of venriculitis and injury to the brain.

E. Exchange transfusions

Exchange transfusions have often been used in Reye's syndrome, although the effect on ICP is controversial. One study documented increases in ICP during the

transfusion [44], while in another study, the ICP decreased or it became easier to manage after the exchange transfusion [33].

F. Other agents

Barbituate coma reduces ICP, by decreasing cerebral metabolism and blood flow. It is an effective method of controlling ICP in intractable hypertension, but requires the patient to be ventilated and nursed in a fully staffed intensive care unit. Other agents such as trishydroxyaminomethane (THAM) reduced ICP in head injured adults. The mechanism by which THAM reduces ICP is not clear, but it has been shown to reduce brain oedema in experimental models of head injury [378] and is thought to increase the CSF capacity to buffer pH with carbon dioxide changes [371].

G. Other interventions

A reduction in the brain temperature to less than 34 °C reduces ICP, by decreasing cerebral metabolism and blood flow. Hypothermia, with a temperature less than 30°C improves the outcome in animal models of ischaemia. Temperatures less than 34 °C are associated with an improved histiopathological outcome, but do not affect the tissue metabolite levels. Patients undergoing hypothermia need to be paralysed and ventilated to prevent the severe acidosis that often develops. Surgical decompression has been used for the control of intractable intracranial hypertension, but requires good neurosurgical facilities.

III THE ROLE OF RICP IN CEREBRAL MALARIA

In order to determine the role of RICP in CM, I shall review the basic pathological features, examine the current hypotheses of the pathogenesis (including the pathophysiological data that support these theories), before discussing the role of ICP in CM.

PATHOLOGY OF CEREBRAL MALARIA

The hallmark of CM is the engorgement of the cerebral capillaries throughout the brain tissue by RBC with and without parasites [13,17,20,38,82,83,347]. Most studies have been conducted on adults, and in those series which include children, differences between adults and children have not been mentioned. The original autopsy studies of African children were from Ghana [87], Uganda [340], and Senegal [182]. More recently, since our clinical observations were published 2 further studies have been conducted in children: - one in Nigeria [348] and an unpublished study in Cote d'Ivoire. In the latter study the brains of 14 children who had PRBC within the venules were examined, although the clinical information was scanty (Sebastian Lucas personal communication).

Macroscopic

Brains packed with PRBC have a slate grey discoloration, which is present on the cut surfaces of the brains of both adults [13,17,82,155,300,341] and children

[87,182,340]. Meningeal vessels are described as congested, with some infiltration and haemorrhage [17,38,82,155,326]. Thomas reported an increase in brain weight of more than 10% in 10 of 13 Ugandan children with CM (all of whom were less than 5 years old) [340], but only one child in the Nigerian study had a heavy brain [348]. The brains appeared swollen with flattened gyri in African children [87,348] and adults [281]. Ventricular compression was seen in 79% of children examined by Lucas and has been reported in non-immune adults [139]. Many pathologists have commented on the presence of vascular congestion with hyperaemia [17,108,155].

Cerebral oedema

Macroscopic oedema is reported in most studies of non-immune children [266,300] and adults [17,155,341], but in only one study of African children [340]. This feature is cited as evidence of BBB breakdown in CM [142,347]. White matter oedema appeared to be marked in the heavier brains of Ugandan children with CM [340], although this may be a post mortem artefact (S. Lucas personal communication). In the more detailed Nigerian study, severe oedema was seen in 5 out of 7 children with CM [348], but oedema was not found (either macroscopically or microscopically) in any of the Ivory Coast children even in those children with the most compressed ventricles (Lucas personal communication). Moreover the incidence of cerebral oedema is similar in patients dying of CM and those dying without CM [279].

Features of tentorial herniation

The pathological features of tentorial herniation, despite being described in the 1930's, have infrequently been reported in CM. Grooving of the uncinate gyri and cerebellar tonsils with a pressure cone effect was described in one textbook [97], but not in others [38,88,117,347,374]. The major papers on the postmortem appearances of CM in adults or children do not mention it [82,139,151,326]. However in a more recent study, "uncal herniation" was found in 70% of Thai adults dying from CM, but also in 60% of the brains of patients with non-CM (NCM) [279]. This suggests that the findings either had little to do with the neurological complications or the criteria used (not stated in the paper) were different from those used by the other pathologists. In the study of Nigerian children 'prominent bilateral uncal gyri and cerebellar tonsils' were found in 4 of the autopsies conducted, but only one had evidence of herniation with focal necrosis of the medulla [348]. Lucas also found cerebellar grooving in 6 out of 14 children with malarious brains, 3 of whom also had uncal grooving. Neither of the studies of West African children found evidence of frank herniation with large midline haemorrhages or distortion of the neuraxis (S. Lucas personal communication).

Petechial haemorrhages

Petechial haemorrhages, described as punctiform or ring haemorrhages are a common pathological feature of CM. These haemorrhages have a blocked central capillary, containing an agglutinated mass of PRBC surrounded by brain tissue which is necrotic and contains demyelinated fibres [38,326] or is a glial reaction.

The haemorrhages are distributed throughout the brain, and are not localised to the brainstem.

Microscopic appearances

Vascular congestion

Cerebral capillaries and venules distended with PRBC and NPRBC are the microscopic hallmark of severe falciparum malaria. In contrast to the peripheral blood, all stages of the parasite are seen within these vessels, with a predominance of young schizonts. This sequestration of mature forms has been documented in adults [13,72,198,326] and in African children [182]. The distended venules are more prominent in the gray matter, where they appear evenly distributed. Arteriolar dilatation has been noted [83], although arteriolar constriction was also described in one study [265].

Granuloma formation

Small malarial granulomas (Durck's nodules) are a distinctive pathological feature of malaria [17,82] associated with ring haemorrhages. They are not found in patients who die shortly after the onset of symptoms [82] and are thought to an advanced stage of repair following the haemorrhage, in which the necrotic tissue has been replaced by neuroglial cells and microglial tissue [82,87,326]. It is likely that these lesions are a non-specific reaction to haemorrhages, as similar lesions are found in other diseases with vessel wall disintegration *eg* typhus fever [347].

Thrombus' formation

The presence of thrombotic lesions in CM is controversial. Some authors have described thrombi in the white and gray matter [13,83], often associated with ring haemorrhages or granulomas, although they do not contain PRBC [326]. In contrast other pathologists have commented on the lack of evidence for organising thrombi in adult brains [139] or in children [87]. Furthermore these deposits do not contain platelets [198].

Cellular elements

The capillary endothelial cells are described as swollen [93,266,304], necrotic or desquamated [13]. These changes appear only in samples taken more than 5 hours after death [251], suggesting that these features are post mortem artifacts. The ultrastructure appears well preserved, with only a few vessels showing patchy degenerative changes [198].

Most pathologists have commented on the lack of inflammatory cells in adults [83,93,198] and African children [340]. However an accumulation of macrophages (with active phagocytosis of PRBC and pigment), neutrophils and plasma cells has been seen in areas of extravasated PRBC [38]. Also an increase in leucocytes in the cerebrum was reported in a single case of CM, but the patient also had acquired immune deficiency syndrome. Moreover some immunoflourescent studies have shown the deposition of falciparum antigens and anti-falciparum antibody on the cerebral vessels [12], often associated with haemorrhages in the white matter [39,232,251]; although this is not an universal finding [198].

Sequestration

The engorgement of capillaries and venules by erythrocytes containing mature stages of *P. falciparum* is attributed to the sequestration of these cells from the peripheral circulation to the deep vascular beds [359]. This leads to an increased concentration of PRBC in these tissues, which is thought to be responsible for the pathogenesis of the complications of falciparum malaria [359].

Many observers report that parasite congested vessels are more prominent in the gray matter than the white [36], and that the cerebrum is more affected than other parts of the CNS. However sequestration of PRBC appears to be greater in the cerebellar vessels than the cerebral vessels in adults [304], but not in African children in particular there was no difference between the gray and white matter (S Lucas personal communication).

Sequestration not only increases *P. falciparum* survival by removing the mature parasites from the circulating blood thereby preventing their destruction by the spleen, but also allows asexual growth and division to occur in a favourable hypoxic environment and may allow more efficient invasion of RBC after schizony [204]. Sequestration varies according to the species of malaria parasite and host. For example in contrast to humans, *P. falciparum* sequestration in the night monkey (*Aotus trivirgatus*) affects in descending order, myocardium, adipose tissue and skeletal muscle with none in the brain [220]. This difference between animal models and humans is one of the factors that invalidates the extrapolation of findings in animals to humans.

Sequestration of PRBC within the brain is not inevitably associated with CM; for non-immune patients, including children, who have died from non-neurological complications *ie* non CM (NCM), have cerebral venules packed with PRBC [198,267]. However, compared to patients with NCM , patients with CM have a greater degree of sequestration in the brain, as determined by the number and percentage of vessels packed with PRBC and a semi-quantitative assessment of the RBC packing within the venules [198,267]. In addition, there is more sequestration within other organs in patients with CM than in those with NCM [198,267]. The degree of sequestration is greatest in the brain, followed by the heart and then the liver, lung and kidney, all of which are greater then the blood [198]. Furthermore there was a strong correlation between the peripheral parasitaemia on admission and PRBC packing in the brain [267]. The degree of PRBC packing appears to be correlated with the depth of coma as measured by a clinical coma scale in one study [279], although other markers of disease severity were not taken into consideration. In contrast, in NCM, there was no relationship between the peripheral parasitaemia and sequestration, nor was there any difference in the degree of parasitisation within the brain compared with that of other organs. Similar studies have not been performed in African children.

Cytoadherence

The mechanisms of sequestration are unknown. Some of the theories such as the permeability hypothesis will be discussed, but the most convincing mechanism is that of cytoadherence.

Cytoadherence, the specific binding of cells to each other is the most convincing explanation for sequestration. PRBC appear to stick to the endothelium and non-parasitised red blood cells (NPRBC). The binding of PRBC to the vascular endothelium appears to be mediated by the attachment of proteins on the surface of the PRBC to receptors on the luminal surface of endothelial cells particularly those in post capillary venules. A number of models have been developed to study this phenomenon, since PRBC stick to different cells *in vitro* (C32 melanoma cells, human umbilical vein endothelium), plastic beads coated with antibodies and even mesenteric venules in an *ex-vivo* model.

Cytoadherence appears to begin when the parasite develops pigment and is the maximal at the late trophozoite/young schizont stage [204]. The binding is pH dependent, with maximal binding occurring at Ph 6.9 [204]. It is inhibited by large shear stresses, thus promoting attachment in the venules where the flow is low [233].

Erythrocytic factors

Most PRBC that bind to other cells of *in vitro* systems (either human amelanotic melanoma cells or human umbilical vein endothelial cells) have electron-dense 'knobs' protruding from their surfaces which appear to be the points of contact between the PRBC and endothelial cells. In the *ex-vivo* model of sequestration only the falciparum infected human RBC with 'knobs' adhered to the vascular endothelium of the rat mesoappendix, reducing blood flow [131]. Recently however, knobless clones have also been shown to adhere [246]. As yet no protein

on the surface of the RBC has been clearly identified as the mediator for the binding, although parasite derived proteins such as *P.falciparum* erythrocyte membrane protein (PfEMP1) sequestrin and ring-infected erythrocyte antigen (RESA), have been implicated [131].

Endothelial ligands

To date five putative molecules have been identified which may act as endothelial ligands. However inconsistencies in the experimental data have provoked disagreement about the significance of their respective roles. Thrombospondin (TSP) is an adhesive glycoprotein involved in a wide range of cell to cell interactions. Anti-TSP monoclonal antibodies inhibit cytoadherence in the rat *ex-vivo* model [287], but not to C32 melanoma cells [131]. The case for CD36, the leucocyte differentiation antigen is stronger. Monoclonal antibodies against CD36 inhibit and reverse the adherence of PRBC to a variety of cells [131]. Also PRBC adhere to the purified CD36 molecules immobilised on plastic beads. The binding of PRBC to C32 and endothelial cells is specifically and competitively inhibited by the purified CD36. TSP and CD36 may interact to promote cytoadherence, with the soluble TSP (produced by endothelial or other cells) acting as a bridge between the PRBC surface proteins and endothelial bound CD36 [131].

More recently a variety of leucocyte adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM) and endothelial cell adhesion cell molecule (ECAM) have been shown to promote binding of PRBC to endothelial cells [131]. ICAM-1 is induced by the release of

cytokines which may have an important role in the pathogenesis (*vide infra*). Both VCAM and ECAM expression are induced in the cerebral endothelial cells of patients with CM, but not in patients who have died from other diseases. However the clinical significance of these molecules remains to be determined [30].

The clinical correlates of these *in vitro* models has been poor. In one study of Gambian children, PRBC from children with CM did not bind more avidly to C32 melanoma cells than isolates from children with less severe disease [204]. Although binding to TSP [131] and CD36 [247], have been shown to be directly proportional to parasitaemia and the degree of binding to CD36 cells correlated with biochemical indicators of disease severity in adult Thai with malaria [128,247], there was no correlation between *in vitro* cytoadherence and coma. Furthermore using the monoclonal antibody OKM5 in immuno-histochemical studies, CD36 cannot be demonstrated on cerebral microvasculature (Berendt personal communication), although it is found in the endothelium of other organs. The initial studies of the other ligands have likewise been unconvincing [247].

Rosetting

Rosetting, the adherence of uninfected RBC to PRBC, is another phenomenon that may play an important role in the pathogenesis of CM. This inter-erythrocytic interaction, defined as the attachment of 2 or more NPRC to PRBC, is pH and heparin sensitive and dependant upon the presence of divalent cations [54]. All *P. falciparum* isolates from Gambian children with CM formed rosettes, whereas only about 60% of isolates from children with non severe malaria did [54,344]. The

mean rate of rosette formation was significantly higher and giant rosettes (aggregates of more than 20 PRBC and 40-50 NPRBC) were seen more frequently in children with CM, than those without. Rosettes can be disrupted by monoclonal and polyclonal antibodies to *P. falciparum*. The plasma of children with CM lacks anti-rosetting activity, while the plasma of children with mild disease could often disrupt rosettes in vitro [54,344]. Further support for the role of this phenomenon in the pathogenesis of CM comes from an *ex vivo* model of falciparum infected RBC causing microvascular obstruction of perfused rat mesocecum [147]. Rosetting aggravated the venule obstruction [147].

Rosetting, however, has not been seen in human post mortem samples. Furthermore the rosettes break up at high flow rates, although they quickly reform at lower shear stresses. Thus the role of rosettes in the pathogenesis has not been established *in vivo* and this phenomenon may simply represent a marker of a different cytoadherent phenotype whose real target is an endothelial receptor.

Clinico-pathological correlation

Many authors, including those who have looked at African children [20,181], have commented on the lack of correlation between the severity of autopsy findings and clinical features [17,104,251,326]. One study did demonstrate a correlation between the degree of PRBC sequestration and a clinical coma scale [279], although this study also found an equal incidence of cerebral oedema and uncal herniation in patients dying from CM and NCM. In the study of Ugandan children, Thomas suggested that CM could be characterised by a clinical history of convulsions or

impairment of consciousness and pathologically by multiple petechial haemorrhages [340]. The presence of pigment in the cerebral vessels was not useful in identifying children with neurological manifestations in this study, although the pigmentation or PRBC were not quantified. Thus the diagnosis of CM in endemic areas remains a clinical diagnosis.

PATHOPHYSIOLOGY OF CEREBRAL MALARIA

Most studies of the pathophysiology of CM have been conducted in non-immune adults and as has been discussed previously there may be significant differences in the pathophysiology of between this group and African children. However the clinical and pathological features of CM in both groups are those of a diffuse encephalopathy.

PATHOGENESIS OF CEREBRAL MALARIA

Since the 1890's when the main pathological features of CM were described, investigators have sought to explain the development of unconsciousness in patients with falciparum malaria. The causes of coma in other encephalopathies are not fully understood. Plum and Posner in their seminal work divided the causes into 2 broad groups: firstly processes diffusely affecting the cerebrum and secondly, localised perturbations that interfere with the reticular activating system. Many

suggestions have been proposed to explain the pathogenesis of CM, which Warrell and Phillips categorised into four, albeit overlapping hypothesises: mechanical, permeability, immunological and toxaemic [262].

a) Mechanical obstruction

In 1893, Laeveran proposed that CM was caused by the blockage of the cerebral vessels by PRBC. Since then the 'mechanical hypothesis' has been favoured by most investigators, although there is considerable speculation about the cause of the obstruction. Dudgeon & Clarke [83] thought that 'thrombus' formation obstructed the blood flow, although the 'thrombi' were found to lack fibrin and platelets. This was later attributed to an increase in fibrinolysis giving rise to an acute transient process of regional intravascular fibrin deposition [275]. Fibrin degradation products are modestly raised in patients with CM and fibrinogen turnover is increased, but other evidence of disseminated intravascular coagulation is not common in CM [260] and spontaneous bleeding is not a feature of CM in African children [354]. In the 1940's, based upon studies of the conjunctival circulation of adults with malaria, Knisley [163] suggested that the PRBC agglutinated forming a "sludge" which caused the obstruction. Thirty years later Miller and colleagues [221] demonstrated that the PRBC are more rigid, and proposed that this caused capillary obstruction. However the latter theory does not explain the concentration of PRBC within the venules since the obstruction would occur at the site of the smallest calibre *ie* capillaries and the concentration of PRBC stacked up behind the occluded vessel should be the same as that in the peripheral blood.

Lactic acidosis as evidence for vascular obstruction

Lactic acidosis is a prominent feature of CM in both Asian adults [367] and African children [364]. Lactic acid is increased in CSF and blood, with higher concentrations in the fatal cases compared with survivors. African children appear to be able to tolerate much higher levels than adults [364]. In a study of Gambian children with severe malaria (46% of whom had CM), the venous lactate concentrations on admission of the fatal cases were almost twice that of the survivors [166]. The lactate concentration 4 hours after admission was the best overall predictor of outcome; better than the presence of hypoglycaemia on admission, depth of coma on admission or 4 hours later or TNF levels. Hyperlacticaemia was more common in younger children and in those with deep coma It was negatively correlated with admission haematocrit. TNF concentrations and packed cell volume were independent predictors of hyperlacticaemia. In the children with CM, admission CSF lactate level was the best predictor of outcome and correlated with venous lactate, but surprisingly was not related to history of convulsions.

Lactate may be produced by the anaerobic glycolysis of both the parasite and the human host. Most is probably derived from the human host, for even with generous estimations of parasite burden, humans would be able to metabolise the lactate produced by the parasites [166]. In the brain, it causes swelling of neuronal cells, enhances the formation of oxygen derived free radicals and interferes with cellular metabolism [100]. Lactic acidosis may contribute to the pathophysiology of CM by promoting cytoadherence [204], impairing gluconeogenesis and cardiac output.

White and colleagues suggest that the lactic acidaemia found in patients with CM supports the mechanical hypothesis since the microcirculatory obstruction causes cerebral hypoxia, which causes the brain to switch to anaerobic glycolysis with the production of lactate. They showed that cerebral lactate production was considerably higher when adults were in coma than on recovery from CM [355], but they did not find evidence that the coma was caused by a local reduction in CBF (*vide infra*).

Cerebral Blood Flow

Warrell, White and colleagues have performed the only study of CBF and cerebral metabolism in CM. They measured total CBF, with a modified Kety-Schmidt method using tritiated water in 12 Thai adults and found the mean CBF (52.2 (+/- 4.0) ml/100g/min), was similar to that found in adults with other encephalopthies. In this study, the CBF did not change significantly when the patients breathed 95% oxygen + 5% CO_2 or when they recovered. Thus the comain CM is not caused by a total reduction in CBF.

Warrell *et al* argued that the CBF was low for the reduced arterial oxygen content of their patients (because they were anaemic) when compared to normocapnic adults with varying haemoglobin levels [47], but the low $PaCO_2$ found in their patients probably invalidates this comparison (Brown personal communication). They were able to demonstrate that CBF was responsive to changes in $PaCO_2$, (thus providing some evidence that chemical vasoparesis is not a feature of adult CM), although CBF did not correlate with absolute levels of arterial pCO_2.

Somewhat surprisingly there was no correlation between CBF and haematocrit or rectal temperature in this study, although other confounding variables such an increase in the viscosity from hyperproteinaemia (acute phase response) may have counteract these effects. Furthermore the technique they used for measuring CBF has not been validated.

This group claimed that cerebral vascular resistance (CVR) was raised in CM and the small, but statistically insignificant fall in the CVR with breathing 95% oxygen + 5% CO_2 and on recovery supported the mechanical obstruction hypothesis of CM. They used jugular venous pressure instead of ICP to calculate CPP (presumably because they could not measure ICP at the time of the CBF measurements) and if one recalculates the CVR using the mean LP CSF pressures presented in their paper the value is decreased. Furthermore the CVR was within the normal range quoted by some authorities. A more likely explanation of the fall in CVR with 5% CO_2 and recovery of coma is the partial resolution of the compensatory hypocapnia their patients exhibited.

Metabolic studies

Warrell and colleagues also reported low cerebral arteriovenous O_2 content differences (the cerebral venous O_2 was higher than normals), oxygen extraction rates and cerebral metabolic rates of O_2 ($CMRO_2$) in the adults with CM [355]. They suggested that these results were caused by the inability of the brain to take up O_2 (because the sequestered parasites interfered with O_2 transport) or utilise the O_2 delivered; either because the brain was "anaesthetized by local metabolic

changes" or because there was "luxury perfusion". However none of these parameters changed with resolution of coma, and the values are similar to those seen in other infectious encephalopathies which do not have microvascular obstruction [256]. Thus the significance of these findings is difficult to determine.

The most significant metabolic findings of this study were the confirmation of increased cerebral lactate production during coma, which decreased with recovery of consciousness. Although the values for the cerebral metabolic rate of glucose were normal during coma (as pointed out by Sharples [311]), they increased significantly only when the patients breathed 95% oxygen + 5% CO_2, (though not on recovery), suggesting that glucose metabolism is limited by the lack of O_2. Thus brain metabolism can be improved, albeit slightly, by better delivery of substrate.

Objections to the mechanical hypothesis

Although mechanical obstruction appears to be the most compelling hypothesis, there are a number of inconsistencies. There are some reports of patients with falciparum malaria who have neurological symptoms, but sequestered parasites were not found in the brain at post mortem [151,341]. In some of these studies other causes encephalopathies were not adequately excluded. Cerebral blood flow was not reduced and the evidence of an increased CVR is poor. Perhaps the most important inconsistency of this hypothesis is that if microvascular obstruction causes coma by reducing CBF, why does it not produce ischaemia and a higher incidence of neurological sequelae?

b) Permeability hypothesis

In the 1960's Maegraith and his colleagues proposed that CM was caused by the stasis of blood secondary to an inflammatory state [199]. They suggested that kinins increase the permeability of the blood brain barrier (BBB), causing an efflux of plasma out of the vessels, thereby concentrating the RBC within the cerebral vasculature and ultimately producing stasis of the blood. They based their hypothesis on the cerebral oedema found at post mortem in humans and especially on their studies of the Rhesus Monkey (*Macaca mulatta*) infected with *P. knowlesi.* In this model, they showed an efflux of albumin from the blood into the CSF [215,216] and since albumin is the protein responsible for 75% of the oncotic pressure, it would draw water into the brain interstitium, causing cerebral oedema. However they did not find a significant increase in CSF albumin, but showed that the protein was transported back into the blood at an almost equally fast rate. The increase in albumin transport did not appear to be associated with a raised ICP, although the pressure was not measured. Furthermore they showed that chloroquine and hydrocortisterone reduced the flow of protein in both directions in the monkeys [199,216]. These experiments lead to the widespread use of steroids in human CM [274,323].

There are important differences between the monkey dying of knowlesi malaria and humans with CM. *P. knowlesi* sequesters preferentially within the liver and the small intestines with hardly any accumulation within the brain. Thus despite rising parasite counts, the infected monkeys retain consciousness until just before death [3].

Blood Brain Barrier in humans with CM

The BBB has been shown to be grossly intact, both in African children [339] and Thai adults [352]. In Zairian children with CM, the concentrations of CSF albumin, IgG and IgM were not raised compared to normal children and were significantly lower than another group of Zairian children, most of whom had bacterial meningitis [339]. The immunoglobin findings contrast with those in Thai adults with CM, as in this group 78% had evidence of intrathecal production of IgG [59], although the studies are not directly comparable. In the non-immune adults, where the CSF:serum albumin ratio was significantly higher in Thais with CM than British controls, there was no significant difference in the ratios during coma compared with recovery nor in fatal cases compared with those who survived [352]. The CSF levels of larger proteins such as α2-macroglobin were not raised [352]. Furthermore the integrity of the BBB appeared intact, since less radiolabelled albumin entered the CSF while the patients were unconscious, than when they recovered. The increase in the CSF:serum ratio of ^{77}bromide reported in this study was thought to be caused by hypoxia interfering with the active transport of the bromide out of the CSF.

Warrell and colleagues suggested that these findings, together with normal LP CSF pressures in most patients [352] and the lack of cerebral oedema on CT scans of adults who survive CM [191], implies that the BBB is grossly intact in adults. However these studies do not exclude the possibility that an abnormal BBB (permeable to smaller molecules) and mild cerebral oedema, not detectable by

computerised tomography, may contribute to the pathophysiology of CM. Indeed, Davis *et al* [79] have shown that there is an increase in permeability of the retinal vessels in adults with acute falciparum malaria, this finding was associated with biochemical indices of severity but not the presence of coma.

c) Immunological hypothesis

The idea that immunological mechanisms might be responsible for CM rose from observations in the 1950s that malnourished children, who were presumably immunodeficient, rarely developed CM [87]. Support for this hypothesis comes from animal models and examination of human brains.

Experimental evidence

Experimental work in the sixties demonstrated that golden hamsters with a neonatal thymectomy [372] or those which were given anti-thymocyte serum were resistant to *P. berghei* infections [373]. During the last decade Grau and colleagues have developed a murine model of CNS involvement using *P. berghei* ANKA in genetically susceptible mice [109]. Initially they showed that $CD4^+$ T cells were essential for the development of the neurovascular lesions [108] and then went on to demonstrate that T-cell dependent macrophage activation lead to the release of cytokines including TNF which mediated the development of these lesions [106]. There are, fundamental differences between rodent models of CNS involvement and humans with CM. In rodents, monocytes are the principal cells that adhere to the endothelium, with little sequestration of PRBC. Immunoglobins are consistently deposited on the cerebral endothelium in mice, but not in humans. Coma is not a

prominent feature of murine malaria; rather the neurological manifestations are limb paralysis, deviation of the head, ataxia and convulsions [109]. Also , cyclosporin prevented the development of neurological complications in mice [107], but was not beneficial in adults with CM (Warrell personal communication).

Human evidence

Although immunological mechanisms are favoured mainly by experimentalists, they have also been proposed by some investigators studying human CM. Based upon pathologic specimens of adults dying in South America, Toro and Roman suggested that CM is a form of disseminated vasculomyelinopathy resulting from a CNS hyperergic reaction to a massive antigenic challenge during a falciparum infection [341]. However perivascular inflammatory response is not a feature of CM, the other features of a disseminated vasculomyelinopathy that are commonly seen in CM and are non-specific and could arise from terminal hypoxia [351]. The more specific features of the disseminated vasculomyelinopathy were not found in all patients. An increase in circulating immune complexes and the depletion of complement occurs in severe falciparum malaria, and in some studies is more common in CM than NCM. However, deposition of immune complexes on the cerebral vessels is not a consistent feature of CM [198] and steroids [129,353] or immunoglobin [332] are not beneficial .

d) Toxaemic hypothesis

Gaskell and Millar [96] were the first to propose that patients with malaria died from an overwhelming toxaemia. The kallikrein-kinin system was shown to be

important in murine and simian models of plasmodium infection, but evidence in humans is lacking. Clark further expanded this hypothesis by suggesting that endotoxins were responsible for the clinical features of severe malaria [63]. Although endotoxins are detectible in patients with falciparum malaria, they are associated with parasitaemia and leucocytosis, but not specifically with CM [22,345].

Oxygen Free Radicals

Clark went on to propose that Oxygen Free Radicals (OFR) are responsible for many of the clinical features of severe falciparum malaria, including CM [64]. He suggested that these substances was responsible for the endothelial injury seen in some animal models and that they contributed to the ischaemic damage. However He went on further to suggest that the extravasated haemoglobin was responsible for the seizures in CM and was a possible cause of coma. The evidence of OFR damage, as detected by products of lipid perioxidation is limited, although a recent trial with desferrioxamine, a potent free radical scavenger appeared to reduce the duration of coma [105].

Cytokines

More recently Clark and colleagues have suggested that the excessive production of cytokines released by the monocytes and macrophages are responsible for the pathogenesis of many of the complications of falciparum malaria, including CM [60]. *P. falciparum* infections have been shown to stimulate monocytes to produce cytokines, principally tumour necrosis factor (TNF) [109], interleukin-1 alpha (IL-

1) [170] and IL-6 [227]. Indeed TNF production significantly increases with schizont rupture and is probably the mediator of the paroxysms of fever associated with schizogony [169].

The interaction between the cytokines and malaria is complex. For example, the fever induced by the TNF release may have beneficial effects in inhibiting the growth of *P. falciparum*, stablising the parasite density and thereby preventing an overwhelming parasitaemia from developing in most cases [169]. Yet TNF may also promote sequestration by up-regulating receptors for adhesion of PRBC to endothelium [30].

Circulating TNF [110,170,307], IL-1 [170] and IL-6 [227] levels are high in African children with falciparum malaria and although there is considerable overlap in TNF concentrations, significant higher concerntrations were found in those with severe malaria compared with non-severe malaria [170,307]. Highest concentrations were associated with hyperparasitaemia [110,170,307], severe anaemia [307], hypoglycaemia [110,170,307] and young age [110,307]. CM was associated with the highest concentrations in Malawian and Gambian children, but not in Zairian children. Furthermore levels in children dying with CM were between 4 and 10 times higher on admission [110,170] and were persistently elevated prior to death [227] than in children who recovered from CM in the Gambia and Malawi studies [110,170], but this association was not seen in the smaller Zairian study. Elevated CSF levels were not found in Malawian children with CM [110], although high levels have been found in Gambian children who developed neurological sequelae

(Kwiatowski personal communication). The latter was association was not present in Indonesian adults who had elevated CSF levels, but did not have neurological sequelae (S.Hoffman personal communication).

There are three major objections to the cytokine hypothesis. Firstly there is considerable overlap between the concentrations associated with severe disease and mild disease. Also other conditions with comparable levels of cytokines manifest with different clinical syndromes, without coma. Secondly, all of the above studies measured total cytokine levels, but most TNF is bound to soluble receptors and only the free active cytokine may be responsible for the pathogenesis. Kwiatowski and Clark suggest that it is the local production, induced by the sequestered parasites (reflected poorly by the systemic levels) that may be responsible (personal communication). Thirdly recent pilot studies using anti-TNF antibodies have shown an ablation of fever, but no effect on outcome [172]. Thus elevated cytokines may be an epiphenomenon, associated with disease severity, but not a major mediator of the pathogenesis of CM.

Nitric oxide

Clark *et al* [61] have further extended their hypothesis to suggest that TNF has a central role in CM by stimulating nitric oxide (NO) production from the vascular endothelium. NO is an important mediator of vascular tone and could certainly mediate vasodilation. It may also promote sequestration by upregulating ICAM-1 and has antiparasite activity.

Clark *et al* propose that NO has profound clinical effects. Nitric oxide can cause seizures, but also interferes with the normal excitatory function of neuronal cells and may cause depression of consciousness. These animal researchers argue further that NO would explain the lack of sequelae, since NO is thought to play a role in other reversible 'encephalopathies' such as morphine narcosis, heat stroke and general anaesthesia *inter alia* [61,62]. However the pivotal role of NO in the pathogenesis of CM must be tempered by the clinical dissimilarities between these encephalopathies and CM. Furthermore inhibition of NO did not prevent vascular lesions in the brain of mice [231].

Other mechanisms of cerebral malaria

Hypoglycaemia

Hypoglycaemia (blood glucose< 2.2 mmol/l) occurs in 11-50% of African children with CM on admission to hospital [42,226,249,365] and is significantly associated with neurological sequelae and death [42,226,333]. In two studies of African children with falciparum malaria, hypoglycaemia was found more commonly in children with CM than those without it [166,365], although a recent report from Tanzania challenges this observation and suggests that hypoglycaemia is not a specific complication of severe malaria, but is found in severely ill fasted children in tropical areas [249].

In children with CM hypoglycaemia is associated with young age [226], high parasitaemia [226], convulsions on admission, deep coma, hepatomegaly and

leucocytosis. The hypoglycaemic children have appropriately low insulin levels with an increase in ketones [249,333,365]. The Thai adults with severe falciaprum malaria develop non-ketotic hypoglycaemia caused by hyperinsulinaemia particularly during pregnancy and after the administration of quinine [366]. Although quinine also increases insulin secretion in African children, the effect is not as marked [149,333] and when it is infused with 5% dextrose, it has not been associated with hypoglycaemia [333]. Counter regulatory hormones such as cortisol[166,333], glucagon [148] and growth hormone [333] are raised. The glycogen stores are diminished in hypoglycaemic children with CM (Molyneux personal communication), but the plasma levels of the gluconeogenic precursors lactate and alanine are raised. This suggests that there is impairment of hepatic gluconeogensis. Raised liver enzymes (5'-nucleotidase, alanine aminotransferase) [333] could be caused by a reduction in hepatic blood flow, or by lactate inhibiting the uptake of the amino acids by the liver. There may be an increase in utilisation of glucose from the anaerobic glycolysis of the PRBC or hypoxic tissue and an increase in basal metabolic produced by the fever.

The level of consciousness rarely improves after the administration of 50% glucose [166,226,333], suggesting that hypoglycaemia is not the cause of the coma in these children. Concern that administration of glucose would exacerbate the concomitant lactic acidosis in hypoxic tissue through the Pasteur effect appears to be unfounded [166,333].

Seizures

Seizures are an important presenting feature of CM, especially in African children, and if witnessed after admission to hospital are associated with a poor outcome [42,226]. In particular prolonged seizures, not easily controlled with diazepam or paraldehyde are associated with the development of neurological sequelae [37] and death [159]. Focal motor and generalised tonic-clonic convulsions are the most common clinically detected seizures [37,159,241], but absences and subclinical seizures that are detected with electroencephalography (EEG) are also common [159].

The cause of the seizures in CM is unclear. Clearly the intracranial sequestration of metabolically active parasites is a potential mechanism, but difficult to investigate. The seizures in CM are unlikely to be simple febrile convulsions (defined as generalised convulsion occuring in association with fever) since they occur more frequently than febrile convulsions in other groups of children and often have a localising features [241]. However there is no difference in the rectal temperatures or ages between those with witnessed seizures and those without [226], but a more detailed study has not been carried out. Other potential causes of seizures in CM are hypoglycaemia and hyponatraemia. In the Malawian study, seizures were not assocaited with hypoglycaemia, and the presence of hypoglycaemia did not influence the effect of witnessed seizures on outcome [226]. Likewise hyponatraemia does not appear to be assocaited with seizures in CM (A Sowumni personal communication).

EEG tracings in African children, either with a 2 lead or 12 lead machine, generally show bilateral diffuse slowing of the brain waves, often asymmetrical, which is compatible with a metabolic encephalopathy [159,181]. There was no correlation with clinical findings, although there is no data on the comparison of conscious level and EEG [181]. In particular the asymmetrical EEG changes were not inevitably associated with clinical signs, although those children that developed hemiplegia, often had pronounced slowing over the contralateral hemisphere [66,250].

Anaemia

Destruction of RBC with a fall in haemoglobin is almost an inevitable consequence of falciparum malaria. Severe anaemia is one of the life threatening complications of *P. falciparum* infections in African children either on its own or associated with CM or acidosis. African children with CM who also have severe anaemia (Hb <60 g/L) are more likely to die or survive with sequelae [42] and take longer to recover consciousness [226]. Whether severe anaemia contributes directly to ischaemia (by reducing oxygen delivery) or simply is a marker of severe disease is unclear.

The anaemia could be caused by many interacting mechanisms. Removal of RBC by the spleen is an important mechanism in adults with splenomegaly, and the spleen is the major site of RBC destruction after the institution of therapy [189]. Dyserythropoiesis is a feature of chronic anaemia caused by *P. falciparum* in Gambian children, but is not a significant factor in the fall of haemoglobin in acute infections [8]. Immune mediated intravascular haemolysis of PRBC and NPRBC

may also play a part, although its role is unclear. However the contribution of malaria in endemic areas is difficult to assess, since nutritional deficiencies, intestinal parasites and haemoglobinopathies also contribute [240].

In children with CM, the lowest haematocrit is reached within the first 24 hours after treatment [226]; in one series 23 percent of children required blood transfusions during the first 24 hours [226]. In non-immune adults without CM, using a simple mathematical model, the fall in haematocrit could be described by a three term equation [78]. The initial fall in haematocrit (during the first few hours) is caused by plasma volume expansion; a zero order fall with a mean half life of 25 hours occurred with the fall in parasitaemia and another fall with a half life of 43 days is associated with a loss of NPRBC. However this model relies on some tenuous assumptions *eg* the number of PRBC that sequester after treatment is small but it is unlikely that quinine used in this study, affected sequestration during the initial phases (Watkins personal communication). This model has not be verified in adults or children with CM.

INTRACRANIAL PRESSURE IN CEREBRAL MALARIA

Raised ICP has been described in CM, but most reports are anecdotal. Raised opening CSFP was reported in non-immune adults [98] and children with CM [338], but not in African children. Indeed based on one report of American soldiers [77], it was suggested that CM should be added to the list of recognised causes of RICP and papilloedema [276].

In most reports of RICP in CM, the technique for measuring opening CSFP was not adequately described and it is hard to exclude false elevations in pressure due to struggling patients or inappropriate manometers. In other reports the opening pressures were not measured, but described as "under pressure". In nearly all of these papers, the definition of CM varied and other causes of coma were not adequately excluded. In a larger and more carefully conducted study of adults, the opening CSFP was normal in most patients and lower in those who died [93,155,352]. These observations, taken in conjunction with the fact that cerebral oedema on CT scan appears to be an agonal event, are used to discount the role of RICP in the pathophysiology of adult CM.

In African children, the situation may be different. Measurements of opening CSFP have not been reported previously, although some authorities have stated that the CSFP is normal [225]. Bulging fontanelle was described as a feature of CM by one author [71], but most reports reporting opening pressures simply describe the pressures as increased [32,291,301]. Although brain stem signs have been reported

in children with CM [226,301], the possibility that these signs are caused by herniation was not entertained. Some authors have claimed that the administration of osmotic diuretics [67,156] and steroids improve outcome, however neither of these therapies have been subjected to randomised trials in African children. Thus the role of RICP in African children with CM has not been adequately examined.

IV. SCOPE OF THIS THESIS

This thesis sets out to examine the role of raised intracranial pressure in children with CM. In particular it attempts to answer the following questions, within the constraints of techniques available in a tropical endemic area:

1. Is ICP raised in African children with CM?
2. Does RICP cause neurological sequelae in this encephalopathy?
3. Is RICP a mechanism of death?
4. What causes RICP in African children with CM?
5. What practicable interventions are available for the treatment of RICP?

These studies were conducted in a rural district general hospital, situated in an endemic area, under conditions similar to those found in most hospitals that African children with CM would be treated. Autopsies, an important piece of evidence for determining the role of RICP in causing death, were not culturally acceptable in this area. However other techniques which are not usually available in African hospitals, have been used to provide data to assess the role of RICP in African children with CM.

2 BACKGROUND, PATIENTS AND METHODS

This thesis is based upon studies which formed part of a collaborative programme between the Kenya Medical Research Institute (KEMRI) and University of Oxford, United Kingdom, funded by the Wellcome Trust, United Kingdom, investigating severe malaria in African children. This chapter provides some background information of the children studied, describes the clinical management and the statistical methods used throughout the thesis.

GEOGRAPHICAL AND ENTOMOLOGICAL BACKGROUND

The studies were conducted at Kilifi District Hospital (KDH), situated in Kilifi, a small town (population approximately 12 000) on the Kenyan coast, 60 kilometres north of Mombasa. The hospital serves the heterogenous population of the town (21%) and the predominately Giriami people who live in scattered rural homesteads in the surrounding areas (79%) (Snow personal communication). Most of the people living outside the town are subsistence farmers; growing maize and cassava and keeping a variety of domestic animals such as goats, cows and chickens. The town dwellers are involved in commercial activities and local government administration.

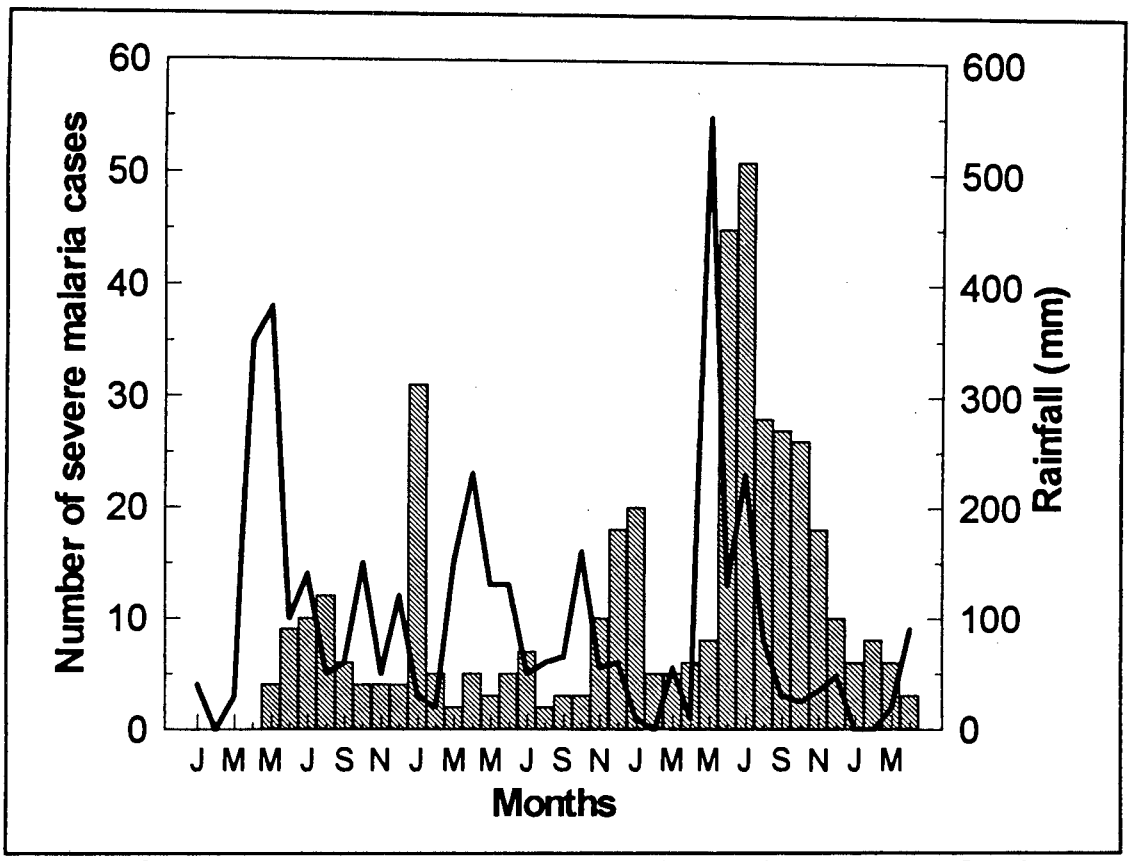


Figure 2.1: Rainfall (line) and number of severe malaria cases (bar chart) admitted to KDH March 1989-April 1992 (Kindly supplied by Dr RW Snow)

The average rainfall in this area is approximately 1000 mm per year. Although rainfall is recorded almost every month, there are two seasons of heavy rainfall per year, the main one from March to July, with a less intense rainfall period from November-January (fig 2.1). The mean daily minimum and maximum temperatures are 22 ^{0}C and 30 ^{0}C with a relative humidity of 70%.

Entomology

Anopheles gambiae s.l. was the predominant vector during the period of study, although only 3.5% of the mosquitos carried sporozoites [207,208]. Ten percent of *An. funestus* are infected, but this species accounts for less than one percent of

mosquitos caught in this area. Other species of mosquito such as *An. coustani, An nili, An squamosus* and *An pharoensis* are also present, but do not carry falciparum parasites. The vectors are present throughout the year, but transmission of infections are limited to 10 months of the year with peak periods from June to August and December to January [208]. The entomological data suggests that residents are exposed to an average of only 4 infective bites per year, although there were 60 infective bites per year in one area. However there does not appear to be an association between the entomologic rates and the incidence of severe malaria infections.

MALARIA IN THE COMMUNITY

Plasmodium falciparum, *P.malariae* and *P.ovale* are the main parasites that infect the inhabitants along the East Coast of Africa. The overall prevalence of falciparum parasitaemia was 34% in children aged 0-9 years who acted as community controls for a case control study of severe malaria. The rate varied from 39% during periods when a lot of children were admitted to KDH with severe falciparum malaria to 25% when admissions with severe malaria were low [325]. The average spleen rate in children aged 0-9 years is 35%. The minimum incidence of mild malaria (symptomatic children with parasitaemia > 5 000 per µl/l who were treated as outpatients at KDH) in children aged 1-4 years was calculated to be 352 and 185 per 1000 in a rural area and Kilifi town respectively.

IDENTIFICATION OF CHILDREN WITH CEREBRAL MALARIA

The studies in this thesis were conducted on children (age <14 years) admitted to the paediatric ward of the KDH from May 1st 1989 to April 30th 1994. The children were initially assessed in outpatients or casualty by clinical officers and then were examined by one of the KEMRI clinicians on admission to the ward. All the children had a fingerprick sample taken for detection of parasites and estimation of the haemoglobin concentration. A primary diagnosis of falciparum malaria was made if other causes of fever were excluded by clinical examination and investigations (chest X-ray, lumbar puncture, blood culture and other microbiological investigations) if clinically indicated. The definition of severe malaria was based upon the recommendations of the World Health Organisation (WHO) [354] (table 2.1).

We modified this definition to take into account the clinical spectrum that we saw in Kilifi (table 2.2). In particular, we considered prostration and hyperparasitaemia as defining criteria. Also we did not exclude children with microcytic anaemia unless there were other features of severe iron deficiency, since iron deficiency is very common in this community.

Table 2.1: WHO criteria for severe falciparum malaria [354]

Defining criteria of severe disease	
1. Cerebral malaria	see text
2. Severe normocytic anaemia	Haemoglobin < 51 g/l) with a peripheral parasitaemia ≥ 10 000 per µl. If RBC are hypochromic and/or microcytic, then haemoglobinopathies or iron deficiency should be excluded
3. Renal failure	Urine output <0.5 ml/Kg/min
4. Pulmonary oedema	
5. Hypoglycaemia	Blood glucose < 2.2 mmol/l
6. Circulatory collapse, shock	Systolic blood pressure < 50 mmHg in children aged 1-5 yrs
7. Spontaneous bleeding/ disseminated intravascular coagulation (DIC)	Bleeding from gums, nose or gastrointestinal tract and/or substantial laboratory evidence of DIC
8. Repeated generalised convulsions	> 2 seizures observed despite cooling
9. Acidaemia/acidosis	Arterial pH < 7.25 or plasma bicarbonate >15 mmol/l
10. Malarial haemoglobinuria	Macroscopic haemoglobinuria associated with acute infection but not antimalarial drugs
11. Post mortem confirmation	Venules/capillaries packed with erythrocytes containing schizonts
Other manifestations	
1. Impaired consciousness	Less marked than unarousable coma
2. Prostration	Unable to sit or walk without an obvious neurological explanation
3. Hyperparasitaemia	Definition varies with population group. In African children >20% parasitaemia
4. Jaundice	Clinically detectable or serum bilirubin > 50 µmol/l
5. Hyperpyrexia	Rectal temperature > 40 ^{0}C

Table 2.2: Kilifi definition of severe malaria

Criteria	Comments
1. Cerebral malaria	Unconscious for at least 1 hour after a seizure. See text.
2. Severe anaemia	Hb < 50 g/l, without evidence of severe iron deficiency
3. Hyperparasitaemia	> 20% erythrocytes parasitised
4. Generalised convulsions	Two or more within 24 hours of admission
5. Prostration	Unable to sit or stand unaided
6. Severe metabolic acidosis	Same as WHO criteria
7. Death with a confirmed diagnosis of malaria.	A child who died with a peripheral parasitaemia and had any of the above criteria

DEFINITIONS USED IN THIS THESIS

Cerebral malaria was diagnosed if a child:

1. was unable to localise a painful stimulus at least one hour after a seizure,
2. had a peripheral asexual parasitaemia,
3. was older than 7 months, and
4. other causes of unconsciousness excluded. For the most part this relied on the following causes:

   a) hypoglycaemia: the conscious level was reassessed when the child became normoglycaemic.

   b) pleocytosis: children with CSF white cell count >20 per litre were excluded, because of the increased likelihood of CNS infection.

   c) hepatic failure: icterus with abnormal liver enzymes.

Other causes of coma could not be excluded, although ammonia concentrations in a small group of children who fulfilled this definition (see chapter 5) were not as high as the concntrations in Reye's syndrome.

Timing of events after admission: events were timed from the onset of antimalarial therapy, since this time was accurately noted. In general this occurred within 1-2 hours of admission to hospital.

Duration of coma was defined as the time from the onset of antimalarial therapy administered after the admission to the time when the child could localise pain, if the assessments were made every 6 hours.

Parasite clearance was the time from the onset of antimalarial therapy administered after the admission to the first of two successive negative blood slides (no parasites detected after counting 200 nucleated cells).

COLLECTION OF CLINICAL DATA

Children with severe falciparum malaria were admitted to a purpose built unit adjacent to the paediatric ward and the clinical and laboratory findings were recorded on a standard proforma (Appendix I). Parenteral antimalarial therapy was started as soon as possible.

The children who were prostrate or unconscious on admission were reassessed an hour later to determine if they fulfilled the criteria for CM. Thereafter a general and neurological examination was performed and recorded on the standard proforma by one of the KEMRI clinicians every 6 hours until the child was able to localise pain or died. Level of consciousness was assessed by the Adelaide coma scale (ACS) [319] and the Blantyre coma scale (BCS) [226] (see table 1.2 in chapter 1).

On discharge, all children had a full neurological examination and the information was recorded on the standard proforma. Outcome was classified as either normal, mild/moderate handicap, severe sequelae or death [305]. (table 2.3).

Table 2.3 : Classification of outcome

Outcome	Criteria
Normal (N)	Normal or difficulty in walking on discharge, which resolves within 2 weeks.
Mild/moderate neurological sequelae (MNS)	Learning or behavioural problems, seizures less frequently than 1 per month, hemiparesis.
Severe neurological sequelae (SNS)	Seizures poorly controlled (>1 per month), spastic quadriparesis, blindness, vegetative state
Death (D)	

LABORATORY INVESTIGATIONS

On admission a blood sample was taken for a thick and thin blood film and a full blood count. Glucose was determined in almost all of the children with CM prior to the onset of treatment. Lactic acid, creatinine, total protein, albumin, total bilirubin and aspartate aminotransaminase were measured in a selected group of patients.

A thick and a thin blood film were prepared for the detection of malaria parasites. The films were stained with 2% Giemsa buffered to a pH of 7.2. Parasite densities were assessed by counting the number of asexual forms per 100 nucleated cells on a thick film and relating this to the total nucleated cell count. If there were more than 10 parasitised erythrocytes per nucleated cell, then the parasitaemia was determined from the thin film by counting the number of RBC with parasites. Full blood counts were performed on a M 530 Coulter Counter (Luton, UK). Platelet counts were performed using the visual method for whole blood [75].

Blood glucose was measured using Dextrostix and a glucose reflectance meter (Reflolux 2, Boehringer, Mannheim, Germany) and subsequently confirmed on site using a glucose oxidase method with an Analox (London, UK) GM6 microstat analyzer. Lactate was measured using a lactate oxidase method (Analox, London, UK). Blood gases were measured with a Corning 178 pH/blood Gas analyzer (Ciba Corning, Halstead, UK) and the measurements reported have been corrected for temperature and haemoglobin. Sodium and potassium concentrations in whole

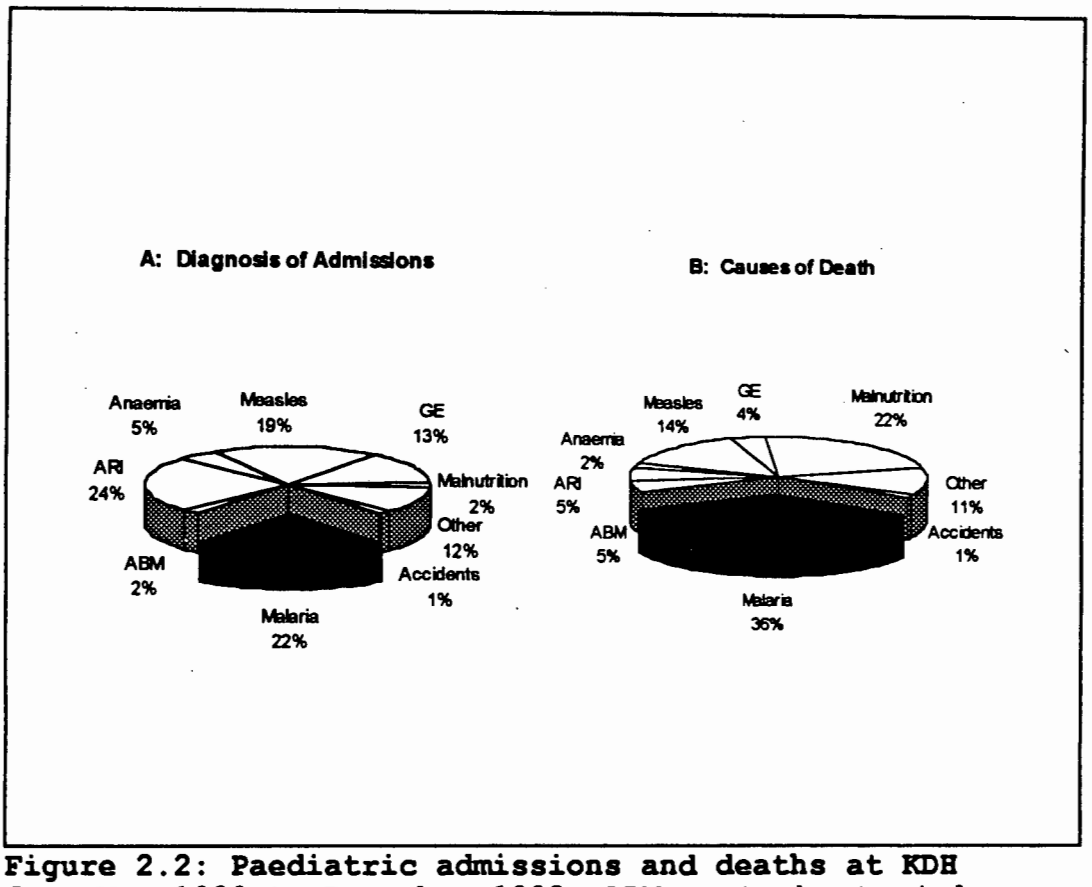


Figure 2.2: Paediatric admissions and deaths at KDH from May 1989 to December 1992. ABM-acute bacterial meningitis, ARI-acute respiratory infection, GE-gastroenteritis.

blood or plasma were determined with a Corning 614 Na^+/K^+ (Ciba Corning, Halstead, UK), urea with a Beckman BUN analyzer 2 (Beckman, Fullerton, USA) Beckman, creatinine with a Beckman creatinine analyzer 2 (Beckman, Fullerton, USA). Ammonia was measured sphectrophotometrically using an enzyme based kit (Sigma, UK).

Cerebrospinal fluid (CSF) was examined microscopically to determine the cell count. CSF glucose and lactate were measured with same devices for plasma estimations. CSF protein was measured by turbidimetric precipitation with 3% trichloroacetic acid.

EPIDEMIOLOGY OF SEVERE MALARIA IN KILIFI DISTRICT

Malaria was the most important cause for children admitted to the paediatric ward at KDH. A primary diagnosis of malaria was made in 22% of admissions and malaria accounted for 34% of the children dying in hospital (fig 2.2). The paediatric admissions were seasonal, following the rainfall pattern (fig 1.1) with two periods of increased admissions *ie* June-August and December-February.

Severe Malaria

The incidence of severe malaria during the period of study is presented in table 2.4 [325]. The average annual hospital recorded incidence of severe malaria in children under 5 years from the surrounding community is 14 per 1000 per year.

These figures represent minimum rates as some children die from severe malaria in the community before they reach hospital. During this period 15 children presented twice with severe malaria and 2 children presented 3 times. None of these children had more than one episode of CM.

Table 2.4: Incidence of severe malaria presenting to KDH [325]

	Incidence per 1000 child-years			
Age (years)	< 1	1-4	5-9	0-9
All categories of severe malaria	13.4	14.2	1.4	8.1
Cerebral malaria	1.6	3.4	0.5	1.9
Severe anaemia	5.3	3.0	0.03	1.9
Malaria mortality	1.0	1.1	0.03	0.6

The incidence of the WHO criteria for severe malaria is shown below (table 2.5) [203]. Many of the manifestations overlapped. CM, respiratory distress and severe anaemia are the most common clinical syndromes. Respiratory distress is defined as an increase in rate and depth of breathing and is associated with a metabolic acidosis. Almost all the mortality in children with hypoglycaemia occurs in those with CM or respiratory distress. The low mortality rate in children with severe anaemia is attributable to blood transfusions being administered promptly.

Table 2.5: Prevalence on admission and associated mortality of severe malaria from in children admitted to KDH from May 1989 to November 1991 [203]

Defining criteria	No. of children on whom admission data was available	Prevalence (%)	Mortality (%)
Cerebral malaria	1844	185 (10.0)	31 (16.8)
Severe anaemia	1816	320 (17.6)	15 (4.7)
Respiratory distress	1833	251 (13.7)	35 (13.9)
Hypoglycaemia	698	92 (13.2)	20 (21.7)
Circulatory collapse	1844	7 (0.4)	5 (71.4)
Renal failure	1844	2 (0.1)	0 (0)
Spontaneous bleeding	1843	2 (0.1)	0 (0)
Repeated convulsions	1842	338 (18.3)	23 (6.8)
Acidosis	110	70 (63.6)	15 (21.4)
Haemoglobinuria	1844	2 (0.1)	1 (50.0)
Other manifestations			
Impaired consciousness	1844	151 (8.2)	9 (6.0)
Jaundice	1806	84 (4.7)	10 (11.9)
Hyperpyrexia	1816	192 (10.6)	3 (1.6)
Hyperparasitaemia	1839	163 (8.9)	7 (4.3)

Cerebral malaria

The admission features of the 226 children with CM who were admitted and examined from May 1989-Dec 1991 are presented in table 2.6. These features are similar to children with cerebral malaria in Malawi [226] and The Gambia [42].

Table 2.6: Clinical and laboratory features of 226 children with CM admitted to KDH from May 1989 to December 1991

	All cases (n=226)	Deaths (n=33)
Age	36.1[18.47]	29.7[12.81]
Male:female ratio	1:1	0.9:1
Fulfilled criteria for CM after admission	42 (18.6%)*	4 (12.1%)*
Seizures: -history before admission (adm)	184(93.4%)*	25 (89.3%)*
- status epilepticus in 24hrs pre-adm	52 (26.4%)*	10 (35.7%)*
- during admission	178(91.8%)*	22 (78.5%)*
Rectal temperature on admission (n=208)	38.7 [1.15]	38.2 [1.16]
Splenomegaly on admission (spleen >2 cm)	77 (34.2)*	12 (37.5%)*
Hepatomegaly on admission (liver >2 cm)	70 (31.3)*	13(40.6)*
Parasitaemia on admission (per µl)		
< 10 000	58	8
10 000 - 99 999	73	13
100 000 - 999 999	75	10
> 1000 000	20	2
Haemoglobin < 50 g/l: on admission	54 (23.8%)	12 (36.4%)
during admission	98 (43.4%)	12 (36.4%)
Glucose on admission (n=208)	4.64 [3.08]	3.98 [4.59]
Hypoglycaemia on admission	45 (21.6%)	17 (58.6)
Hypoglycaemia during admission	63 (29.4%)	21 (70.0)
Transfusion administered	63 (28.0%)	7 (21.2)

[ ] = standard deviation

* = percentage of the number of cases in which complete data was collected.

During this period, 33 (14.6%) children died during admission, 38 (16.8%) had neurological deficits on discharge from hospital, while the remainder either had difficulty in walking or were discharged fully recovered.

CLINICAL MANAGEMENT

Children were nursed in the supine position, unless they were vomiting, in which case they were turned into the lateral decubitus position to prevent aspiration. A nasogastric tube was inserted and the contents of the stomach aspirated. Urinary catheters were not inserted routinely, except in the children with high creatinine levels and those undergoing intracranial pressure monitoring.

Chemotherapy

The children were treated with a number of antimalaria regimens that were being investigated during the 4 years of the study:

a) From May 1st 1989 - March 1990 children were randomised into groups of three to receive one of the following regimens:

i) Quinine dihydrochloride (Paris Chemicals, St Cloud, France) 20 mg salt/Kg (16.35 mg base/Kg) infused intravenously (IV) over 2 hours, followed by 10 mg salt/Kg (8.17 mg base/Kg) every 12 hours,

ii) low dose IV quinine dihydrochloride 10 mg salt/Kg, followed by 5 mg salt/Kg every 12 hours, with all infusions given over 2 hours

iii) intramuscular (IM) quinine dihydrochloride 20 mg salt/Kg, followed by

10 mg salt/Kg every 12 hours; quinine was diluted 1:5 in sterile water and was injected into the anterior thigh.

The first four doses were given parenterally, thereafter children able to take oral medication were given quinine sulphate to complete five days treatment [254].

b) From April 1990 to June 1991 children were randomised in pairs to receive either IM quinine dihydrochloride 20 mg salt/Kg, followed by 10 mg salt/Kg every 12 hours for a total of 6 doses or the same regimen plus IM sulphadoxine/ pyrimethamine (SP) (Fansidar^{R} parenteral, Hoffman La Roche; 25 mg/Kg sulphadoxine 1.25mg/Kg pyrimethamine) given on admission [243].

c) From July 1991 to June 1992 children received either IM or IV quinine dihydrochloride as a loading dose of 20 mg salt/Kg and 12 hourly maintenance dose of 10 mg/Kg until they could take oral medication when they were given a single dose of SP orally. For IM injections quinine was diluted 1:5 in sterile water and the loading dose was split and given into both thighs whilst the maintenance doses were administered into alternate thighs [369].

d) Since July 1992 children have been randomised as part of a multicentre trial of arthemether/quinine, to receive either IV quinine dihydrochloride 20 mg salt/Kg, followed by 10 mg salt/Kg every 8 hours or artemether 3.2 mg/Kg IM followed by a daily dose of 1.6 mg/Kg for a total of 5 days.

Antimicrobial therapy

Prophylactic antimicrobials were not prescribed. However with the decision to defer the LP until the child was neurologically stable (see chapter 3), Chloramphenicol (25mg/Kg) was given to cover the possibility that the child had acute bacterial

meningitis. Other infections were treated with chloramphenicol (septicaemia), benzylpenicillin and gentamicin (chest infections), cotrimoxazole (urinary tract infections) and erythromycin (superficial skin infections).

Intravenous fluids

Children were resuscitated or rehydrated on admission if required with 0.9% Normal saline or a plasma expander (Haemacel). Thereafter children with CM were given intravenous 4% Dextrose 0.18% Na Cl at a rate of 3ml/Kg/hr, until they were able to take fluids by mouth, after which they were given fluids *ad libitum*.

Routine investigations

Finger pricks were performed 6 hourly by the KEMRI nursing staff for parasite count and glucose estimation. In general children had at least daily estimations of haemoglobin, electrolytes and creatinine or urea. Urine collections and repeat blood cultures were performed if the child had a persistent fever or developed a fever after parasite clearance.

Hypoglycaemia

Dextrose 50% (0.6-1 ml/Kg) was administered as a bolus dose if a blood glucose <2.2 mmol/l was detected either by dextrostix, glucometer or Analox method. Blood glucose was rechecked an hour later and if low, 50% dextrose was again administered and the intravenous fluid was switched to 10% dextrose.

Blood transfusions

Blood (10-20 ml/Kg) was administered to children with severe anaemia (Hb <51 g/l) who had signs of respiratory distress or who had cool peripheries and those with a parasitaemia greater than 20%. The blood was administered over 5 hours, often preceded by Furosemide 1 mg/Kg IV.

Seizures

Most generalised seizures lasting more than 5 minutes were initially treated with Diazepam 0.3 mg/Kg IV. If the seizure persisted the Diazepam was repeated or Paraldehyde (0.1 ml/Kg IM) was given. Thereafter Phenobarbitone (10-15 mg/Kg IM) or Phenytoin (15-18 mg/Kg IV) was administered. Blood glucose was checked and hypoglycaemia treated. Temperatures above 38.0^{0}C were treated with fanning, paracetamol suppositories and regular tepid sponging.

ETHICAL PERMISSION

The non-invasive clinical studies described in this thesis were performed under the aegis of ethical permission granted by the KEMRI ethical committee for studies in the pathophysiology of severe falciparum malaria. The parents of the child were asked for permission in their home language to perform the transcranial Doppler studies and the computerised tomographic scans. Each of the drug studies was submitted for specific clearance from the ethical committee. The protocol for intracranial pressure monitoring was submitted to the KEMRI ethical committee

and the ethical committee at Great Ormond Street hospital, London for reasons discussed in chapter 5.

DATA COLLECTION AND ANALYSIS

The data recorded on the specially designed proformas (Appendix I) was entered into DBASE IV v2.01 (Ashton Tate, USA) which was installed on an IBM PC 50. The graphs were created with Freelance Graphics (Lotus) and the data was analyzed using two statistical packages; SPSS for windows v6.0 (SPSS UK Ltd) and Epi Info v5.0 (Centres for Disease Control, Atlanta , Georgia).

Descriptive statistics

Means and 95% confidence intervals are used to describe normally distributed data, otherwise medians and ranges are used.

Univariate analysis

Analysis of variance (ANOVA) was used to analyze data with a normal distribution and equal variance. Kruskal-Wallis analysis of variance is used for non parametric analysis of variance. Paired Students t-test was used for continuous variables. Comparisons of proportions were performed using Chi square or Fisher's exact test when the expected frequency in the cell is less than 5.

Differences are regarded as significant if the probability of the test statistic is less than 5%. Test values are not reported if the findings did not reach this level,

however the differences are reported as not being significant.

Multivariate analysis

Multivariate analysis was performed on some data sets. Logistic regression methods was used to identify variables which appeared to be related to outcome. Variables were selected according to their significance indicated by univariate analysis, their clinical importance and the completeness of the data sets examined. Analysis was conducted with multiple stages, reducing the number of each variable at each stage.

Regression and correlation

Regression analysis was calculated by the least squares method, if the following conditions are met:

1. the outcome variables had abnormal distribution
2. equal variance for each value of the predictor variable
3. the relation between the 2 variables was linear.

SUMMARY

The studies presented in this thesis are conducted on Kenyan children who live in a malarious endemic area and as such are probably representive of most African children with this encephalopathy. The diagnosis of CM is strictly defined, the clinical care and methods of analysis are described.

3 LUMBAR PUNCTURE OBSERVATIONS

INTRODUCTION

The simplest method of measuring raised intracranial pressure (RICP) the opening CSF pressure (CSFP) is at lumbar puncture (LP). Estimations of ICP made at LP have been used since 1888, when Queckenstedt first described the technique. Amost without exception the presence of RICP in encephalopathies, was first documented at LP. Our original observations of IH in children with CM were made at LP.

A number of factors need to be taken into account in the interpretation of the opening CSFP. The measurement assumes that the pressure is equal within the CSF cranio-spinal axis, which only occurs if the CSF is able to flow freely throughout the axis. Furthermore CSFP may not accurately reflect the ICP if the pressure within the cranium is changing rapidly [188]. The patient should be in the lateral decubitus position, so that the venous pressure is close to the atmospheric pressure and then the midline of the body can be taken as the level of reference [80]. The recordings should be undertaken in a quiet and relaxed child, since

crying can increase the ICP up to 25 mmHg [253] and flexion of the limbs and torso will also increase the abdominal and venous pressures, thereby elevating the ICP [28].

The CSFP measured with a fluid manometer is influenced by the amount of fluid removed during the measurement and the capillary action of the fluid in a glass tube. Since fluid is removed from the system to measure the pressure, this technique tends to underestimate the 'true' pressure. This is particularly important in the presence of RICP, as the volume/pressure response will be increased and thus aggravate the discrepancy. Capillary action of the CSF in the tube, however will tend to raise the pressure recorded in narrow bore tubes [213]. At normal intracranial pressure, an increase of 8mm CSF was measured in tubes in comparison to pressures recorded with a mercury manometer [213]. To address these problems, a specially designed non-displacement strain gauge pressure transducer has been designed [222]. This device has a sloping diaphragm (so that air bubbles are removed as the transducer is introduced into the spinal needle) and allows the opening CSFP to be measured with minimal loss of fluid. Non-displacement transducers are more accurate and may be safer [222].

PATIENTS AND METHODS

Initially we performed an LP on all children with CM at admission, to exclude CNS infections. However after a child with RICP died within 3 hours of an LP with signs of herniation (see case history 1, index case in results), we changed our policy to delay the LP until the child was neurologically stable, but covered the possibility of acute bacterial meningitis as the cause of coma with antimicrobials.

Lumbar Puncture

Lumbar punctures were performed with the child in the lateral decubitus position. A 22 G spinal needle was inserted between L2/L3 or L3/L4 vertebrae, then the child was deflexed such that the hips were < 45 degrees flexed and the head was in the neutral position. The opening pressure was recorded only if the child was quiet and there was a swing with respiration. The Queckenstedt test was not performed because it is considered dangerous in intracranial disease. Lumbar punctures were not performed in children with papilloedema.

Measurement of lumbar CSFP

Opening CSFP was measured in 2 groups of children with CM.

A. Admission CSFP

26 children had CSFP measured with a spinal fluid manometer (Waretex, USA) within 6 hours of admission from May 1989 to July 1990. The manometer had a calibre of 1.5 mm (measured with Raborne calipers with

an accuracy of 0.1 mm), which elevated the pressure measured by 3.3 mmHg (4.5 mm CSF or 4.9 mm H_2O) by capillary action in a stationary column of fluid at sea level. This is the maximum possible rise due to capillary action, but this influence is likely to be considerably less in a fluctuating column of fluid. A volume of 0.61 ml CSF was required to measure a pressure of 20 mmHg. Blood pressures were measured at the time of the LP with a sphygmomanometer.

B. CSFP after admission

35 children had CSFP measured with a non-displacement transducer (Gaeltech, Isle of Skye, UK), when they were neurologically stable and recovering consciousness (either flexing briskly to or localising pain). The transducer was calibrated from zero to 20 mmHg before each measurement and was sterilised in 2% glutaraldehyde between the measurements. In 13 children a comparison was made between CSFP measured with the non-displacement manometer and the spinal manometer.

CSF biochemistry

During 1989-1992, the CSF glucose (Analox, UK) was measured in 178 children with CM, CSF lactate (Analox,UK) in 54 and CSF protein in 52. In the remainder of cases, the tests were not performed within an appropriate time interval for accurate measurement or the results were not recorded.

RESULTS

Index case

The following case alerted us to the dangers of RICP in children with CM.

Case History 1 (Patient No. 265/90)

RH was a 3 and a half year old girl, who presented with 3 day history of fever and seizures. On admission she was flexing to pain, had features compatible with the diencephalic syndrome *ie* sluggish and constricted pupils, with full deviation of the eyes on oculocephalic reflexes and hyperreflexia. She had absent corneal reflexes and retinal haemorrhages in the left fundus. The parasiteamia was 201 000 per μl, blood glucose normal, Hb 44 g/l and she was not acidotic. The opening CSFP shortly after admission was 28 mmHg. The LP needle was connected to a transducer (Hewlett Packard), mannitol 1 g/Kg was administered over 15 minutes. Thirty minutes after the end of the infusion, the CSFP had dropped to 13 mmHg. During this period her breathing became more stertorous (repiratory rate 52/min) and 3 hours after admission, she had features of the pontine stage of herniation with no motor response. An hour later she had a respiratory arrest with a good cardiac output (blood pressure was not measured), and was intubated and hand ventilated. At this stage her pupils were dilated and unresponsive and thus fulfilled the criteria for the medullary stage of herniation. She was hand ventilated for about 40 minutes, during which she remained unresponsive, before attempts at resuscitation were discontinued.

Opening CSFP

All the opening CSFP measured on admission were above the normal range for children (figure 3.1). The mean (95% CI) opening CSFP was 16.7 (6.1 - 27.3) mmHg and mean CPP at the time of the LP was 52.6 (25.6 - 79.6) mmHg. Three children had opening CPP less than 40 mmHg; one died (CPP=38.0 mmHg) whilst the other two with lower CPP (30.3 and 31.3 mmHg) survived without sequelae. There was no significant differences in CSFP or CPP between the fatal cases and those who survived. There was no association between opening CSFP measured on admission and blood or CSF concentrations of glucose and lactate,

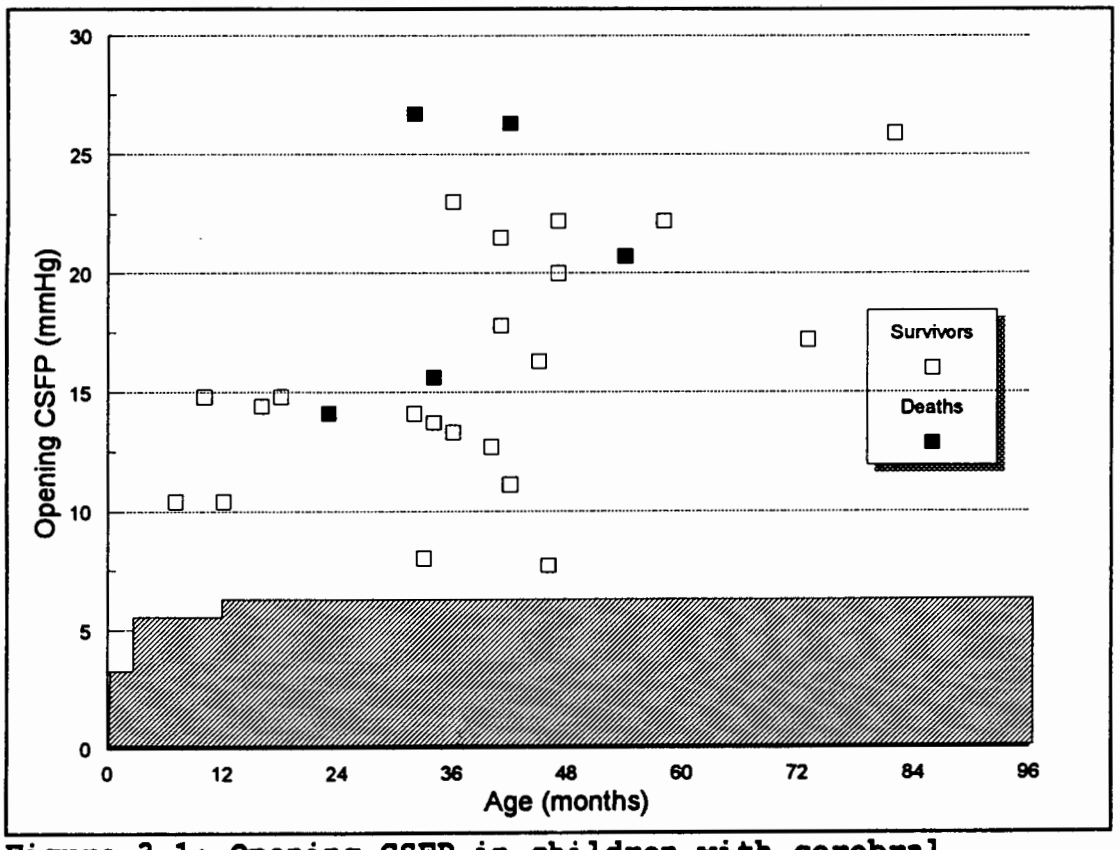


Figure 3.1: Opening CSFP in children with cerebral malaria, recorded on admission to KDH (May 1989-June 1990)

parasitaemia, haematocrit, the presence of retinal haemorrhages or the depth of coma as measured by the Adelaide motor response (Chi square, $p>0.5$). The only child who did not have a history of seizures during the 24 hours prior to admission, had an opening pressure of 20 mmHg.

The CSFP measured after admission are illustrated in figure 3.2. The pressures did not appear to be higher shortly after admission, although the periods of unconsciousness varied. Measurements with the non-displacement transducer correlated with the manometer ($r = 0.746$, standard error of estimate 2.97, $p = 0.0034$). The mean difference (non-displacement - manometer) was -2.12 mmHg with a standard deviation 2.85 mmHg.

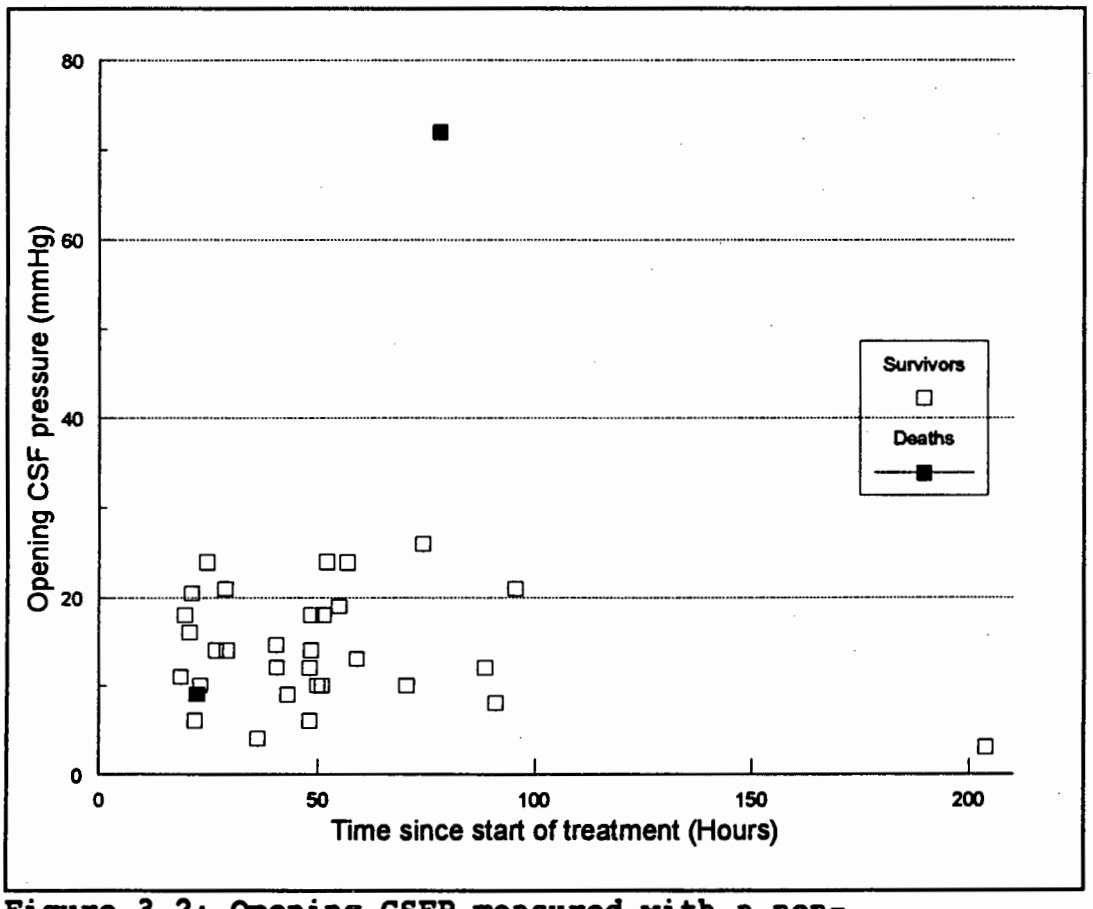


Figure 3.2: Opening CSFP measured with a non-displacement transducer after admission

There was no significant difference in the mortality rate between the patients who had an LP on admission and those in whom the policy was to defer the LP until they were neurologically stable (9/55 (16.4%) vs 24/170 (14.1%), $X^2=0.17$, $P>0.05$). Likewise there was no difference in the time of death from admission between these two periods (median (range): 6 (0-91) hrs vs 5 (0-55) hrs respectively).

Children who have deteriorated following LP, despite being assessed as neurologically stable *ie* coma score improving and the absence of brain stem signs, as is illustrated in the following case history:

Case History No.2 (132/92)

This was a 23 month old boy who presented with a 2 day history of fever, vomiting, irritability and seizures occured on the morning of admission. On admission he was deeply unconscious (Adelaide coma score (ACS): verbal 1, motor 1, with eyes open but no response to painful stimulus), had dilated sluggish pupils but no other brain stem signs. His fundi were normal. He was hypoglycaemic, acidotic with a parasitaemia of 176 000 per μl and Hb 89 g/l. He was treated with quinine and chloramphenicol. During the first 12 hours after admission he appeared to improve after his seizures (5 in 6 hours) had been controlled (ACS 232). However 36 hours after admission, he had episodes of decorticate posturing (provoked by touch) associated with dilated sluggish pupils. He was given mannitol every 4 hours during this period. The posturing lasted for 24 hours, after which he started to improve again (coma scores 232, pupils normal

and brisk). By this time he was aparasitaemic and had remained normoglycaemic since shortly after admission. The following day his coma scores were unchanged. He had an LP to exclude a CNS infection. His opening CSF pressure was 72 mmHg. He was immediately given mannitol, which reduced his pressure to 37 mmHg within 30 minutes. His CSFP rose again to 70 mmHg, only coming down to 58 mmHg with a second dose of mannitol. Thereafter he developed ataxic breathing and his pupils became fixed and dilated (fundi normal) and then he stopped breathing, his heart rate slowed. Resuscitation was unsuccessful.

CSF biochemistry

The CSF was macroscopically clear (by definition) and had a white cell count <20 cells/ml. A CSF protein >0.45 mg/l was significantly associated with death ($P=0.010$, 2 tailed Fisher's exact test) (table 3.1). The CSF lactates were significantly higher in children who died compared to those who survived ($p = 0.003$, 2-tailed t-test with pooled variance estimate). There was no difference in the glucose values between the groups.

Table 3.1: CSF biochemistry in children with cerebral malaria

Outcome	Protein (g/l)			Glucose (mmol/l)			Lactate (mmol/L)		
	n	median	No.(%) >0.45	n	mean	95%CI	n	mean	95%CI
All	52	0.28	21(40)	178	3.12	2.90,3.33	54	3.05	2.35,3.75
Normal	37	0.66	11(30)	128	3.07	3.58,3.19	37	2.87	2.06,3.68
SNS	10	0.37	6(60)	34	3.11	2.92,3.30	10	1.83	1.10,2.56
Death	5	1.58	5(100)	15	3.59	2.14,5.04	7	5.76	3.43,8.09

DISCUSSION

These results indicate that RICP is a feature of CM in Kenyan children. All the opening CSFP on admission were above the accepted normal range in children [222]. There was no correlation between opening CSFP or estimated CPP and outcome, although the only child with pressures recorded above 40 mmHg died. Furthermore there was no correlation between CSFP and a variety of clinical and biochemical markers of poor prognosis. However CSF protein and lactate values were higher in children who died, although there was no correlation between these variables and the CSFP.

CSFP measurements in other encephalopathies

The opening CSFP in these children with CM were similar to or higher than pressures measured in Reye's syndrome and ABM; encephalopathies in which RICP is thought to be an important determinant of outcome. In a group of 12 children with Reye's syndrome with a similar degree of coma (Lovejoy score <3 [18], the CSFP were lower than those measured in children with CM. In the study of opening pressures in children with ABM, most of whom were conscious, the median opening CSFP was 15 (range 8-70 mmHg) [223]. In neither study was an association between CSFP and outcome demonstrated.

A single measurement of raised CSFP simply indicates that RICP is a feature of the encephalopathy, for in most encephalopathies opening ICP does not predict

maximal pressure. Also the development of herniation is not dependent upon the actual level of ICP, but may occur at low pressures, if a pressure gradient between the supratentorial space and the spinal spaces has developed. Similarly a single estimation of CPP is unlikely to be a useful prognostic indicator. Although a minimum CPP <40 mmHg had been associated with a poor outcome in other encephalopathies [157,329], opening CPP does not predict minimal CPP. The single estimations of blood pressure measured with sphygmomanometer and the CSFP are not directly comparable to the data collected during monitoring of ICP and arterial blood pressure.

CSFP measurements in CM

Raised opening CSFP have subsequently been documented in African [185,350], Thai [360] and Vietnamese (D Bethel personal communication) children with CM. In comparison to pooled (but similar) data of children from Banjul, Blantyre and Sokloe, Thailand [360], the mean (95% CI) opening CSFP was 4.4 (1.8, 7.1) mmHg lower in survivors and 9.3 (3.2-15.4) mmHg lower in those who died than the CSFP recorded in the Kilifi children ($p < 0.001$) [360] (fig 3.3). The significantly higher pressures measured in the Kilifi children compared to elsewhere in the world, may have been caused by the difference in the manometers. For the measurements in The Gambian children, 0.7 ml of CSF was removed to measure a pressure of 7.4 mmHg [350], compared to 0.61 ml for a pressure of 20 mmHg in this series. The capillary action of the smaller calibre tubes that we used, appears have been offset by the influence of the removal of

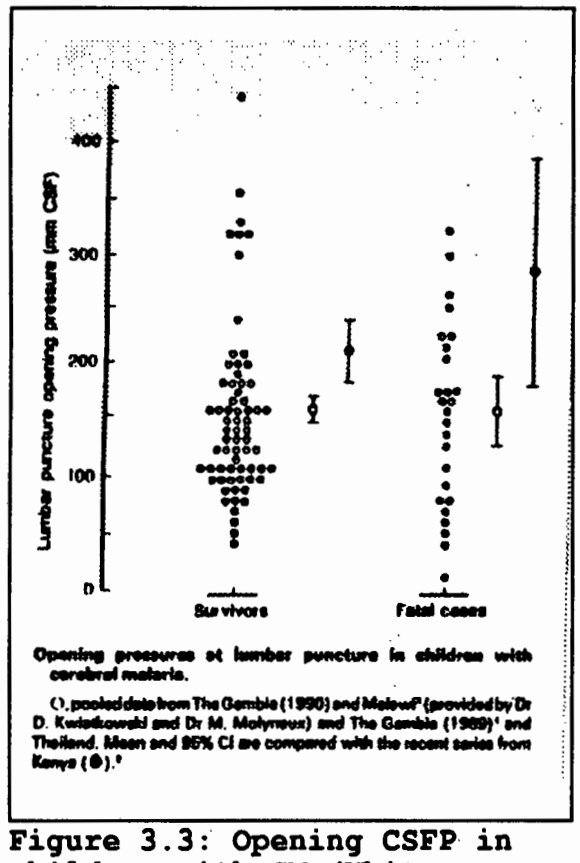


Figure 3.3: Opening CSFP in children with CM (White [360])

CSF, since the non-displacement transducer consistently measured higher pressures than the fluid manometer. Thus we think our acute data is more likely to represent the situation than the data from other units.

As found in other studies, there was no association between opening CSFP or CPP in any of these studies and outcome. Two patients with CPP less than 40 mmHg in this study survived without sequelae.

There was no correlation between opening CSFP and the clinical features of CM in this study or that of Gambian children. In the Malawian study, CSFP were significantly higher in those with papilloedema, and these children had a poorer outcome than those without papilloedema [185]. However there was no association between opening CSFP and extramacular oedema or other retinal findings in this study. There was no difference between the mean CPP in the survivors and the children who died in our study or The Gambian study.

Comparison between CSFP in adults and children with CM

The measurement of CSFP has been pivotal in the arguments about the role of IH in CM. The finding of normal CSFP in 80% of adults and the fact that the patients who died had lower pressures than the survivors [352] is used to refute the role of RICP in CM. These observations have not been substantiated in Vietnamese adults, in which CSFP was significantly higher in those who died compared to those who survived [81].

The mean opening CSFP are lower in children than adults with CM. Although the upper limit of normal is lower in children, the significance of the relative IH in the 2 groups are difficult to determine, since there is lack of data on the ICP at which herniation is likely to be precipitated in adults and children. The reduced pressure volume index documented in children [309], suggests that children are less likely to tolerate small elevations of ICP. Furthermore, children have lower blood pressures and in those with moderately raised ICP, CPP may be reduced to a critical level.

Dangers of LP

In endemic areas an LP is performed in children with CM to exclude other CNS infections. However the discovery of RICP in children with CM and the rapid deterioration, with the development of brain stem signs compatible with herniation in one child following LP prompted us to reconsider the timing of the LP. Thus we decided to delay the LP until the child was neurologically stable, but to cover the possibility of ABM, by administering antimicrobials.

There has been a slight, though not significant decrease in the mortality with the deferment of the LP This result could be attributed to improved management of these children by a more experienced and a larger staff. Furthermore this policy did not completely prevent neurological deterioration following unexpected high opening CSFP measured at LP when the child was thought to be stable (see case history 2). In the Gambian study, no obvious neurological deterioration was detected following LP [350]; however the examination of brain stem signs was not part of the protocol. The dangers of LP are further discussed in chapter 8.

CSF biochemistry

Lactate

The increased CSF lactate concentration and the assocaition of high levels with death in this study, confirm the findings in other studies of CM [226,364]. The differences in mean concentrations of lactate in children who die, between the groups of African children (9.1 mmol/l in Gambian children, 5.76 mmol/l in this study and 5.3 mmol/l in Malawian children) may be explained by analysing stored samples in these studies, rather than performing the tests on fresh samples (Peter Warn personal communication). The significantly lower concentrations of lactate in children who survived with sequelae in this study contrasts with the higher levels in the Malawian study (mean 7.0 (SD,4.8) mmol/l) and may be a function of our policy to delay the LP.

The CSF lactate concentrations are similar to those found in ABM and thus does

not help distinguish between these encephalopthies. Indeed similar concentrations are aslo found in tuberculosis menigitis, head injury and meningeal disemination of Non-Hodgkins lymphoma. In studies of head injury CSF lactate concentrations correlated with ICP levels [100], but no such association was found in the Kenyan children; probably because opening CSF pressures may not reflect the ICP pattern and that the sequestered parasites may contribute to the lactic acidosis.

The role of lactate in the pathophysiology of encephalopathies is unclear. It is usually thought to be produced by anaerobic glycolysis and thus acts as a marker of ischaemia or tissue hypoxia. Lactic acid interferes with sodium/potassium pumps on the cell membrane (causing the neuronal cells to swell), increases intracellular calcium (thus promoting the activity of degradative enzymes) and increases the formation of oxygen free radicals. All of these factors may combine to cause death of neuronal tissue. However other factors such as the glucose level (hypoglycaemia protects against ischaemia) and the fact that lactate can be utilised by neurons as a source of energy [100] complicate the interpretation lactate's role.

Protein

An increase in the total CSF protein is a non-specific marker of neurological disease [92]. In most conditions it is associated with an increased permeability of the blood brain barrier (BBB). The protein concentrations are higher in the lumbar region, probably because of an increased permeability of the lumbar subarachnoid space [92]. In this study, 40% of the children had elevated protein concentrations,

considerably higher than the 10% reported in Zairian children [24]. As the elevated CSF protein is not an universal finding, it is unlikely that the BBB breakdown is a major pathogenic feature of CM. The highest protein levels were associated with death.It is difficult to determine if this is an agonal event or an important mechanism of death.

SUMMARY OF LP FINDINGS

The findings at LP suggest that RICP is a feature of CM in children, but no correlation between CSFP and poor prognostic indices or outcome was found. These findings do not support a role for IH in the pathogenesis or pathophysiology of CM, but since the measurements represent single points in the course of the illness, these results do not refute IH as an important determinant either.

4 BRAIN STEM SIGNS

INTRODUCTION

Brain stem signs are common in children with CM and are associated with a poor outcome in most studies[226,301]. However in none of these reports was the hypothesis that the brain stem signs were caused by transtentorial herniation entertained. After finding raised opening cerebrospinal fluid pressure (CSFP) in the children with CM and documenting signs compatible with herniation in one child following LP (case history no. 1), we reviewed the clinical records to determine the incidence of brain stem signs and the relationship of these signs to outcome.

In our original report, we documented constellations of brain stem signs compatible with transtentorial herniation in all children who died with CM (Appendix III [237]). Furthermore 7 of the 12 children who died, had evidence of passing through 2 or more stages of herniation. However we were unable to confirm the mechanism of death in these children, since we could not obtain consent for autopsies from the children's guardians.

One of the controversies that arose from this publication, was the specificity of the clinical signs for herniation [171,358,360]. Similar brain stem signs to those documented could be caused by the systemic complications of malaria *eg* hypoglycaemia or the sequestration of the parasites within the brain stem. The criteria we used was based upon Plum and Posner's descriptions of the clinical features in adults, with intracranial tumours. The clinical diagnosis of herniation in other paediatric encephalopathies has varied and since few studies have autopsy data, the significance of clinical signs suggestive of herniation has not been firmly established in this population group.

Since our original publication we have extended our observations of the brain stem signs in CM. This chapter presents the results of further analysis. In particular, I identify the brain stem signs that were most reliably detected by the clinicians working at the hospital and determined which of these signs were associated the development of neurological sequelae and death. Thereafter I examine the relationship between clinical syndromes of herniation and death with the aid of a computer programme to remove any potential bias of the original study. I did not include neurological sequelae in this analysis, since the tomographic patterns in survivors are not compatible with transtentorial herniation causing neurological sequelae (see chapter 6). Finally I attempt to determine the cause of death in these children.

PATIENTS AND METHODS

Interobserver analysis

Twenty five children with CM were examined by the 3 clinicians who were responsible for most of the observations from May 1989 to December 1991. The clinicians had initially agreed on the examination technique and drawn up a manual which was referred to during the study. The examinations were performed within 12 hours of admission and at least 1 hour after any seizure. None of the children was ventilated at the time of the examination, nor had any child been given any sedative drugs except diazepam to terminate a seizure. The 3 clinicians examined each child within 1 hour of each other, with the other clinicians out of the room. The signs were categorised (table 4.1) and recorded on separate proformas. The results were not discussed between the clinicians at any point during the study.

Statistical analysis

The variation between observers was measured by the proportion of agreement (PA), disagreement rate (DR) [336], Cohen's Kappa (Kc) [94] and the fixed sample size kappa or concordance rate (Kn) [168]. The PA is simply the number of times the observers agree on the sign. The DR rate is a measure of the amount of discrepancy between 2 observers when they are using an ordinal scale to assess a sign. Values range from 0 to 0.5, the lower values reflecting less disagreement. Kappa statistics take into account the influence of chance in determining the agreement between observers and can be considered as the proportion of agreement beyond that expected by chance [168]. Kc is most commonly used (included for

comparison purposes) and adjusts for guessing by using the marginal totals. The Kn assumes that each of the categories have equal chance of being guessed correctly, without taking into account the marginal totals. Kappa values of 0 imply the responses are likely to have been due to chance, while a value of 1 represents perfect agreement. The following are generally accepted, although arbitrary guidelines for the interpretation of Kappa: 0 - 0.2, slight agreement; 0.21 - 0.40, fair agreement; 0.41 - 0.60, moderate agreement; 0.61 - 0.80, substantial agreement and >0.81 almost perfect agreement [269]. Weighted means of the statistics are presented as the 3 clinicians did not each examine all the patients [168].

Brain stem signs

All children admitted with CM had a full neurological examination, including an assessment of their brain stem performed by a KEMRI clinician. Subsequently the neurological examinations were performed every 6 hours until the children died or regained consciousness (defined as the ability to localise pain). Children who survived had a neurological examination on discharge from hospital. The results were recorded on a proforma (Appendix I), from which the data was entered into a data base (DBase IV version 2.01, Ashton Tate, USA). For the analysis, the respiratory pattern were reclassified as abnormal respiration for scores 1-4 (table 4.1) and abnormal posture for decerebrate or decorticate posture. Outcome was classified as normal, neurological sequelae (mild or severe as described in table 2.3) or death.

Table 4.1 : Classification of Clinical Signs

Position	1. Decerebrate 2. Decorticate 3. Normal
Respiratory pattern	1. Apnoea 2. Ataxic 3. Gasping 4. Cheyne-Stokes 5. Hyperpnoea 6. Normal breathing
Pupil reaction	1. No reaction 2. Sluggish 3. Brisk
Pupil size	1. Dilated 2. Constricted 3. Midpoint
Fundal appearances	0. Not visualised 1. Papilloedema 2. Haemorrhages 3. Full veins 4. Normal
Spontaneous eye movements	1. None 2. Abnormal movements eg ocular bobbing 3. Roving dysconjugate 4. Roving conjugate 5. Orientating
Horizontal Oculocephalic Reflex	1. None 2. Minimal 3. Full deviation 4. Normal
Corneal reflexes	1. Absent 2. Weak 3. Brisk
Motor response to a painful stimulus applied to the sternum	1. No response to pain 2. Extends limbs to pain 3. Flexes to pain 4. Localises painful stimulus 5. Obeys commands
Limb Tone	1. Decreased 2. Increased 3. Normal
Limb Reflexes	1. Decreased 2. Increased 3. Normal
Plantar Reflexes	1. Extensor 2. Equivocal 3. Plantar

Signs of herniation

I wrote a programme in Dbase IV (Appendix IV) to analyse the clinical data for:

a) signs that have been used for the diagnosis of herniation in children with acute bacterial meningitis (ABM). Two criteria were used, one from a retrospective analysis of clinical notes [130] and another set from a smaller series which had better post mortem data of herniation [277].

b) the criteria we used in the original publication (Kilifi criteria), split into the stages of herniation described by Plum and Posner ie diencephalic (KD), midbrain/upper (KMB), lower pontine (KP), medullary (KMD) and uncal (KU).

c) a stricter set of criteria also based upon Plum and Posner's stages that further attempts to exclude the influence of systemic disturbances and the signs which had a poor interobserver agreement (table 4.2).

The criteria used for each of these classifications is presented in table 4.4, together with the results of the analysis.

Review of the clinical notes

After the programme had been run, the notes of all children who had died were examined, including the comments which were not entered into the database, and the cause of death was classified into one of the categories shown in table 4.2.

Table 4.2: Criteria for cause of death

Cause of death	Criteria
Brain stem death	Respiratory arrest with a good cardiac output Pupillary dilatation + either ataxic or Cheyne-Stokes breathing and/or decerebrate posturing
Acidosis	Base excess less than -20 with hyperpnoea and cardiac-respiratory arrest
Severe Anaemia	Haemoglobin less than 50 g/l The following signs of heart failure: Respiratory rate > 60/min Intercostal recession Cool peripheries
Undetermined	

RESULTS

Interobserver agreement

Table 4.3 shows the interobserver reliability as assessed by the proportion of agreement (PA), disagreement rate (DR), Cohen's kappa (Kc) and the concordance rate (Kn). There was most agreement between the clinicians about the position and the pupillary responses, with moderate agreement about respiratory pattern, motor response to pain and fundal appearances. There was fair agreement about all the other signs except for the plantar response and pupillary size. In the ACS, there was substantial agreement about the eye signs and moderate agreement about the motor response, but less agreement about the verbal response. There was moderate agreement about the summated response. Assessment of the Blantyre coma scale was similar (data not shown)

Table 4.3 : Interobserver Agreement between 3 Clinicians

	Pa	DR	Kc	Kn
Position	0.75	0.09	0.29	0.56
Respiratory pattern	0.53	0.09	0.13	0.43
Adelaide coma score				
eye response	0.60	0.06	0.67	0.93
motor response	0.73	0.07	0.48	0.67
verbal response	0.60	0.06	0.28	0.50
summated response	0.40	0.06	0.42	0.37
Pupil reaction	0.69	0.13	0.33	0.53
Pupil size	0.40	0.30	0.30	0.11
Fundal appearances	0.56	0.17	0.27	0.45
Spontaneous eye movements	0.40	0.17	0.12	0.26
Oculocephalic Reflex	0.47	0.14	0.08	0.29
Corneal reflexes	0.58	0.18	0.32	0.37
Motor response	0.62	0.10	0.38	0.48
Limb Tone	0.51	0.16	0.30	0.28
Limb Reflexes	0.56	0.12	0.30	0.34
Plantar Reflexes	0.45	0.20	0.13	0.18

Clinical features

The main neurological features detected on admission which were associated with death are (table 4.4): a summated ACS less than 6, Adelaide verbal score of 1, abnormal respiration, no spontaneous eye movement and absent pupillary responses. Abnormal respiration was the most predictive sign.

Table 4.4: Clinical features present on admission associated with death

	N	Normal n = 151	Sequelae n = 38	Death n = 33	Statistical analysis for death*
Age (months):	222				No association between age
< 12		12	3	2	bands and outcome, not
13 - 24		28	10	12	even when categorised into
25 - 36		46	12	8	above or below 36 months
37 - 48		31	8	8	
> 48		34	5	3	
Summated ACS	220				For score < 6
< 6		20	3	11	FE 0.0024, OR=3.97 (1.55,
6-8		87	26	12	10.11). Otherwise NS
> 8		44	9	8	
Adelaide VS	220				For score = 1 χ^2=12.28,
1		31	10	16	p=0.00043, OR=3.85 (1.64,
2		113	27	15	9.06). Otherwise NS
≥ 3		7	1	0	
Abnormal respiration	222	15 (10)	6 (16)	10 (26)	FE: p=0.011; OR=3.48 (1.33, 8.99)
Spont. EM:	214				For no spontaneous eye
none		36	13	16	movement, χ^2=9.75,
roving		103	21	12	p=0.0018, OR=3.42 (1.43,
orientating		8	4	1	8.20)
Corneal reflex	192				
absent		16 (12)	9 (28)	7 (26)	NS
Pupil dilation	213	23 (15)	3 (8)	1 (4)	NS
Absent pupil	214				FE: p=0.083,
responses		6 (4)	4 (11)	4 (15)	OR=3.08(0.74,11.95)
Fundal haemorrhages	155	8 (7)	1 (4)	4 (25)	NS
Abnormal posture	221	14 (9)	3 (8)	2 (6)	NS
Oculocephalic	193				
none		19 (14)	4 (12)	10 (37)	FE: p= 0.01; OR=3.67
minimal		65 (49)	19 (56)	10 (37)	(1.36, 9.78)
full dev/normal		48 (36)	11 (32)	7 (26)	
Reflexes:	214				
increased		50 (34)	13 (38)	13 (46)	NS
decreased		34 (22)	10 (29)	9 (32)	NS
Tone:	207				
increased		42 (29)	10 (32)	9 (32)	NS
decreased		47 (33)	12 (31)	10(36)	NS
Plantars:	205				
extensor		60 (42)	14 (40)	10 (37)	NS

* Statistical results: FE - Fisher's exact test 2-tailed p value, NS - not significant (p >0.05), OR - Odd's ratio (5%, 95% confidence intervals)

There was a linear trend between the summated ACS (grouped as in the table 4.4) and death (χ^2=4.153, p=0.042); and the grading of the oculocephalic reflex and death (χ^2=4.119, p=0.042). There was no relationship between age of the child and death. Assessment of the BCS gave similar results to the ACS *ie* there is an association with the summated score and verbal response, but not with the other components. There is no significant association between other neurological signs recorded (spontaneous movement, absent vertical oculocephalic, bruxism, absent gag reflex, cranial nerve lesions and hemiparesis (see Appendix I).

There was an association between hypoglycaemia on admission and a lack of eye opening in response to pain (AVS=1) (χ^2=7.82, p=0.02) or spontaneous eye movement (χ^2=4.10, p=0.043) and decreased reflexes (χ^2=8.13, p=0.004). However there was no association between hypoglycaemia and the brain stem signs used to diagnosis herniation, in particular abnormal respiration, position, pupillary reaction or size, and the oculocephalic response.

Univariate logistic analysis (with a cut off at p=0.1) identified the following signs on admission as predictors of deaths: summated ACS < 6, AES = 1, AVS = 1, abnormal respiration, no spontaneous eye movement, pupillary dilation, absent pupillary response to light, no oculocephalic response, increased tone, increased or decreased reflexes. Abnormal respiration and dilated pupils are the clinical signs that predicedr death when this data is fitted stepwise to derive a minimum main effect model (table 4.5).

Table 4.5: Logistic regression: minimum main effect model for signs detected on admission (but taking into account hypoglycaemia) for predicting death

Variable	Degrees of Freedom	p value
Abnormal respiration	2	<0.0001
Pupillary dilation	3	0.0045
Oculocephalic reflex	4	0.0001
Hypoglycaemia	1	0.0090

Signs of herniation

The number of children fulfilling the various definitions of herniation are shown in table 4.6. Of the children who died, 18% fulfilled Rennick's criteria of herniation, 27% fulfilled Horwitz's criteria, 30% fulfilled a modified Plum & Posner definition and 42% fulfilled the original Kilifi definition. There was a significant association between death and the clinical features of herniation as defined by Rennick's or Horwitz's criteria, and those of midbrain or uncal syndromes (PPMB, KMB and KU). Furthermore brain stem dysfunction fulfilling the criteria of Horwitz, KD, KP, KMD and KU is associated with a trend towards sequelae and death (X^2=12.5, P=0.002; X^2=6.58, P=0.037; X^2=8.73, P=0.013; X^2=13.78; P=0.002; X^2=8.95, P=0.011 respectively).

On the data recorded during the 6 hourly examinations, 2 children had the features of more than one of Plum and Posner's stages of herniation, one with PPMB and PPMD died and the other with PPMB and PPU survived with severe sequelae. Three children had 2 or more features of our original criteria for herniation, 1 died after passing through KPD, KPP and KMB, whilst the other 2 survived although they had developed features of the diencephalic and midbrain syndromes.

Table 4.4 Criteria for herniation syndromes

Criteria for herniation		Survivors n = 189	Death n = 33	Statistical tests*
Horwitz et al [130] ≥ 2 of these signs simultaneously Excluded if convulsing at the time of the examination	1. Pupils: one or both fixed & dilated 2. Respiration: Cheyne-Stokes or apnoea 3. Position: decerebrate or decorticate or hemiplegia 4. Oculocephalic reflex absent	19	9	FE= 0.018 OR=3.36 (1.24,8.98)
Rennick et al [277] > 2 of these signs simultaneously Excluded if deterioration caused by seizures	1. Pupils: one or both fixed & dilated 2. Resp: irregular/ Cheyne-Stokes/ apnoea or arrest 3. Decerebrate or decorticate posturing or no response to a painful stimulus	7	6	FE=0.006 OR=5.78 (1.57,21.1)
Kilifi definition [237]: excluded if blood glucose <2.2 mmol/l or a seizure within 1 hour of the clinical signs				
Diencephalic (KD) 4 or more of these signs simultaneously	1. Pupils: small or midpoint, reactive to light 2. Respiration: Cheyne-Stokes 3. Oculocephalic: full deviation 4. Decorticate posturing +/- flexor response to pain 5. Hypertonia, hyperreflexia with extensor plantars	47	4	NS
Midbrain /upper pontine (KMB) 3 or more of the following	1. Pupils: midpoint and fixed 2. Respiration: hyperventilation 3. Oculocephalic: minimal deviation 4. Decerebrate posture +/- extensor response to pain	3	1	NS
Lower pontine (KP) 3 or more of the following	1. Pupils: midpoint and fixed 2. Respiration: shallow or ataxic 3. Oculocephalic: no response 4. Flexion of legs only or no response to pain 5. Flaccidity with extensor plantars	3	2	NS
Medullary (KMD) 2 or more of the following	1. Pupils: fixed and dilated 2. Respiration: slow, irregular or gasping 3 Respiratory arrest with adequate cardiac output	2	4	FE=0.005 OR=12.9 (1.9,107.0)
Uncal (KU) 2 or more of the following	1. Pupils: unilateral fixed & dilated 2. Unilateral ptosis 3. Oculocephalic: minimal deviation 4. Hemiparesis	2	3	FE=0.024 OR=9.35 (1.2,84.2)
Modified Plum & Posner excluded if blood glucose <2.2 mmol/l or a seizure within 1 hour of the clinical signs				
Diencephalic (PPD) No absent oculocephalic, roving dysconjugate eye movements or dilated pupils	1. Pupils: small or midpoint 2. Hypertonia or hyperreflexia 3. Cheyne-Stokes respiration or decorticate posturing	9	1	NS
Midbrain/upper pontine (PPMB)	1. Pupils fixed 2. Oculocephalic minimal or absent, or decerebrate posturing	6	4	FE=0.045 OR=4.21 (0.9,18.3)
Lower pontine (PPP)	1. Pupils fixed 2. Oculocephalic absent 3. No response to pain or extensor plantars or ataxic respiration	1	1	NS
Medullary (PPMD)	1. Pupils fixed and dilated 2. No motor response to pain +/- respiratory arrest	0	1	NS
Uncal (PPU)	1. One pupil dilated 2. Oculocephalic dysconjugate +/- unilateral decorticate or hemiplegic posture	8	3	NS

* NS = non significant (P > 0.05), FE= Fisher's exact test (2-tailed), OR=Odds ratio (5%,95% confidence intervals)

Cause of death

From the examination of the clinical notes of the children who died, 12 children had brain stem signs, 5 fulfilled the criteria of acidosis, 1 died with profound hypoglycaemia and in the remaining 15 the cause of death could not be determined from the information recorded in the notes. In this latter group, 3 children had a cardiorespiratory arrest without acidosis or severe anaemia, 3 children had a respiratory arrest without brain stem signs being recorded and in the other 9 children little information was available. Children with severe anaemia usually died on admission before they could be neurologically assessed or did not fulfil the criteria for CM.

DISCUSSION

The data presented in this chapter, establish that brain stem signs in children with are associated with death. Some of these signs are reliably detected by the clinicians who were present at most of the deaths and are similar to the clinical syndromes of herniation (as defined by various criteria).

Cause of death

There appear to be at least 2 distinct clinical syndromes in children with CM dying after admission to hospital; one in which there is evidence of brain stem compromise and the other associated with systemic metabolic disturbance. In the first group, the children die with signs compatible with herniation as diagnosed by

4 different, albeit overlapping criteria. This includes a set of criteria (modified Plum & Posner) which uses signs that are reliably detected by the clinicians who performed the examinations. In the children dying with systemic disturbances, brain stem compromise is not evident until the child has collapsed.

The proportion of children dying from either of these mechanisms cannot be accurately estimated from these data since in nearly a half of the children here was a lack of data. However more children died with brain stem signs than systemic metabolic disturbances.

Interobserver variation

Disagreement between observers in the interpretation of brain stem signs would influence the significance of these signs. In this study, as has been shown in other studies, there is considerable disagreement between clinicians eliciting brain stem signs [306], adding another variable to the interpretation of this clinical data. However we were able to establish that some of the signs used in the diagnosis of herniation can be reliably detected, in particular the distinction between decerebrate and decorticate posturing, pupillary reaction to light, respiratory pattern and motor response.

The differences in assessment of clinical signs may be explained by one or more of the following factors: i) the experience and training of the observers, ii) the stability of the sign over the period it is being assessed, iii) the number of categories that the results are classified into and iv) the distribution of the scores

amongst the categories (Newton *et al* in preparation). The instability of the clinical signs during the initial stages of the assessment of an acute encephalopathy may be important. The child's condition sometimes changed during the examination and it has been shown that the patient's position at the start of the examination may influence the motor responses elicited [40]. Hence the stimulation of a previous examination may aggravate the disagreement measured in these unventilated children. Categories recorded should reflect important pathophysiological events or provide useful prognostic information. Interobserver variability can be reduced by decreasing the number of categories. The addition of other categories even if they are easy to elicit and seemingly increase the sensitivity of the scale, will adversely influence the agreement between observers.

Neurological signs

The neurological signs most strongly associated with death are the summated ACS, verbal response of the ACS, abnormal respiration, spontaneous eye movement, pupillary reaction, and oculocephalic reflexes. Most of these signs form part of the herniation syndromes and are reliably elicited by clinicians, thus would be useful for the development of a prognostic index.

Brain stem signs compatible with herniation

The present analysis using more exclusive and stricter criteria, on a larger set of patients than our original observations, identifies signs of herniation associated with death in 18-42% of children. This represents the absolute minimum incidence, since the exclusive criteria are strict. In our original report, brain stem signs

suggestive of herniation were identified in all of the children who died. These signs were identified by inspection of the clinical case notes. Not surprisingly, most of these signs were seen during the agonal phases but they were recorded by a group of clinicians, most of whom were unaware that herniation might be a mechanism of death. The restriction of the analysis to the recorded six hourly examinations removes any possible bias of a retrospective survey, but also excludes significant stages from the analysis if they occurred between the recorded examinations or the signs were suggestive of a transition between two stages. Furthermore this analysis will not detect the rapid progression through the clinical syndromes of herniation during the agonal phases.

Signs of herniation in other paediatric encephalopathies

There have been a few reports in children with ABM, which support the association between brain stem signs and the presence of herniation at necroscopy. Williams [368] described a 4 year old child with Haemophilus meningitis, who over a period of 16 hours deteriorated from being stuporous, with normal respiration and small reactive pupils though having sluggish oculocephalic reflexes and withdrawing briskly from a painful stimulus, to having a respiratory arrest with fixed dilated pupils with an absent oculocephalic reflex after a period of decerebrate spasms. The child died three days later and a post mortem on the day of the death revealed a swollen oedematous brain with uncal grooving and a cerebellar pressure cone. Likewise in Horwitz's series, the only child with uncal herniation confirmed at autopsy had clinical signs of a rostrocaudal progression, unilateral dilation of a pupil and a respiratory arrest [130]. In Rennicks' larger

study of children with ABM, six children had herniation diagnosed at post mortem, although they did not describe the features that they used to identify herniation pathologically [277]. In five children, the level of consciousness was impaired and ventilation was required. Three had fixed or dilated pupils, three had abnormal respiration and two had an abnormal posture. However, one child who was unconscious and ventilated with pupillary abnormalities did not have unequivocal evidence of herniation. Thus in ABM which has some similarities to CM *ie* raised ICP, CSF lactic acidosis, but also has obvious differences *ie* severe cerebral oedema following the breakdown of the BBB: brain stem signs similar to those that are observed in children with CM are associated with herniation at post mortem.

The specificity of brain stem signs

The argument against the association between brain stem signs and herniation in CM, rests upon the presence of these signs in adults with CM (who do not have evidence of herniation at post mortem (NJ White personal communication) or on magnetic resonance imaging (S. Krishna, personal communication)) and the observations that children often recover after developing some of these signs [171]. Complications of CM may also produce brain stem signs, without evidence of herniation. Seizures are common in children with CM; over a third of children with brain stem signs compatible with herniation were removed from the analysis because they had a seizure within 1 hour before the signs were detected. It is possible the brain stem dysfunction persists for longer after a seizure than the one hour specified here. Furthermore seizures may also produce brain stem signs without more conspicuous signs of ictal activity such as twitching of the limbs

[159].

Metabolic perturbations such as hypoglycaemia, hyponatraemia and acidosis may also be associated with disturbance of brain stem function. Hypoglycaemia may produce an array of neurological signs including decerebration [45,302] and other signs of brain stem dysfunction [257]. In this series hypoglycaemia was associated with low scores of the Adelaide eye response, spontaneous eye movements and decreased reflexes, but not with the signs of herniation. Children with hypoglycaemia were excluded from the analysis of the herniation syndromes thus eliminating this factor as a confounding variable. Although it was a significant factor in predicting death in the logistic regression, the removal of this parameter from this analysis did not effect the significance of the other results. The effect of localised cerebral hypoglycaemia induced by the metabolically active sequestered parasites or anaerobic glycolysis could not be eliminated in this study. Acidosis is associated with brain stem signs [19], although it is usually associated with other causes of an encephalopathy. Also hyponatraemia has also been associated with brain stem dysfunction [167], although its contribution to the clinical signs is more difficult to define.

SUMMARY OF CLINICAL FINDINGS

The clinical data presented in this chapter, in conjunction with the raised opening CSFP documented in the previous chapter suggest that RICP may be an important determinant of death. There is substantial evidence, using a variety of clinical criteria, that a significant proportion of children dying with CM have brain stem signs compatible with herniation. However post mortem evidence of herniation could not be obtained to support this interpretation and other causes of brain stem dysfunction could not be excluded.

5 ICP MONITORING

INTRODUCTION

Raised intracranial pressure (RICP) plays a major role in the pathophysiology of some encephalopathies (see chapter 1), but clinical signs and non-invasive techniques do not reliably detect increased intracranial pressure (ICP). Thus monitoring ICP invasively is necessary to detect and describe the natural history of intracranial hypertension (IH). Furthermore ICP monitoring provides information on the intracranial compliance, either directly through the measurement of the pressure volume index (chapter 1) or indirectly by monitoring the effect of events such as seizures on ICP. Finally ICP monitoring is essential in the evaluation of therapies, improves the control of ICP and also identifies potentially harmful interventions.

The role of ICP monitoring in improving the outcome of encephalopathies is controversial. Although the mortality of severe Reye's syndrome appeared to drop with the institution of ICP monitoring [342]; other changes in management were

introduced at the same time and no randomised trials were published. Thus some clinicians argue that any benefit from continuous measurement of ICP does not justify the small, but significant risks of this invasive procedure. The proponents of ICP monitoring point out that ICP is the major cause of death in encephalopathies and monitoring is the only reliable way to detect RICP and refine therapy [289]. Furthermore they suggest that early and aggressive treatment may reduce the number of patients who develop intractable IH.

The most dependable method to monitor ICP in children is invasively through the skull. Intraventricular methods are considered the standard since the pressures in the supratentorial compartment are transmitted to the ventricles. Furthermore cerebrospinal fluid (CSF) can be removed through the catheter to reduce ICP and assess intracranial compliance. However the complications of this technique *ie* risk of infection (particularly ventriculitis), damage to brain tissue, intracerebral haemorrhage and blockage of the catheters. have restricted its use. Recently, fiberoptic devices have been developed to overcome the problems of damping and blockage of the fluid filled systems and can measure ICP accurately in various compartments of the cranium. The risk of complications from these devices are lower than the fluid filled intraventricular methods, particularly if they are inserted into the subarachnoid space or the brain parenchyma [73].

METHODS

Preparation for ICP monitoring

The decision to conduct ICP monitoring was made in August 1990, during the preparation of the paper on opening CSFP (Appendix III). The study was approved by the ethical committees of the Kenya Medical Research Institute and Institute of Child Health, London (Appendix V). I was trained in the insertion of ICP monitors by the Department of Neurosurgery, Hospital for Sick Children, Great Ormond Street, UK (Appendix V); as was Dr Jane Crawley who continued the monitoring after I had left Kilifi in August 1993. A room on the KEMRI paediatric unit was refurbished and designated as an intensive monitoring room. Ethical approval for the study and all the equipment had been obtained by December 1st 1991. Thereafter every child with CM was assessed as a potential candidate for ICP monitoring.

Criteria for ICP monitoring

The criteria for ICP monitoring changed during the study. During the first part of the study, the criteria were based upon a consensus of opinions expressed by practising neurosurgeons, a paediatric neurologist, together with a review of the literature and an analysis of the clinical features that were associated with a poor prognosis in children with CM. These criteria (criteria A) were:

i) a child who fulfilled the criteria for CM

ii) normoglycaemia and seizure free during the hour prior to the examination

& iii) had the following clinical signs:

a) lack of withdrawal, extension only or no response to pain

b) decerebrate/decorticate posturing

or c) one of the following brain stem signs:

dilated and sluggish pupils, or minimal or absent

oculocephalic reflexes.

From October 1st 1992 to August 1st 1993, the criteria were made less rigorous to determine whether ICP was raised earlier in the course of the disease and if treatment could prevent intractable IH (see discussion). In addition to children who fulfilled the criteria A, children who did not flex to pain briskly (criteria B) were considered for monitoring. After August 1st 1993, the original criteria (criteria A) were reinstated, since over half of the children with criteria B did not develop IH which required treatment.

The following exclusion criteria were applied, irrespective of the criteria used:

(i) platelet count < 40 $x10^9/l$, because of the risk of intracranial bleeding

(ii) severe uncompensated metabolic acidosis (pH < 7.1 with base excess < -20), since the child was likely to die from systemic causes.

(iii) evidence of spontaneous bleeding.

After the child was identified as a candidate for ICP monitoring, another clinician assessed the child to ensure the criteria had been fulfilled. Blood glucose was

rechecked. The procedure was fully explained to the parents in their vernacular by one of the KEMRI nurses as outlined in Appendix V. Consent was accepted if both the nurse and the attending physcian thought that the parents understood what the procedure entailed, in particular that a hole would be drilled in the child's head and that there was no guarantee that the monitoring would produce a good outcome.

Insertion of ICP transducer

A fiberoptic device (OLM ICP monitoring kits, model 110-4B, Camino Laboratories, San Diego, USA) was used to monitor the ICP. A new kit was used for each child. The monitor was inserted in the intensive care room of the KEMRI paediatric unit. The contents of the room were removed and the room was disinfected before each insertion. The procedure was performed under full sterile conditions, with the operator fully gowned up. General anaesthetic was not used, though Diazepam (0.3 mg/Kg intravenously) was given if the child was restless with posturing. After the head was shaved, the skin was cleaned with 2% chlorhexidine solution. The subcutaneous tissue over the non-dominant hemisohere was infiltrated with 2% lignocaine down to the periosteum. A 0.5 cm incision was made 2 cm anterior to the coronal suture in the midpupillary line, down to the bone. A 2.7 mm burr hole was made with the specially provided drill bit. The dura often had to be perforated with a needle. The Camino bolt was screwed manually into the skull to a depth of 3-5 mm. The catheter was connected to the pre-amp lead and zeroed to air before being inserted into the bolt. The wave form was verified and the opening ICP was noted. The ICP was displayed

as a digit on the Camino monitor (model 420) and the wave pattern and the mean ICP were displayed on a Hewlett Packard monitor.

Safety

After the ICP bolt was inserted, a doctor was present on the unit during the entire time of monitoring, except at times when the ICP had been lower than 20 mmHg for longer than 3 hours, in which event a KEMRI nurse was present. Although there was not a policy to use prophylactic antibiotics for the risk of infection from the ICP monitor, all the children were given IV chloramphenicol and benzylpenicillin until a LP was performed to exclude bacterial infection.

Treatment of RICP

The child was nursed in the dorsal decubitus position, with the head flat and in the midline position A nasogastric tube was inserted to prevent the aspiration of the stomach contents.

Mannitol was administered prior to the onset of monitoring if the child had:

i) unilateral pupil dilation

ii) decorticate or decerebrate posturing

iii) prolonged seizures (lasting > 30 minutes)

The indications for treatment of RICP during monitoring were based upon standard practice outlined in the literature [222] and discussions with practising neurosurgeons

and neurologists. Thus mannitol was administered for the following indications:

i) ICP > 20 mmHg for longer than 20 minutes.

ii) spikes of ICP > 20 mmHg, with more than 3 lasting longer than 3 minutes, or with less than a 5 minute interval between each.

iii) CPP < 50 mmHg for longer than 20 minutes.

Different doses of mannitol (0.25 to 1.0 g/Kg), sometimes with the addition of furosemide (1 mg/Kg) were used to establish the smallest dose which was effective.

Dopamine infusions were started if the CPP was less than 40 mmHg and mannitol had not raised the CPP above 50 mmHg. The infusion was started at a dose of 2.5 micrograms /Kg/min and was titrated against the CPP and the mean arterial pressure (MAP), to a maximum dose of 25 micrograms/Kg/min.

Removal of ICP monitor

The monitor was removed if the ICP was less than 20 mmHg for 12 hours and/or the child was beginning to localise pain. An LP was performed before the bolt was removed, the opening CSF pressure was measured with a non-displacement transducer (Gaeltech, Isle of Skye, UK) and the supratentorial pressure was noted. A CT scan was performed in 14 children after the removal of the bolt to detect any intracranial complications of CM or the ICP monitor (see chapter 6).

Data collection

The MAP was measured with a intra-arterial line (usually in the radial or dorsalis pedis artery, although the femoral artery was used in patient 332/92) connected to a pressure transducer (HP 1290C, Hewlett Packard, Andover, USA) and displayed together with rectal temperature and electrocardiographic pattern on a monitor (HP 7834A, Hewlett Packard, Andover, USA). The MAP and ICP data were sampled at least every 30 seconds in the children monitored during 1992 and 1993 and this data was stored on a Dell 320 N PC using a programme written for the collection of Near-infra Red Spectroscopy data (Onmono, Hamamatsu, Japan). After the malfunction of the programme due to a power failure, all ICP and MAP were recorded on a sheet at 15-minute intervals. During 1994 the software was not available, thus the ICP and MAP were recorded at least every 15 minutes (more frequently if the ICP was greater than 20 mmHg) by attendant nurses and doctors.

Data analysis

All the stored data was viewed, to identify maximum ICP, minimum CPP, ICP waves and time spent with ICP >20 mmHg, ICP >40 mmHg, CPP <70 mmHg, CPP <50 mmHg, CPP <40 mmHg. The changes in ICP and MAP with seizures, decerebrate/decorticate posturing, and some clinical signs (pupillary dilatation, yawning) were also assessed from this data.

Pressure waves

The pressure waves were classified as follows:

A-waves: abrupt rise in ICP to above 50 mmHg, with the ICP remaining at this level for 5-20 minutes, before returning to the baseline [194,217].

B-waves: sharp peaked waves occurring at a frequency of 0.5 to 2 minutes [194,217].

C-waves: rhythmic oscillations of an amplitude less than 20 mmHg, occurring at 4-8 per minute [194].

plateau-like waves: similar to A waves, but with an ICP of 20-50 mmHg at the plateau.

tented waves: elevations in ICP to greater than 20 mmHg, lasting 5-20 minutes.

Intracranial hypertension

The ICP and CPP findings were classified as follows:

Severe intracranial hypertension (SIH): ICP >40 mmHg for longer than 15 minutes continuously and CPP <40 mmHg for more than 15 minutes continuously.

Intermediate intracranial hypertension (IIH): ICP >20 mmHg for longer than 15 minutes and CPP <50 mmHg for more than 15 minutes continuously.

Mild intracranial hypertension (MIH): maximum ICP 10-20 mmHg for longer than 15 minutes continuously and minimum CPP >50 mmHg.

Normal intracranial pressure (NICP): maximum ICP <10 mmHg and minimum CPP >50 mmHg.

Outcome

Outcome was defined as in chapter 2. In particular the children who survived with spastic quadriparesis, intractable epilepsy and/or poor vision were classified as having severe neurological sequelae (SNS), whilst children with hemiparesis, learning difficulties or seizures that were controlled with anticonvulsants were regarded as having mild/moderate neurological sequelae (MNS). Good outcome refers to children who survived with MNS or were normal on discharge, poor outcome includes children with SNS or those who died.

RESULTS

Children monitored

From December 1st 1991 to 1st April 1994, 26 children were identified for ICP monitoring on the clinical criteria. Eighteen children had ICP bolts inserted. Two children were admitted in the absence of Dr Crawley or me. The others were excluded because parents refused consent (n=1), the parents were not available to give consent (n=2), the platelet count was less than 40 000/l (n=2) or there was severe uncompensated metabolic acidosis (n=1).

The clinical, laboratory and CSF features of the children who had ICP monitoring (arranged in increasing degree of IH), are shown in tables 5.1, 5.2 and 5.3 respectively.

Table 5.1: Clinical features of children who had ICP monitoring

Patient Number	Age (months)	Prior to Admission			On Admission				During Admission					Discharge
		Duration of fever (days)	Duration of coma (hrs)	Seizures[a]	ACS (VME)[b]	Brain stem signs[c]	Fundi[d]	MAP (mmHg)	Seizures[a]	Worst ACS[b] (hrs post Rx)	Brain stem deterioration[c](hrs post Rx)	Fundi[d]	Duration of coma (hrs)	CNS sequelae
220/93	24	4	2	GTC x5	232	No	Hg	63	PM x 5	232	No	Hg	12	None
214/93	21	2	17	None	234	No	N	68	? SCS[f]	232	No	N	39	None
210/93	71	3	8	S-PBG	242	No	N	82	S-GTC	111 (30)	36	Hg	77	None
056/93	35	4	24	GTC x5	131	Yes	N	77	None	132 (26)	18	Hg	68	None
055/94	77	3	16	None	234	No	N	73	GTC x1	222 (19)	19	N	49	None
002/94	17	6	36	S-PBG	231	Yes	N	72	None	?	7	N	96	Mild
374/92	19	3	1	GTC x2	232	No	N	63	S - PM	122 (18)	11	N	48	None
232/92	81	1	9	PM x2	232	Yes	N	NR	S- GTC	110 (19)	19, 36	N	87	Mild
207/93	51	4	10	GTC x3	234	A CR[g]	N	77	None	132 (6)	6	N	36	None
128/94	23	3	0	None	344	No	N	NR	PMx10, PBG x5	?	10	Hg	90	None
080/94	40	5	24	T x7	232	No	N	87	PM x2	?	26	Hg	96	None
421/93	53	3	0	None	243	No	N	77	PM x 4	232 (12)	No	Hg	36	None
185/93	84	1	15	S-T	232	No	NR	70	S -GTC	132 (6)	No	N	18	None
175/93	24	3	17	S-GTC	233	Yes	N	63	PBG x2	132 (20)	No	N	44	None
230/92	42	2	26	GTC	232	No	N	85	GTC x2	222 (12)	12, 40	Hg	120	None
332/92	24	3	0	GTC x 3	232	No	N	-	GTC x4	122 (60)	6, 24	Hg,Pap	>140	Severe
386/92	30	1	3	None	131	Yes	N	UR	PM x 1	222 (18)	15	N	>140	Severe
094/94	36	3	6	None	110	Yes	Pap	80	None	?	18, 23, 24	Pap	-	Died

[a] Seizures: GTC-generalised tonic clonic, PM-partial motor, T-tonic, S-status, SC-subclinical, PBG-partial becoming generalised.

[b] Adelaide coma scale: V-verbal, M-motor, E-eye opening.

[c] Brain stem signs: one or more of the following signs: pupillary dilatation + sluggish response to light, absent corneal reflexes, minimal or absent oculocephalic reflexes, decerebrate posturing.

[d] Fundal appearances: N-normal, Hg-haemorrhage, Pap-papilloedema, NR- not recorded

[e] Mean arterial pressure (MAP): NR-not recorded, UR-unrecordable (because it was too low)

[f] Intermittent episodes of upward eye deviation, associated with increases in ICP and higher amplitude on the cerebral CAM monitor

Abs CR = absent corneal reflexes only

Table 5.2: Laboratory investigations of children who had ICP monitoring

Patient Number	Blood Haematology and Biochemistry on admission												During admission (hrs post onset of Rx)			Time to clear parasites (hrs)
	Parasite count (per μl)	Hb (g/l)	WBC ($x10^9$/l)	Platelet count ($x10^9$/l)	Glucose (mmol/l)	Arterial blood			Lactate (mmol/l)	Na (mmol/l)	Ammonia (μmol/l)	Urea (mmol/l)	Highest parasite count (/ul)	Episodes of hypo-glycaemia	Lowest Hb (g/l)	
						pH	pCO_2 (kPa)	BE								
220/93	3 090	34	61.8	120	2.7	7.37	2.0	-14.5	9.7	134	108	18.1	28200	None	BTX	37
214/93	49 742	49	26.6	99	5.4	7.28	2.0	-17.2	6.2	150	117	9.2	Adm	None	BTX	42
210/93	3 848	60	7.4	56[b]	5.6	-	-	-	5.8	135	67	1.1	7 900(6)	None	38 (96hrs)	48
056/93	242 880	69	28.2	96	2.3	7.33	3.2	-10.5	9.6	141	-	25.5	496800	None	49 (72hrs)	60
055/94	80 340	83	8.3	66	5.1	-	-	-	2.7	134	90	4.2	220 000	None	63 (36hrs)	64
002/94	1 377	83	44.5	268	4.5	7.26	1.9	-17.8	2.0	148	?	28.4	Adm	None	64(23hrs)	12
374/92	36 580	43	11.8	96	4.0	7.4[b]	1.9[b]	-11.0[b]	_	134	-	3.9	174 900	None	BTX	57
232/92	1 200	110	11.2	160[b]	5.5	7.51	3.8	+2.2	1.1	134	144	3.6	Adm	None	100 (24hrs)	66
207/93	45 144	86	10.2	78	5.0	7.51	3.3	-0.1	2.2	128	67	3.9	1261900	None	46 (168hr)	44
128/94	10 535	31	21.5	240[b]	2.4	7.28	2.1	-17.5	11.1	142	113	10.8	356000	None	BTX	69
080/94	3 060	83	9.0	49	3.5	7.44	3.7	-3.5	1.4	138	121	5.1	Adm	None	52 (96hrs)	12
421/92	9 200	50	10.0	52[b]	5.0	7.42	3.2	-0.15	5.1	133	51	1.7	302400	None	BTX	33
185/93	15 200	81	16.0	290	5.6	7.39	2.4	-11.1	0.9	130	92	3.0	Adm	None	76 (12hrs)	20
175/93	4 293	48	15.9	43	4.3	7.43[b]	3.3[b]	-6.6[b]	3.9	135	75	4.0	576 000	None	BTX	60
230/92	1108800	111	6.2	65[b]	0.7	7.43[b]	4.6[b]	-0.8[b]	1.9[b]	140	232	Cr 90	Adm	40	BTX	90
332/92	92 520	60	18.6	171[b]	6.7	7.49[b]	2.8[b]	-5.4[b]	8.2[b]	136	144	9.4	585 000	72	BTX	66
386/92	37 269	132	36.9	139[b]	<2.2	6.90	3.3	-26.1	3.4[b]	144	34	6.6	72 700	18, 26, 29, 36	87 (90hrs)	48
094/94	310200	54	41.1	247	3.4	7.22	3.4	-15.3	8.9	140	?	5.6	534 00	None	BTX	Died

[a] BTX- blood transfusion

[b] Performed at the start of ICP monitoring, not on admission.

Table 5.3: CSF in children monitored

Patient Number	Time of LP since onset of Rx	Cell count		Glucose		Lactate (mmol/l)	Protein (g/l)
		WBC[a] ($x10^6$/l)	RBC[b] ($x10^6$/l)	Concentration (mmol/l)	CSF/blood ratio		
220/93	12	4(all P)	2	3.2	-	2.9	-
214/93	22	6 (5 L)	6	5.0	-	-	0.45
210/93	52	0	4	3.9	-	2.7	-
056/93	29	0	2	6.0	0.76	0.2	0.20
055/94	72	4	4480	3.0	0.73	2.1	0.20
002/94	30	0	98	4.0	1.05	-	0.12
374/92	33	0	8	1.5	-	-	0.27
232/92	27	0	0	1.7	0.63	1.6	-
207/92	19	0	8	3.7	0.73	-	0.14
128/94	25	0	2	2.9	0.76	1.8	0.54
080/94	70	6(all P)	1	3.3	0.69	1.6	0.26
421/92	-3	0	0	3.2	0.64	-	0.08
185/93	45	0	0	3.7	-	0.6	0.18
175/93	30	2	8	-	-	-	0.21
230/92	80	0	0	2.4	0.92	1.7	-
332/92	18	0	6	1.5	0.63	9.4	-
	215	0	0	-	-	-	-
386/92	29	0	0	2.1	0.72	2.4	-
	151	0	150	4.4	0.92	-	0.04
094/94	Post mortem	0	0	4.4		6.3	0.49

[a] WBC = white blood cells, L = lymphocytes, P= polymorphs
[b] RBC = red blood cells

None of the children had any micro-organisms grown from blood taken on admission or CSF from the LP. In the 3 children with mild leukocyte pleocytosis (table 5.3), 2 had seizures prior to the LP and none had other evidence of CNS infection *ie* normal CSF/blood glucose ratio and CSF protein concentrations.

Table 5.4: ICP monitoring in children with cerebral malaria

Patient Number	Time from start of treatment to onset of Mx (hrs)	Duration of Mx (hrs)	ICP					CPP				No. of mannitol infusions	Pattern of IH
			Opening (mmHg)	Maximum (mmHg)	Time spent > 20 mmHg	Time spent > 40 mmHg	Pressure waves[a]	Opening (mmHg)	Minimum (mmHg)	Time spent < 50 mmHg	Time spent < 40 mmHg		
220/93	3	10	10	16	0	0	None	54	54	0	0	0	MIH
214/93	2	20.5	15	19	0	0	? B	(50)	55	0	0	0	MIH
210/93	32	22	16	17	0	0	None	64	64	0	0	0	MIH
056/93	23	9	10	17	0	0	None	48	40	6	0	0	MIH
055/94	28	31	6	20	< 0.1	0	?	84	51	0	0	0	MIH
002/94	8	22	7	24	< 0.1	0	?	70	60	0	0	0	MIH
374/92	16	18	14	?	?	0	None	75	?	?	?	0	MIH
232/92	15	18	14	26	0.2	0	None	(61)	46	0.6	0	1	IIH
207/93	4.5	18	14	22	0.5	0	None	(46)	36	10	3	0	IIH
128/94	42	50	21	31	2.0	0	?	49	45	0.1	0	1	IIH
080/94	29	66	15	56	3.65	0.1	?	69	31	0.1	0	3	IIH
421/92	16	23	20	43	1.5	0.1	P & B	72	43	0.7	0	1	IIH
185/93	1.5	20.5	23	56	6.8	0.3	None	57	45	0.5	0	1	IIH
175/93	8	36	32	32	14.5	0	None	43	35	17.8	0.7	2	IIH
230/92	49	32	28	49	21.9	0.9	B,T	51	34	3.6	0.3	6	IIH
332/92	13	122	13	95	63.2	13.9	B, C & T	60	32	23.9	1.4	26	SIH
386/92	22	92.5	9	> 60	> 30	?	B & T	42	< 30	> 6	?	8	SIH
094/94	10	16.5	25	158	7.3	4.5	?	55	2	3.3	3	5	SIH

[a] A = Lundberg's A-waves, B = Lundberg's B-waves, C = Lundberg's C-waves, P = plateau type waves, T = tented waves (defined in the text)
[b] () opening CPP calculated from blood pressure measured with sphygmanometer
[c] ? Excessive drift during ICP monitoring, hence unable to determine accurately

Summary of ICP findings

In this group of children, selected on the basis of 2 overlapping sets of criteria, 3 children had SIH, 8 had IIH, while in the remaining 7, the ICP was elevated, but did not rise above 20 mmHg for more than 15 minutes (table 5.4). This classification includes 2 children in whom the ICP monitor drifted by 16 mmHg (386/92) and -11 mmHg (374/92) due to a faulty pre-amplifier cable. The wave pattern was preserved throughout the monitoring and the ICP responded rapidly to mannitol or seizures.

Patient No.386/92 had pressures compatible with SIH since the maximum ICP could be estimated as greater than 60 mmHg (since the maximum ICP recorded was 80 mmHg) and the minimum CPP (31 mmHg) was recorded shortly after the insertion of the monitor. The CSFP recorded at LP 2 hours later was similar to the ICP, indicating that the monitor had not drifted considerably during that period. The other child (374/92) had pressures compatible with MIH, although this could not be ascertained with the same degree of confidence.

Opening ICP and CPP did not predict maximal ICP or minimum CPP respectively (fig 5.1). Only one child had the maximum ICP recorded at the insertion of the ICP monitor and he developed IIH. In the other children who developed either IIH or SIH, five had an opening ICP less than 20 mmHg, including the two who survived with SIH. Of the children with a minimum CPP less than 40 mmHg, all had an opening CPP greater than 40 mmHg, including 2 who had opening CPP less than

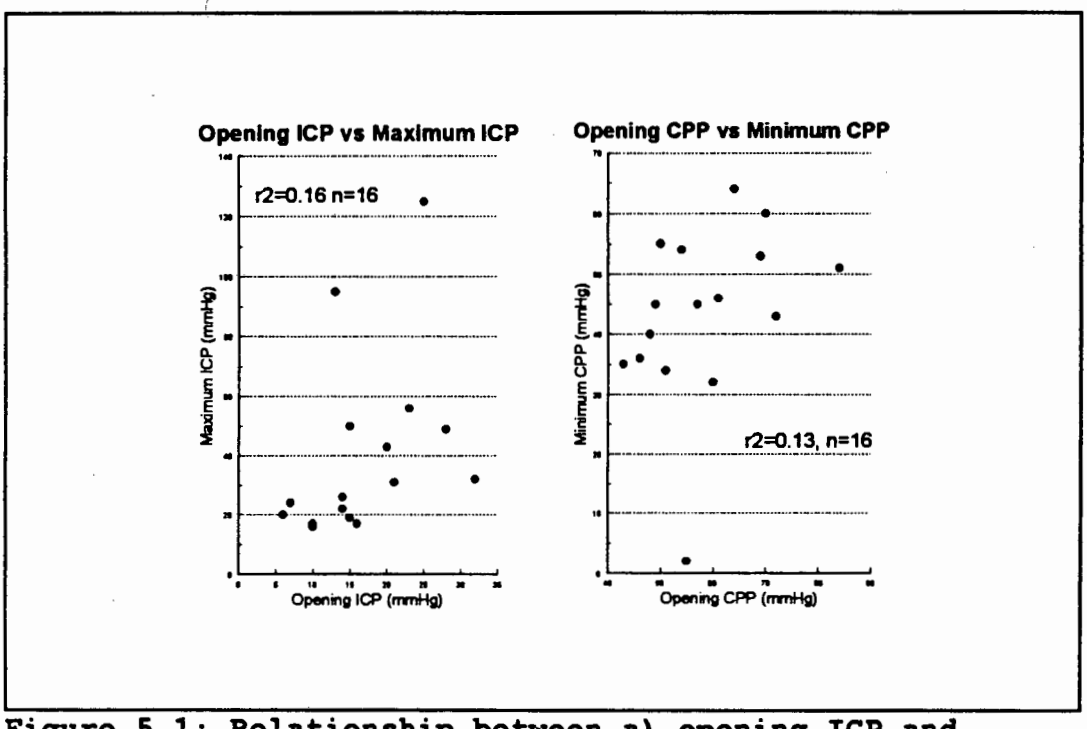


Figure 5.1: Relationship between a) opening ICP and maximum ICP, b) opening CPP and minimum CPP

50 mmHg. Two children had their minimum CPP recorded at the time of insertion of the ICP monitor.

Outcome

In this series of 18 children, one child died, two had SNS and two had mild neurological sequelae. The three children with a poor outcome all had SIH, while one child with mild sequelae had IIH and the other had MIH.

Death and severe neurological sequelae

The child who died (094/94) was admitted with opisthotonic posturing and papilloedema. The opening ICP was 25 mmHg and CPP 55 mmHg (fig 5.2). During the first 11 hours of monitoring, 3 doses of mannitol prevented the ICP

from rising above 30 mmHg and the CPP from dropping below 55 mmHg. Thereafter the ICP rose to a peak of 153 mmHg (CPP 2 mmHg) despite a further 2 doses of mannitol. The child died with evidence of uncal herniation, progressing to the medullary syndrome.

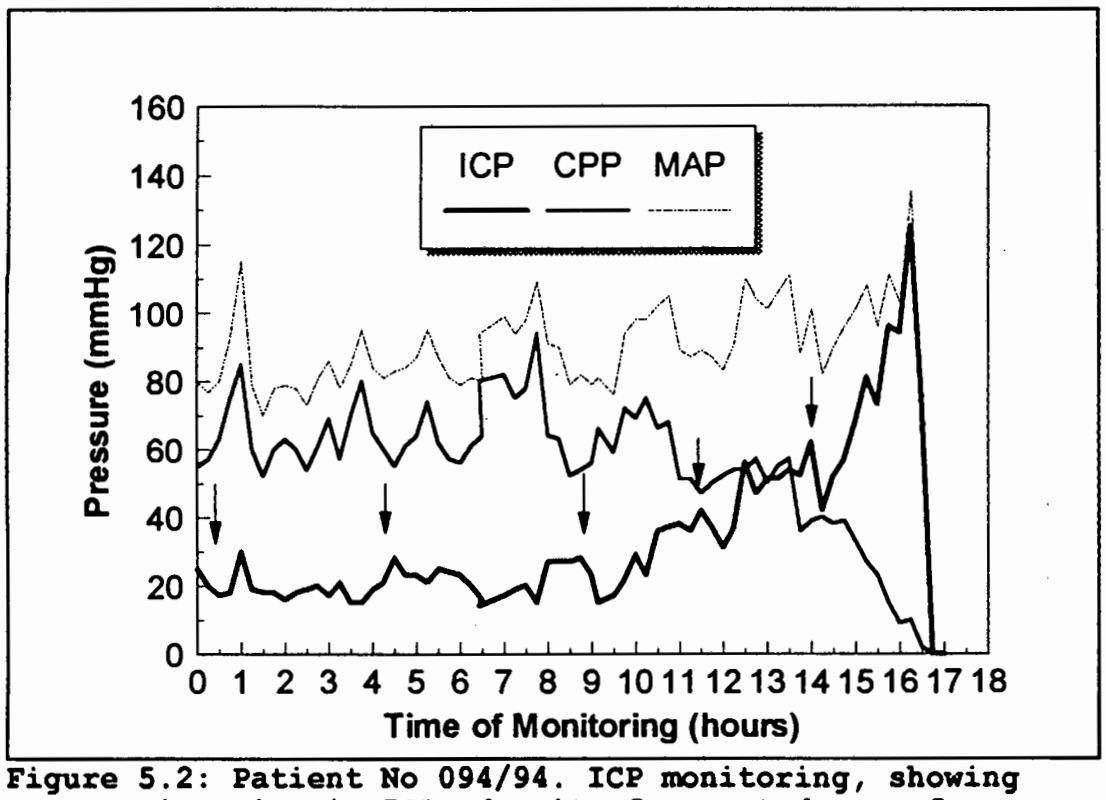


Figure 5.2: Patient No 094/94. ICP monitoring, showing progressive rise in ICP, despite frequent doses of mannitol (arrows).

The other 2 children with SIH were discharged from hospital with severe neurological sequelae. One child (332/92) was blind, did not respond to his mother voice, although he startled to loud noises He could not talk and had bilateral fisting with a spastic quadriparesis. He died 4 months after discharge with a respiratory illness. The other child (386/92) was irritable, unable to talk, could visually distinguish between light and dark only, and had a spastic quadriparesis.

Mild neurological sequelae

A 6 year old child with IIH (No 232/92) had learning difficulties which impeded his promotion at school. Another 18 month old child (002/94) who also had a history of status epilepticus, was discharged with right hemiparesis, right visual field defect and right sided sensory inattention. These defects improved over a period of 12 months. All the other children survived without any sequelae.

Relationship between ICP or CPP and outcome

In this small series a maximum ICP above 60 mmHg (P = 0.001, Fisher's exact test 2-tailed) and CPP below 35 mmHg (P = 0.005, Fisher's exact test 2-tailed) were strongly associated with a poor outcome (fig 5.3). Furthermore there was an association between a minimum CPP less than 38 mmHg (p=0.025, Fisher's exact test, 2 tailed) or maximum ICP > 40 mmHg (p=0.04, Fisher's exact test, 2 tailed) and poor outcome, as has been found in other encephalopathies. The maximum ICP and minimum CPP compatible with a good outcome was 56 mmHg and 34 mmHg respectively.

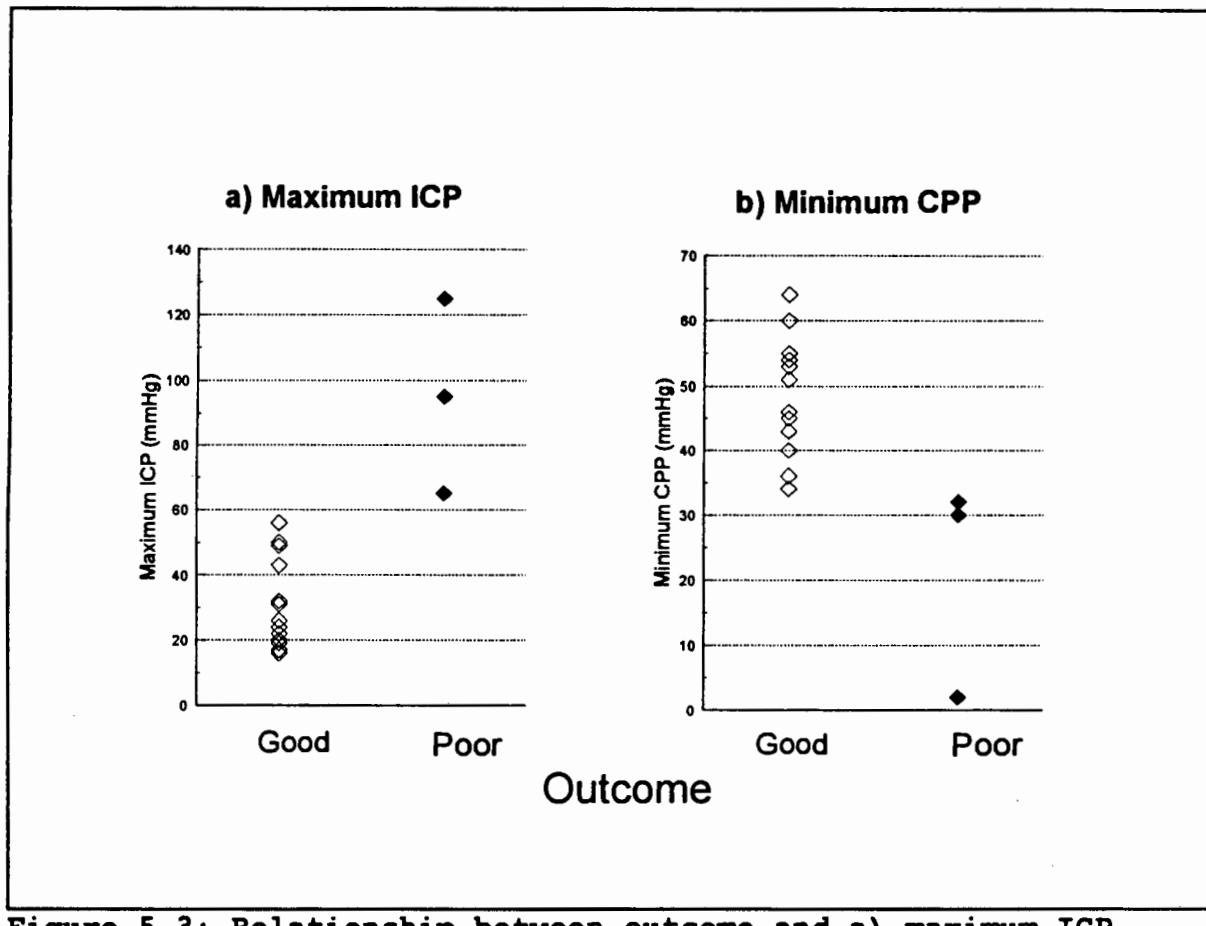


Figure 5.3: Relationship between outcome and a) maximum ICP and b)minimum CPP

A Patterns of Intracranial Hypertension

i) Severe Intracranial Hypertension

The course of the child who died with SIH is described above. The other 2 children with SIH (nos 332/92 and 386/92) had similar patterns of IH, with an opening ICP of 13 and 9 mmHg respectively, an initial period of 10-12 hours during which the ICP was not critically raised (< 20 mmHg), thereafter developed

intractable IH with little response to frequent doses of mannitol. These children were monitored for 122 hours and 92.5 hours respectively, before the monitor was removed (because the children had been neurologically stable for at least 24 hours and they were becoming restless).

In the child who died (09/94), the maximum ICP and minimum CPP were measured 16 hours after the monitoring began, during the agonal stages. In one of the children who survived (332/92) the maximum ICP and minimum CPP were recorded at 33 hours and 97 hours respectively. The other child with SIH (386/92) was admitted hypoglycaemic with an unrecordable blood pressure before the intractable intracranial hypertension developed. The times and values of the maximum ICP and minimum CPP could not be determined accurately in this child because of the drift in the monitor.

B-waves and T-waves were recorded in both children who survived with SIH and one child had prominent C waves documented. Child no 332/92 had 7 episodes of B waves of which 2 were associated with clinical signs. The B waves only appeared during the later part of the monitoring in child No 386/92. In the child who died, the ICP was not collected frequently enough to detect pressure waves.

ii) *Intermediate Intracranial Hypertension*

The 8 children with IIH had a median opening ICP of 20.5 (range 14-32) mmHg and the median of the maximum ICP was 37.5 (range 22-56) mmHg measured at

12.5 (range 2-18) hours after onset of monitoring or 51(12-63) hours after onset of treatment. Four children had minimum CPP less than 40 mmHg, recorded median 22 (3-35) hours after the initiation of monitoring. These children were monitored for a median of 22 (range 18-36) hours. Two of these children developed B-waves. One also had plateau like waves, although the ICP was less than 40 mmHg and lasted only 3 minutes, thus did not fulfil the criteria for Lundberg's A-wave.

iii) *Mild Intracranial Hypertension*

In the 7 children with MIH the opening ICP had a median of 14 (range 10-16) mmHg and the maximum ICP a median of 17 (range 16-19) mmHg. The children were monitored for a median of 18 (range 9-22) hours before the ICP bolt was removed because of low ICP. None of these children had clearly defined B-waves.

B Relationship of ICP to clinical signs

i) *Clinical signs as indications for ICP monitoring*

Eleven children were monitored having fulfilled criteria A; all 3 children with SIH fulfilled these criteria, 4 out of the 8 children with IIH had these criteria, whilst they were also fulfilled by 4 of the children with MIH. Thus the sensitivity of these criteria in predicting the development of SIH or IIH is 64%, while the specificity is 43%.

The association between the individual signs used as indications for ICP monitoring and the pattern of ICP that subsequently developed is shown in table 5.5. Sluggish

pupils were the most predictive signs, associated with the development of IIH or SIH (p=0.004, 2 tailed Fisher's exact test) and with a trend towards increasing severity of IH (Chi square for linear trend (Mantel extension)=5.005, p=0.025). If children who were unresponsive following frequent seizures are excluded, then the 2 children who could only extend to pain (Nos 230/92 and 386/92) developed IIH and SIH respectively. Other brain stem signs such as the oculocephalic reflexes, gag reflex and bruxism were rarely severely impaired prior to monitoring and therefore are unlikely to contribute much to the decision to insert a monitor.

Table 5.5: The relationship between clinical signs elicited before the onset of ICP monitoring.

Clinical Sign	SIH (n=3)	IIH (n=8)	MIH (n=7)
Adelaide Motor Score 1 or 2	2	2	3
Blantyre Coma Score 0	0	0	1
(summated) 1	1	4	1
2	2	4	5
Decerebrate posturing	2	2	2
Pupils sluggish	2	5	0
Pupils dilated	1	0	1
Absent or weak corneal reflex	1	3	2

In the group of 14 children in whom all the components of the Adelaide coma scale were tested, a worst summated score of less than 6 prior to monitoring was associated with the development of SIH (p=0.038, 2 tailed Fisher exact test), but not with SIH and IIH combined. There was not a significant relationship between the worst summated Blantyre coma score prior to monitoring and ICP pattern.

ii) *Clinical signs during monitoring*

(a) Fundal appearances

Two children had papilloedema. The child who died with intractable IH (094/94) was admitted with papilloedema, whilst the other child (332/92) developed papilloedema after a documented period of SIH. There was a strong association between papilloedema and SIH (p=0.02, 2 tailed Fisher exact test). There was no association between fundal haemorrhages and severity of IH (p= 0.519, 2 tailed Fisher exact test).

(b) Pupillary signs

The most reliable sign of RICP during monitoring was sluggish dilated pupils. In patient 230/92, spikes of ICP above 40 mmHg were associated with dilatation of the left pupil and a definite sluggish response to light. After the spike the pupils, although dilated, reacted briskly to light (see fig 5.4).

(c) Decerebrate posturing

Twenty three episodes of decerebrate posturing occurred in 4 patients (Nos. 230/92, 374/92, 386/92 and 185/93). The ICP immediately prior to the onset of the posturing was a median of 23 mmHg (range 11-28) and rose to median of 28 (range 12-49) mmHg. The MAP rose with every episode, although CPP decreased in 27% of episodes.

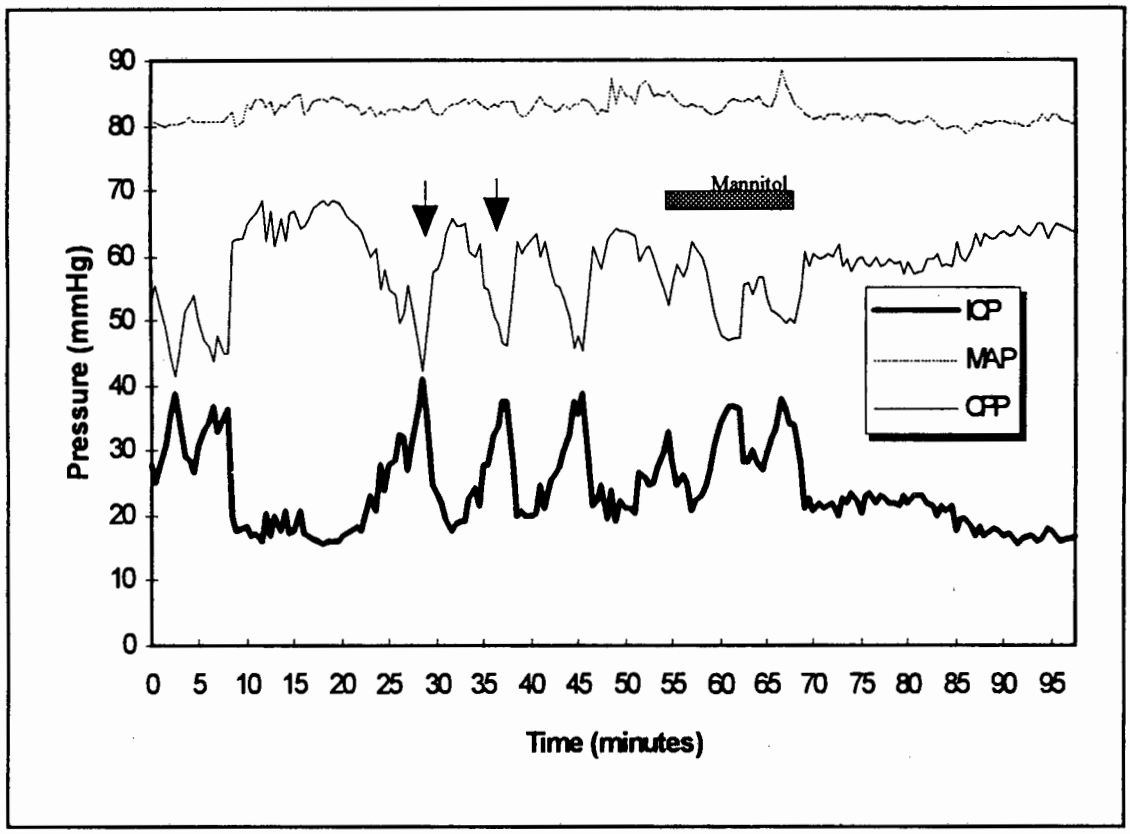


Figure 5.4: No. 230/92. Tented waves associated with sluggish dilated left pupil (arrows) and abolition of waves with mannitol

iii) *Duration of coma*

The 2 children with SIH were unconscious for greater than 144 hours and although they eventually regained consciousness, one remained in a vegetative state, whilst the other was severely handicapped. There was no significant association between IIH or MIH and the duration of coma prior to monitoring or that recorded during admission. Furthermore there was no association between the presence of IIH or SIH during monitoring and the total duration of coma >72 hours (p= 0.587, 2-tailed Fishers exact test) or duration of coma > 48 hours after onset of treatment (p= 0.587, 2-tailed Fishers exact test).

iv) *ICP and seizures*

Twelve of the 18 children presented with seizures and 14 children had clinically detectable seizures after admission. Seizures were associated with transient elevations of ICP (table 5.6) often persisting after the clinical manifestations had ceased. The CPP improved during most episodes because of the concomitant increase in MAP (table 5.6). Generalised seizures were associated with the greatest rises in ICP, particularly if they were manifest clinically. In 3 children with IIH and status epilepticus (232/92, 185/93 & 175/93), after the seizures were controlled the ICP decreased and no further doses of mannitol were required (Appendix VI).

Table 5.6: ICP changes with seizures

Clinical Number	Type of seizure[a]	Number of seizure	Initial measurements in mmHg, median (range)		Percent change in measurements median (range)		Duration of rise in ICP (mins)
			ICP	CPP	ICP	CPP	
214/93	ED	8	14.4 (1.2)	69.5 (3.5)	+61(12.1)	-19.0 (3.8)	4.5 (1.8)
210/93	PM	4	9.3 (1.2)	68 (2.0)	+47 (56.5)	0 (6.9)	-
002/94	PM	1	8	69	+150	NR	NR
374/92	PM lasting > 1 min	2	7.5	57	+86.6	+35.5	2
	PM lasting <1 min	25	?	?	0	0	-
	GTC	1	6	56	+118	+8.9	5
128/94	PM	1	15	71	+40	NR	30
	PBG	1	10	70	+390	-45.7	90
185/93	PBG	6	13 (9-18)	53 (48-57)	+216 (88-467)	+5 (+2 to+7)	20 (13-24)
	GTC	4	17 (14-19)	51 (48-53)	+136 (89-142)	+3 (-1 to +3)	3(1-11)
384/92	PM	1	15	49	+66	-18	8

[a] Seizures: ED-eye deviation, GTC-generalised tonic clonic, PBG-partial becoming generalised, PM-partial motor,
[b] NR-not recorded
? Unknown, because of drift in the monitor

C. ICP and laboratory parameters

There was no association between opening ICP, maximal ICP or pattern of IH and the following blood tests: parasitaemia (admission or maximum), haemoglobin (admission or minimum), pCO2, base excess, lactate (on admission or maximum), glucose or ammonia (tables 5.2 & 5.3). Neither was there an association between opening ICP, maximal ICP or pattern of IH and CSF protein or lactate (tables 5.2 & 5.4).

The ammonia levels were raised (> 50 μmol/l) in 10 out of 11 cases. One child (No 230/92) had a very high concentration and hypoglycaemia, which were compatiable with Reye's syndrome. However he did not have evidence of liver dysfunction, had a very high parasite count and responded well to antimalarial therapy.

D. Response of ICP to treatment

i) *Mannitol*

All the children with SIH and IIH were given mannitol and it reduced the ICP in every administration that was monitored. The response to mannitol varied with the pattern of IH. In the children with IIH, the lowest ICP reached after mannitol infusion was a median of 10 mmHg (range 4-17), a median of 57 minutes (range 25-90) minutes after the infusion, and the time it took for the ICP rise to above 20 mmHg again was 120 (range 62-180) minutes. The response of ICP to mannitol in one child with IIH (No 230/92) is illustrated in figure 5.6.

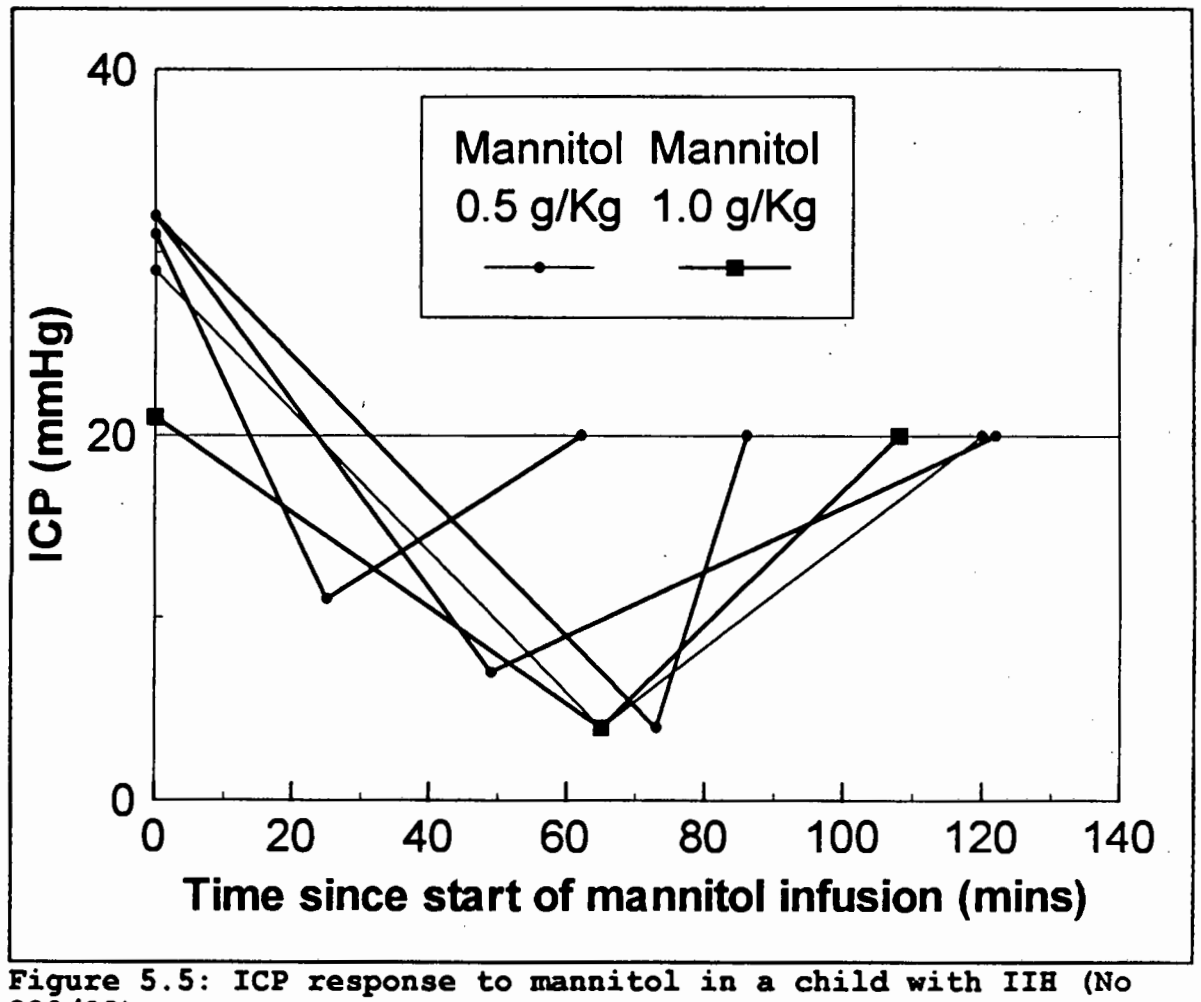
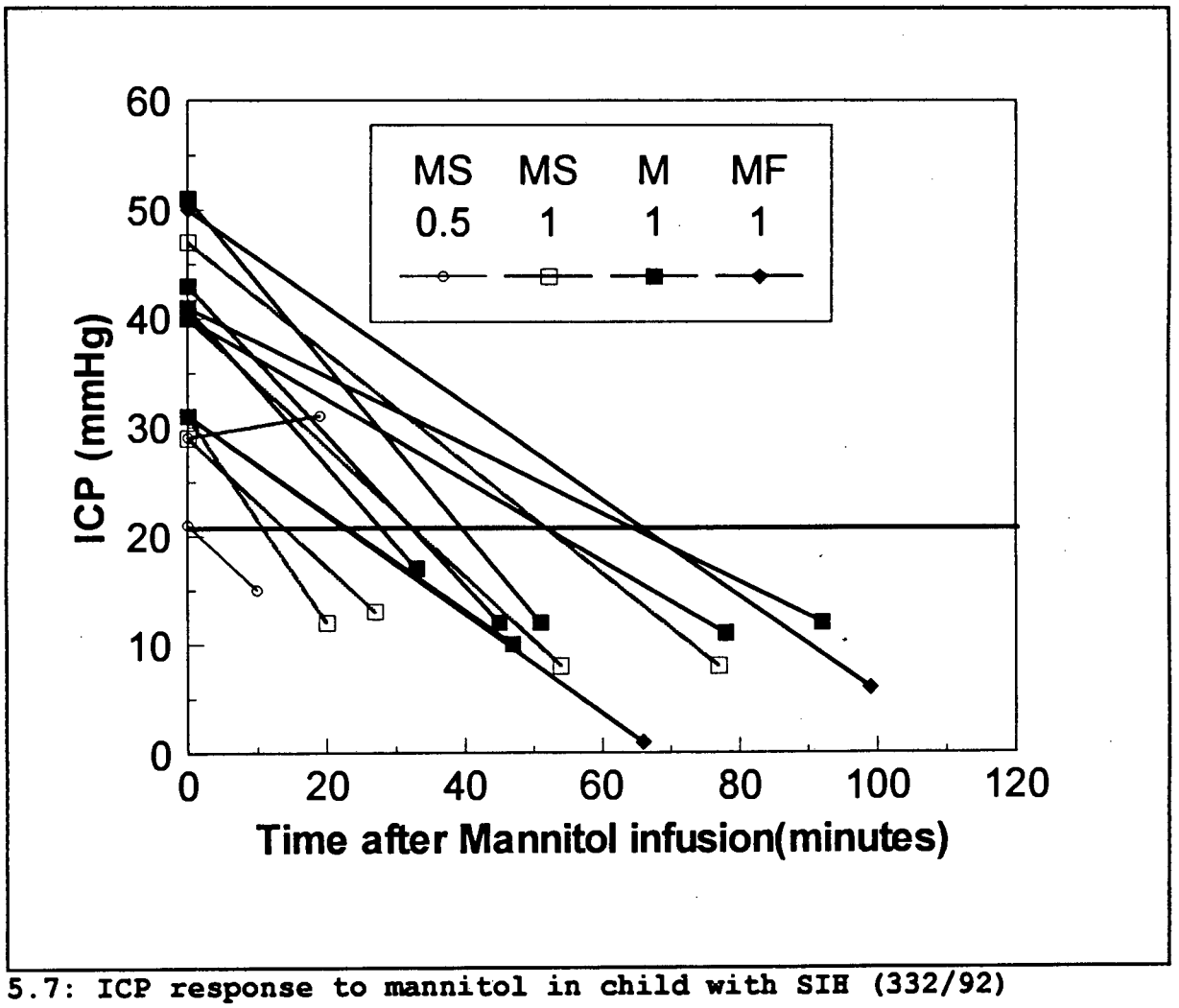


Figure 5.5: ICP response to mannitol in a child with IIH (No 230/92)

In the 3 children with SIH, the response was more variable and did not appear to be affected by the preparation or dose used (figure 5.7), the duration of administration or level of initial ICP. In 7 instances amongst the 3 children, mannitol did not reduce the ICP to below 20 mmHg. In patient 332/92, the time of the lowest ICP after the infusion was a median of 46 (range 10-99) minutes (fig 5.7) and time taken for it to return to 20 mmHg was a median of 97 (range 11-179) minutes. A mannitol/sorbitol mixture was used to replace mannitol in some patients as this is the mixture that is freely available in Kenya. The other children with SIH

had an even more variable response and in the child who died the last dose of mannitol caused only a transient reduction in ICP and did not prevent the child developing signs of the medullary stage (fig 5.2).



5.7: ICP response to mannitol in child with SIH (332/92)

ii) *Ventilation*

Hand ventilation with a face mask was tried in 4 children (Nos 230/92, 332/92, 386/92 & 175/93) on 9 occasions. On all occasions, hand ventilation caused the child to struggle and in one child (No. 230/92) the ICP rose by 15.3% , before decreasing.

iii) *Head position*

The ICP was lowered by mean 9 (sd 4.9) mmHg when the head was returned to the midline on 4 occasions. Nursing the child in the lateral decubitus position was associated with a range of 3 - 9 mmHg increase in ICP.

iv) *Raising blood pressure*

Dopamine infusions were used in the 2 children with SIH who survived to improve CPP and specifically to treat hypotension in one (386/92). The infusions improved the CPP, but the ICP also increased (Appendix VI).

v) *Blood transfusions*

Although 8 children had blood transfusions during monitoring, only 3 had blood transfusions during a period in which mannitol was not given (see appendix VI). In 2 children (214/93 & 128/94), the ICP rose by 12 and 2 mmHg during the transfusion , but the CPP also increased by 17 and 13 mmHg. In the other child (220/93) the ICP and CPP decreased by 4 and 9 mmHg respectively (Appendix VI).

Intracranial vs Cerebrospinal fluid pressure

In 11 children the ICP and the CSFP were recorded during LP. Overall the pressures measured in the 2 sites were similar, in particular there was no evidence of a pressure gradient (figure 5.7).

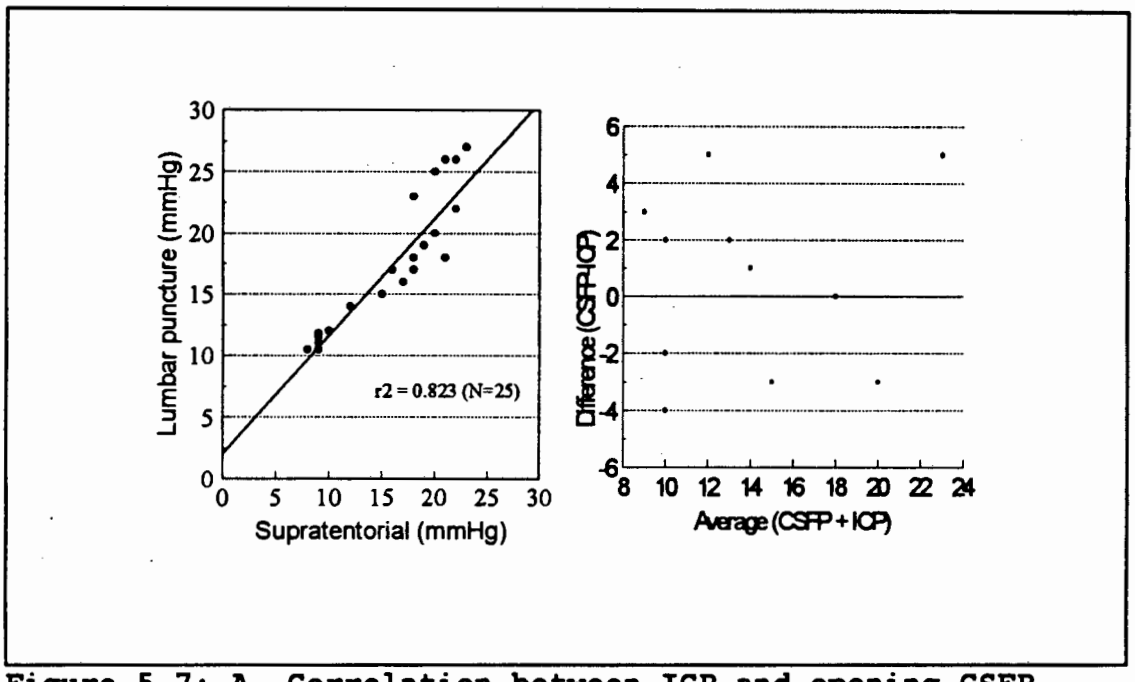


Figure 5.7: A. Correlation between ICP and opening CSFP. B. Difference between ICP and CSFP plotted against average.

DISCUSSION

Intracranial pressure monitoring confirmed the observation made at LP, that Kenyan children with CM have RICP, and extended these observations by showing that opening ICP does not predict maximal ICP and that in some children critically high levels of ICP develop. The children with a CPP below 31 mmHg had a poor outcome and the lowest CPP were recorded in children who developed severe neurological sequelae or died. Seizures increased ICP, particularly those which were partial becoming generalised. Mannitol was effective in reducing ICP, although some children developed intractable IH despite early treatment with mannitol.Other simple measures such as keeping the head in the midline reduced the ICP, but hand ventilation with a face mask aggravated the situation.

Ethical considerations

The measurement of raised opening CSF pressures and the documentation of clinical signs compatible with herniation prompted us to consider monitoring ICP in children with CM. However as in any encephalopathy, we had to address the major considerations about instituting ICP monitoring *ie* the prognosis of the underlying brain lesion, whether the monitoring could be carried out safely and accurately and if monitoring would alter management [320].

Prognosis of CM

The prognosis of most children who survive CM is good, but since there is clinical evidence of trantentorial herniation in the children who died, reducing the ICP improve the oucome. As ICP can only be monitored invasively, all of us involved in this project were keen to establish that other informed clinicians thought that ICP monitoring would be potentially useful in this encephalopathy. Thus we submitted the proposal to two ethical committees: one at KEMRI to ensure that Kenyan doctors thought ICP monitoring in CM was acceptable and the other one at the Institute of Child Health, London to establish that paediatricians with a wide experience of managing encephalopathic children thought that ICP monitoring was appropriate.

Safety and accuracy

Considerations about safety and accuracy were outlined by Lundberg in his original monograph on ICP monitoring [194]. He suggested that six requirements needed to

be considered before invasive ICP monitoring is instituted: i) the procedure should cause as little trauma as possible, particularly to the brain; ii) the risk of infection should be neglible; iii) there should be no leakage of CSF which would interfere with the measurements and act as a portal of entry for infection iv) prolonged recording should be possible without interfering with patient care or comfort; v) measurements should not be affected by diagnostic or therapeutic procedures) and vi) ideally the apparatus should be reliable, durable and simple to use.

Safety of ICP monitoring at Kilifi

We needed to establish that we could perform ICP monitoring safely at the Kilifi unit, despite the lack of access to on call neurosurgical or neuroradiological services. Thus I spent six weeks learning how to insert ICP monitors into children under the guidance of neurosurgeons at the Hospital for Sick Children, Great Ormond Street, London UK. Furthermore the unit at Kilifi was refurbished, so that an air conditioned, sealed room was designated for ICP monitoring. The microbiological facilities at the unit were already excellent and additional antibiotics *eg* third generation cephalosporins were obtained to treat potentially serious infections.

To date we have encountered few complications. There was slight subarachnoid bleeding on the CT scan of 3 patients (see chapter 6), but none had clinical symptoms or signs referable to the bleeds. Another child developed a superficial skin infection which responded quickly to treatment.The child who died with

progressive IH during ICP monitoring had a clear post mortem CSF, suggesting that a CNS infection or intracranial bleed did not contribute to the death. Thus we established that ICP monitoring could be performed safely in rural Africa.

Fiberoptic monitor

We chose to use a fiberoptic method of ICP monitoring because it is accurate, has a low risk of infection, does not require insertion into the ventricles (which is difficult in children with swollen brains, particularly in the absence of neuroradiological facilities) and has been safely used in children with acute encephalopathies [329].

The fiberoptic device consists of a miniature transducer which is connected to an external monitor with a fiberoptic cable. It can be inserted percutaneously into the ventricles or abutting the brain parenchyma, or placed surgically into the subarachnoid space. The intraparenchymal measurements show excellent correlation (although they are slightly higher), with intraventricular measurements in animals [73] and adults [56]. In the children with CM there was a good correlation between the ICP measured with this system and the opening CSFP. However in adults with intraparenchymal haemorrhages following head injury [299] the Camino fiberoptic system measurements were higher than the intraventicular measurements in 66% of the readings, with mean difference of 9.8 mmHg [299].This is not relevant to our studies as intracranial haemorrhage is not a feature of CM (chapter 6). Fiberoptic devices have a much lower rate of infection and bleeding in both adults and

children [252,329] than intraventricular methods, and are more reliable than subarachnoid or epidural monitors. The major disadvantage of fibreoptic catheters is that CSF cannot be removed, thus intracranial compliance cannot be tested nor CSF drained during management.

Criteria for monitoring

One of the predicaments of ICP monitoring is the identification of patients with RICP. The clinical signs associated with RICP either occur too infrequently or are inconsistently associated with RICP to be useful in deciding the indications for monitoring [288]. We initially chose deep coma and brain stem signs, clinical features which had been associated with poor outcome in CM (see chapter 2), as the indications to start monitoring. Sixty three percent of children with these indications had either IIH or SIH, although the monitoring was instituted 13-49 hours after admission. However the failure to prevent intractable IH in two children (332/92 & 286/92) and the possibility that we had missed periods of high ICP by waiting for brain stem signs to develop, prompted us to relax the indications to include children who did not have brain stem signs and had a flexor response to pain (though not brisk). With these criteria, monitoring was instituted earlier in seven children, four developed IIH and the remainder had MIH which was not treated with mannitol. Whether the introduction and treatment of ICP monitoring earlier prevented the development of SIH in this group is difficult to establish and would require a randomised controlled trial or many more patients.

Patterns of RICP

The patterns of IH in these children with CM were different, probably reflecting the heterogeneity of this clinical syndrome.

Severe intracranial hypertension

The child who died with SIH had a high opening pressure which was initially reduced by mannitol, before he developed intractable IH. In the other two children who developed SIH, the ICP was less than 20 mmHg for the first 6-12 hours of the monitoring. Thereafter they developed intractable IH 24 hours after admission, despite the frequent administration of mannitol. The ICP bolts were removed when they still had a high ICP but were neurologically stable. Both these children survived with severe neurological sequelae. It is unlikely that a period of RICP occurred before the onset of monitoring since other children monitored earlier in their illness only had a mild elevation of the ICP. The development of intractable IH in these children was not prevented by the prompt administration of mannitol.

Intermediate and mild intracranial hypertension

The children with IIH had higher ICP at the beginning of monitoring, but the ICP responded briskly to mannitol. The ICP peaked within twelve hours of admission and the bolt was removed when the ICP was less than 15 mmHg. Three of these children (Nos 232/92, 185/92 & 128/94) had generalised status epilepticus after admission and the ICP fell after the seizures were controlled. However it is difficult to determine the influence of mannitol on the outcome of this group, as

there are no appropriate controls (discussed further in chapter 8).

In the children with MIH, the highest ICP was recorded shortly after the insertion of the bolt and since significant IH was not documented, the bolt was removed within twenty four hours.

Maximum ICP

The highest ICP recorded was 158 mmHg in the patient (094/94) who died with intractable IH. This pressure was associated with the signs of medullary stage of herniation. Although there are no established levels at which herniation develops; post mortem evidence of herniation has been documented in a child who had a maximum ICP of 62 mmHg in one report, although most children with herniation had pressures greater than 50 mmHg [214]. The presence of A-waves provides some indication at which level of ICP signs of herniation (aniscoria, decerebration and, fixed and dilated pupils) will develop in adults since herniation occurs when the ICP reaches 70 mmHg in the presence of A-waves, but only above 120 mmHg without A-waves [125]. These observations have not been confirmed in children.

Minimum CPP

In this series 6 children had a minimum CPP less than 38 mmHg, a level associated with poor outcome in other paediatric non-traumatic encephalopathies [222]. Only three of these children had a poor outcome, all with a minimum CPP <34 mmHg, but one child with a minimum CPP of 31 mmHg survived without

sequelae. This may be is a reflection of the younger age of these children in comparison to those from the series of children with non-traumatic coma. The lower levels of CPP at which some children survive has been documented in other series [273] and may be differ between encephalopathies. An accurate assessment of the critical levels at which sequelae develop, would require inserting the ICP monitor earlier and studying more children.

Pressure waves

Further evidence for reduced intracranial compliance is supported by the presence of pressure waves in four children. A plateau of increased ICP was seen in only one child (421/92), although the rise in ICP was not as high and did not last as long as that associated with A-waves in adults [194]. Tented wave patterns were seen in the two children with SIH. These patterns are thought to be equivakent to A-waves in infants with intracranial hypertension and expandable skulls [253], *eg* infants with hydrocephalus or after decompression [194]in whom A-waves are not. However the age at which A-waves become apparent has not been determined, although they have been recorded in children older than 5 years [253]. If the tented waves seen in one child have the same significance as A-waves, then the presence of this type of wave suggests critically.

B-waves

B-waves were seen in four children. These waves are thought to be produced by fluctuations in blood volume, caused by the phasic dilatation and constriction of the

small regulating arteries [236]. Although similar vascular oscillations occur under normal conditions, the amplitude is small. Conspicuous B-waves appear only in conditions with reduced intracranial compliance. The amplitude of the B-waves increases as the lower limit of CBF autoregulation is reached and B-waves disappear before vasoparalysis occurs [21]. Of note is the relative absence of B-waves during the early part of the monitoring in patient 386/92 despite SIH, suggesting autoregulation was impaired. The occurrence of respiratory abnormalities, increased rigidity and tonic flexion of the arms with B-waves, as seen in patient 332/92, has been described previously [194] and is thought to presage irreversible brain damage [194].

Seizures and ICP

Seizures occurred in most of these children and appeared to be an important cause of RICP. An increase in CBF with seizures is thought to be the main cause of the rise in ICP [95,209], but brain cell swelling or cerebral oedema may also contribute, particularly during prolonged seizures. The rate of ICP elevation with seizures is dependent upon electrical spike frequency, intracranial compliance [95] and the type of seizure (the largest ICP increases have been documented during generalised seizures [209]). In this study partial motor seizures lasting less than 1 minute were not associated with increases in ICP, however if the seizure lasted more than 1 minute the ICP rose. Generalised seizures were associated with greater increases in ICP, particularly if the onset was focal. The persistent elevation of ICP after the clinical features of the seizure have stopped is well documented and will

be aggravated when the compliance is reduced. Intermittent tented waves may also be caused by subclinical seizures [209], but I was unable to document this phenomenon.

Blood pressure

Hypotension was probably an important determinant of the outcome in patient No 386/92. This child was admitted with bradycardia and hypoglycaemia, and although he did not have a cardiac arrest, cardiac output only improved after the administration of atropine. The ICP was mildly elevated at the start of monitoring, but the MAP was only 50 mmHg. After resuscitation and correction of the metabolic acidosis, the ICP rose and this child developed SIH. He developed B-waves, which are associated with intact autoregulation, only towards the end of the monitoring period, despite high ICP levels earlier. Hypotension is more likely to be impair autoregulation than an increase in ICP [219].

Anaemia

Anaemia is almost inevitable in a severe falciparum infection and could contribute to RICP, by increasing CBF. There was no relationship between haemoglobin level (or packed cell volume) and opening ICP or maximum ICP, although it improved the CPP. In the three children in whom it could be assessed, increasing the haematocrit with a blood transfusion did not consistently decrease the ICP. Thus it seems unlikely that anaemia *per se* is a major mechanism in the pathogenesis of RICP in these children.

Clinical signs

Unilateral pupillary dilatation with a poor response to light was the sign most consistently associated with RICP, particularly spikes of ICP. All episodes of unilateral pupil dilatation were associated with high ICP, reaching up to 95 mmHg. Bilateral sluggish pupils were often present after seizures and not necessarily associated with high ICP. Decerebrate posturing, which is thought to be a sign of RICP [45] was inconsistently associated with pressures above 20 mmHg, although the pressure always rose, albeit by small amounts on some occasions. There was no relationship with absent corneals, minimal oculocephalic responses or weak gag reflexes and RICP. However the measurement of ICP at one site in the supratentorial compartment does not exclude the possibility of pressure gradients in the brain stem causing these signs. The development of papilloedema in only 2 patients is not surprising, as this is not a sensitive sign of RICP in acute encephalopathies. Yawning and sighing often occurred in children with IIH or SIH towards the end of monitoring as the child woke up, and were generally followed by reductions in ICP.

Treatment

The level at which treatment of ICP should be instituted has not been established. Most authorities recommend keeping the ICP below 25 mmHg both in adults [288] and children [310], although in head injury, there appeared to be an improved outcome in an uncontrolled trial if treatment was instituted when the ICP reached 15 mmHg [297]. There is more evidence to suggest a CPP below 40 mmHg is

associated with poor outcome in other paediatric encephalopathies, implying that CPP should be kept at least above this level and probably above 50 mmHg [310]. For the development of an empirical regimen that could be applied in other African hospitals, we examined simple interventions for the treatment of ICP. We decided to treat the ICP when the pressure rose above 20 mmHg with a CPP lower than 50 mmHg, so that the least number of doses could be used.

Osmotherapy

Mannitol was effective in reducing ICP in all children with IH, but it did not prevent the development of SIH in 3 children despite being administered before the intractable IH started. Mannitol, an osmotic diuretic, has long been thought to work by simply reducing brain water content, although recently it has been proposed that the major mechanism of action is a reduction in CBV, caused by the decrease in blood viscosity inducing vasoconstriction [229]. Both of these mechanisms are probably important, for mannitol requires an intact BBB and autoregulation to be effective. The effectiveness of mannitol is further dependent upon the level of ICP at which the treatment is instituted, the dose and rate of administration, the amount of mannitol already present [209] and the addition of other diuretics [284]. Smaller doses of mannitol eg 0.25 g/Kg have been shown to be as effective as larger doses, although the reduction does not persist as long [205]. Larger doses are associated with a rebound phenomenon, probably because high concentrations of mannitol can disrupt the BBB particularly if administered quickly [209].

We choose to examine an intermediate dose (0.5 g/Kg) administered over 20 minutes. This regimen was effective in all the children with IIH in whom it was given, although it may need to be repeated as frequently as every 2 hours to maintain the ICP below 20 mmHg in children with persistant IH. The use of a smaller dose (0.25 g/Kg) in one child was not as effective as the higher dose, although the ICP did not rise above 20 mmHg for any significant period. Mannitol initially decreased ICP and improved CPP in the children with SIH, but it did not prevent the development of intractable IH and it became less effective in reducing spikes of ICP, despite doubling the dose. The loss of efficacy may be due to an impairment of either the BBB and/or autoregulation leading to a rebound phenomenon [100]. The addition of frusemide did prolong the period of ICP below 20 mmHg in these children as it has done in other encephalopathies.

Hyperventilation

Hand ventilation with a face mask in these unparalysed and unventilated children provoked increases in ICP, before decreasing it and thus may be dangerous as it may precipitate herniation. The adverse effect was not only caused by positive thoracic pressure generated, but also by the child struggling against the face mask. Furthermore 15 of the 18 children monitored were hypocapnic (pCO_2 <3.5 KPa, to compensate for a metabolic acidosis) and thus hyperventilation is unlikely to reduce ICP further, but may cause a critical reduction in CBF.

Head position

The ICP rose when the head was rotated to either side and decreased when the head was returned to the midline. When the child was turned into the lateral decubitus position for an LP, there was a small rise in supratentorial ICP which came down slightly, but remained elevated after deflection of the legs.

Pressure gradients

There was no evidence that the supratentorial pressures were higher than those below the foramen magnum at the time of LP. Indeed, given that the fiberoptic device is probably under reading the intraventricular pressure [299] and the fibreoptic pressures were generally less than those measured in the lumbar space, a gradient opposing tonsillar and uncal herniation appeared to exist when the LP was performed. However these measurements were performed in the absence of brain stem signs.

SUMMARY OF ICP MONITORING

The data presented in this chapter shows that RICP is a feature of severe CM in Kenyan children. Critically high pressures were associated with death and severe neurological sequelae. Furthermore the child who died had clinical features of herniation associated with very high pressures. Although SIH is associated with severe neurological sequelae, a causal relationship could not be established. The patterns of IH in these children are not similar, since some had mildly raised ICP initially before developing intractable IH, whilst others had moderate ICP during the early part of the admission. Clinical signs are poor at reflecting RICP and no

signs were identified (except pupillary dilation) which could used to institute monitoring or treatment. Mannitol is effective in reducing ICP in this encephalopathy, but does not prevent the development of intractable IH in all children. There is not enough data, as yet, to propose an empirical regime for the treatment of RICP.

6 COMPUTERISED TOMOGRAPHY

INTRODUCTION

The cause of the intracranial hypertension (IH) in children with CM is unknown, but the most likely causes are an increase in cerebral blood volume (CBV), cerebral oedema or acute hydrocephalus. In other encephalopathies computerised tomography (CT) is useful in identifying space occupying lesions and acute hydrocephalus. Gross cerebral oedema, especially if vasogenic, has a distinctive tomographic appearance. An increase in CBV is associated with reduced tomographic densities in children with head injury [48]. However milder degrees of cerebral oedema and small increases in blood volume are not reliably detected.

In a CT study of 10 adults with CM, cerebral oedema was detected in 2, during the agonal stages [191], although recently there has been a case report of cerebral oedema detected by CT scan in an adult patient who has survived [258]. Other causes of RICP were not seen. However, as intracranial hypertension is not thought to play an important role in the pathophysiology of CM in adults, tomographic findings in adults may not reflect the situation in African children.

Thus CT was performed on children who had ICP monitoring to investigate the cause of RICP and detect intracranial complications of monitoring.

PATIENTS AND METHODS

Fourteen children who had ICP pressure monitoring were scanned at the earliest possible time after the removal of the monitor, when they were neurologically stable but still unconscious (not yet able to localise pain). Scans were not performed earlier, as the children had to be transferred to other hospitals in Mombasa 60 kilometres away for the CT to be performed. They were also not performed on children who died and 3 children with mild intracranil hypertension (MIH). Six children were scanned with the Siemens Somatogram DR and 10 scans were performed with the Shimadzu SCT-3000TE. Contrast Iopamidol (300mg/Kg) was given to 6 patients, 4 during the acute scan and one on a follow-up scan.

The scans were examined by me and the findings confirmed by Dr Brian Kendall, Department of Radiology, Great Ormond Street, UK. Brain swelling was assessed by examining the size of the following cerebrospinal fluid (CSF) spaces: (a) the cerebral sulci; (b) the perimesencephalic and chiasmatic cisterns; (c) the ventricular system The swelling was graded as outlined in table 6.1 [330]. The Evans ratio, the(width of the frontal horns divided by the internal skull diameter (fig 6.1) was used to compare the ventricular size on the scans performed during the acute phase to those on recovery .

Table 6.1: Criteria for grading brain swelling in CT scans [330]

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

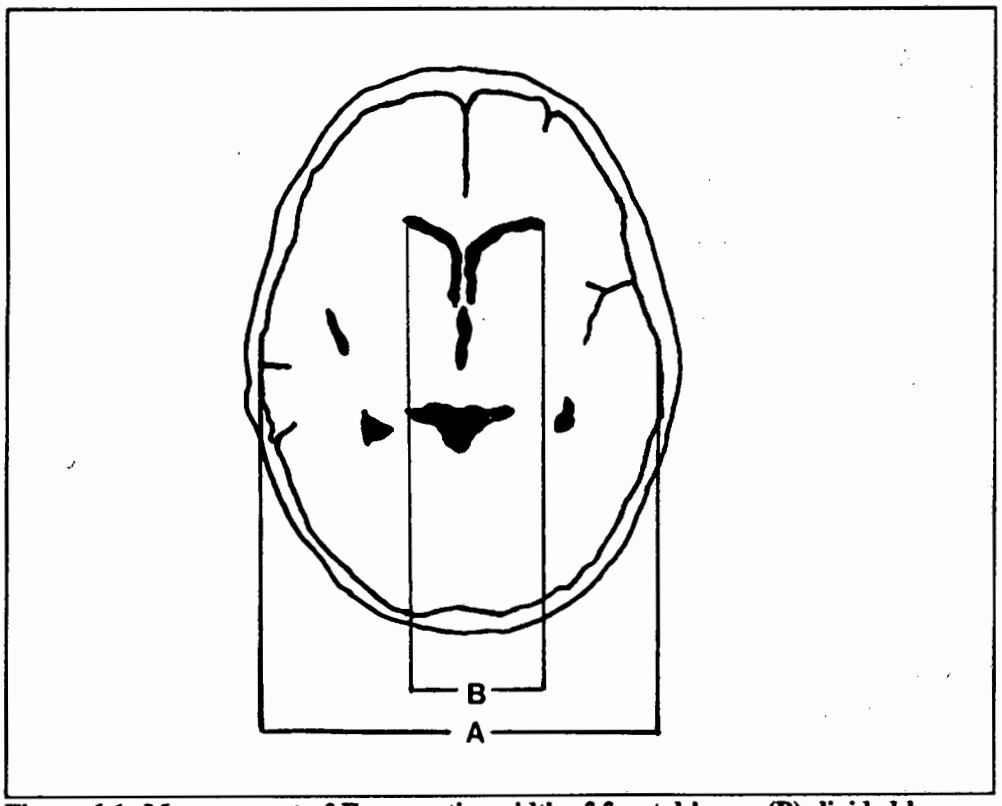


Figure 6.1. Measurement of Evans ratio: width of frontal horns (B) divided by internal skull diameter (A)

RESULTS

The clinical and laboratory features of the children scanned are presented in chapter 5 (tables 5.2 and 5.3). The CT appearances are described in table 6.2 and the patterns of intracranial hypertension are classified as outlined in chapter 5. The children were scanned 3 to 9 (median 5) days after the onset of the illness and 1.4 to 6 (median 3.2) days after the onset of coma.

Diffuse Brain swelling

Four children had clear evidence of diffuse brain swelling (DBS), as defined by loss of sulci (n=4), loss of spaces around the cisterns (n=2) and resolution of the swelling without atrophy on the follow up scans (n=2) (figure 6.2). Two of these children had diffuse hypodensity of their brains associated with severe intracranial hypertension (SIH). The other two had normal density and the brain swelling had resolved 12-24 days after the initial scans. Of the 10 children whose scans did not have evidence of swelling, one child with intermediate intracranial hypertension (IIH) had conspicuously small ventricles. Increased tomographic density was not present in any of these children. One child had decreased density in the left parietal region (*vide infra*) associated with status epilepticus. None of the children had the CT features of vasogenic oedema, acute hydrocephalus or a midline shift.

Brian swelling was associated with IIH or SIH (Fisher exact test, $p = 0.015$) and with a duration of coma after admission longer than 96 hours (Fisher exact test, $p = 0.011$), but there was not a significant relationship between degree of swelling and total duration of coma. Brain swelling was not associated with the following admission parameters: summated ACS, parasitaemia or lactate.

Changes in tomographic density

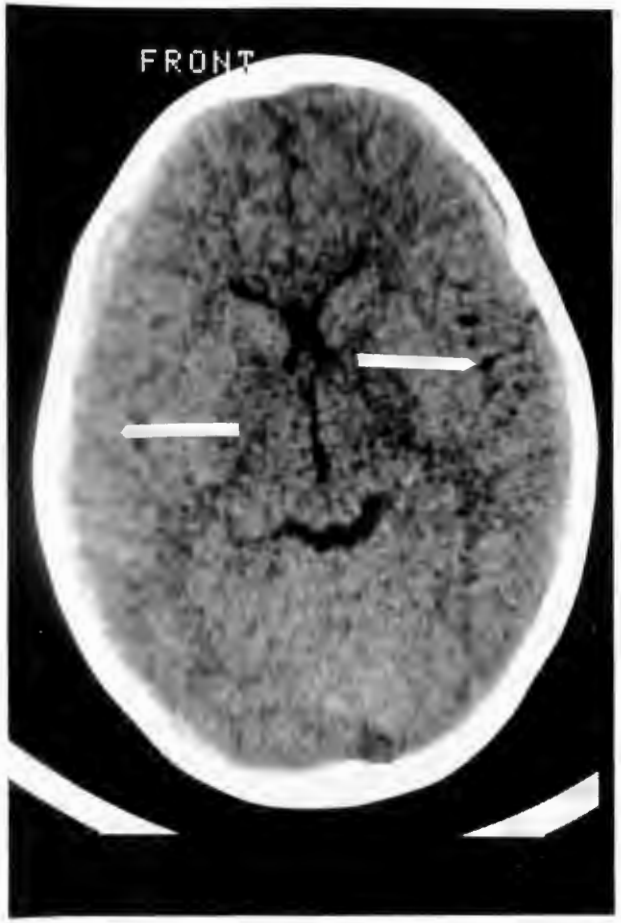
Three children had areas of hypodensity on their CT scans. Two children (both with DBS) had diffuse low tissue density and loss of gray/white matter differentiation involving the cerebral hemispheres (fig 6.3) compatible with an ischaemic or hypoglycaemic insult. Both were unconscious for longer than 140 hours. One child (No. 332/92) had diffuse low density of 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 left frontal and parietal regions (figure 6.3). The other child with diffuse changes (No. 386/92) had a typical superficial watershed distribution on the initial scan together with low density of the basal ganglia and subsequently an intracerebral haemorrhagic lesion in the watershed area between the left middle and posterior cerebral arteries, which enhanced with IV contrast (figure 6.4). The third child presented with status epilepticus, had a hypodense region in the left parietal region and survived with a right hemiparesis, sensory inattention and visual field defect. None of the children had any evidence of thalamic or posterior fossa abnormalities. Only one child (338/92) had enhancement with contrast, associated with generalised infarction on the follow up scan. Generalised hypodensity on the acute scans was associated with prolonged coma, and cerebral atrophy on the convalescent scans in the children who had severe neurological sequelae.

Complications of ICP monitoring

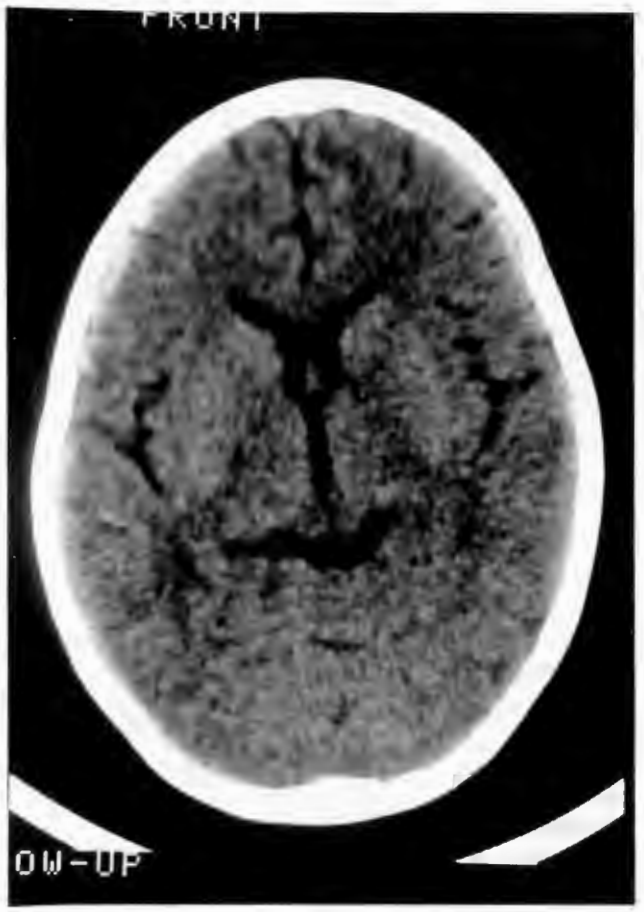
Three of the children had evidence of blood in the CSF on their CT scans. None of the children had intracerebral haemorrhages or evidence of parenchymal damage.

Table 6.2: CT appearances of 14 children who had ICP monitoring

Patient No	Acute Scan					Convalescent Scan	
	Time since onset of coma (days)	Time since admission (hours)	ICP pattern	CT Scan Appearances	Grade	Time since initial scan (days)	CT Scan Appearances
056/93	6	44	MIH	Normal scan	N	-	-
220/93	2	20	MIH	Normal scan	N	-	-
207/93	1.4	26	MIH	Normal scan	N	-	-
214/93	1.8	2.7	MIH	Normal scan	N	-	-
374/92	4	48	MIH	Normal scan	N	-	-
232/92	4	84	MIH	Normal scan	N	120	Mild cerebral atrophy
002/94	3.5	44	MIH	Hypodensity of left parietal region	N	-	-
185/93	2	24	IIH	Normal scan	N	-	-
210/93	2.7	57	MIH	Normal scan ? small ventricles	N	-	-
175/93	3.2	47	IIH	Normal scan with small ventricles	N	-	-
421/92	3	40	IIH	Swollen brain	1	12	Normal scan
230/92	4	72	IIH	Swollen brain	1	24	Normal scan
332/92	6	148	SIH	Hypodensity of hemispheres, not involving basal ganglia or posterior fossa. Not watershed distribution.	1	70	Cerebral atrophy with infarction of right ant. & post. regions (with occipital sparing) & left parietal regions.
386/92	5	120	SIH	Generalised hypodensity of hemisphere & basal ganglia, with sparing of the posterior fossa. Watershed distribution	3	11	Generalised infarction of hemispheres & basal ganglia with enhancement of watershed area between posterior & middle cerebral arteries



A



B

Figure 6.2: CT scans of patient No 230/92. (A) Acute scan: diffuse brain swelling with loss of sulci (arrows) and compression of the ventricles.(B) Convalescent scan: resolution of brain swelling, with increase in the sulci and ventricles but without atrophy

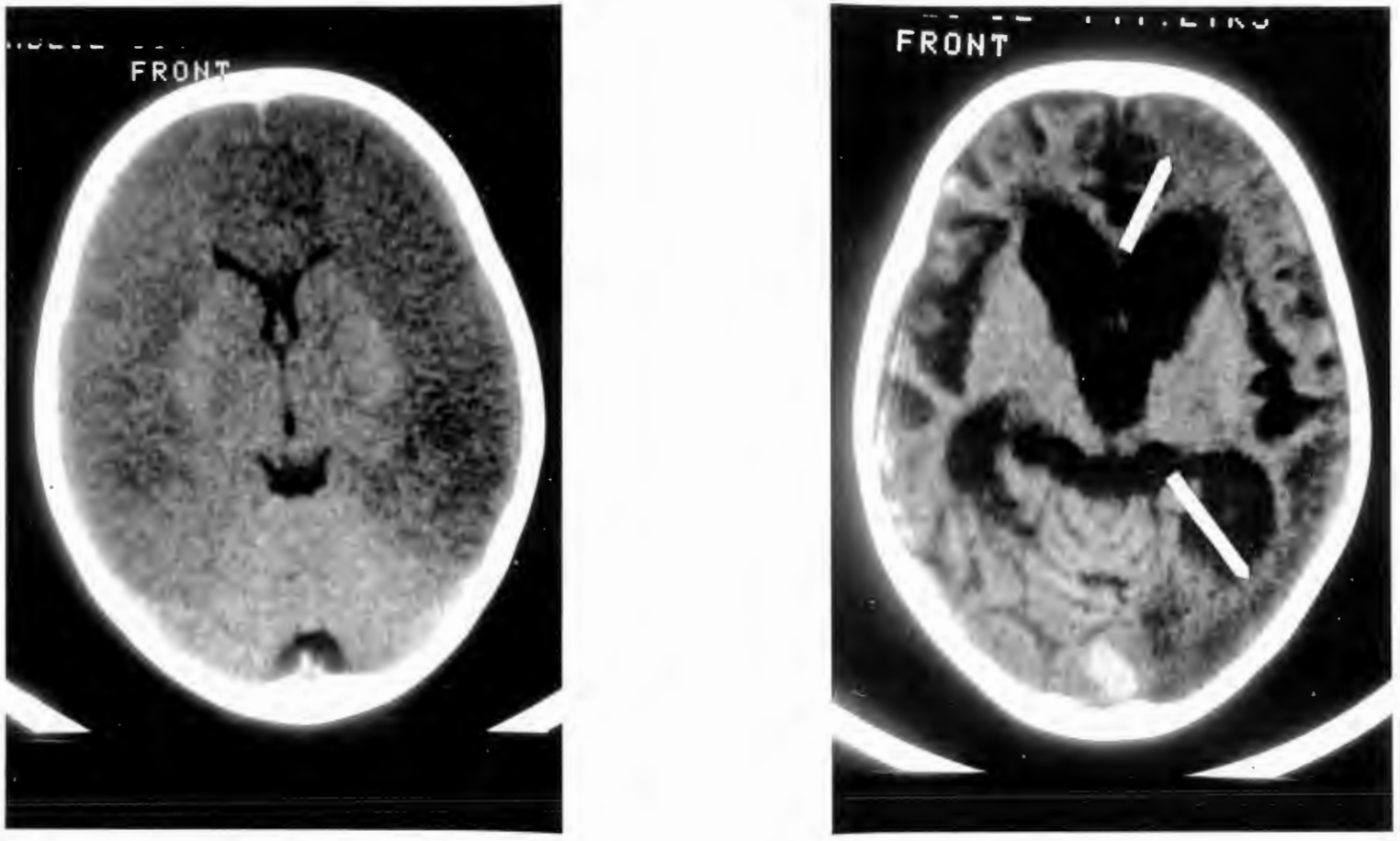


Figure 6.3: CT scans of patient No. 332/92. A) Acute scan: Diffuse brain swelling with generalised hypodensity, loss of gray/white matter differentiation, but preservation of the basal ganglia and the cerebellum. B) Convalescent scan: Cerebral atrophy with hypodense areas, suggestive of infarction in the left frontal and parietal regions (arrows).

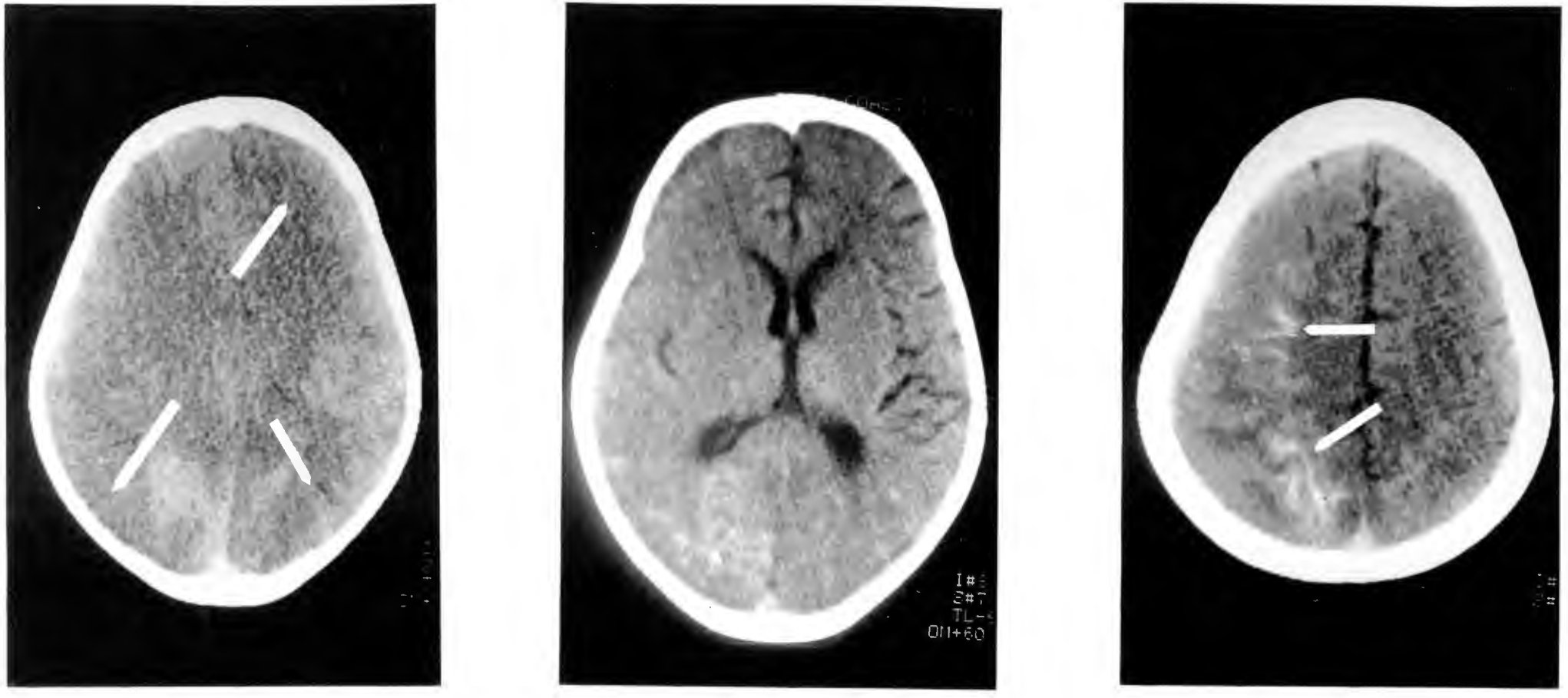


Figure 6.4: CT scans of patient No. 386/92. A) Acute scan. Diffuse brin swelling with generalised hypodensity involving the basal ganglia and the watershed areas (arrows). B) Convalescent scan. Cerebral atrophy with infarction in the hemispheres and the basal ganglia. C) Convalescent scan. Enhancement of the watershed area between the right posterior and middle cerebral arteries (arrows).

DISCUSSION

Five children had conspicuously abnormal scans during the acute phase of the illness. DBS was present in 4 children and was associated with more severe IH, whilst another child with MIH had hypodensity in the left parietal region. In 2 children DBS was associated with normal tomographic densities and complete resolution of the swelling on follow up scans. The cause of the IIH in these children is unclear. In the other 2 children DBS was associated with widespread low density on the initial scans, suggestive of cytotoxic oedema and severe cerebral atrophy with infarction on the convalescent scans. Both these children had SIH and survived with severe neurological sequelae. Acute hydrocephalus and vasogenic oedema could be excluded as causes of intracranial hypertension in these children.

Brain swelling

DBS is characterised on CT scan by small ventricles, absence of sulci and compression of the perimesencephalic and chiasmatic cisterns with resolution on follow-up scan [48,334]. DBS may resolve quickly [48]; thus the possibility that swelling had disappeared by the time some of the normal scans were performed cannot be excluded. In head injury, DBS occurs more commonly in children than adults [90] and has been associated with greater tomographic density in the white matter, reflecting an increase in blood volume [48]. In the 2 children with the most severe swelling, the tomographic densities were decreased throughout the

cerebrum, without CT evidence of vasogenic oedema, suggesting cytotoxic oedema. In the two CT scans with DBS without low density, the tomographic densities in white matter were normal. Therefore there is no CT evidence for an increase in blood volume, although this technique may not be sensitive enough, even with the use of contrast medium, to detect small increases in CBV [100,259].

In the children with CM, the most severe swelling occurred in those with the highest ICP, whether or not there was also low density. The degree of brain swelling correlated with the subsequent measurement of ICP in a study of children with non-traumatic coma [330]. However the CT appearances could not be used to predict the ICP, since some children with normal scans developed raised ICP and children with focal abnormalities in the basal ganglia or cerebral hemispheres had a loss of CSF space without a generalised increase in ICP [330]. Whether CT scans can be used to predict ICP in children with CM remains to be determined.

Contrast enhancement was seen in only one child (386/92); this was present on a follow up scan and the enhancement was localised to an area of infarction. None of the children had evidence of a breakdown in the BBB (as suggested by generalised enhancement) or other tomographic features of vasogenic oedema such as loss of gray/white matter differentiation. However CT may not be able to demonstrate mild degrees of oedema, particularly if the decreases in tomographic density are counteracted by increases in blood volume.

Neurological sequelae

The CT patterns of children who developed neurological sequelae in this study and a more extensive series (Appendix VII, [242]) are heterogenous. The acute CT scans of 2 children who developed sequelae showed a watershed distribution of damage; one child had SIH and the other child had MIH. In the child with SIH, the watershed distribution may have been caused by a precipitate drop in CPP [9,161], although this was not detected during the period of monitoring. However this appearance has also been seen on a CT scan following hypoglycaemia [136], and thus the repeated episodes of hypoglycaemia may also have contributed. The other child (002/94) presented with status epilepticus. Critically high ICP or low CPP were not recorded during the period of ICP monitoring, but may have occurred before the monitoring started. The more diffuse changes as seen in the other child (332/92) are more likely to be seen in a moderate but prolonged decrease in CPP [9], although seizures may also contribute [11]. In the larger series hypodensity was not associated with hypoglycaemia or status epilepticus (Appendix VII).

SUMMARY

Brain swelling is a feature of children with severe CM and is associated with the highest ICP. Features of cytotoxic oedema were associated with SIH, but a causal relationship could not be established. The cause of IIH in the other two children with DBS cannot be determined. Most children with CM, including a few children with IIH, have normal CT scans.

7 TRANSCRANIAL DOPPLER MONITORING

INTRODUCTION

Transcranial Doppler (TCD) sonography was devised by Aaslid and colleagues during the early 1980's [7], as a non-invasive technique for measuring blood flow velocity in the basal cranial arteries. Since then, the measurements have been shown to be reliable and reproducible in both adults [119,154] and children [34,160]. In addition to being non-invasive, the technique is safe [4], and repeated examinations of the intracranial circulation can be performed. TCD has been used for the assessment of intracranial occlusive disease [154], arteriovenous malformations [119] and to investigate cerebral haemodynamics in subarachnoid haemorrhage (especially vasospasm) [52,119], bacterial meningitis [34,101,119] and during cardiopulmonary by-pass [51,119]. More recently it has been used to monitor ICP and CPP in unconscious patients [123,162,282,298,314] and it has been used as an aid for the diagnosis of brain death [35,123,158].

Principle

TCD is based upon the phenomenon described by Christian Johann Doppler in

1842, which when applied to blood flow can be stated as: the shift in the frequency of the sound wave reflected from moving red cells to that from the emitted frequency is proportional to the velocity of the blood. Thus

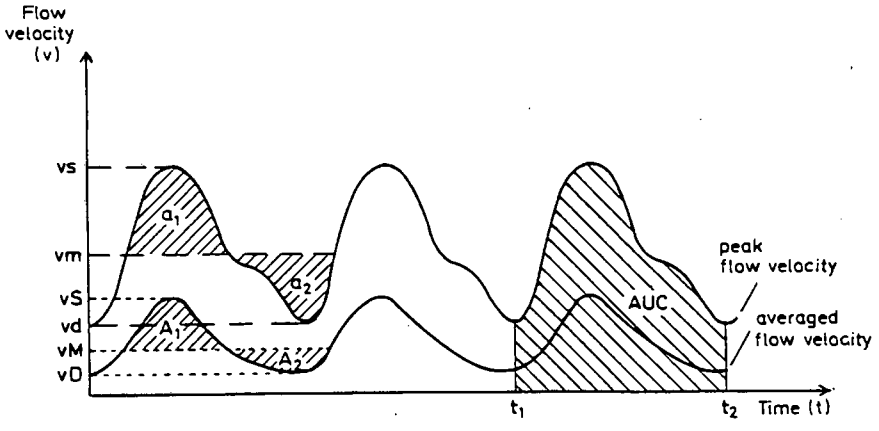
$$Velocity = \frac{c * f_d}{2 * f_t * \cos\Theta} \quad \ldots\ldots\ldots\ldots\ldots\ldots equ\ 7.1$$

where c is the velocity of sound through human tissue (~1560 m/sec at 37°C); f_d=Doppler shift frequency, f_t = transmitted frequency and Θ = the intercept angle between the vessel and the Doppler insonation. The angle Θ is a major determinant of the accuracy of the measured velocity, for when Θ < 10°, the error is less than 2% (as cosine Θ is between 1 and 0.985), but when Θ is 35° the velocity will be raised by 18% .

Although the Doppler principle has been used to measure blood flow velocities in peripheral vessels since the 1960s [119] and in intracranial vessels in neonates through an open fontanelle in the 1970s [271], it was only when a machine became available that could deliver 2 MHz signals (which can penetrate thin parts of the temporal bone), that the basal cranial arteries in older subjects could be examined [7]. In modern devices it is possible to transmit the ultrasound in pulses (thus the direction of blood flow can be determined) and to vary the receiving time, allowing the measurements to be sampled from a specified depth.

The basal cranial arteries can be examined by through various windows. The terminal part of the internal carotid artery (ICA), middle cerebral artery (MCA),

anterior cerebral artery (ACA), anterior and posterior communicating arteries may be examined via the transtemporal approach; the carotid siphon and ophthalmic artery through the orbit and the posterior cerebral artery (PCA), basilar and vertebral arteries through the foramen magnum window [5]. The Doppler signal contains a spectrum of frequencies representing the parabolic velocity profile of blood cells in the vessel, which, after transformation by Fast Fourier frequency spectral analysis, can be displayed real time on a screen or recorded on an audiotape. The systolic peak flow velocity (vs), mean peak flow velocity (vm) and end diastolic flow velocity (vd) may be derived from the envelope curve of the



Parameters of the Doppler signals: $a_1 = a_2$, $A_1 = A_2$

Figure 7.1: Parameters of Doppler signals from Bode [34]

Doppler frequency spectra, while the averaged mean flow velocity (vM) is derived from all the registered velocities (figure 7.1).

Various indices of vascular resistance can be calculated from these parameters, which are largely independent of the angle of insonation. The most commonly used indices are Goslings pulsatility index (PI) and Pourcelet's resistance index (RI) where:

$$Pulsatility\ Index = \frac{(Vs-Vd)}{Vm} \quad \text{.....equ 7.2}$$

$$Resistance\ Index = \frac{(Vs-Vd)}{Vs} \quad \text{.....equ 7.3}$$

Clinical applications

Doppler sonography reliably measures changes in CBF in animals [331], neonates [114] and is used in normal adults and children [160]. However its usefulness in monitoring CBF in unstable unconscious patients remains to be determined. TCD measurements such as vm and PI have been used to monitor the ICP in children with head injury, hydrocephalus [294] and bacterial meningitis [101]. The mean peak sytolic velocity (vm) and RI correlated with ICP in adults with intracerebral haemorrhages [162]. Asymmetrical reductions in vm and increases in PI were associated with an increase in ICP and a decrease in CPP produced by intracranial haematomas [314] and are thought to represent ICP gradients [53]. TCD waveforms have been used to monitor ICP and CPP in head injury [154,298]. TCD sonography has also been used to detect impaired CBF autoregulation by demonstrating

velocity dependent upon MAP [6,51,99,101], although this use was not validated by observations in a lapine model of subarachnoid haemorrhage [235].

TCD has been shown as a reliable technique to confirm brain death in adults [123,282] and children [35,162]. In one study, brain stem death occurred in all ventilated children with a vm of the MCA (MCAV) less than 10 cm/sec. Furthermore a direction flow index (DFI), where

$$DFI = 1 - \frac{R}{F} \quad \ldots\ldots\ldots\ldots\ldots\ldots equ\ 7.4$$

(R was the area under the maximum velocity envelope of the reverse part of the sonogram and F was the area under the forward flow envelope [158]) of less than 0.8 was also associated with brain stem death. The bad prognosis of reverse flow during diastole *ie* DFI <1 was confirmed in another study of children [35] and both studies demonstrated a reverbatory pattern associated with an arrest of intracranial blood flow. In a study of adults dying with progressive ICP, diastolic flow velocity progressively decreased (with an increasing PI) until there was no flow during diastole, followed by reverse flow during diastole [123].

I undertook TCD monitoring to examine the cerebral haemodynamics of children with CM and to determine if TCD could be used to monitor ICP or CPP non-invasively.

PATIENTS AND METHODS

The basal cranial arteries of 63 children with severe malaria were examined with TCD. Sixty children fulfilled the criteria for CM, including 6 children who were monitored during their agonal phases. Three other children who died with severe acidosis or severe anaemia were also monitored during their agonal phases. In 10 children the left middle cerebral artery (LMCA) was monitored with TCD during ICP monitoring.

Ultrasound recordings were made with a 2Mz pulsed transcranial Doppler (EME to 2-64B, Uberlingen, Germany). The MCA was identified using techniques described by Aaslid [7] and was insonated trans-temporally at a depth of 3 to 5 cm. The spectral analysis of the signals was displayed real time and recorded on an audiocassette deck (Technics M30). Mean peak flow velocities (vm) and Gosling's pulsatility index averaged over 10 cardiac cycles were recorded. The DFI was calculated in the children who were monitored during the agonal phases of their illness.

An assessment of MCA CO_2 reactivity was attempted in 4 children with CM, by administering 5% CO_2 + 21% O_2 + 74% N_2 via a face mask. The test was aborted if the child struggled against the face mask or the ICP rose above 25 mmHg. The test was abandoned if a change greater than 1.0 KPa could not be accomplished within 5 minutes.

RESULTS

There was no significant relationship between the TCD findings on admission, the minimum or maximum velocity or PI during admission and outcome, defined as death or survivors, or poor or good outcome.

TCD and ICP monitoring

The clinical features of the children with ICP monitoring are described in chapter 5. In 10 children who had ICP monitors inserted, the correlation between the MAP and MCAV, and the ICP or CPP and PI are shown in table 7.1. There was a significant correlation between ICP and MCAV, and ICP and PI in one child (No 332/92) who had SIH. In the other child with SIH (No. 386/92) there was a strong correlation between MAP and MCAV (r^2 = 0.65, 0.76-0.84 5-95% CI) suggesting autoregulation was impaired as MCAV was dependant upon MAP. This child had a long period during which there were no B-waves present (see chapter 5) and had evidence of diffuse ischaemia on the CT scan (chapter 6); she survived with severe neurological disability. A significant correlation between MAP and MCAV was not detected in any of the other children. There was a significant correlation between CPP and MCAV, and CPP and PI in the 2 children with SIH (Nos 332/92 and 386/92), despite an excessive drift of the ICP monitor in patient 386/92. The relationship between CPP and PI was significant in patient 332/92 (PI = -0.0092(CPP) + 1.3533) and in patient 386/92 (PI = -0.0079(CPP) + 1.044). Similar relationships were not documented in any of the other children, all of whom survived without sequelae.

Table 7.1: TCD measurements in children with ICP monitoring

Clinical Number	Pattern of IH*	Duration of TCD Mx (hrs)	Number of TCD readings	Changes during the TCD monitoring		MACV vs MAP			PI vs ICP			PI vs CPP		
				Haematocrit (%)	pCO_2	Range of MAP	r	CI (5%, 95%)	Range of ICP	r	CI (5%, 95%)	Range of CPP	r	CI (5%, 95%)
220/93	MIH	10.3	26	10.8-18.3	2.8-3.9	68 - 81	-0.33	-0.64, 0.07	5-14	0.50	0.13, 0.74	68-87	-0.08	-0.46, 0.31
214/93	MIH	20.3	51	26.1	1.5-3.6	75 - 102	0.19	-0.10, 0.44	7-19	-0.20	-0.45, 0.08	75-102	-0.05	-0.37, 0.23
210/93	MIH	21.0	53	15.2-25.3	3.7-5.2	76-84	0.14	-0.14,0.39	8-17	0.11	0.16,0.37	76-84	0.10	-0.18,0.36
207/93	MIH	18.7	43	34.0 -24.0	3.9-3.7	54 - 82	-0.05	-0.34, 0.26	12-22	-0.23	-0.5, 0.07	54-82	-0.34	-0.58, -0.04
421/92	IIH	24.1	123	15.6 -29.2	4.0-4.5	66 - 107	-0.23	-0.39,-0.05	7-44	0.10	-0.08, 0.27	44-105	-0.22	-0.38, -0.04
185/93	IIH	20.3	60	28.3 -24.4	2.4-4.8	69 - 99	0.07	-0.19, 0.32	11-32	0.08	-0.18, 0.33	68-107	-0.03	-0.28, 0.23
175/93	IIH	35.3	129	17.6 -22.7	3.3-4.5	63 - 81	-0.04	-0.21, 0.13	8-34	0.07	-0.10, 0.24	57-81	-0.28	-0.43, -0.11
230/92	IIH	25.9	85	19.2 -16.9	4.4-5.4	71 - 93	0.37	-0.54,-0.17	11-42	0.2	-0.01, 0.4	38-79	-0.13	0.02, -0.33
332/92	SIH	50.2	248	19.4 -33.1	3.8-4.7	68 - 114	-0.29	0.08, -0.40	4-52	0.73	0.67, 0.79	31-87	-0.71	-0.77,-0.64
386/92	SIH	89.7	257	36.2 -27.6	1.6-4.5	46 - 128	0.80	0.76, 0.84	5-69	-0.37	-0.47,-0.26	31-110	-0.78	-0.78,-0.66

*Severe intracranial hypertension (SIH): ICP >40 mmHg for more than 20 minutes continuously and CPP <40 mmHg for more than 20 minutes continuously.
Intermediate intracranial hypertension (IIH): ICP >20 mmHg for more than 20 minutes continuously and CPP <50 mmHg for more than 20 minutes continuously.
Mild intracranial hypertension (MIH): maximum ICP 10-20 mmHg for more than 20 minutes continuously and minimum CPP >50 mmHg.

CO_2 reactivity

An assessment of the reactivity of the cerebral vessels to CO_2 was attempted in 4 children at least once, including one child (332/93) 3 times. However, this test proved to be extremely difficult to perform on unventilated children as they would hyperventilate and struggle against the mask.

Table 7.2: CO_2 reactivity

Patient Number	Initial Measurements				End of CO_2 run measurements				Comments
	pCO_2	MCAV	PI	ICP	CO_2	MCAV	PI	ICP	
332/92	3.8	164	0.65	10	4.7	150	0.74	21	no intermediate CO_2 values
332/92	3.67	146	0.73	15	3.72	150	0.69	24	child hyperventilating & struggling
386/92	2.7	94	0.78	23	4.4	74	0.97	30	ICP rose rapidly
421/92	4.0	112	0.63	15	4.5	108	0.70	17	child struggling, unable to increase pCO_2 further

TCD monitoring during agonal phases

Nine children with severe malaria were monitored during the agonal phases of their illness before ICP monitoring was instituted. The clinical features and results of the TCD monitoring are presented in table 7.3. Of the 6 children with CM, 3 had progressive increase in PI followed by a DFI < 0.80, all died with clinical signs compatible with transtentorial herniation. This is best illustrated by the sonograms recorded in patient No 265/90 (case history 1) (Figure 7.2). Sonogram A was recorded shortly after admission, when the child had features of the diencephalic syndrome, whilst sonogram B, showing reverse flow during diastole was registered

after she had a respiratory arrest and was being hand ventilated. In the other three, reverse flow throughout diastole was not documented and a DFI < 0.8 was not recorded despite continuous monitoring during the agonal phases (Figure 7.3). One of these children had evidence of brain stem dysfunction (pupils fixed and dilated after a cardiac arrest) during the agonal stages, the other two were admitted with severe acidosis and had cardio-respiratory arrests. Of the 3 children who did not have CM, but died of severe anaemia and acidosis, none had reverse diastolic flow or a DFI < 0.8.

Table 7.3: Admission characteristics and TCD findings in children who died

Patient No.	Clinical syndrome[a]	Age (months)	Duration of history (days)	Seizure[b]	Admission					Hypoglycaemia (<2.2 mmol/l)	Time of death after onset of Rx (hrs)	Signs of brain stem compromise	BP after diastolic reverse flow	Maximum PI
					Blood press.	ACS[c] (VME)	Parasite count (per μl)	Hct (%)	pH, BE					
265/90	CM	44	3	S-TC	96/70	131	201 000	15.1	NR	N + 0	2	Y	NR	4.42
384/91	CM	9	6	S-TC	142/80	111	39 710	10.2	,-18.1	A + 0	2	Y	160/85	2.69
419/91	CM	24	3	S-TC	56/40	234	273 600	13.7	NR	NR	4	Y	78/40	4.17
329/91	CM	27	2	TC	116/70	232	81 200	30.2	7.01,-27.4	A + 0	8	N	NR	1.36
420/91	CM	42	4	PM	112/60	214	288 080	21.7	7.28,-17.7	A + 0	13	N	NR	1.23
479/91	CM	16	2	S-PBG	80/30	232	252 725	20.7	6.96,-25.1	N + 0	1	N	NR	2.08
335/91	AA	8	2	None	UR	234	21 440	10.4	7.23,-20.7	A + 3	28	N	NR	1.56
362/91	MA	26	2	S-TC	86/-	144	2 500	NR	7.31,-17.8	N + 0	1	N	NR	1.34
365/91	HA	41	3	TC	124/58	344	2397000	17.3	7.19,-21.0	A	2	N	NR	1.52

[a] Complications: AA = Anaemia and metabolic acidosis, CM = cerebral malaria, HA = Hypoglycaemia and metabolic acidosis MA = metabolic acidosis
[b] Seizures: S-TC = status tonic-clonic, TC = tonic clonic, PM = partial motor, S-PBG = status partial becoming generalised
[c] Adelaide Coma Scale (Verbal, Motor, Eye opening components)
[d] blood gases measurements done after child arrested shortly after admission

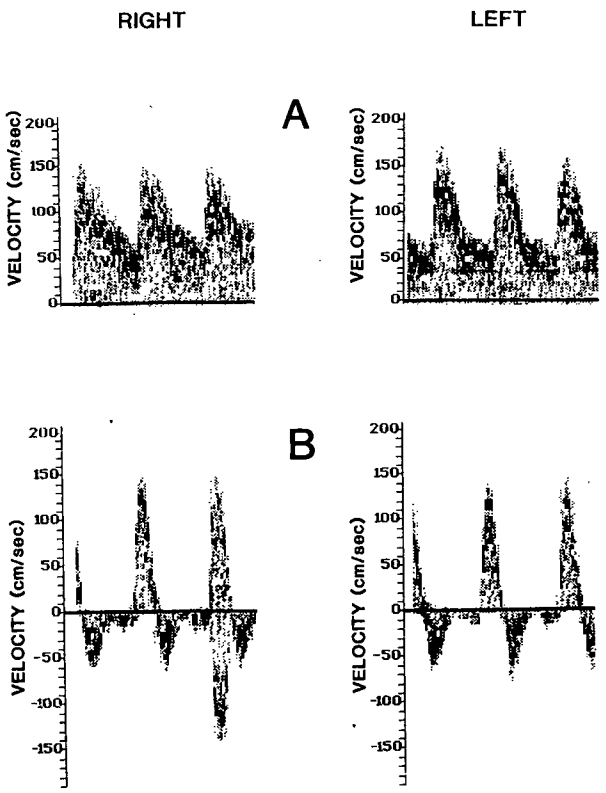


Figure 7.2: Sonograms of patient 265/90. A) On admission. B) 3 hours later associated with signs of herniation

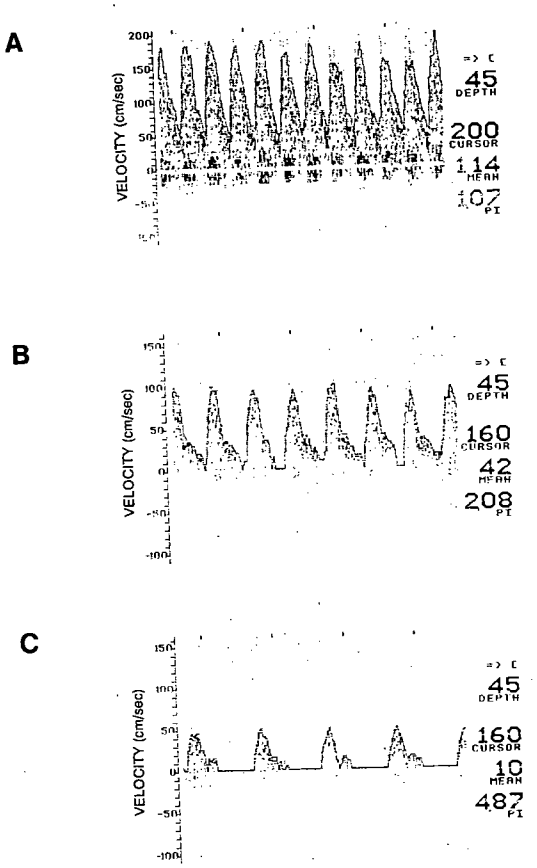


Figure 7.3: Sonograms of patient No. 479/91. A) On admission. B) 30 minutes after admission, shortly before a cardiac arrest. C) 1 hr after admission, after first resuscitation, but before second cardiac arrest

DISCUSSION

Half of the children dying from CM had sonographic features of progressive IH. In the two children with SIH who had ICP and TCD monitoring, there was a correlation between CPP and PI, but no relationship was found in the other children with less severe IH. In the child with SIH who did not have B-waves, TCD provided further evidence that autoregulation was impaired.

Technical aspects

The accuracy of TCD sonography depends upon the operators knowledge of the anatomy and physiology of the cerebral arteries and his skill and experience of the technique [4]. The coefficient of variation for an experienced operator for vm is 2-8% and for the resistance indices it is 1-4% [34]. Recordings from the MCA are most reliable in children, because ICA and ACA are more difficult to insonate, as the ACA has more anatomical variations than the MCA and in older children is insonated at a less favourable angle [34]. These difficulties are aggravated by commercial instruments in which the change of depth occurs in 5 mm steps, thus making the identification of the carotid bifurcation and following the ACA and PCA difficult. Thus for repeated recordings the MCA is generally reported.

Parameters influencing TCD measurements in malaria

There are many physiological parameters that influence the TCD measurements, but in these children with CM, the most important to consider are:

a) *Age*. In normal German children, the vm increases with age, from 28 cm/sec in neonates to 80 cm/sec at 1 year and peaking at 92 cm/sec at 6 years. The RI decreases with age from 0.71 in neonates to 0.58 at 1 year, before reaching a nadir of 0.50 at 6-9.9 years [34]. Thus in this group of children with CM, a difference of up to 15% can be anticipated in any interpatient comparisons.

b) *Haematocrit*. There are no studies specifically showing the relationship between haematocrit and the Doppler measurements in children other than neonates who have high haematocrits. Some children were included in a study which demonstrated an exponential increase in vm with decreasing haematocrit, (described by the formula: $vm = 181.e^{-0.025(Hct)} - 15.9$) and a weak linear relationship between PI and haematocrit [41]. However all the subjects with haematocrits less than 25% had sickle cell disease, which may be associated with cerebral vessel abnormalities. Thus this equation may not reflect the relationship between haematocrit and vm in children with malaria.

c) *Carbon dioxide*. A change in vm of 21.8% per KPa pCO_2 has been demonstrated in one study which included normal children [160]. However the CO_2 responsiveness is likely to be different in acidotic children with CM.

d) *Miscellaneous*. Other factors that may influence Doppler measurements in children with CM are those that decrease the viscosity of the blood *eg* temperature or those that increase the viscosity *eg* aggregation of RBC (either rosetting or rouleaux formation) and/or an increase in the viscosity of the plasma caused by an acute phase response. However these are thought to play a relatively insignificant role in comparison to the above factors (Newton *et al* in preparation).

Monitoring ICP and CPP with TCD

In this study, there was a significant correlation between CPP and PI or MCAV in the 2 children with SIH, despite changes in pCO_2, haematocrit and in one child, a drift in the ICP monitor. These data suggest that CPP is the major determinant of CBF in children with SIH. The lack of correlation between ICP or CPP and the TCD measurements in most children with CM, is probably caused by the confounding variables mentioned in the previous paragraph and the fact that most children did not have severe intracranial hypertension and autoregulation is preserved. In other studies that have shown significant correlations between ICP and TCD parameters such as vm or RI, the patients have been stable adults with intracranial bleeds [162], or ventilated head injured adults with high ICP [298]. Even more significant correlations have been described between CPP and the TCD parameters, particularly PI, but again these findings were described in ventilated adults with head injuries who had a stable $PaCO_2$ [57].

Autoregulation

In only one child was there a significant correlation between MAP and MCAV, despite a 1.9 KPa change in $PaCO_2$ and an 8.6% change in haematocrit, suggesting impaired autoregulation. This interpretation is further supported by the presence of a clearly discernable break point in the relationship between PI and CPP (despite a drift in the ICP monitor), such that there is a linear relationship between CPP and PI below a CPP of 59 mmHg. Such patterns have been described in adults with head injury and interpreted as exhaustion of autoregulation [57]. None of the other

children, (including patient No 332/92 who developed severe neurological sequelae, but had only modest changes in CO_2 and insignificant changes in haematocrit during the monitoring period) had evidence of impaired autoregulation, although the data was uncorrected for haematocrit or CO_2. However autoregulation was not formally tested by altering the blood pressure and changes in vessel diameter cannot be excluded [164].

CO2 reactivity

The rigorous assessment of CO_2 reactivity was abandoned in these unstable children, because of concerns of precipitating herniation and aggravating the acidosis. However the marked increase in ICP in response to the administration of CO_2, suggests that the vessels are responsive to changes in CO_2, as the rise in ICP is probably caused by vasodilation. Although RICP may cause the loss of CO_2 reactivity (*ie* vasomotor paralysis) during progressive decompensation [174], the two children with SIH in whom CO_2 reactivity was tested, were very sensitive to an increase in CO_2.

Brain death

Two types of sonographic appearances were recorded during the agonal phases. Three children had evidence of a progressive increase in PI (despite maintaining their blood pressure), associated with reverse flow throughout diastole (fig 7.2), culminating in a DFI of less than 0.8. All these children had evidence of brain stem compromise, compatible with transtentorial herniation during the agonal phases.

These appearances have been described in children [158] and adults [123] with low CPP caused by RICP and suggest that RICP is directly contributing, if not the main cause of death. The other 3 children also had a rise in PI, but this was not associated with reverse flow throughout diastole. Instead, a reverbatory pattern with a short low forward velocity flow in systole counterbalanced by an even shorter flow in diastole was seen (figure 7.3). This pattern was associated with a poor cardiac output (detected by an unmeasurable blood pressure) and systemic acidosis. Only one of the children had evidence of brain stem signs (but did not fulfil the criteria for herniation) before a terminal cardiorespiratory arrest. The reverbatory pattern has been documented in children [158] and adults [123] with RICP, but also occurs in children with brain stem death not associated with generalised RICP [35]. Although the brain stem signs may have been missed during the attempted resuscitation before the cardiorespiratory arrest occurred, it appears that these children died of severe acidosis rather than a brain stem death.

SUMMARY

TCD sonography provided further evidence that some children with CM die with progressive IH. The technique may be useful for monitoring CPP in children with SIH, but it is of little use in monitoring children with less severe IH. TCD could be used to detect children with impaired autoregulation, although this is uncommon in CM.

8 DISCUSSION

This thesis establishes intracranial hypertension (IH) as a feature of cerebral malaria (CM) in Kenyan children and presents evidence to support the hypothesis that IH is a determinant of poor outcome in some children.

Prior to these studies, IH was dismissed as an important component of the pathophysiology of CM, even by some authorities on paediatric malaria [225], based mainly upon the findings in adults. In the few anecdotal reports of RICP in African children, IH was not suggested as a determinant of outcome. Some clinicians thought that cerebral oedema was responsible for the coma in CM and advocated the use of osmotic diuretics to improve the level of consciousness [68,156]; but none of these authors suggested RICP caused brain tem herniation.

In this thesis, ICP was raised in all the children with CM and in some cases critically high pressures were reached. Severe intracranial hypertension (SIH) was associated with a poor outcome: all the children with ar. ICP above 50 mmHg or a cerebral perfusion pressure (CPP) less than 32 mmHg either died or survived with severe neurological sequelae. Further evidence of reduced intracranial compliance in some children, was suggested by the presence of B-waves detected during ICP

monitoring and the marked brain swelling detected by computerised tomography (CT). Clinical signs compatible with transtentorial herniation were present in at least a third of the children who died, including three children who also had transcranial Doppler sonographic evidence of progressive IH during the agonal phases. Mannitol reduced the ICP in all cases. Athough it controlled the ICP in children with intermediate intracranial hypertension (IIH), it did not prevent or control severe intracranial hypertension (SIH) in other children.

MEASUREMENT OF ICP

Opening CSF pressure

Opening CSF pressure (CSFP) was raised in all children with CM on admission and most children who had an lumbar puncture performed (LP) during recovery. These observations were confirmed by other studies of African children [237, 350, 360]. Correlation between high CSFP and poor outcome was not found in any of these studies, but this is not surprising as a single measurement of CSFP represents only one point in time and as the data from the ICP monitoring clearly demonstrates, the opening ICP and CPP do not predict the maximum ICP or minimum CPP. The CSFP measured in African children were similar to those in non-immune adults with CM [352], but because of a higher upper limit for normal in adults, the pressures are considered raised in only 20% in this latter group.

ICP monitoring

The ICP monitoring confirmed the LP measurements; *ie* RICP is a feature of CM in Kenyan children and established that the highest ICP and lowest CPP were associated with death and severe neurological sequelae. Furthermore, in the child who died during monitoring, signs of herniation appeared as severe ICP developed. Intracranial pressure monitoring also demonstrated that mannitol effectively controlled the ICP in children with IIH and although this agent reduced the ICP in children with SIH, it did not prevent or contol intractable IH.

ICP monitoring in cerebral malaria

The role of ICP monitoring in CM still needs to be determined. From an ethical point of view, ICP monitoring in CM can be classified as 'therapeutic research' [244]. It provides information that can be used to manage the individual child's IH and in addition, it may provide data for an empirical regimen that can be used in African children with CM. However the benefits of ICP monitoring must be consider in the light of the following factors:

i) in African hospitals, particularly those without neurosurgical and neuroradiological facilities, the risk of causing an intracranial catastrophe is undetermined. In sophisticated centres, such as Great Ormond Street, London, the risk of serious infection or bleed is less than one percent (Harkness personal communication). It is reassuring to note that we have not had any life threatening complications so far.

ii) there have been no controlled trials that show an improvement in outcome with ICP monitoring in any encephalopathy. Indeed there was not a significant

difference in head injured adults between the administration of mannitol when the ICP reached 25 mmHg and an empirical regimen of mannitol given every 2 hours [322], although a type II statistical errror could be possible.

iii) the treatment of RICP detected with monitoring may prevent children dying from herniation, but might also increase the incidence of severe neurological sequelae. This outcome may be undesirable in developing countries, which have limited facilities and/or resources to cater for children with severe handicap.

iv) the findings in African children may not be applicable to non-immune individuals. Intracranial pressure did not rise above 25 mmHg in six non-immune patients with CM who have been monitored; one child treated in London (Kirkham personal communication) and five adults in Austria (Wagner personal communication).

Thus ICP monitoring still must be considered as a research tool and not part of the standard clinical management of CM. However it can be performed safely in African hospitals and centres that have the facilities and staff, should consider adding this procedure to the management of African children with CM.

ROLE OF INTRACRANIAL HYPERTENSION IN CEREBRAL MALARIA

RICP could contribute to the pathophysiology of CM by causing death, neurological sequelae or even coma.

Intracranial hypertension as a cause of death

RICP causes death by producing compression of the brain stem from transtentorial herniation or ischaemia following a profound reduction in CPP. Although we were unable to perform necropsies on the Kenyan children, three pieces of evidence suggest that some of these children died from herniation. Firstly at least a third of the children who died had clinical evidence of herniation as assessed by strict clinical criteria that have been used in other studies. Secondly, of the six children with CM who were monitored with transcranial Doppler during their agonal stages, three had sonographic evidence of progressive IH associated with the clinical signs of herniation. Finally, the one child who died during ICP monitoring had the highest ICP recorded and the clinical features of uncal and midbrain stages of herniation developed as the ICP rose to the critically high pressures.

The following factors should be taken into consideration when assessing the significance of RICP as a cause of death:

i) IH is the only mechanism of death in these children with CM, for some children undoubtly died with severe metabolic acidosis, severe anaemia or intractable hypoglycaemia. Clearly, when considering intervention studies, it is important to establish the proportion of children that die with RICP. The ICP

has been monitored in only child who died and although the data is compelling, the incidence of critically high ICP during the agonal phases remains to be determined.

ii) the clinical signs used for the diagnosis of herniation are not specific. The signs have been documented in the absence of RICP in other encephalopathies and were present in the children in this thesis when the ICP was moderately raised (*eg* respiratory abnormalities or extensor posturing occurred in children with ICP <20 mmHg). Thus other processes affecting the brain stem cannot be excluded

iii) although the transcranial Doppler findings during the agonal stages are convincing, they do not establish IH as the cause of the death, but may represent an agonal phenomenon.

iv) there is little pathological evidence to support herniation as a cause of death. Brain swelling and oedema were seen at autopsy in African children [340], but transtentorial herniation was only reported in African children [348] after we had published our original observations [237]. The lack of autopsy evidence for herniation may be explained by the difficulty of recognising central herniation, particularly by general pathologists with little training in neuropathology. Furthermore a critical factor in the development of herniation is the size of the tentorial opening [263]. The aperture may vary considerably between the heterogenous peoples of Africa, perhaps explaining the lack of pathological evidence in some areas.

Intracranial hypertension as a cause of neurological sequelae

Raised ICP produces brain damage by reducing the CPP or compressing the basal cerebral arteries during transtentorial herniation. The patterns of ischaemic damage documented on CT scans were heterogenous (Appendix VII). The expected distribution of damage from herniation with prominent involvement of structures in the territory of the posterior cerebral artery was not seen in this study. Thus in CM, herniation is likely to be a terminal event rather than a cause of neurological sequelae.

In this study, two children with minimum CPP less than 34 mmHg developed severe neurological sequelae, including one child who had a watershed distribution of ischaemic damage on his CT scan. Two other children with a minimum CPP of 46 and 60 mmHg, also developed sequelae. Both these children had status epilepticus and developed mild sequelae. In addition, three children with minimum CPP less than 40 mmHg, which is usually associated with a poor outcome in other studies [102, 222, 329], survived without sequelae. Thus a low CPP may be an important cause of severe sequelae, although a causal relationship remains to be established. Clearly it is not responsible for the development of all sequelae.

The minimum CPP that was associated with a poor outcome in these children with CM was lower than those recorded in other encephalopathies [157,222,329], suggesting that CPP may not be a reliable estimate of cerebral perfusion in CM. The critical minimum CPP depends upon the encephalopathy, age of the child and the extent of the damage within the brain [49]. For example, CPP is a poor

predictor of cerebral perfusion in oedematous tissue [49]. Furthermore a low CPP does not necessarily imply a low cerebral blood flow (CBF), as a CPP below the autoregulatory range was associated with an high global CBF in one study of head injured adults [308]. In CM, the CPP is unlikely to reflect the perfusion pressure of capillaries blocked with sequestered erythrocytes, particularly if luxury perfusion is an important component of the pathophysiology. These considerations may make it difficult to determine a critical level of CPP at which to institute treatment.

Other features of CM, such as seizures, hypoglycaemia, lactic acidosis and degree of sequestration may also be important determinants of sequelae in CM. The heterogenous patterns of damage found on the CT scans (Appendix VII) suggests that the sequelae are caused by several, possibly interacting mechanisms. Global reduction in CPP produces diverse patterns; from borderzone ischaemia (with a precipitous reduction in CPP), to diffuse ischaemia (with a moderate, but prolonged reduction in CPP) [9]. The contributory effects of the other factors cannot be easily identified from the CT scans. Thus, although the mechanisms of damage caused by status epilepticus and hypoglycaemia are different from low CPP, they may produce additive neuropathological changes when CPP is reduced. Furthermore it is possible that there is a synergistic interaction between lowered CPP and sequestration of parasite infected cells. Sequestration may lead to reduced peripheral perfusion and since the cytoadherence of parasitised red blood cells (PRBC) is enhanced by low shear stress [234], a decrease in CPP from any cause may promote sequestration in areas of low flow.

Intracranial hypertension as the cause of coma

Raised intracranial pressure can produce coma by reducing CBF or causing compression of the brain stem. It is not the level of ICP *per se* that causes the disturbance in consciousness, but rather the rate at which IH develops.

In CM, there is little evidence to suggest that RICP is a primary pathogenic mechanism responsible for coma. Critically high ICP (>20 mmHg) was not documented in all children with CM (although the high ICP may have been missed since the monitoring was started after the onset of coma), there was no correlation between ICP and depth of coma and the highest pressures in the children were not documented shortly after admission, but often occurred 12 hours later when the children was improving. Raised intracranial pressure, however, may prolong the duration of coma, by reducing perfusion in the vessels packed with sequestered parasites.

Role of ICP in adults

The role of RICP in the pathophysiology of CM in adults was dismissed on the basis that most adults had a normal opening CSFP (with lower pressures in those who died), the blood brain barrier (BBB) was intact [352] and cerebral oedema only occurred as an agonal event [191]. Although adults can die with an acute respiratory arrest, this is much more common in children and in adults, respiratory arrest is associated with other evidence of severe disease [353] (NJ White personal communication). The lack of intermediate or severe IH in the 6 non-immune patients who had ICP monitoring (page 219) would also support this conjecture.

Recent studies from South East Asia, however have provided evidence supporting a role for RICP in non-immune patients with CM. In a study of Vietnamese adults, although the CSFP measured were similar to those in the Thai adults [352], the pressures were higher in the patients who died [81]. The reason for this discrepancy is not clear. In a Magnetic Resonance Imaging (MRI) study of 24 Thai adults, gross brain swelling and transtentorial herniation were found in 2 of the 4 patients who died. The scans were performed after the patients had a respiratory arrest and thus may have been secondary to hypoxia (NJ White personal communication). This study also showed that there was an increase in cerebral volume during the acute stages, but the MRI appearences were not compatiable with cerebral oedema. Lastly, some adults do have evidence of uncal grooving and tentorial herniation [279]. Thus RICP may be a feature of adult CM, although the evidence would suggest that it is not as an important factor as in African children.

CAUSES OF RICP IN CM

The possible causes of RICP in CM are an increase in cerebral blood volume (CBV), cerebral oedema or acute hydrocephalus. There was no tomographic evidence of acute hydrocephalus or vasogenic oedema in the acute scans, although the two children who developed severe sequelae had scans compatible with cytotoxic oedema. Also the MRI study of adults with CM also supports our hypothesis that CBV is increased in CM [237]. Thus an increase in CBV is the most likely cause of RICP in most children with this encephalopathy, although some authorities would disagree [268].

Increased CBV

Cerebral blood volume could be increased by physiological factors which increase CBF and/or an increase in stagnant cells *ie* the sequestrated erythrocytes within the cerebral venules (table 8.1).

Table 8.1: Possible causes of increased CBV in CM

Increased CBF and CBV	Increased venous capacitance
Seizures	Sequestration
Anaemia	Venous outflow obstruction secondary to sequestration
Hyperthermia	
TNF induces NO to cause vasodilation	
Hypoxia	
Lactic acidosis	

Sequestration

Sequestration of parasites could increase the CBV in a number of ways. The sequestered mass of parasitised erythrocytes, may represent a 'diffuse space occupying lesion' increasing the amount of space the vascular compartment occupies within the cranium. This mechanism may be particularly important in a synchronous infection since sequestration could increase the volume of the vascular component quickly and lead to a rapid rise in ICP. Furthermore compensatory vasodilation of the vessels adjacent to the occluded vessels would aggravate the increase in CBV. Finally sequestration may impede venous outflow from the cerebral circulation, thereby increasing CBV.

Sequestration may be a more important cause of RICP in African children than non-immune adults, since children have higher peripheral parasitaemias and thus by implication (although not proven) a larger sequestered mass in a smaller volume cranium. This consideration may be particularly important in children aged 1-4 years old when fusion of the sutures prevents any skull expansion and explain the age distribution of children dying from CM.

Seizures

Seizures raise ICP by increasing the CBF and producing cerebral oedema. A six to nine fold increase in CBF has been documented in animals [212] and in humans the elevation of CBV persists after the seizure has stopped [100]. During the seizure, CBF increases as a result of an elevation of blood pressure, pulse rate and vasodilation, in response to the increased metabolic demands of the brain. Although the rise in CBF more than compensates for increased brain metabolism during the initial stages of the seizure, the CBF decreases to pre-ictal values in prolonged seizures [212]. Thus seizures may account for some of the acute increases in ICP, but they are unlikely to be wholly responsible for the sustained increase in ICP.

Anaemia

The rapidly falling haematocrit in malaria may contribute to the increase in CBF. Anaemia increases CBF by decreasing the viscosity of the blood and reducing the oxygen content [132]. In this study there is little data to support anaemia as a major cause of RICP in CM. There was no relationship between the haemoglobin level and the opening CSF pressure or the pattern of RICP during monitoring and

the effects of blood transfusion on ICP during monitoring were variable.

The relationship between anaemia and RICP in these children could be influenced by a number of confounding factors. Arterial oxygen content is an important determinant of CBF in normocapnic individuals [47] and CBF increases exponentially when the PaO_2 drops below 60 mmHg if the $PaCO_2$ is constant [343]. However in severe malaria the influence of oxygen is likely to be overridden by the compensatory hypocapnia that many of these children exhibit. Systemic hypoxia promotes the opening of arterio-venous shunts in the brain, but it is unclear what the effects of localised hypoxia secondary to vascular obstruction would have on the cerebrovascular haemodynamics of surrounding vessels.

Fever

Fever is another universal feature of CM. Hyperpyrexia increases cerebral metabolism which in turn raises CBF [89]. This adaptive response is limited since an increase in temperature has been shown to aggravate ischaemia in experimental models [100].

Metabolic causes of an increase in CBV

A number of metabolic factors may also contribute to an increase in CBV. Lactic acidosis is associated with an increase in CBF and luxury perfusion in many encephalopathies [177]. Lactate *per se* does not raise the CBF, but the accompanying acidosis increases the CO_2 and causes vasodilation [89]. In this study there was no relationship between lactate and opening CSFP or ICP.

Systemic levels may not accurately reflect the concentrations in the cerebral vessels packed with metabolically active schizonts. The hypocapnia found in children with CM may override this mechanism.

The increased concentrations of tumour necrosis factor (TNF) found in children with CM, may also increase the CBV. TNF is a major pyrogen and induces the release of nitric oxide, a potent vasodilator; although in malaria free haemoglobin (from the intravascular haemolysis) may inhibit this action [133]. TNF may increase the CBV despite the presence of hypotension, as in experimental model of endotoxinaemia [120].

Hypoglycaemia increases CBF in rats [89] and piglets (Ichord personal communication), but this response has not been documented in humans [317] and thus is unlikely to contribute to the increased CBV.

Cerebral oedema

Cerebral oedema contributes to the RICP in some children. The tomographic appearences of cytotoxic oedema (see page 50) were found on the acute CT scans of the children who had SIH. Since SIH may have caused the cytotoxic oedema (reduced perfusion), it is unclear if the SIH was the cause or effect.

Severe vasogenic oedema is unlikely to be a major component of the pathophysiology of CM in children, since most children did not have the characteristic raised CSF protein levels [92] or the distinctive tomographic features

of vasogenic oedema. Increased capillary permeability is a feature of adult malaria [79], but is associated with systemic complications such as renal failure which are rare in children. Cerebral oedema may contribute to death, since children who die have elevated CSF protein levels and cerebral oedema is often seen at autopsy in African children. However these findings are more likely to be an agonal event or a postmortem artifact (Sebastian Lucas, personal communication).

Systemic perturbations such as hyponatraemia may promote fluid accumulation within the interstitial spaces [100], but there is no evidence to support the role of it increasing the ICP in children with CM.

THE EFFECTS OF RICP

Cerebrovascular haemodynamics in CM

The effect of RICP on the cerebrovascular haemodynamics was difficult to examine in these unventilated children. Sonographic evidence for impaired autoregulation was found in only one child who had SIH and developed diffuse ischaemia, but autoregulation was not properly tested in any of these children (by inducing changes in blood pressure) and the TCD assessment did not take into consideration the other confounding variables.

In CM, a number of factors may affect autoregulation. Seizures perturb autoregulation, although the effect is transient [15] and is probably only clinically significant in prolonged convulsions. Acidosis is associated with impaired

autoregulation in many encephalopathies [100], but since hypocapnia quickens the autoregulatory response [6], its effect in CM may be minimal.

Little useful data was collected on CO_2 reactivity in these children with CM, since most tests had to be aborted. However the rise in ICP in response to CO_2 suggests that the vessels retain their reactivity. The compensatory hypocapnia may be an important factor in controlling the ICP in these children. Some children had very low CO_2 levels, which if the cerebral vessels were fully reactive, might cause a critical reduction in CBF, resulting in ischaemia.

Clinical signs of RICP

One of the disappointing aspects of the ICP monitoring in these children was the lack of association between raised ICP and clinical signs. The ICP monitoring in these children was unique, in that the children were not paralysed and thus there was an opportunity to document clinical signs associated with rises in 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. In Reye's syndrome, pupillary dilatation and loss of pupillary reflexes were associated with low CPP [346]. Decerebrate posturing is often regarded as a sign of RICP [46], but the children with CM, two children had repeated episodes of decerebrate posturing when the baseline ICP was less than 20 mmHg and the episodes of posturing did not become more frequent as the ICP increased. Finally as in Reye's syndrome [346], a Cushing reflex, infrequently accompanied a low CPP.

The lack of clinical signs reflecting RICP 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 benefit of ICP monitoring. Most paediatric authorities would institute ICP monitoring in an unconscious child [180] with a summated Glasgow coma score less than 8 [103,157,201,206,245,310] or features compatible with Lovejoy stage 3 (table 1.6) [49,58,201]. As yet there is not enough data to provide reliable indications for ICP monitoring in CM, although children with pupillary abnormalities and an Adelaide coms score less than 6 are more likely to develop severe IH.

MANAGEMENT OF RICP IN CHILDREN WITH CM

There are three immediate concerns, besides the cause of the IH, that a clinician must address in the management of the unconscious child with RICP: reduction of the ICP, prevention of factors that increase the ICP further and the indications of an LP to determine the cause of the encephalopathy.

Reduction of RICP

Treatment of RICP should be guided by the underlying mechanisms [49], but in Africa potential therapies are limited to improving nursing care, fluid regimens, osmotherapy, steroids and other pharmaceutical agents. Other modalities *eg* hyperventilation, barbiturate coma or hypothermia, have been used in specialised centres, but are not as effective as osmotic diuretics [138] and are unlikely to be practical solutions for use in rural African hospitals.

Osmotic Diuretics

Osmotherapy has been used in children with CM previously. Kingston reported an improved outcome in Liberian children who were given 30% urea in 10% invert sugar after they had deteriorated or were in prolonged coma [156], but a randomised control trial has not been conducted. Similarly the administration of mannitol (1 g/Kg) every 8 hours was reported to improve the level of consciousness [67] and perhaps outcome [68] in Ghanian children. Again these observations were not part of a randomised trial, did not have historical controls and thus their significance is difficult to determine. Neither of these therapies are recommended by the WHO [354].

Mannitol

Mannitol was effective in reducing ICP in children with CM, and we have observed instances when neurological improvement occurs after administration (see figure 5.4). However, frequent administration of mannitol did not prevent the development of intractable IH in three children (although one child 386/92 probably had hypoxic/ischaemic encephalopathy following poor cardiac output), and during the period of severe IH, its effectiveness was limited. This failure may be the result of the criteria for the treatment used in this study, for a significant improvement in outcome was reported in a study of head injured adults, using historical controls, by reducing the level of ICP at which mannitol was given, from 20 mmHg to 15 mmHg [297]. This study has not been substantiated by a randomised control study and most authorities still recommend that treatment of ICP should be instituted when the ICP reaches 20 mmHg. Furthermore, lowering

the level of ICP at which treatment of ICP begins, may increase the number of doses administered and lead to the development of the rebound phenomenon [137].

A major question to arise from our observation is whether osmotherapy contributed to the outcome in the group with IIH. Mannitol effectively reduced the ICP in these children and they all survived with a good outcome. However, establishing cause or effect would be difficult, requiring a large randomized study. More data are required on the safety and efficacy of an optimal regimen before such trials could be recommended.

Besides the treatment of RICP, mannitol could have some other potentially therapeutic effects in malaria. It may improve the blood flow through the partially occluded capillaries and venules by reducing the viscosity of the blood, but the increase in 'blood flow' would be at the expense of a reduction in erythrocyte flow and hence the delivery of oxygen. Mannitol has been shown to lyse PRBC containing schizonts, however the concentrations required are 10 times higher than those achieved with osmotherapy (S Krishna, personal communication). It is also a free radical scavenger, although the role of oxygen free radicals in malaria is not established.

Mannitol would aggravate the mild dehydration that commonly occurs in children presenting with CM (Sowunmi *et al* in preparation) and may precipitate renal failure. Dehydration may also reduce the blood pressure in unstable patients, reducing oxygen delivery, thereby aggravating lactic acidosis.

Glycerol

Glycerol is another osmotic agent that may be useful for controlling ICP. It has been used safely in adults with malaria, as a tool for testing gluconeogenic pathways (S.Krishna personal communication) It can be used by the brain as a source of energy. However, it is associated with an increased incidence of the rebound phenomenon [26], increased haemolysis, the pharmacokinetics in children is very variable. Furthermore, in comparison to mannitol, it is more difficult to administer and is not widely available throughout Africa.

Other osmotic agents

Urea in invert sugar, the osmotic agent used in Liberian children with CM, is not as effective as mannitol or glycerol in reducing ICP in other encephalopathies. It was associated with a greater incidence of the rebound phenomenon and the reports of toxicity with this preparation have limited its use [91]. Thus although it has been used in children with CM, the other osmotic agents should be tested first.

Steroids

Corticosteroids reduce ICP in some encephalopathies, principally by reducing cerebral oedema. They are most effective against vasogenic oedema, particularly that surrounding tumours, but are rarely beneficial in diffuse encephalopathies [91]. They do not appear to work in other types of oedema, in particular they are not useful in cytotoxic oedema following ischaemia or hypoxia [100]. The mechanisms by which steroids work are unknown, though they were shown to reduce CSF production, promote CSF absorption [100] and improve the vascular integrity.

Steroids have not been shown to be beneficial in two studies of non-immune patients (principally adults) with CM, [129,353]. In these studies, steroids were associated with a prolonged duration of coma and an increase incidence of complications (mainly gastrointestinal bleeding). However neither of these studies examined the effect of steroids on ICP and similar clinical trials have not been conducted in African children.

Other agents

Desferroxamine is an iron chelating agent, lowers ICP in experimental models by reducing oxygen free radicals [134]. In African children with CM, it appears to reduce the duration of unconsciousness [105], but its effect on ICP has not been examined, although it is unlikely to be able to control RICP on its own.

High CSF lactate concentrations are strongly associated with death in children with CM. The interaction between lactate and RICP is complex, since IH may develop following ischaemia (for which lactate is a marker), or RICP may produce the ischaemia. Agents such as trishydroxyaminomethane (THAM) may improve the outcome by lowering the ICP and neutralising the harmful effects of the lactic acidosis.

Other agents which interfere with the pathophysiological processes in CM *eg* anti TNF antibodies [172], may also lower ICP, but are unlikely to be useful in the acute reduction of ICP.

Other interventions

Non pharmacological interventions may be useful in reducing ICP in children with CM. Positioning the head in the midline reduces ICP by promoting venous drainage, but children are more likely to aspirate vomitus in this position, thus insertion of a nasogastric tube and draining the stomach contents is essential.

Hypothermia is effective in reducing ICP by reducing cerebral metabolism [26]. However it should not be undertaken lightly since it causes a metabolic acidosis particularly if shivering is not suppressed by an adequate paralysis [100]. The effect on ICP of maintaining normothermia in encephalopathies associated with pyrexia is undetermined.

Improving CPP by increasing blood pressure

Hypotension is not a recognised feature of CM in African children, although 0.3% of the children studied in this thesis had a systolic blood pressures less than 50 mmHg. In children with CM, hypotension is associated with hypoglycaemia and acidosis. It may also be caused by dehydration in which case it responds to intravenous fluids. The administration of IV fluids, particularly blood, increased the ICP in some children, but also improved the CPP. Inotropic agents may have a role to play in the management of SIH in CM, although their effect needs to be monitored to assess the role of any parallel increase in ICP.

Prevention of increases in ICP.

Three practical measures may be important in preventing rises in ICP: effective anticonvulsant therapy, temperature control and improved oxygen delivery. Seizures not only increase ICP, but if they are prolonged can produce neuronal damage by excitotoxin release and other biochemical perturbations [192]. A single intramuscular dose of phenobarbitone (3.5 mg/Kg) reduced the incidence of seizures in adults with CM from 54 to 13 %, but an improvement in outcome could not be shown [363]. In Kenyan children, a 10 mg/Kg IM injection did not prevent seizures [370]. Adequate temperature control will prevent the rise in ICP associated with an increase in CBF to meet the higher metabolic rates and may prevent the occurrence of seizures. Oxygen delivery may also prevent the rises of ICP. The obligatory reduction of haemoglobin in malaria reduces the oxygen delivery and may aggravate the IH, by increasing the CBV further. Oxygen delivery could be improved by blood transfusions, the administration of compounds that carry oxygen or even oxygen administered via a nasal prong.

Timing of LP in CM

Lumbar punctures are performed in unconscious children, principally to exclude central nervous system infections [46]. This indication is even more pertinent in children presenting with the clinical features of CM, since CM is essentially a diagnosis of exclusion and it cannot be differentiated from ABM clinically [373]. Lumbar punctures are regarded as dangerous in the presence of RICP, since they may precipitate transtentorial herniation. The incidence of this complication is difficult to determine. In adults with RICP from brain tumours 1.2% of those with

papilloedema had neurological deterioration within 24 hours of the procedure, while 12% without papilloedema had similar outcomes [165]. From this data and a review of a further 418 patients, the estimated risk of serious complications following LP in the presence of papilloedema was less than 1.2%. Further reports from neurosurgical units [84] and adults with subarachnoid haemorrhages [85], would suggest that the risk of deterioration is even higher in patients without papilloedema. However in none of these reports was the incidence of neurological deterioration determined in those patients who did not have a LP.

In ABM the likelihood of neurological deterioration appears to be increased in children who are unconscious, present with a history of disturbed consciousness for more than 4 days or have localising signs [29]. In countries with CT facilities, it is now recommended that children presenting with coma should have empiric treatment started immediately (depending upon the clinical suspicion) and the LP delayed until a CT scan is performed to exclude brain swelling. These recommendations could not be followed in most African hospitals because of the lack of CT facilities.

Most tropical physicians agree that an LP should be performed on children with CM to exclude other CNS infections, however the timing of the procedure is controversial. Most authorities still recommend that the LP should be performed on admission [70,171,358,360]. We elected to defer the LP until the child is neurologically stable, and cover the possibility of ABM causing the encephalopathy by administering both antimalarials and antibiotics. Although, we have not

significantly reduced the mortality with this policy (it would need a large study to show such a difference), this policy still seems prudent. It may, however be difficult to maintain in some African hospitals [112].

FUTURE RESEARCH

The data presented in this thesis establishes that RICP is a feature of Kenyan children with CM, which may be associated with brain swelling caused by an increase in CBV. It also suggests that SIH is an important determinant of poor outcome in some children.

In order to establish the proportion of children dying from herniation, detailed autopsies need to be performed, paying particular attention to the brain stem. These studies should include careful documentation of the clinical signs before death and if possible ICP monitoring, to establish the relationship between the ICP levels, brain stem signs and post mortem findings. These studies would also provide useful clinical data that may be applied to other encephalopathies as well, but may indicate that other processes affect the brain stem and are responsible for the clinical syndromes seen in CM. In particular, it would be important to document the patterns of sequestration within the brain and any relationship that these patterns have with the clinical syndromes.

The contribution of IH to producing neurological sequelae relies on collecting more data on ICP during the course of the illness. Non-invasive techniques *eg* TCD are

unlikely to provide adequate information, although continuous monitoring of the EEG pattern may provide data on cerebral perfusion.

Most African hospitals are not able to undertake ICP monitoring safely, although more information is clearly needed to develop an empirical regimen. Thus centres that are able to institute ICP monitoring, should collect further information to establish the incidence of SIH in CM, to identify clinical signs that may be useful in predicting SIH, document the natural history of RICP and further define the most appropriate therapy.

Computerised tomography may be useful in determining the causes of the RICP in CM, if the scans could be performed earlier and repeated during the course of the illness. Further CT scans of children who develop neurological sequelae, particularly combined with detailed monitoring during the acute illness may further delineate the major mechanisms of damage. Other sophisticated neuroradiological investigations would also help elucidate the pathophysiology of RICP, in particular magnetic resonance imaging is good at detecting herniation and white matter oedema [268]. Unfortunately these devices are unlikely to be placed in the areas where most African children with CM are seen.

Osmotic diuretics are the most practicable measure to control ICP in most African hospitals. The most effective agent still needs to be identified. Mannitol should be thoroughly investigated first, since it reduces ICP in most cases and is readily available throughout Africa. The optimal dose and manner of administration still

needs to be determined, particularly before a large scale randomised trial is considered. Glycerol would also warrant investigation. Other agents that reduce ICP and interfere with the pathophysiological processes in malaria, such as THAM should also be considered. Investigation of the BBB, using small molecular substances such as inulin to detect minor perturbations would provide information that would help decide which osmotic agent was most appropriate.

Accurate measurement of CBF and CBV would provide information to support or refute the hypothesis that an increase in CBV is a major cause of RICP in these children. However the measurements would have to be repeated frequently in these children with rapidly changing cerebral haemodynamics (*eg* changing CBF from fluctuating temperatures and dropping haemoglobin). Most techniques would be difficult to perform accurately in this setting. We have tried using Near Infra-red spectroscopy (NIRS) to measure CBF and CBV, but need to validate the techniques before we can interpret the data.

SUMMARY

This thesis establishes that raised intracranial pressure is a feature of cerebral malaria in Kenyan children and presents evidence that supports the role of intracranial hypertension as a determinant of poor outcome in some children Raised intracranial pressure is not caused by vasogenic oedema or acute hydrocephalus, but is likely to be caused by an increase in cerebral blood volume. Mannitol was effective in reducing ICP and may improve the outcome in some African children with cerebral malaria, but requires further study.

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APPENDIX I: CLINICAL PROFORMA

Proforma used for the collection of the clinical data in 1991, modified from proformas of 1989 and 1990.

Key

CS = Coding Sheet
EM = Eye Movements
N/A = Not Applicable
OC = Oculocephalic reflex
OV = Oculovestibular reflex
UMNVII = Upper Motor Neuron VII
Y/N = Yes/No

Organisms:
S. pneu = *Streptococcus peumoniae*
H. influ = *Haemophilus influenzae*
N. men = *Neisseria meningitidis*
S. typhi = *Salmonella typhi*

Drugs:
Pen = Benzylpenicillin
Amp = Ampicillin
Chlor = Chloramphenicol
Gen = Gentamicin

KILIFI UNIT

FRONT SUMMARY SHEET

1.KEMRI NUMBER : ..... |_|_|_| |_|_|

2. STUDY NUMBER: ..... |_|_|_| |_|_|

3. ..... |_|_|_| |_|_|

4. ..... |_|_|_| |_|_|

HOSPITAL NUMBER : ..... |_| |_|_|_| |_|_|

FIRST NAME : .....

SURNAME : .....

SEX : M/F ..... |_|

AGE : _____years_____months

DATE OF ADMISSION : ..... |___|___|___|

5. DATE OF START OF THERAPY : ..... |___|___|___|

6. TIME OF START OF THERAPY : (24 hr clock) ..... |___|___|

7. DIAGNOSIS : _____ .....|_|_|_|.|_|

8. _____ ..... |_|_|_|.|_|

9. _____ ..... |_|_|_|.|_|

10. STUDIES: _____ |_|_|

_____

|_|_|

_____

|_|_|

_____

|_|_|

Coded by |___| Checked by |___| Entered by |___| Re-Entered by |___|

PRESENTING HISTORY

[_] [_|_] [_|_]

ADDITIONAL HISTORY

1. Informant : (relationship) _____ |_|_|

2. Time since last food 1.<12hrs; 2.12-24hrs; 3.>24hrs |_|

CNS

3. How long has the child been - irritable (in days)..... |_|
   - drowsy (in days)..... |_|
4. - unconscious (in hours)..... |_|
   - photophobia (Y/N)..... |_|

SEIZURE

6. Did the child have seizures (Y/N) ..... |_|
   Ask informant to demonstrate the fit

7. Did the seizure start in one site?(Y/N) ..... |_|
   If so, where: _____ |_|

8. Were they any jerking movements (Y/N)..... |_|
   Did the child go stiff?(Y/N) ..... |_|

9. Were both sides equally invovled (Y/N)..... |_|
   If not, which side : 1.Right 2.Left ..... |_|
   Which side did the eyes deviate 1.Right 2.Left 3.Neither |_|

10. Was there loss of consciousness? (Y/N) ..... |_|
    Did the seizure last more than 5 min (Y/N)..... |_|

11. What type of seizure:_____ [_|_]

12. How many seizures did s/he have this illness? ..... [_|_]
    How many seizures dis s/he have in 24 hours? ..... [_|_]

13. When was the last seizure? (hours) ..... [_|_|_]
    When was the first seizure during this illness? (days) [_|_]

14. Has the child had any previous seizures (Y/N)..... [_]
    Were these associated with fever (Y/N)..... [_]
    Do any of the siblings or parents have convulsions (Y/N) |_]

15. Did mother have any problems during her pregancy (Y/N).... [_|_]

16. Was the birth complicated (Y/N) ..... [_]
    If so, how? _____ . [_|_]

17. After birth did the child have:

any problems with breathing (Y/N) . [_]
any problems with feeding (Y/N) . [_]
jaundice (Y/N)..... [_]
seizures (Y/N)..... [_]

PAST MEDICAL HISTORY
==========

18. Has the child got a healthcard (Y/N) ..... [_]
When was it issued? ..... [_]\[_]\[_]

19. Has the child been admitted to hospital previously (Y/N)..... [_]
How many times ..... [_|_]
Source of information 1.health card 2.history 3.both..... [_]

20. When was the last admission ..... [_]\[_]\[_]

21. What was the diagnosis (CS): _____ ..... [_|_|_].[_]

22. Diagnosis of other admissions : _____ ..... [_|_|_].[_]

23. _____ ..... [_|_|_].[_]

24. Has the child received any blood transfusions (Y/N) ..... [_]
Has anyone in the family received a blood transfusion (Y/N) .....[_]

TREATMENT HISTORY
==========

25. Has the child received any medication in the last 14 days? (Y/N) [_]
Where was it issued _____ ..... [_]

26. Was it: a) Chloroquine (Y/N) ..... [_]
When was last dose? 1.<24 hrs; 2.24-48; 3.48-72; 4.>72 [_]
How many doses? ..... [_]

27. b) Aspirin (Y/N) ..... [_]
When was last dose? 1.<24 hrs; 2.24-48; 3.48-72; 4.>72 [_]
How many doses? ..... [_]

28. c) Fansidar (Y/N)..... [_]
When was last dose? 1.<24 hrs; 2.24-48; 3.48-72; 4.>72 [_]
How many doses? ..... [_]

29. d) Other What? _____ [_|_]
When was last dose? 1.<24 hrs; 2.24-28; 3.48-72; 4.>72 [_]
How many doses? ..... [_]

30. e) Other What? _____ [_|_]
When was last dose? 1.<24 hrs; 2.24-28; 3.48-72; 4.>72 [_]
How many doses? ..... [_]

31. Is the child allergic to any medication (Y/N)..... [_]
If so, what _____ .. [_|_]

Before the child was ill, could s/he :

32. sit unsupported? (Y/N)..... [_]
stand " (Y/N) ..... [_]
walk " (Y/N) ..... [_]

33. grasps object with fingers (Y/N) ..... [_]
say 2 words together (Y/N) ..... [_]
say his/her name (Y/N)..... [_]
say a sentence (Y/N) ..... [_]

34. drink from a cup (Y/N) ..... [_]
wash self (Y/N) ..... [_]
plays with other children (Y/N) ..... [_]
dresses self (Y/N)..... ..... [_]
go to school (Y/N)..... [_]

ADDITIONAL HISTORY
==========

35. Is there any additional history Y/N ..... [_]

ADMISSION EXAMINATION

36. Date of Examination	[_|_]\[_|_]\[_|_]
37. Time of Examination	[_|_]:[_|_]
38. Condition : 1.Quiet; 2.Unco-operative; 3.Crying	[_]
39. Temperature : Axillary (centigrade)	[_|_].[_]
40. Rectal (centigrade)	[_|_].[_]
41. Skin	[_|_].[_]
Central peripheral gap	[_|_].[_]
42. Weight (kg)	[_|_].[_]
43. Head Circumference (cm)	[_|_].[_]
44. Hydration: Is there decreased peripheral perfusion (Y/N)....	[_]
deep breathing (Y/N)	[_]
decreased skin turgor (Y/N)	[_]
45. Are there any abnormalities of the skin? Y/N	[_]
If so, what? (CS) _____	[_]
46. Is there any evidence of sepsis? Y/N	[_]
If so, what? (CS) _____	[_]

CARDIOVASCULAR

47. Pulse: rate / min	[_|_|_]
	systolic
diastolic	
48. Blood Pressure : Lying	[_|_|_] .. [_|_|_]
Cuff size (cm) _____	
49. JVP (cm)	[_|_]
50. Auscultation: 1.Normal; 2.Gallop 3. Flow murmur 4.Other	[_]

RESPIRATORY

51. Cough : (Y\N)	[_]
Resp. rate : breaths per minute.....	[_|_]
Resp. Distress : (Y\N)	[_]
52. Chest : 1.Normal; 2.Abnormal	[_]
Specify : _____	[_|_]

GIT

53. Mouth: 1.Normal; 2.Ang. chelitis; 3.Ulcer; 4.Gingivitis; 5.Candidiasis; 6.Other [_]

Hackett Score

1
2
3
4
5

54. Distension:(Y/N) ..... [_]
55. Liver: cm below costal margin in MCL ..... [_|_]
56. Spleen: cm below costal margin in MCL .... [_|_]
Hacket score ..... [_]

NERVOUS SYSTEM EXAMINATION

57. General 1.Awake; 2.Drowsy; 3.Unconscious; 4.Agitation [_]
Fontanelles 1.Normal; 2.Sunken; 3.Bulging; 4.N/A ..... [_]
Signs of meningism (Y/N)..... [_]
Neck stiffness(Y/N)..... [_]
Kernigs sign (Y/N)..... [_]

58. Any CNS medication _____ ..... [_|_]
When was it given? (hours) ..... [_|_]
Route of administration (1.IV 2.IM 3.PO 4.PR)..... [_]
59. Dose (mg) ..... [_|_|_]

60. Resp. pattern :- 7.normal; 6.abd/hyperinflated 5.hyperpnoea (depth); 4.Cheyne-Stokes; 3.ataxic; 2.gasping; 1.apnoea ..... [_]

61. Position:1.Decerebrate; 2.Decorticate; 3.Normal ..... [_]
1.Opisthotonic 2.Hemiplegic 3.Normal ..... [_]

62. Spontaneous movements (Y/N) ..... [ ]
If yes 1.Normal 2.Abnormal, specify _____ [ ]

Coma scales

	Verbal	Motor	Eyes
63. Adelaide	[_]	[_]	[_]
64. Blantyre	[_]	[_]	[_]
65. Seshia Scale :-	[_]		
66. Reaction Level Scale	[_]		

	R	L
67. Pupil reaction :-(Strong torch)1.None;2.Sluggish;3.Brisk	[_]	[_]
68. Pupil size :- 1.Dilated; 2.Constricted; 3.Midpoint ...	[_]	[_]
69. Spontaneous eye movements :-1.None; 2.Other abn EM; 3.Roving dyscon; 4.Roving conj; 5.Orienting	[_]	[_]

If the child has impaired consciousness

70. Corneal reflex :-(Touch cornea with cotton wool) **R L**
    1.Absent; 2.Weak; 3.Brisk..... [_] [_]
71. Withdrawl from pain:- (Y/N)..... [_] [_]
72. Response to supraorbital pain as in Adelaide coma score..... [_]
73. Fronto-orbicular reflex :- 1. Absent; 2. Present ..... [_]
74. Oculocephalic: Vertical (Rotate head briskly up and down)
    1.Absent; 2.Present ..... [_] [_]
75. Horizontal (Rotate head side to side)
    1.none; 2.minimal movement.; 3.full deviation; 4.normal... [_] [_]
76. Oculovestibular (Head tilted back 30°, 20ml ice water)
    1.no eye movement; 2.minimal.dysconjugate. 3.tonic-conjugate.4.normal [_] [_]
    Time to return to midline (sec)..... [_|_|_]
77. Bruxism (Y/N)..... [_]
    Gag reflex :-(Touch pharynx with spatula)
    1.Absent; 2.Weak; 3.Brisk ..... [_]

78. TA angle (angle made by flexing foot) (degrees) ..... [_][_]

79. Fundi:-4.normal;3.full veins;2.haemorrhage; 1.papilloedema;
    0. inadequate view ..... [_] [_]

80. Cranial nerve lesions: 1.none 2.UMNVII 3.other [_] [_]
    Cerebellar signs (Y/N)..... [_]

81. Limb Tone :- 1.Decreased; 2.Increased; 3.Normal . [_] [_]
83. Plantars :- 1.Upgoing; 2.Equivocal; 3.Downgoing .. [_] [_]

84. Any localising Features: (Y/N)..... [_]
    If so, what_____ [_|_|_]

EYES AND ENT

==========

R L

85. Eyes 1.Normal; 2.Conjunctivitis; 3.Sepsis; 4.Other..... [_] [_]
86. Ears : 1.Normal; 2.Wax; Abnormal-specify: ..... [_] [_]
87. Throat : 1.normal; 2.pharyngitis; 3.follicular tonsilitis;
    4.other specify (CS) ..... [ ]

PROSTRATION

==========

88. Can the child sit unsupported? (Y/N)..... ..... [_]
    Can the child drink? (Y/N)..... [_]
    Did the child vomit it? (Y/N) ..... [_]

OTHER CLINICAL SIGNS

89. What: _____ [_|_]

    Where: _____ [_|_]

90. What: _____ [_|_]

    Where: _____ [_|_]

DIAGNOSIS: _____

Complications: _____

_____

_____

MANAGEMENT PLAN:

Signature _____

LABORATORY INVESTIGATIONS

On Admission

1. KEMRI Number ..... [_|_|_|_] [_|_]
2. Date ..... [_|_]\[_|_]\[_|_]
3. Time of Sample ..... [_|_]:[_|_]

☐ BLOOD SLIDE

count/100 WBC ..... [_|_|_]
count/500 RBC ..... [_|_|_]
4. percentage parasitaemia ..... [_|_].[_]
5. mm3 (asexual) ..... [_|_|_|_|_|_]
6. Malaria pigment 1.None 2.Present 3.Alot [_]
Gametocytes 1.None 2.Present ..... [_]

☐ EDTA (0.5ml)

7. Full Blood Count: WBC..... [_|_].[_]
8. RBC ..... [_].[_|_]
9. Hgb..... [_|_].[_]
10. Hct..... 0.[_|_|_]
11. MCV..... [_|_|_].[_]
12. MCH..... [_|_].[_]
13. MCHC..... [_|_].[_]

14. Differential: Neutrophils ..... [_|_]
15. Lymphocytes ..... [_|_]
16. Eosinophils ..... [_|_]
17. Monocytes ..... [_|_]
18. Basophils ..... [_|_]
19. Nucleated RBC / 100 WBC ..... [_|_|_]

20. Blood Film: RBC size 1.Normocytic 2.Microcytic..... [_]
shape _____ [_|_]
21. WBC Hypersegmented nucleus (Y/N)..... [_]
Toxic granulation (Y/N)..... [_]
Lymphocytes 1.Normal 2.Reactive ..... [_]
Atypical Monocytes (Y/N)..... [_]

☐ FLUORIDE/OXALATE (0.2ml)

22. Glucose (mmol/l) ..... [_|_].[_]
23. Lactate (mmol/l) ..... [_|_].[_]

☐ HEPARIN (2ml)

24. Sodium (mmol/l) ..... [_|_|_]
25. Potassium (mmol/l) ..... [_|_].[_]
26. Creatinine (micromole/l) ..... [_|_|_]
27. Reserve (Y/N) ..... [_]

BLOOD GASES (0.3ml arterial)

28. pH ..... [_].[_|_]
29. pO2 ..... [_|_].[_]
30. pCO2 ..... [_|_].[_]
31. HCO2 ..... [_|_].[_]
32. Base Excess [_] [_|_].[_]

BLOOD CULTURE (1ml)

33. Organism: 1.No growth 2.S.pneu 3.H.influ 4.N.men 5.S.typhi
    Other _____ [_]

34. Sensitivity to: 1.Pen 2.Amp 3.Chlor 4. Gent
    Other _____ [_|_|_|_]

35. Resistant to: 1.Pen 2.Amp 3.Chlor 4. Gent
    Other _____ [_|_|_|_]

CSF

==

1. KEMRI Number ..... [_|_|_|_] [_|_]
2. Date ..... [_|_]\[_|_]\[_|_]
3. Time of Sample ..... [_|_]:[_|_]
4. Appearence: 1.Clear; 2.Blood stained; 3.Turbid ..... [_]

5. Pressure: Spinal manometer(cm H2O) [Only if child calm] [_|_].[_]
6. Gaeltech mmHg ..... [_|_].[_]
7. Microscopy: Red cells (x106/l) ..... [_|_|_|_|_|_]
8. Polymorphs (x106/l) ..... [_|_|_|_|_|_]
9. Lymphocytes(x106/l) ..... [_|_|_|_|_|_]

10. Biochemistry: Glucose mmol/l ..... [_|_].[_]
11. Lactate mmol/l ..... [_|_].[_]
12. Protein mmol/l ..... [_|_].[_]

13. Blood Glucose mmol/l ..... [_|_].[_]
14. Lactate mmol/l ..... [_|_].[_]

15. Organism: 1.No growth 2.S.pneu 3.H.influ 4.N.men 5.S.typhi
    Other _____ [_]

16. Sensitivity to: 1.Pen 2.Amp 3.Chlor 4. Gent
    Other _____ [_|_|_|_]

17. Resistant to: 1.Pen 2.Amp 3.Chlor 4. Gent
    Other _____ [_|_|_|_]

18. Stored Y/N ..... [_]

MICROBIOLOGICAL FORM

☐ BLOOD CULTURE (1ml)

1. KEMRI Number ..... [_|_|_|_] [_|_]
2. Date ..... [_|_]\[_|_]\[_|_]
3. Time of Sample ..... [_|_]:[_|_]

4. Organism: 1.No growth 2.S.pneu 3.H.influ 4.N.men 5.S.typhi
   Other _____ [_]

5. Sensitivity to: 1.Pen 2.Amp 3.Chlor 4. Gent
   Other _____ [_|_|_|_]

6. Resistant to: 1.Pen 2.Amp 3.Chlor 4. Gent
   Other _____ [_|_|_|_]

☐ URINE

1. KEMRI Number ..... [_|_|_|_] [_|_]
2. Date ..... [_|_]\[_|_]\[_|_]
3. Time of Sample ..... [_|_]:[_|_]

4. Microscopy: Red cells (x106/l) ..... [_|_|_|_|_]
5. WBC (x106/l) ..... [_|_|_|_|_]
6. Casts (Y/N) ..... [_]

7. Organism: 1.No growth 2.S.pneu 3.H.influ 4.N.men 5.S.typhi
   Other _____ [_]

8. Sensitivity to: 1.Pen 2.Amp 3.Chlor 4. Gent
   Other _____ [_|_|_|_]

9. Resistant to: 1.Pen 2.Amp 3.Chlor 4. Gent
   Other _____ [_|_|_|_]

☐ STOOL

1. KEMRI Number ..... [_|_|_|_] [_|_]
2. Date ..... [_|_]\[_|_]\[_|_]
3. Time of Sample ..... [_|_]:[_|_]

INTENSIVE PROGRESS SHEET

1. Number..... [_|_|_|_] [_|_]
2. Date ..... [_|_|_|_|_|_]
3. Time ..... [_|_].[_|_]
   Time since onset of therapy ..... [_|_|_]

4. General Observations (CS) [_|_|_]

5. [_|_|_]

6. Number of seizures since the last examination [_|_|_]
7. Recovery times1.drinking; 2.sitting; 3.standing; 4.walking [_]

8. Temperature: Axillae ..... [|].[ ]
9. Rectal ..... [|].[ ]
10. Skin ..... [|].[ ]

11. Pulse ..... [_|_|_]
12. Blood Pressure ..... [_|_|_]\[_|_|_]
13. Respiratory Rate ..... [_|_|_]
14. Resp. pattern :- 7.normal; 6.abdominal/hyperinflated chest
    5.hyperventilation(depth); 4.periodic(Cheyne-Stokes)
    3.ataxic; 2.gasping; 1.apnoea ..... [_]
15. Auscultation ..... [_|_]
16. Position: 1.Decerebrate; 2.Decorticate; 3.Normal ..... [_]
    1.Opisthotonic 2.Hemiplegic 3.Normal ..... [_]
17. Spontaneous movements (Y/N) ..... [_]
    If yes 1.Normal 2.Abnormal, specify [_]

COMA SCALES

	Verbal	Motor	Eyes
18. Adelaide	[_]	[_]	[_]
19. Blantyre	[_]	[_]	[_]

20. Reaction Level Scale ..... [_]
21. Seshia Scale :- ..... [ ]

22. Response to supraorbital pain as in Adelaide coma score..[_]

	R	L
23. Withdrawl from pain:- (Y/N).....	[_]	[_]
24. Spontaneous eye movements :- 1.None; 2.Other abnormal 3.Roving dysconj;4.Roving conjugate; 5.Orienting	[ ]	
25. Pupil reaction :-(Strong torch)1.None;2.Sluggish;3.Brisk	[ ]	[ ]
26. Pupil size :- 1.Dilated; 2.Constricted; 3.Midpoint ...	[ ]	[ ]
27. Fundi:-4.Normal;3.Full veins;2.Haemorrhage; 1.Papilloedema; 0. Inadequate view	[_]	[_]
28. Corneal reflex : 1.Absent; 2.Weak; 3.Brisk.....	[_]	[_]
29. Fronto-orbicular reflex :- 1. Absent; 2. Present	[ ]	
30. Vertical oculocephalic reflex :- 1.Absent; 2.Present	[_]	[ ]
31. Horizontal OC :- 1.None; 2.Min; 3.Full deviation; 4.Norm	[_]	[ ]

32. OV:- 1.Absent; 2.Min.dysconj: 3.Tonic-conj; 4.Norm..... [_] [_]
Time to return to midline (sec)..... [_|_|_]
33. Cranial nerve lesions: 1.None 2.UMNVII 3. Other ..... [_] [_]
34. Bruxism Y/N..... [ ]
Gag reflex :- 1.Absent; 2.Weak; 3.Brisk ..... [_]

35. Limb Tone :- 1.Decreased; 2.Increased; 3.Normal ..... [_] [_]
36. Reflexes :- 1.Decreased; 2.Increased; 3.Normal ..... [_] [_]
37. Plantars :- 1.Upgoing; 2.Equivocal; 3.Downgoing ..... [_] [_]
38. TA angle (angle between leg & foot) (degrees) ..... [___][___]

39. Other signs: _____ [_|_|_]

40. _____ [_|_|_]

Other notes

CLINICAL PROGRESS SHEET (use after the child has regained consciouness)

1.	KEMRI Number	[_|_|_|_] [_|_]
2.	Date	[_|_]\[_|_]\[_|_]
3.	Time of Sample	[_|_]:[_|_]
4.	Any seizures since the last examination _____	[_|_|_]
5.	Recovery Times1.Drinking; 2.Sitting; 3.Standing; 4.Walking Symptoms	[_]
6.	Temperature Axillae	[_|_].[_]
7.	Rectal	[_|_].[_]

DISCHARGE

1. CLINICAL NUMBER ..... [_|_|_|_] [_|_]
2. DATE ..... [__ /__ /__]
3. Any symptoms ..... [_|_]
4. ..... [_|_]

EXAMINATION

5. Temperature (C) ..... [_|_].[_]
6. Weight (kg) ..... [|].[ ]
7. Height (cm) ..... [| |].[ ]
8. MAC (mm) ..... [| |]
9. Head circumference (cm) ..... [|].[ ]

10. Pulse (beats per minute) ..... [| |]
11. BP Sitting ..... [|]/[|]
12. Auscultation 1.Normal; 2.Flow murmur; 3.Other . [ ]

13. Respiratory Rate (breaths per minute) ..... [|]
14. Auscultation 1.Normal; 2.Crackles; 3.Wheezes; 4.Other [ ]

15. Liver (cm) ..... [|]
16. Spleen (cm) ..... [|]
17. Hackett score ..... [_]

18. Is there any induration at the injection sites (Y/N) [_]

CNS EXAMINATION

19. Is the child fully conscious? (Y/N) ..... [_]
20. Does the child continue to have fits? (Y/N)..... [ ]
21. Does the child recognise mother? (Y/N)..... ..... [ ]
    respond to his name? (Y/N)..... [ ]
    say "mama"? (Y/N)..... [ ]
    say other single words? (Y/N..... [ ]
22. ask for a drink? (Y/N..... [ ]
    put 2 words together? (Y/N)..... [ ]
    speak sentences? (Y/N)..... [ ]
    hold a conversation? (Y/N)..... [ ]
23. Can the child see? 1.No 2.Large objects (e.g.for navigation only) 3.A cashew/smartie 4.A Hermeseta 5.100s &1000s [ ]
    If possible also test with each eye separately..... [_] [_]
24. Fundi:-4.N; 5.Optic atrophy;3.Full veins;2.Hgs;1.Papill [_] [_]
25. Can the child hear? 1.Definitely 2.Probably 3.No..... [_] [_]
26. Cranial nerve lesions: 1.None 2.UMNVII 3. Other ..... [_] [_]
27. Does the child have cerebellar ataxia? - gait... [ ] [_]
    - arm [ ] [ ]

28. dystonic posturing?- arms..... [ ] [ ]
- legs [ ] [ ]

29. 1.Chorea 2.Athetosis 3.Tremor... [ ] [ ]
30. 1.Hemiparesis (Y/N)..... [ ] [ ]

31. Limb Tone :-1.Decreased; 2.Increased; 3.Normal ..... [_] [_]
32. Reflexes :- 1.Decreased; 2.Increased; 3.Normal ..... [_] [_]
33. Plantars :- 1.Upgoing; 2.Equivocal; 3.Downgoing ..... [_] [_]

34. Gait: 1.Unable; 2.Hemiplegic; 3.Ataxic; 4.Unsteady; 5.Normal [_]
34. Are there any other neurological features (Y/N) ..... [_]
Please describe them on the other side.

Comments

SUMMARY FORM

(to be completed after the follow up examination)

1. Clinical Number..... [ ] [| |] [|]

OUTCOME

2. Outcome 1. Survived; 2. Neurological sequelae; 3.Died . [ ]
3. Duration of hospital stay : (days) ..... [|]
4. Time of death (hrs after start of treatment) : ..... [| |]
5. Specify sequelae : [|]
   [|]

COMPLICATIONS

6. Hypoglycaemia - on admission Y/N ..... [ ]
   - recurrences (no.) ..... [ ]
   - did level of consciousness improve with Rx .. [ ]

7. Blood transfusion given : Y/N ..... [ ]
   Number ..... [|]

8. Infections Y/N ..... [ ]
   Specify [|]
   [|]

9. Convulsions - history of convulsions during this illness Y/N [_]
   - did the child convulse on admission Y/N . [_]
   - how many convulsions during admission . [_|_]
   - was there any laterialising signs Y/N [_]
   - did any last >20 minutes Y/N ..... [_]

10. Renal failure : Y/N ..... [ ]
    Spontaneous bleeding : Y/N ..... [ ]
    Pulmonary oedema : Y/N ..... [ ]

RECOVERY TIMES

(Time (hours) to reach)

Frequency of assessment 1.Daily; 2.12 hourly; 3.8 hourly; 4.6 hourly; 8.3 hourly

11. Aparasitaemia: frequency of assessment ..... [_]
    (2 negative blood slides) ..... [| |]
12. Defeverence: frequency of assessment ..... [| |]
13. Coma score Time taken to localise pain (6 hourly) .. [| |]
14. Time taken to Blantyre coma score 5 (6 hourly [_|_|_]
15. Drinking: frequency of assessment ..... [_]
    ..... [| |]
16. Sitting unsupported:frequency of assessment ..... [_]
    ..... [| |]
17. Standing unsupported:frequency of assessment ..... [_]
    ..... [| |]
18. Walking: frequency of assessment ..... [_]
    ..... [| |]

COURSE

19. Initial parasitaemia ..... [| | | | |]
20. Maximum parasitaemia : mm3 (asexual) ..... [| | | | |]
21. Time of maximum parasitaemia (hours) ..... [|]
22. Initial HCT ..... 0.[| |]
23. Minimum HCT ..... 0.[| |]
24. Time to minimum HCT after admission : hours ..... [|]
25. % fall in HCT ..... [|]
26. Parasitaemia at day 14 Y/N ..... [_]

FOLLOW-UP OBSERVATIONS

1. Clinical Number: ..... [| | |] [|]

   Name : _____

2. Date : ..... [| |]
3. Days since admission : ..... [|]

COMPLAINTS

4. Specify : [|]

5. [|]
6. Does the child continue to have fits? (Y/N)..... [ ]
   What type are they _____ [_]_]

7. Does the child recognise mother? (Y/N)..... ..... [ ]
   respond to his name? (Y/N)..... [ ]
   say "mama"? (Y/N)..... [ ]
   say other single words? (Y/N..... [ ]
8. ask for a drink? (Y/N..... [ ]
   put 2 words together? (Y/N)..... [ ]
   speak sentances? (Y/N)..... [ ]
   hold a conversation? (Y/N)..... [ ]

EXAMINATION

9. Temperature ..... [|].[ ]
10. Pulse (beats per minute) ..... [| |]
11. BP Sitting ..... [|]/[|]
12. Auscultation 1.Normal; 2.Flow murmur; 3.Other ..... [ ]

13. Respiratory Rate (breaths per minute) ..... [|]
14. Auscultation 1.Normal; 2.Crackles; 3.Wheezes; 4.Other [ ]

15. Liver (cm) ..... [|]
16. Spleen (cm) ..... [|]
17. Hackett score ..... [_]

18. Is there any induration at the injection sites (Y/N) ..... [_]

CNS EXAMINATION

19. Can the child see? 1.No 2.Large objects (e.g.for navigation only) 3.A cashew/smartie 4.A Hermeseta 5.100s &1000s [ ]
    If possible also test with each eye separately..... [ ] [ ]
    20.Fundi:-4.N; 5.Optic atrophy;3.Full veins;2.Hgs;1.Papill [_] [_]
21. Can the child hear? 1.Definitely 2.Probably 3.No..... [ ] [ ]

22. Cranial nerve lesions: 1.None 2.UMNVII 3. Other ..... [_] [_]
23. Does the child have cerebellar ataxia? - gait... [ ] [ ]
- arms.... [ ] [ ]
24. dystonic posturing?- arms..... [ ] [ ]
- legs..... [ ] [ ]
25. 1.Chorea 2.Athetosis 3.Tremor..... [ ] [ ]
26. Hemiparesis (Y/N)..... [ ] [ ]

27. Limb Tone :- 1.Decreased; 2.Increased; 3.Normal ..... [_] [_]
28. Reflexes :- 1.Decreased; 2.Increased; 3.Normal ..... [_] [_]
29. Plantars :- 1.Upgoing; 2.Equivocal; 3.Downgoing ..... [_] [_]
30. Gait: 1.Unable; 2.Hemiplegic; 3.Ataxic;
4.Unsteady; 5.Normal [_]
31. Are there any other neurological features (Y/N) ..... [_]
Please describe them on the other side.

32. Investigations: Parasitaemia ..... [_|_|_|_|_]
33. Haemoglobin ..... [_|_].[_]

Comments

APPENDIX II: SELECTED CASE HISTORIES

Histories and clinical progress of patients referred to in the text

Key

ACS = Adelaide Coma Score
CS = Coding Sheet
EM = Eye Movements
hg = haemorrhages
IM = Intramuscular
Invest = Investigation
IV = Intravenous
N/A = Not Applicable
PO = Per Os
OC = Oculocephalic reflex
O/E = On Examination
OV = Oculovestibular reflex
UMNVII = Upper Motor Neuron VII

265/90 RH

22/7/90 A 3.7 year old girl who was admitted with 3 day history of fever and seizures. She had persistant generalised seizures during the morning of admission. She was given Diazepam in outpatient department.

O/E Rectal temp 38.0°C, BP 86/70
RR 52/min, deep & rapid
3cm liver, 4cm hepar
Flexing to pain, no eye opening or verbal response
Sluggish and constricted pupils, with full deviation of the oculocephalic reflexes and hyperreflexia. She had absent corneal reflexes and retinal haemorrhages in the left fundus. Generalised hypertonia and hyperreflexia

Invest The parasiteamia was 201 000 per mm^3, blood glucose normal, Hb 44 g/l. She was not acidotic or hypoglycaemic

Clinical course

14:15	Quinine started
16:00	LP performed. Opening CSFP was 28 mmHg. The LP needle was connected to a transducer,
16:05	Mannitol 1 g/Kg was administered over 15 minutes and within 30 minutes of the end of the infusion, the CSFP had dropped to 13 mmHg. During this period her breathing became more stertorous (RR 52/min)
16:20	No motor response. Respiratory arrest with a good cardiac output (BP was not measured). She was intubated and hand ventilated. At this stage her pupils were dilated and unresponsive. Transcranial Doppler showed reverse flow during diastole.
17:00	Hand ventilation stopped

132/92 JN

26/5/92 A 23 month old boy who presented with a 2 day history of fever, vomiting and irritability. On the morning of admission, he had two generalised tonic-clonic seizures and did not regain consciousness after the second seizure. He was convulsing on presentation to the hospital. and given diazepam in casualty

O/E Rectal temperature 37.8, BP 90/60
No liver or spleen palpable
He was deeply unconscious (Adelaide coma score: verbal 1, motor 1, with eyes open, but no response to painful stimulus. Normal posture. Pupils dilated & sluggish, with roving conjugate eye movements. Absent corneals. Full deviation of oculocephalic reflexes.

Invest Parasitaemia 37180 Hb 86 g/l
Glucose 1.8 mmols/l
Blood gas not done (machine not working)

Clinical course

	04:00-	3 seizures
	08:40	Eyes respond to painful stimulus. Hippus. Absent corneals. Given Paraldehyde
	08:40- 09:20	3 generalised seizures, given Phenytoin
	11:30	Improved, corneals present, withdrawing from pain, spontaneous movement
	16:20	Decorticate posturing. Given mannitol
	23:00	Partial seizure of L hand & mouth
28/5/92	08:35	Decorticate posturing. Pupils dilated & sluggish. Fundi normal Minimal oculocephalic reflex. Given mannitol
	16:35	Intermittent posturing
	22:30	No more posturing
29/5/92	08:40	Stable overnight, no more posturing. Flexing to pain Pupils still smaller & brisker than previously, but not normal.
	10:30	LP performed. Opening CSFP 72 mmHg Given mannitol
	10:53	CSFP 37 mmHg
	12:00	CSFP 70 mmHg Given mannitol
	13:00	CSFP 60 mmHg
	14:00	Ataxic respiration, then respiratory arrest Hypotonic. Fixed dilated pupils
	14:30	Certified dead

230/92 S K

28/6/92 4 year old boy, presented with 2 day history of fever. Twenty hours before admission, he had a single generalised convulsion, after which he never regained consciousness.

O/E Temp 38.2 °C BP 108/78
1 cm liver, no spleen palpable
ACS: 232, normal posture, no brain stem signs, fundi normal.
Generalised hypotonia and hyporeflexia.

Invest Parasitaemia 1108 800, Hb 107 g/l
Blood glucose 0.7 mmol/l

He was given 50% dextrose and started on quinine, chloramphenicol and benzylpenicillin

28/92	0:00	5hrs post treatment he appeared lighter, saying recognisable words, but not localising a painful stimulus.
	20:20	Seizure (generalised) lasting 3min
29/9	02:00	Definite deterioration: odd almost athetoid movements of the arms and face. Yawning, grimacing. Extending but not withdrawing from to pain. Pupils sluggish, but midpoint. Corneals brisk. Increased tone and reflexes. Mannitol administered 0.5mg/Kg
	09:00	Improved, flexing to and withdrawing from pain. Pupils brisk, midpoint with intact corneals. Tone and reflexes normal now. No fundal haemorrhages
	17:30	ISQ
	23:00	Partial seizure, lasting 1 min. Although reported unchanged, pupils dilated and sluggish. Full veins. Tone and reflexes increased.
	06:45	Deterioration now only extending to pain, but withdrawing pupils dilated and sluggish
	09:30	Still extending to pain, but pupils and corneals brisk. Fundi clear
	15:30	Extending and not withdrawing from pain. Pupils midpoint and sluggish. Full veins. Corneals brisk, oculocephalic full deviation. Hypertonia and hyperreflexia
	21:00	Pupils now brisk and dilated otherwise ISQ
01/7	03:00	Improvement in that flexing to and withdrawing from pain. But L pupil very sluggish and dilated, while R dilated and brisk. Fundal veins dilated with blurred disc margins. Corneals brisk. Hypertonia and hyperreflexia. Mannitol 0.5g/Kg administered
	04:00	Pupils brisk and equal
	10:15	Eyes wide open, but open wider in response to pain. Now extending but withdrawing from pain. Pupils dilated, brisk with full veins. Corneals brisk. Hypertonia and hyperreflexia

	16:15	Moaning and flexing to pain. haemorrhage on L side.
	21:00	Waking up. Flexing and withdrawing. Pupils midpoint and reacting briskly. fundal haemorrhages bilateral. Generalised hypertonia and hyperreflexia.
2/7	03:00	Improving but flexing upper limbs and extending lower limbs. Other clinical signs ISQ (A)
	09:30	ISQ
3/7	09:00	Orientating, asking for mother.

Discharge

6/7/92 Fully conscious, holding a conversation.
No further seizures reported since 29/6.
Vision and hearing intact
Normal gait, no localising signs.

13/7/92 No seizures otherwise well.

232/92 N M

29/6/92 8 year old boy, presented with a one day history of fever and 2 seizures. He did not regain consciousness after the second seizure, which occurred 9 hours prior to admission

O/E Temp 39.3 °C,
Liver & spleen not palpable
Decorticate posture in response to pain
Hippus, absent corneal reflexes, full oculocephalic eye movement
Generalised hyperreflexia and hypertonia

Invest Parasitaemia 1200/µl Hb 92 g/l
Respiratory alkalosis, normoglycaemic

Clinical Course

29/6	04:50 -11:00	14 generalised tonic-clonic seizures witnessed, each lasting 1-3 min, all associated with temp>38.0 Normoglycaemic. Given Diazepam 2.5 mg IV at 05:15 & 06:10, phenytoin 285 mg IV at 07:35 & phenobarbitone 280mg IM at 10:00.
	12:15	Seizures continue, given paraldehyde 6mls IM
	12:30	Another seizure Diazepam 5mg IV
	14:35	Mannitol 0.5 mg/Kg IV, remains unresponsive, pupils dilated & sluggish. Minimal oculocephalic response
	15:00	ICP monitor inserted
	19:00	Hyperventilating, with eyes open but not moving, Very unresponsive (ACS 111) not withdrawing from pain. Pupils dilated, sluggish with absent corneal reflexes. Generalised hypotonia and hyporeflexia. Plantars equivocal
	22:05	Pupils reacting briskly to light
30/6	05:00	More responsive, flexing to pain, pupils constricted & sluggish. Corneals weak. Decreased tone & reflexes
	10:00	ICP monitor removed
	12:30	ISQ
	22:20	Pupils more responsive, flexes legs only in response to pain.
1/7	05:00	Unresponsive (ACS 111) Pupils mid point and brisk. Absent corneals hypotonia and hyporeflexia
	16:30	Flexing and withdrawing from pain, pupils normal but corneals still absent
	23:00	Pupils sluggish & corneals weak otherwise ISQ
2/7	08:55	ISQ
	11:00	CT scan
	15:30	localising to pain
3/7	08:55	drinking, talking, sitting LP performed
4/7		transferred to ward 1

Discharge

8/7/92 Behavioural abnormalities: visual hallucinations, "irrational"
Fully conscious, responding to his name and saying single words, but does not appear to recognise his mother.
sees large objects only, fundi normal. Hears
no localising signs
unsteady gait. No seizure

11/8/92 No more hallucinations, but the mother thought he did not think as quickly as he used to. She had not noticed any memory problems.
Able to hold a good conversation, although did appear to have a blunt affect.
No vision, hearing problems detected
No localising signs. No seizures.

15/9/92 Now has tremor of L hand, with past pointing, but no other signs of cerebellar disease. Otherwise no other localising signs.

332/92 D M

5/8/92 2 year old boy, presented with a 3 day history of fever. Had 3 convulsions in the 24 hours prior to admission, regaining consciousness after each one. Had another convulsion on admission, before which he was localising pain.

O/E Apyrexial, normotensive
Normal posture, flexed briskly to pain
No brainstem signs, fundi normal

Invest Parasitaemia 92 1660/µl Hb 60 g/l
Glucose 6.7 mmols/l
Not acidotic. Urea 9.4

Clincal Course

5/8	23:00	1.5 hrs post seizure , drowsy, localising to pain
6/8	00:00	Generalised seizure, lasting 11mins.
	02:00	Generalised seizure, lasting 5mins.
	02:30	Generalised seizure, lasting 12mins.
		During this 3 hour period started becoming agitated and then started decerebrate posturing, but thought to be too light for ICP monitoring
	05:00	Deterioration - decerebrate, opisthotonic posturing
		Flexes arms, but extends legs to pain. Withdraws from pain. Midpoint pupils reacting briskly to pain. Conjugate eye movement. Corneals brisk. Generalised hypertonia and hyperreflexia
	11:00	ICP monitor inserted
		Not posturing
	17:00	Exam ISQ. Normal tone/reflexes
	22:00	Episodes of increased tone/reflexes
		yawning. brain stem signs still intact.
7/8	04:00	Haemorrhages noted in L fundus.
		remainder of exam ISQ
	11:20	L fundal hg and dilated veins
	16:00	No eye movements, otherwise ISQ
	19:52	Episode of bradycardia 120->99 BP 90/42
		pupils midpoint, but sluggish
		corneals weak
	20:30	Pulse 96, ICP 40
		attempted intubation
		Hand ventilated ICP increased
	21:36	Condition worse: p 99/min, BP 90/45 cool
		extremities, poor respiratory effort. Withdraws from pain. Pin point pupils, with absent corneals.
		Decreased tone & reflexes. ICP 35 mmHg

	23:00	Improved: p 100-110/min, Temp 35.5 ICP 20-30. Pupils now sluggish, but reactive. Corneals present.
	23:05	BP 90/45 ICP 16
8/8	01:00	BP 100/50
	04:00	ACS 132 yawning Pupils midpoint & brisk, but no eye movement of the open eyes Haemorrhages in R fundus, L not visualised, brisk corneals Increased reflexes, normal tone with extensor plantars ICP 34 rectal temp 35.9
	10:20	ISQ except that legs extending to pain although arms flex
	16:45	ISQ
	22:05	ISQ
9/8	04:00	ISQ
	11:55	ISQ Fundi show full veins, haemorrhages & blurred discs
	22:21	ISQ
10/8	10:40	ISQ
	17:25	ISQ reacting more briskly to pain
11/8	04:37	ISQ
	13:05	ISQ
	13:45	ICP removed
	15:00	CT scan
12/8	08:30	ISQ Anterior fontanelle full.
13/8	09:00	More spontaneous movement. Appropriate cry for stimulation. Still only flexing to pain, but with brisk withdrawal. Clear disc margins. Brain stem intact. Roving conjugate eye movement, brisk midpoint pupils. Brisk corneals. Full deviation of oculocephalic. Bilatateral hyperreflexia and hypertonia.
14-16/8	"Awake", though still only flexing to pain hypertonia	
17-24/8	Can drink	

Discharge

24/8/92 Vegetative state, unable to recognise mother, respond to his name or speak. Does not appear to see, although blinks in response to a loud noise. Generalised spasticity with some dystonic movements. Unable to sit or feed himself.No further seizure witnessed since 6/8. (P)

386/92 S M

10/9/92 A 2 and half year old girl, presented with a 10 day history of diarrhoea and vomiting. No history of seizures.
Hypotonic, bradycardic with slow shallow respiration.
Dehydrated >10%.
Resuscitated with IV fluids, oxygen, atropine and 50% glucose

O/E Unrecordable blood pressure. Temp 38.0
Normal posture
Flexed to pain, but otherwise no response
Pupils dilated, but reactive. Corneals present. Fundi normal
Minimal oculocephalic responses
Generalised hypotonia and hyporeflexia

Invest Parasiteamia 37 269/µl Hb 132 g/l
H 6.9, pCO_2 3.3, pO_2 29.9, BE -26.1
Glucose unrecordable on admission
Na 144, K 5.3, Urea 6.6

Clinical Course
Started on Quinine, Benzylpenicillin, Chloramphenicol,
Within 1.has of starting therapy he was much more vigorous, moving limbs, although by 3.5 hrs he was noted not to be moving his L side much.

	22:30	localising to pain, restless and passing bloody diarrhoea
11/9	09:00	deteriorated, vomited coffee ground vomitus, extending to pain only, unable to withdraw.
	11:45	ICP monitoring started
	17:00	able to withdraw on the R side only. Still only extending to pain
12/9	00:50	hyperpnoea, looks as though becoming acidotic. Flexing to and withdrawing from pain on both sides. Salivation prominent.
	08:10	ISQ, still salivating
	13:45	ISQ, salivation and yawning
	22:15	ISQ
13/9	09:50	ISQ, ICP high
	17:40	ISQ, ditto
	19:05	ICP had been running at 50. Profuse vomiting, despite frequent aspiration which produced little. Still had brisk pupils, corneals and withdrawing from pain. Given Mannitol
14/9	07:30	ISQ
	16:20	ISQ
	23:40	ISQ. no fundal hg
15/9	09;00	Went for CT scan
	12:50	ISQ
	22:50	ISQ
16/9	09:30	ISQ
	23:00	ISQ

17/9	09:25	ISQ
18/9	09:30	ISQ
19/9	11:35	ISQ flexing to pain, withdrawing. Brisk midpoint pupils, conjugate eye movement, increased tone and reflexes. Tolerating N/G feeds
20-24/9	ISQ irritable	
25-30/9	Able to drink, but unable to support the head or sit. Becoming less irritable.	

Discharge

2/10	Irritable. Unable to support his head, but able to drink and eat. Not responding to his name. ? can see light & dark hearing probably intact, quietens to mothers voice No abnormal movements Bilateral hyperreflexia and hypertonia. No evidence of hemiparesis.
16/10	Slight improvement

421/92 A N

8/10/92 4 and half year old boy, presented with a 3 day history of fever. No seizures.

O/E Temp 39.4 BP 110/69
Prostrate, unable to sit, but could localise pain.
No brainstem signs

Clinical Course

9/10	00:37	4 short (0.5-1 min) seizure, starting in R arm,
	01:20	spreading to the mouth, then involving L arm also.
	10:30	Had deteriorated: hyperventilating, flexing to pain, sluggish withdrawal from pain. Roving conjugate eye movements, with brisk midpoint pupils. Right sided retinal haemorrhages. Increased tone, but normal reflexes Associated with increase in parasitaemia.
	14:15	ISQ
	14:30	ICP monitor inserted
	22:00	more hg developed otherwise ISQ
10/10	06:40	Full veins and sighing
	13:20	clinically ISQ
	14:25	bolt removed
	16:00	CT scan
	21:00	localising to pain
11/10	08:35	Much improved, but still not drinking, sitting
12/10		Drinking, obeying commands, head lag
13/10		Talking

Discharge

14/10/92 Fully conscious, able to hold a conversation
Normal vision, hearing, gait
No localising signs

056/93 S K

8/2/93 Admitted with a 4/7 history of fever. The day prior to admission had multiple generalised convulsive seizures lasting about 2 mins each. During the 24 hrs prior to admission had 5 seizures. She was treated with chloroquine prior to admission and given diazepam 10mg IV prior to examination.

O/E On admission Temp 40.6
p 200/min BP 110/60
RR 60/min deep breathing, nasal flaring and intercostal recession
Chest clear
3cm hepar, 3cm spleen
Unconscious, flexing to pain only
Normal posture
Pupils constricted, sluggish with no eye movements
Minimal horizontal oculocephalic
Generalised hyporeflexia, hypotonia with equivocal plantars

	12:00	Started on Quinine, Benzylpenicillin and Chloramphenicol
	15:20	p148/min BP 80/52 Flexing, opening eyes and moaning to pain pupils midpoint reacting briskly full deviation of oculocephalic movements
	18:00	ISQ
09/2	00:00	ISQ
	10:00	Retinal haemorrhages noted for the first time Hardly withdrawing ICP monitor inserted - opening pressure 11 mmHg
	14:00	ISQ
	18:15	ISQ
	19:30	LP performed: press 14mmHg
	20:00	Monitor removed
	23:30	ISQ
10/2	08:10	Localising pain Pupils midpoint but sluggish
	10:30	CT scan performed in Mombasa

Discharge
Recovered with a mild left hemiparesis which improved within1week.

094/94

10/2/94 3 year old girl who presented with a 3 day history of fever. On the day of admission, she started vomiting and had opisthotonic posturing, lapsing into coma 6 hours prior to admission.. No history of seizures.

Examination Temp 40.0 BP 100/70
Opisthotonic posturing, aggravated by stimulation
Extending to pain, grunt with no eye opening.
Midpoint pupils reacting briskly to light. Corneal reflexes intact
Roving spontaneous eye movements, full deviation of eyes in oculocephalic reflex. Fundi ? disc swelling.

Investigations 310 200 /µl Hb 45 g/l
Normoglycaemic. pH 7.21, pCO_2 3.4, BE -15.3.
Lactate 8.9 mmol/l
Na 134, K 4.7, Creatinine 60µmols/l

Clinical Course

	18:00	Opisthotonic posturing, accompanied by slow activity on EEG Given 3mls 50% Dextrose-dextrostix low.
	22:00	Posturing continues. Pupils midpoint, but sluggish. Absent corneals.
11/2/94	01:00	ICP monitor inserted. Agitated. Given mannitol (see Appendix VI)
	09:50	ISQ
	10:40	Hippus. Increased tone on R side
	14:40	R pupil larger than L
	15:40	Pupils equal size Haemorrhages and disc swelling noted.
	16:00	EEG flat.
	16:45	R pupil dilated, unreactive. L pupil small and sluggish.
	17:20	Ataxic respiration, pupils fixed and dilated
	17:30	Gasping, respiratory arrest.

APPENDIX III:

Intracranial pressure in African children with cerebral malaria

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Intracranial pressure in African children with cerebral malaria

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Opening lumbar cerebrospinal fluid (CSF) pressure was measured with a paediatric spinal fluid manometer in 26 of 61 Kenyan children (mean age 39 months) with cerebral malaria. In all cases pressure was above normal (mean [SD] 22·6 [7·4] cm CSF, range 10·5–36). Clinical features of our patients suggest that intracranial hypertension is important in the pathogenesis of cerebral malaria in children, especially as a cause of death. We suggest that raised intracranial pressure is secondary to increased cerebral blood volume. Lowering intracranial pressure may significantly reduce the mortality and morbidity of cerebral malaria. The potential risks and benefits of lumbar puncture should be considered carefully in patients with suspected cerebral malaria.

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Introduction

Plasmodium falciparum infection is one of the commonest causes of acute encephalopathy in children. Cerebral malaria (CM) in children has a 10–40% mortality,[1] even when effective antimalarial drug concentrations are achieved rapidly.[2] The exact cause of death is often obscure. We have measured intracranial pressure (ICP) in African children with CM to determine whether intracranial hypertension contributes to the pathophysiology of this condition.

Patients and methods

Ethical permission for the study was granted by the Kenya Medical Research Institute (KEMRI), and informed written consent was obtained from childrens' parents or guardians. Since May, 1989, we have identified children admitted to the Kilifi District Hospital, Kenya, who fulfilled the World Health Organisation definition of CM[1]—ie, they were unable to localise pain, had peripheral parasitaemia, and other causes of coma were excluded. On admission, a full clinical history was taken and a physical examination done. Blood was obtained for a complete blood count, glucose determination, and preparation of thick and thin blood films for peripheral parasite counts.

Lumbar puncture (LP) was done in all children, except those with signs pathognomonic of brainstem herniation or raised ICP (eg, papilloedema). (Since July, 1990, we have delayed LP until the return of consciousness, although antimicrobials to cover for meningitis are given from the time of admission.) LP was done with the child in the lateral decubitus position. A 22 G spinal needle was used, and, where possible, cerebrospinal fluid (CSF) pressure was measured with a paediatric spinal fluid manometer. Excessive flexion was avoided and pressure was recorded only if the child was quiet and there was a swing in pressure with respiration. Maximum height above the spine reached by the column of fluid was recorded as the opening pressure in cm CSF. Closing pressures were not measured since this would have required the removal of too large a volume of CSF. Less than 1 ml of CSF was removed for microscopy, culture, glucose, and lactate. In 2 children, a pressure transducer (Hewlett Packard) was connected to the spinal needle for measurement of CSF pressure for up to 30 min. Blood pressure was measured as close to the time of LP as possible so that cerebral perfusion pressure could be estimated from the difference between mean arterial pressure and lumbar CSF pressure. In 10 children, transcranial pulsed doppler ultrasonography ('TC2-64B', Eden Medizinische Elektronik, Überlingen, Germany) of the middle cerebral arteries[3] was done frequently during admission.

Children were given parenterally either a loading dose of 20 mg/kg quinine dihydrochloride followed by 10 mg/kg every 12 h, or a 10 mg/kg loading dose with 5 mg/kg every 12 h thereafter. Parenteral therapy was continued until the child could swallow, when quinine sulphate was given orally. Each patient received 10 doses of quinine.

Children had a full neurological examination at least every 6 h until they became conscious and were able to localise pain. These clinical data were analysed retrospectively for combinations of physical signs (table I) compatible with uncal herniation or with one of the four stages of central cerebral herniation—ie, diencephalic, upper pontine, lower pontine, or medullary. The minimum criteria required to define a herniation syndrome were decided before data were analysed. Uncal herniation could be diagnosed with only two of four criteria present, since partial third-nerve palsy is unlikely to be due to any other cause in an unconscious child. For diagnosis of diencephalic syndrome, it was decided that four of five criteria should be present, since some of the signs also occur in diffuse bilateral hemispheric dysfunction due, for example, to drug or metabolic effects. Diagnosis of upper pontine (three of four criteria), lower pontine (three of five), and medullary (two of three) syndromes was uncomplicated. If a herniation syndrome was documented during hypoglycaemia or within 1 h of a seizure, data were excluded from analysis. Differences between groups were analysed with Fisher's exact test.

Results

Between May, 1989, and August, 1990, 586 children with a primary diagnosis of malaria were admitted, of whom 61 fulfilled the definition of CM (mean [SD] age 39 [21·6] months, mean duration of disease 3·8 [2·6] days). Table II shows the clinical and laboratory features of these children on admission. 47 patients had LP on admission. Opening pressure was measured reliably in 26 children. No opening pressure was recorded in the remaining children because manometers were not available during the first 5 months of study (19), the child was struggling (3), or because LP was deferred until 24 h after consciousness had been regained (13).

The figure shows opening pressure in 26 patients plotted against age, compared with the normal range.[4] Mean (SD) opening pressure was 22·6 (7·3) cm CSF [16·7 (5·4) mm

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TABLE I—HERNIATION SYNDROMES IN CHILDEN WITH CM

—	Diagnostic criteria	Number (%) of patients with syndrome (if more than 1 documented, worst given)		
		Survivors (n=49)	Deaths (n=12)	p
No herniation	..	32 (65)	0	..
Herniation				
Total		17 (35)	12 (100)	0·001
Uncal	Unilateral mydriasis and unilateral fixed pupil Unilateral ptosis Oculocephalic and/or oculovestibular minimal deviation Hemiparesis	1 (2)	2 (25)	Not significant
Diencephalic	Cheyne-Stokes respiration Small or midpoint pupils reactive to light Oculocephalic and/or oculovestibular full deviation Flexor response to pain and/or decorticate posturing Hypertonia and/or hypereflexia with extensor plantars	15 (31)	0	0·05
Midbrain/upper pontine	Hyperventilation Midpoint pupils, fixed to light Oculocephalic and/or oculovestibular minimal deviation Extensor response to pain and/or decerebrate posturing	1 (2)	1 (8)	Not significant
Lower pontine	Shallow or ataxic respiration Midpoint pupils, fixed to light Oculocephalic and/or oculovestibular no response Flexion legs only or no response to pain Flaccidity with extensor plantars	0	2 (16)	0·05
Medullary	Slow, irregular, or gasping respiration Pupils dilated and fixed to light Respiratory arrest with adequate cardiac output	0	7 (62)	<0·001

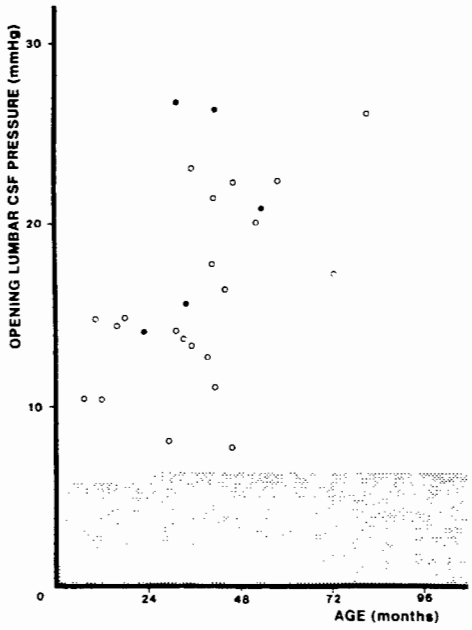
Hg]. Mean cerebral perfusion pressure at LP was 52·6 (13·8) mm Hg (range 30·3–88·3). LP was repeated in 2 children, because of recrudescence of fever. 1 child had opening pressures of 10·5, 21, and 14 cm CSF (8, 16, and 10 mm Hg) at admission, 54, and 115 h after start of treatment, respectively. The other child had an opening pressure of 31 cm CSF (23 mm Hg) at admission and 29 cm CSF (21 mm Hg) at 84 h after start of treatment. He also had the lowest recorded cerebral perfusion pressure (30·3 mm Hg), and was left with dystonic motor disorder, delayed language, and cortical blindness at 3-months follow-up. CSF pressure fell from 21 to 10 mm Hg and from 20 to 9 mm Hg in the 2 children in whom it was measured with a transducer, 30 min after a 1 g/kg bolus dose of mannitol. Extensor posturing with Cheyne-Stokes respiration and absent gag was seen 12 h later in 1 of these children; hypoglycaemia was excluded. Posturing ceased after a further bolus of mannitol and a full recovery was made. Of those studied with transcranial doppler ultrasound, forward flow was observed in 9 of 10 throughout diastole during every study; all survived. The tenth child had normal middle cerebral artery sonograms at admission; however, after 3 h, when brainstem reflexes were absent and the child was being hand ventilated, there was reverse flow throughout diastole with low velocity and a direction-of-flow index similar to that seen in brainstem death.[5]

12 of the 61 children (20%) died, all in coma, between 10 min and 24 h after admission. The fontanelle was closed in all, and 10 had had an LP. Herniation was observed in all 12 patients who died but in only 17 of 49 (35%) survivors ($p < 0·001$) (table I). No survivors showed rostro-caudal progression from the diencephalic or midbrain/upper pontine syndromes. However, clinical deterioration consistent with central cerebral herniation was seen in 7 of the 12 who died. Diencephalic and medullary syndromes were documented in 3 of those who died, and the lower pontine stage was also seen in 1 of these children. 2 of those who died were seen initially during the midbrain/upper pontine stage and 2 during the lower pontine stage; all deteriorated rapidly to the medullary stage. Partial third-nerve palsy was documented in a survivor, who had an opening pressure greater than 30 cm CSF, after she awoke from 48 h of coma. 2 children with signs of uncal herniation had rapidly deteriorating brainstem function and died. Thus, 9 of the 12 children who died had clinical deterioration compatible with the rostro-caudal progression of brainstem herniation. Of the other 3 deaths, 1 child died on admission with a medullary syndrome and 2 had acute

TABLE II—PRESENTING FEATURES (NUMBER/%) OF 61 CHILDREN WITH CM

History	
Convulsions	51 (83·6)
Vomiting	34 (55·7)
Irritability	33 (54·1)
Drowsiness	47 (77)
Examination	
Response to pain	
Localising	4*(6·6)
Flexion	40 (65·6)
Extension	13 (21·3)
None	4 (6·6)
Blantyre coma scale[2] (summated)	
4	1 (1·6)
3	7 (11·5)
2	16 (26·2)
1	21 (34·4)
0	16 (26·2)
Fundal haemorrhages	5 (8·2)
Papilloedema	1 (1·6)
Investigations	
Parasitaemia	
< 10 000	9 (14·8)
10 000–99 999	18 (29·5)
100 000–999 999	27 (44·3)
> 1 000 000	7 (11·5)
Hypoglycaemia (< 2·2 mmol/l)	17 (28·3)

*Subsequently deteriorated to fulfil criteria for CM.[1]



Lumbar CSF pressures in 26 children with CM compared with the normal range at different ages (shaded).

Survivors are represented by open circles and those who died by closed circles.

respiratory difficulties with signs of medullary failure, 3 and 6 h after routine examination found no evidence of a herniation syndrome. 9 of those who died had respiratory arrest with adequate cardiac output, and circulation was maintained during hand ventilation for up to 4 h. Respiratory and cardiac arrest was apparently simultaneous in the remaining 3 deaths. Necropsy was not possible.

Discussion

Raised ICP is a feature of many encephalopathies,[6] and is associated with poor outcome.[7] Raised pressure at LP in children with CM has been noted previously,[8,9] and opening pressure was raised (greater than 20 cm H_2O) in 33 (21%) of 157 Thai adults with CM in whom opening and closing pressures were recorded.[10] Lower opening pressure in fatal cases was cited as evidence that intracranial hypertension is not important in the pathophysiology of CM. However, opening pressure correlates poorly with maximum ICP in other central nervous system infections[6] and a single measurement may be misleading. Furthermore, in most adults, the cause of death is complicated and is not primarily neurological. This is not the case in African children.

In our series, all childen with CM had raised opening pressures. Abnormally high lumbar CSF pressures have also been found in a study from The Gambia (N. J. White, personal communication). Vomiting, irritability and drowsiness—non-specific symptoms of raised ICP in children—were all prominent in our patients.

Clinical signs of herniation were documented in 35% of survivors and in all the deaths. Uncal herniation and/or rostro-caudal progression in 75% of those who died suggest that brain shift due to supratentorial cerebral swelling and intracranial hypertension is the mechanism leading to death. Other causes—such as parasite sequestration in the brainstem—cannot be excluded, however, since necropsy was not possible. Transcranial doppler recordings in 1 child who died were similar to serial recordings in head-injured patients with brainstem death secondary to intracranial hypertension.[5,11] Low cerebral perfusion pressure could also account for some of the neurological sequelae[12] seen in this and other series.[13] These data support the view that intracranial hypertension has an important pathophysiological role in determining outcome of African children with CM.

Raised ICP may be caused by cerebral oedema, acute hydrocephalus or an increase in cerebral blood volume. Cerebral oedema has been documented at necropsy in young children;[14] however, the blood-brain barrier does not appear to break down in CM,[10] and in adults with CM cerebral oedema was uncommon and seemed to be agonal;[15] acute hydrocephalus was not seen. An acute increase in cerebral blood volume in CM has not been suggested previously. The distinctive histopathological feature of CM is sequestration of large numbers of malaria-infected erythrocytes in the cerebral microvasculature.[16] If cerebral blood flow remains normal, as in adults,[17] this sequestered mass would be expected to increase cerebral blood volume. Peripheral parasitaemia (and therefore, perhaps, the sequestered mass) is usually higher in children with CM than in non-immune adults. In addition to this space-occupying effect, the parasites produce lactate,[18] which may act as a vasodilator and further increase cerebral blood volume. "Luxury perfusion"—ie, cerebral blood flow in excess of metabolic demand—may be a consequence of metabolic acidosis[19] and is common in other paediatric encephalopathies with diffuse cerebral swelling.[20] In response to a reduction in cerebral perfusion pressure, caused by either intracranial hypertension or a decrease in blood pressure, autoregulatory vasodilatation occurs, leading to an increase in cerebral blood volume which in turn induces a further increase in ICP and reduction of cerebral perfusion pressure.[21] All the children in this series who died had closed fontanelles; a pliable skull may protect the infant from a dangerously high ICP.

The management of intracranial hypertension depends upon its pathogenesis. Urea[22] and mannitol[23] may be of benefit in children with CM, but controlled trials have not been conducted. In this series, mannitol infusion led to a reduction in CSF pressure in 2 children in whom monitoring was possible, and clinical improvement of 1 of these children on another occasion. If intracranial hypertension is important in the pathogenesis of CM, regimens aimed at reducing ICP or maintaining cerebral perfusion pressure might substantially reduce mortality and morbidity. Information about the temporal aspects of intracranial hypertension, which can only be gained from continuous invasive monitoring, will be required before this approach can be adopted, because the clinical burden of childhood CM is borne by centres without intensive monitoring facilities.

LP is recommended in comatose children in the tropics, and has been thought mandatory in CM to exclude meningitis and other causes of coma.[1] However, benefits must be weighed against the risk of herniation. Though there is no clear evidence that children with severe encephalopathies who die do so because of LP, it is important for doctors to be aware of the possibility of raised ICP. It may sometimes be appropriate to delay LP until the child is neurologically stable. Our practice in children presenting in coma with peripheral parasitaemia is to give antibiotics and antimalarials until consciousness improves

and meningitis can be excluded. An osmotic diuretic should be available if LP is to be done.

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Cutaneous vasoconstrictor response to glucocorticoids in asthma

PETER H. BROWN SURUJPAL TEELUCKSINGH
SIMON P. MATUSIEWICZ ANDREW P. GREENING
GRAHAM K. CROMPTON CHRISTOPHER R. W. EDWARDS

The aim of the study was to find out whether asthma patients whose airways obstruction is sensitive (CS) or resistant (CR) to corticosteroid treatment also differ in their cutaneous vasoconstrictor response to a potent topical glucocorticoid. Corticosteroid resistance was defined by failure of forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate to improve by at least 15% after a 2-week trial of corticosteroids (prednisolone 20 mg daily for 1 week, then 40 mg daily for 1 week) despite more than 15% improvement with inhaled beta agonists. Beclomethasone dipropionate in concentrations of 3 μg/ml, 10 μg/ml, 30 μg/ml, and 100 μg/ml was applied to forearm skin; the site was occluded under plastic and the degree of blanching assessed after 18 h. CS asthmatic subjects (n = 31), asthma patients with mild airways obstruction (n = 26), asthma patients taking long-term prednisolone (n = 13), and healthy volunteers showed similar vasoconstrictor responses. In CR asthmatic subjects (n = 15), the response (expressed in terms of either blanching intensity or the proportion of patients showing a positive response) was significantly lower than that in the CS group at concentrations of 3 μg/ml ($p < 0.01$), 10 μg/ml ($p < 0.01$), and 30 μg/ml ($p < 0.05$), but not at 100 μg/ml. This resistance to glucocorticoids in the skin, together with reported evidence of glucocorticoid resistance in peripheral blood leucocytes, suggests a general defect in the ability of tissues to respond to glucocorticoids in CR asthma.

Lancet 1991; **337**: 576–80.

Introduction

Most patients with chronic asthma respond well to inhaled corticosteroid therapy, and acute exacerbations of

ADDRESSES: **Department of Medicine, Northern and Western General Hospitals, Edinburgh, UK** (P. H. Brown, MRCP, S. Teelucksingh, MRCP, S. P. Matusiewicz, MRCP, A. P. Greening, FRCP, G. K. Crompton, FRCP, Prof C. R. W. Edwards, FRCP). Correspondence to Dr P. H. Brown, Respiratory Unit, Northern General Hospital, Ferry Road, Edinburgh EH5 2DQ, UK.

APPENDIX IV: COMPUTER PROGRAMME TO ANALYSE CLINICAL DATA

See table 4.6 for definition of criteria:

hor	Horwitz
npmb	Kilifi midbrain
npmd	Kilifi medullary
npd	Kilifi diencephalic
npp	Kilifi pontine
npu	Kilifi uncal
oth	Other
ppd	Plum & Posner diencephalic
ppmb	Plum & Posner midbrain
ppmd	Plum & Posner medullary
ppp	Plum & Posner pontine
ppu	Plum & Posner uncal
ren	Rennicks

```
* Programme to detect features of herniation from DBase files
*  CRJCN 20/7/93

close all
use cmadm in 1
use cmipr in 2

select 1
select 2

repl all ren with 0,hor with 0, oth with 0, ppd with 0, ppmb with
0, ppp with 0, ppmd with 0, ppu with 0, npd with 0, npmb with 0,
npp with 0, npmd with 0, npu with 0

replace all ren with ren+1 for substr(puprxn,1,1)="1" .or.
substr(puprxn,2,1)="1" .or. substr(pupsize,1,1)="1" .or.
substr(pupsize,2,1)="1"
repl all ren with ren+1 for val(respat)<5
repl all ren with ren+1 for position="T" .or. position="D" .or.
admot="1"

replace all hor with hor+1 for (substr(puprxn,1,1)="1" .or.
substr(puprxn,2,1)="1") .and. (substr(pupsize,1,1)="1" .or.
substr(pupsize,2,1)="1")
repl all hor with hor+1 for val(respat)<5
repl all hor with hor+1 for position="T" .or. position="D" .or.
position="H"
repl all hor with hor+1 for ochorizon="11"

repl all oth with oth+1 for (substr(puprxn,1,1)="1" .or.
substr(puprxn,2,1)="1") .and. (substr(pupsize,1,1)="1" .or.
substr(pupsize,2,1)="1") .and. (position="T" .or. position="B")

repl all ppd with ppd+1 for pupsize="22" .or. pupsize="33"
repl all ppd with ppd+1 for tone="II" .or. reflex="II"
repl all ppd with ppd+1 for respat="4" .or. position="T"
repl all ppd with 0 for ochorizon="1" .or. pupsize="11"

repl all ppmb with ppmb+1 for puprxn="11"
repl all ppmb with ppmb+1 for ochorizon="1" .or. ochorizon="2"
.or. position="B"

repl all ppp with ppp+1 for puprxn="11"
repl all ppp with ppp+1 for ochorizon="1"
repl all ppp with ppp+1 for admot="1" .or. plantars="UU" .or.
position="B"
```

```
repl all ppmd with ppmd+1 for puprxn="11" .and. pupsize="11"
repl all ppmd with ppmd+1 for admot="1"

repl all ppu with ppu+1 for substr(pupsize,1,1)="1" .or.
substr(pupsize,2,1)="1"
repl all ppu with ppu+1 for substr(ochorizon,1,1)="2" .or.
substr(ochorizon,2,1)="2" .or. position="H"

repl all npd with npd+1 for pupsize="22" .or. pupsize="33"
repl all npd with npd+1 for tone="II" .or. reflex="II"
repl all npd with npd+1 for val(respat)=4
repl all npd with npd+1 for admot="3" .or. position="T"
repl all npd with npd+1 for ochorizon="3"

repl all npmb with npmb+1 for puprxn="11"
repl all npmb with npmb+1 for ochorizon="2"
repl all npmb with npmb+1 for admot="2" .or. position="B"
repl all npmd with npmb+1 for val(respat)=5

repl all npp with npp+1 for puprxn="11" .or. pupsize="33"
repl all npp with npp+1 for ochorizon="1"
repl all npp with npp+1 for admot="1" .or. position="B"
repl all npp with npp+1 for tone="DD" .and. plantars="UU"
repl all npp with npp+1 for val(respat)<4

repl all npmd with npmd+1 for puprxn="11" .and. pupsize="11"
repl all npmd with npmd+1 for admot="1"
repl all npmd with npmd+1 for val(respat)<3

repl all npu with npu+1 for (substr(pupsize,1,1)="1" .or.
substr(pupsize,2,1)="1") .and. (substr(pupsize,1,1)="1" .or.
substr(pupsize,2,1)="1")
repl all npu with npu+1 for ochorizon="2"
repl all npu with npu+1 for position="H"

set printer on

? "Rennick's criteria for herniation"
list clinum for ren>1
? "Horwitz's criteria for herniation"
list clinum for hor>1
? " Other criteria"
list clinum for oth=2
? " Plum & Posner Diencephalic stage"
list clinum for ppd=3
? " Plum & Posner Midbrain stage"
list clinum for ppmb=2
? " Plum & Posner Pontine stage"
list clinum for ppp=3
```

```
? " Plum & Posner Medullary stage"
list clinum for ppmd=2
? " Plum & Posner Uncal stage"
list clinum for ppu=2
? " Newton Diencephalic stage"
list clinum for npd>3
? " Newton Midbrain stage"
list clinum for npmb>2
? " Newton Pontine stage"
list clinum for npp>2
? " Newton Medullary stage"
list clinum for npmd>1
? " Newton Uncal stage"
list clinum for npu>1

set printer off
close all
```

APPENDIX V: COMPETENCY AND ETHICAL PERMISSION TO CONDUCT ICP MONITORING

1. Certificate of competency in inserting ICP monitor

2. Ethical permission from Kenya Medical Research Institute

3. Approval from the ethical commitee of Hospital for Sick Children, Great Ormond Street, London, UK.

4. Sheet used to describe the procedure to the parents. Each of these points was translated into the parents home language by an attendant.

The Hospitals for Sick Children *Special Health Authority*
GREAT ORMOND STREET, LONDON WC1N 3JH
Telephone: 071-405 9200 Ext.
Telegrams: GREAT LONDON WC1
PATRON: HER MAJESTY THE QUEEN
CHAIRMAN: MRS. C. BOND, S.R.N., S.St.J.
GENERAL MANAGER: SIR ANTHONY TIPPET, K.C.B., C.B.I.M

FROM
THE DEPT. OF PEDIATRIC NEUROSURGERY

TO WHOMSOEVER IT MAY CONCERN 18.10.91

This is to confirm that Dr. Charles Newton has worked in conjunction with our unit over the last six weeks. During this time he had the opportunity to introduce the Camino Sudural Intracranial Pressure monitoring system in a number of our patients under the direct supervision of our Senior staff members. We have found him reliable and competent to conduct this procedure safely and with due care.

Mr. W.F.J.Harkness F.R.C.S.
Consultant Pediatric Neurosurgeon

KENYA MEDICAL RESEARCH INSTITUTE

Mbagathi Road
P.O. Box 54840
Nairobi, Kenya.

Date 15th August 91

Address all correspondence
to Director
Telegrams: "KEMRI" NAIROBI
Telephone: 722541/2/3/4 Nairobi

Our Ref: KEMRI/RES/7/3

Your Ref:

Dr. CRJC Newton

Thro' The Director
CRC
NAIROBI

Forwarded 19/8/91 IM

RE: SSC PROTOCOL NO: 212 ENTITLED "THE COURSE AND TREATMENT OF INTRACRANIAL HYPERTENSION IN CHILDREN WITH CEREBRAL MALARIA" BY CRJC NEWTON ET AL

During the 41st meeting of the National Ethical Review Committee meeting the above protocol was granted approval for you to start on your work.

Kindly let the undersigned know that Dr. I. Mwangi has appended his signature to the "Approval of Research Protocols by KEMRI Centres" form.

G.A.O SEKO
FOR: SECRETARY
NATIONAL ETHICAL REVIEW COMMITTEE

The Hospitals for Sick Children Special Health Authority
GREAT ORMOND STREET. LONDON WC1N 3JH
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CHAIRMAN: MRS. C. BOND, S.R.N., S.S.t.J
GENERAL MANAGER: SIR ANTHONY TIPPET

31 May, 1991

Dr F Kirkham
Senior Lecturer in Paediatric Neurology
INSTITUTE OF CHILD HEALTH

Dear Dr Kirkham,

ETHICAL COMMITTEE APPLICATION NUMBER 934: RAISED INTRACRANIAL PRESSURE IN CHILDREN WITH CEREBRAL MALARIA: ITS DURATION AND RESPONSE TO TREATMENT

I write to inform you that this application was approved at a meeting of the Ethical Committee on 15th May, 1991.

Yours sincerely

Helen Lavan

Helen Lavan
SECRETARY TO THE STANDING COMMITTEE ON ETHICAL PRACTICE

DRAFT INFORMATION TO BE GIVEN BEFORE OBTAINING CONSENT

1. Your child has a severe form of malaria. He/She is extremely ill and requires very careful treatment which has already been started.

2. As you can see your child is deeply unconscious, because of work done here over the last two years we now know that one of the problems with children who are unconsciouss with malaria is that the brain swells and this is not good for them. This happens sometimes in other diseases and in those diseases there is a way of treating the swelling that is very helpful in protecting the brain from damage.

3. This treatment involves measuring how swollen the brain is by putting a thin wire a small distance through the bone of the skull and connecting it to a machine to measure the pressure. This looks like the wires that are already connected to your childs head (EEG Monitor) but the difference is that the wire must go through the bone itself. Drugs can then be given to keep the pressure at the correct level to try and prevent damage to the brain.

4. We cannot guarantee that this will definitely help in malaria but we do know that it definitely helps in other similar conditions and we believe that this will be true in malaria.

5. The reason that we are explaining this to you is that we want parents to know as much as possible about the problems of their children and because we cannot carry out this new treatment without your permission as it involves a small operation to insert the wire. This operation takes about 5 minutes and involves making a small hole in the

.../2

skull with this instrument (The parent to be shown the instruments and recording device), and passing this wire into the hole. There will be no need for a general anaesthetic as your child is already deeply unconsciouss.

6. Any operation carries a risk of problems but in this case the risks are very small. In 80 such operations carried out at the hospital where we have trained in this technique only two children have had problems which were definitely related to the operation. In one case the area around the wire became infected and this was successfully treated with antibiotics. In another case a stitch had to be placed in the skin to stop watery fluid leaking from the hole. In neither case did the child suffer long term harm. We think this is a very low risk compared with the possible help that this method of treatment may give.

7. It is important that you understand fully what we have told you and if there is anything at all that you wish to know about the treatment or anything else about your childs condition we would like you to ask us now. If you decide that you do not wish your child to have this treatment we will continue to give the very best care that we can with the treatment that has already been started.

APPENDIX VI: ICP MONITORING

This appendix presents the charts of some of the children who had ICP monitoring, with an accompanying description of the clinical course during the monitoring.

Key

Numbers: refer to points in the clinical description

Arrows: mannitol infusions

Rectangles:

Red :blood transfusions (BTX)

Green: seizures

Purple: opisthotonic posturing

Black: events described in the text

Patient No. 230/92

This child was admitted fulfilling the criteria for CM, without any brain stem signs. Initially he appeared to improve, but 12 hours after admission deteriorated with yawning, athetoid movements and sluggish pupils (ICP monitor was not inserted as it was being used to monitor patient No. 232/92). He was given mannitol and made a dramatic improvement, but 36 hours after admission there was a further deterioration, pupils became dilated and sluggish. He could only extend to pain. The ICP monitor was inserted, with an opening ICP of 28 mmHg and CPP of 51 mmHg. During the first 24 hours of monitoring, the child had raised ICP with frequent fluctuations in pressure. Mannitol (arrow) was given repeatedly.

1. Typical B-waves (B) were documented, sometimes but not inevitably, associated with episodes of hyperpnoea.

2. A seesaw pattern of ICP was associated with a cyclical breathing pattern.

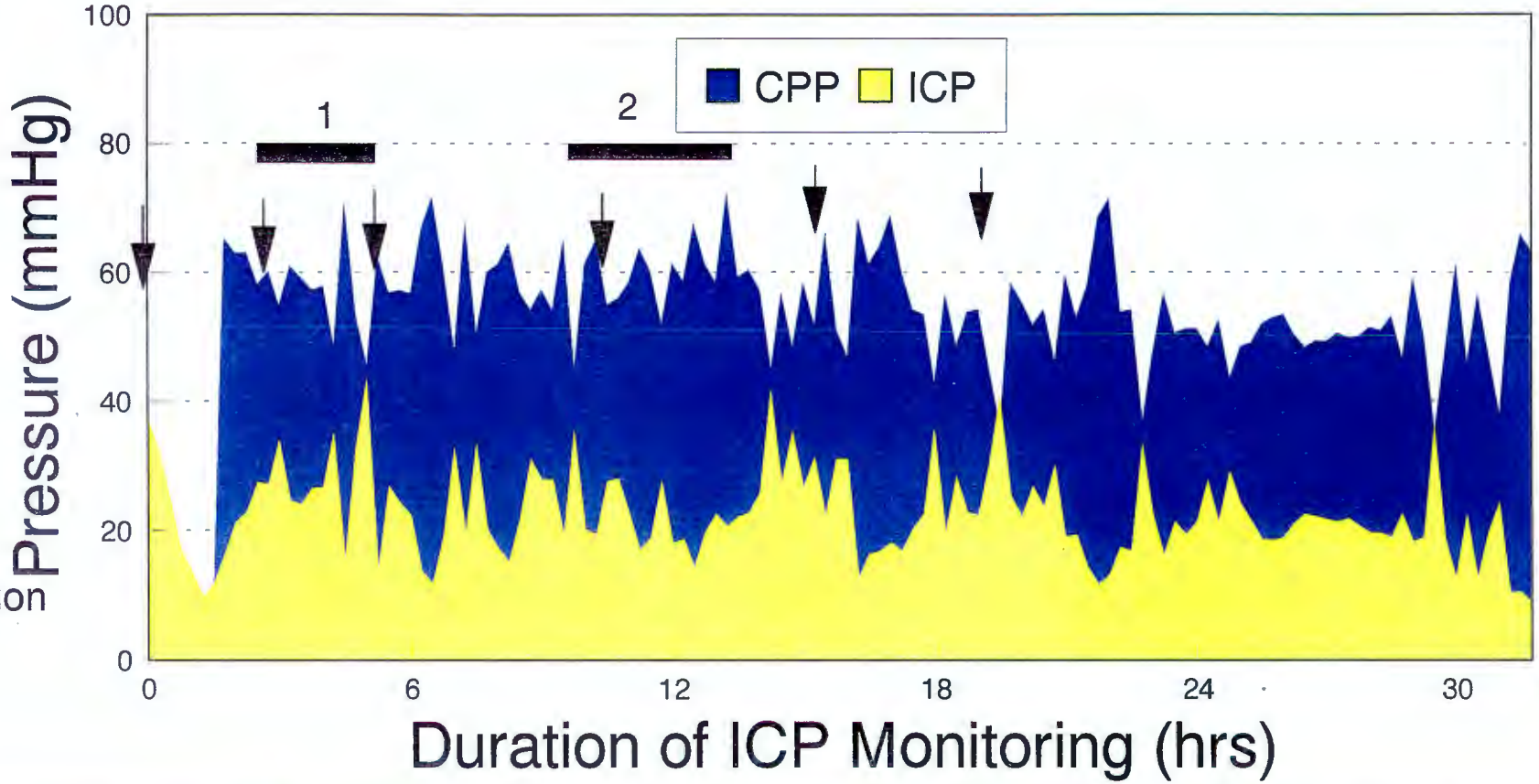
This was followed by 3 occasions when the ICP rose to above 40 mmHg (only one spike shown) during 14-16 hours after the onset of monitoring. These rises were associated with pupillary dilation, with the left pupil much more sluggish than the right. Spikes of ICP were often terminated with sighs.

For the last 8 hours of monitoring, the ICP was much more stable, although often high. The ICP bolt was removed when the child began to wake up and cry.

230/92

4 yr old boy admitted unconscious for 26 hrs, following a seizure

Monitoring started 48 hrs after admission

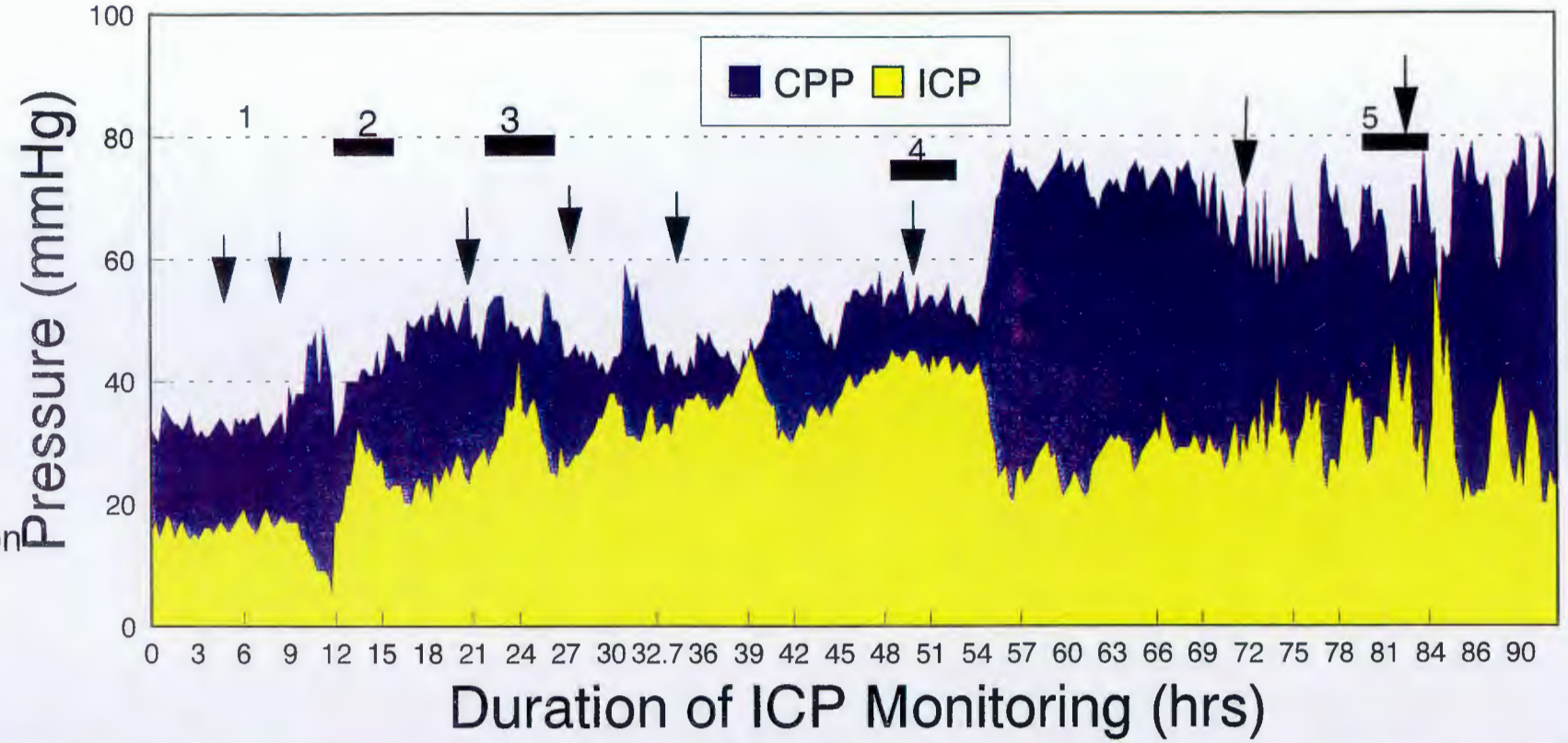


Time (hrs)	Admission	0	8	16	23
ACS	9	7	7	7	7
Brain stem	N	N	N	N	N
Posture	N	N	N	N	N
Parasitaemia	8740	1056	920	0	0
Hb	45	43	42	93	-
pH	7.42	7.47	7.44	7.40	-
pCO2	3.2	4.0	4.5	4.2	-
BE	-7.5	-0.8	-0.2	-3.8	-
Glucose	5.0	5.5	5.3	-	-
Sodium	133	-	-	-	-

386/92

30 month old girl presented with hypoglycaemia, shocked & acidosis

Monitoring started 22 hrs post admission
Monitor drifted by +16 mmHg



Time (hrs)	Admission	0	5	12	20	36	46	56	80	96
ACS	5	6	6	6	7	7	6	6	7	7
Brain stem	Y	N	N	N	N	N	N	N	N	N
Posture	N	N	DCT	N	N	N	N	N	N	N
Parasitaemia	37269	59187	-	2890	630	0	0	0	0	0
Hb	132	139	-	99	100	95	-	-	93	-
pH	6.9	7.29	-	7.23	7.29	7.37	-	-	7.45	-
pCO2	3.3	2.1	-	2.8	2.9	3.1	-	-	4.0	-
BE	-26.1	-15.6	-	-16.8	-14.3	-10.0	-	-	-1.1	-
Glucose	<2.2	2.1	-	1.5	14.5	2.7	-	-	6.4	-
Sodium	144	124	-	130	120	121	-	-	125	-

Patient No. 386/92

The clincal course is describe in Appendix II. The interpretation of the ICP pattern of this patient is complicated by the excessive drift that occurred during monitoring.

The child was admitted hypoglycaemic, acidotic with a low blood pressure. He was resuscitated with haemacel. The following day the acidosis had improved (although he still had a pH 7.29 with a BE -15.6) and the MAP was between 50 and 55 despite normal hydration. The child had a further episode of hypoglycaemia prior to monitoring. The ICP monitor was inserted, the opening ICP 17 and CPP 26 mmHg. Haemacel was again administered and a dopamine infusion (D) was started increasing the MAP to above 65 mmHg.

1. An LP performed 6 hrs after the start of monitoring, confirmed that the ICP had risen to 17 mmHg and mannitol (arrow) was given to raise the CPP to above 50 mmHg. Thereafter the MAP was maintained above 70 mmHg.
2. The ICP rose above 20 mmHg. The child had tented waves (T) 24 and 80 hours after monitoring started.
3. After 36 hours of monitoring, the child had frequent episodes of yawning and sighing, most of which appeared to be precipitated by spontaneous increases in ICP, followed by significant reductions.
4. B-waves appeared associated with a sustained rise in ICP. The waves disappeared with the administration of mannitol, after which there was a significant reduction in the baseline. This may have been caused by the fault in the monitor.

5. B-waves appeared superimposed on 2 plateau waves 85 hours after the start of monitoring. In the first A-wave the ICP monitor readings increased from 32 to 52 mmHg, but levelling off with B waves (amplitude 2-3 mmHg) at 48 mmHg for 14 minutes (MAP increased from 98 to 105 mmHg) (fig 5.3). This was associated with the child opening her eyes, staring, followed by nystagmus to the right. The pupils were dilated but acted briskly to light and the depth of breathing increased. There was generalised hypotonia, but the child was able to withdraw briskly from pain. The second 'plateau' type wave occurred 5 minutes later, had similar increments in pressure with superimposed B-waves, but was not associated with any clinical signs and only lasted for 4 minutes.

The monitor was removed 7 hours later because the child appeared to be waking up with a lot of normal spontaneous movement, coughing and reacting briskly to nursing procedures. The ICP was 16 mmHg on removal of the monitor.

An LP performed the following day, when the child was aparasitaemic, showed fluctuations of ICP between 9 and 24 mmHg measured with the Gaeltech non-displacement transducer.

The child was discharged 19 days after admission irritable, unable to talk, light/dark vision spastic quadriparesis.

before presumably responding to the mannitol that had been started 1 minute before the seizure. CPP not calculated since arterial line was blocked.

7. Data lost due to computer malfunction

8. Reappearance of B-waves

C waves and other irregular fluctuations of ICP appeared throughout the course of monitoring, but were not associated with clinical signs. Initially mannitol rapidly decreased the ICP. However the response did not persist, despite mannitol administration every 2-6 hours in an effort to control the ICP. Thereafter the intracranial hypertension became intractable with little response to 2 hourly administrations of mannitol. The ICP was allowed to remain between 20 and 40 mmHg as long as the CPP was above 50 mmHg as the child was becoming dehydrated. Bagging with a face mask was attempted on 4 occasions, but the child became restless and the ICP rose from a median of 43 (range 38-47) to 69 (64-77). A dopamine infusion was given for 8 hours, 112 hours after the onset of monitoring, because of difficulty in maintaining the CPP above 50 mmHg.

The bolt was removed 122 hours after the insertion of the monitor because the child had been neurologically stable for the last 48 hours and was becoming restless. An LP which was performed 4 days after the removal of the monitor (to exclude meningitis as a cause of the fever that the child subsequently developed) and the opening CSFP was 9 mmHg..

The child was discharged 19 days after admission with severe neurological sequelae. (See Case History, Appendix II)

Patient No. 332/92

The clincal course is describe in Appendix II

During the first 10 hours of monitoring the ICP remained below 20 mmHg with CPP above 50 mmHg.

1. LP was performed.
2. The ICP rose and this was associated with a dilatation of the pupils (although reacting very briskly) and hypertonia.
3. 12 hours after the monitoring started, B-waves (ICP 15 - 21 mmHg) appeared (black rectangle), associated with restlessness and episodic fisting with extension of left elbow, flexion at the wrist and extended legs with plantar flexed feet appeared. The pupils were still dilated and the limbs hyperreflexic. The waves lasted for 50 minutes, disappearing spontaneously.
4. The B-waves reappeared (black rectangle) nearly 2 hours later as the ICP drifted upwards to 20 mmHg, and this time they were associated with hyperventilation, generalised hypertonia with the left leg spontaneously flexing at the hip and knee, but both feet plantar flexed, left arm externally rotated and both pupils dilated, but reacting briskly to light. The waves disappeared after the administration of mannitol.
5. Examination of the fundi 2 hours after the onset of the second period of B-waves revealed fundal haemorrhages which had not been detected 6 hours earlier.

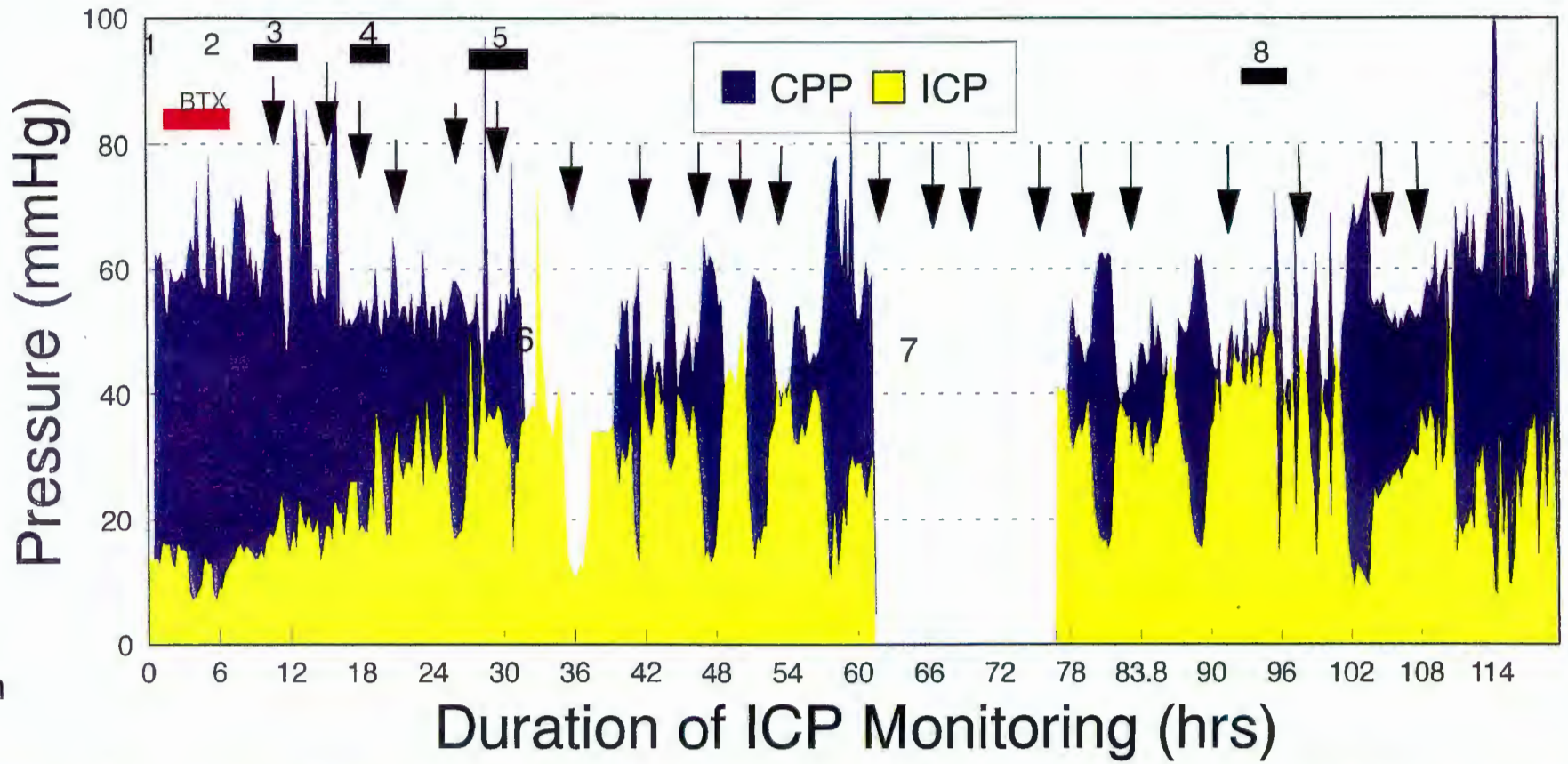
B-waves reappeared briefly at 26, 31 and 47 for 4, 30 and 5 minutes respectively, but these episodes were not associated with any clinical signs.

6. The closest pattern resembling an A wave was precipitated by a seizure 33 hours after admission, with the ICP rising from 43 to 78 mmHg for 6 minutes,

332/92

2 yr old boy presented with seizures, but did not have any seizures during the monitoring

Monitoring started 13 hrs after admission



Time (hrs)	Admission	0	12	24	48	72	96	120
ACS	7	6	9	7	5	6	6	7
Brain stem	N	Y	Y	N	N	N	N	N
Posture	N	N	N	N	N	N	N	N
Parasitaemia	92520	65880	-	30380	85446	0	0	0
Hb	60	42	-	85	79	79	89	102
pH	7.49	7.45	-	7.35	7.45	7.45	7.43	-
pCO2	2.8	1.9	-	3.5	4.0	4.0	4.12	-
BE	-5.4	-11.9	-	-9.4	-2.0	-2.0	-2.2	-
Glucose	6.7	2.4	-	4.0	4.1	3.0	3.4	4.6
Sodium	136	140	-	-	138	140	137	132

Patient No. 421/92

This 4.5 year old boy was admitted prostrated with malaria but was able to localise pain. During the first 12 hours he had 4 partial motor seizures, after which he was only able to withdraw sluggishly from pain. He developed fundal haemorrhages, but no other brain stem signs. The ICP monitor was inserted 4 hours later.

1. During the first 3 hours of monitoring he developed plateau like waves, in which the ICP increased from 15 mmHg to 22 mmHg for about 5 minutes only. There was no change in the clinical condition and the waves disappeared with mannitol.

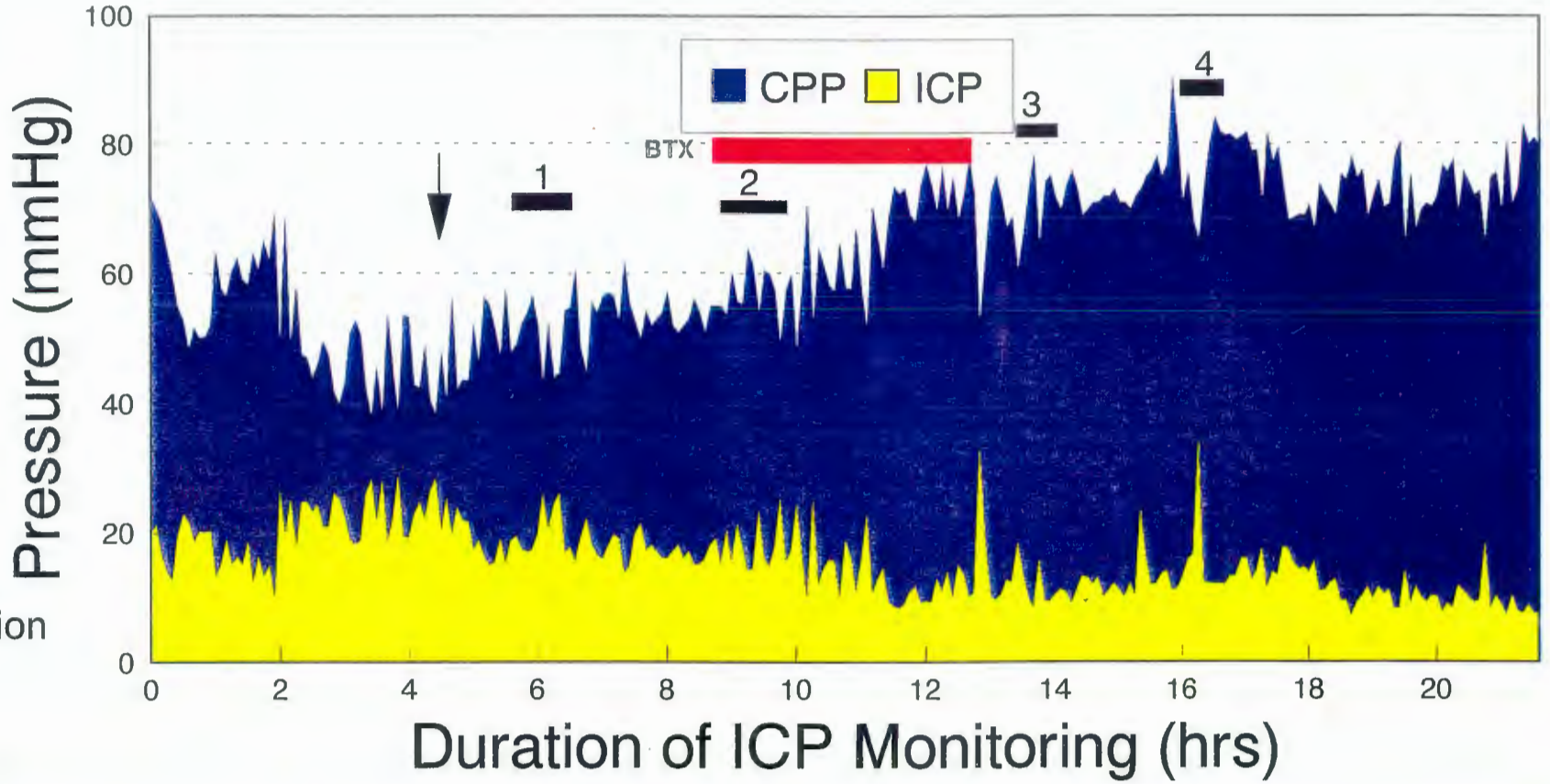
2,3,4. The child had runs of small amplitude (ICP remained less than 20 mmHg) B-waves (B) 9, 13 and 15 hours after the commencement of monitoring.

Thereafter he made an uneventful recovery.

421/92

4 yr old boy admitted conscious, but prostrate, deteriorated after seizures

Monitoring started 16 hrs after admission



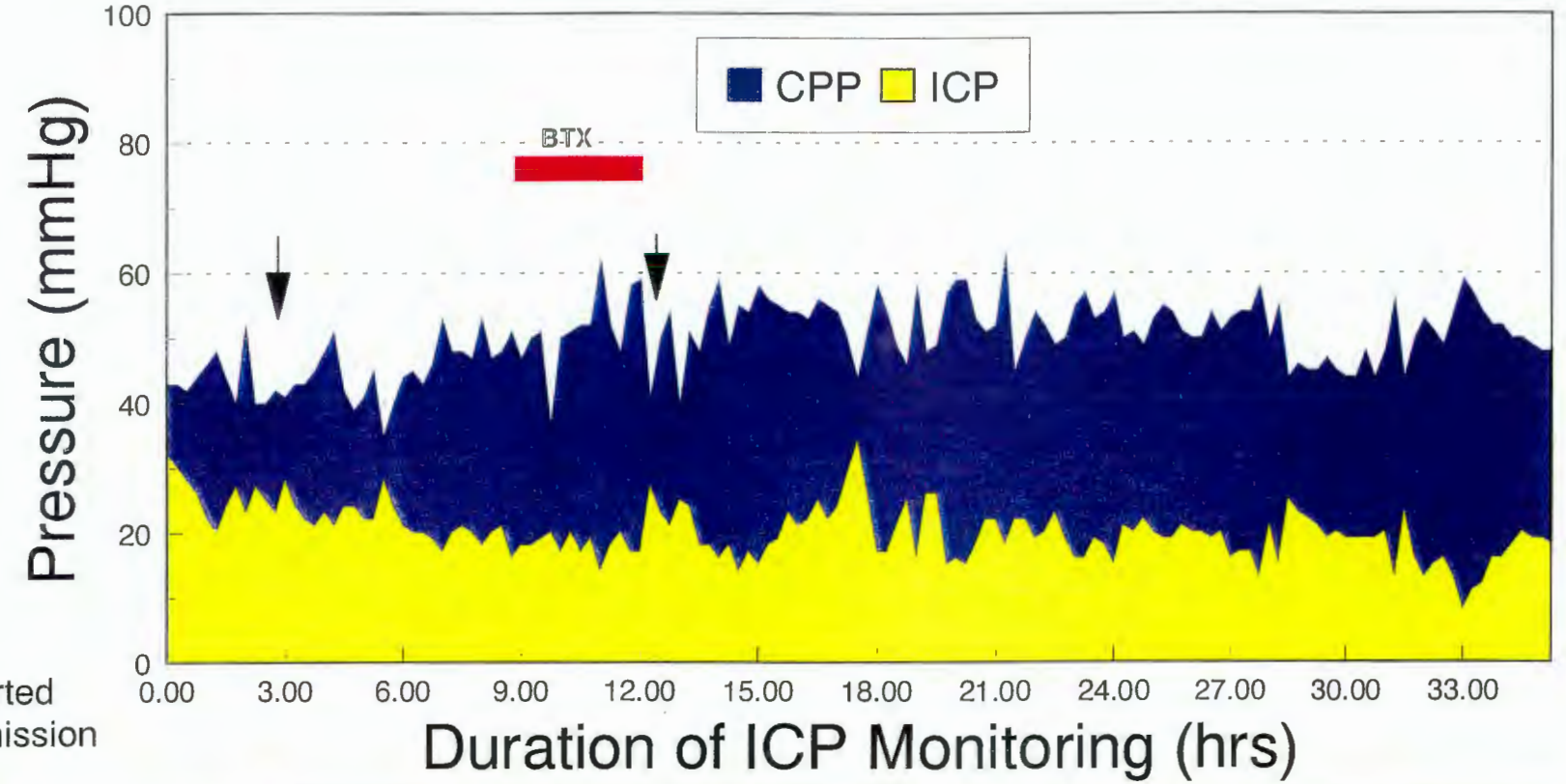
Time (hrs)	Admission	0	8	16	23
ACS	9	7	7	7	7
Brain stem	N	N	N	N	N
Posture	N	N	N	N	N
Parasitaemia	8740	1056	920	0	0
Hb	45	43	42	93	-
pH	7.42	7.47	7.44	7.40	-
pCO2	3.2	4.0	4.5	4.2	-
BE	-7.5	-0.8	-0.2	-3.8	-
Glucose	5.0	5.5	5.3	-	-
Sodium	133	-	-	-	-

Patient No 175/93

2 year old girl admitted with a history of status epileticus, who on admission reacted briskly to pain, but 6 hours later deteriorated with the development of hypertonia, sluggish withdrawal from pain and sluggish pupils. Opening ICP was 32 mmHg, which dropped to 17 mmHg with mannitol (arrow). However the ICP rose to above 20 mmHg within 90 minutes, but we elected not to give mannitol as the CPP had increased to above 50 mmHg and although the ICP trace was reactive, no waves were documented. The blood transfusion produced an increase in the ICP and CPP, but after the transfusion had finished, the MAP dropped, reducing the CPP. A second dose of mannitol (arrow) was administered since the CPP was below 50 mmHg. After an initial reduction in the ICP, the pressure rose to above 20 mmHg, but not above 30 mmHg and was not treated because the CPP remained 50 mmHg. Thereafter the ICP fell spontaneously and the bolt was removed when the child started responding to his name.

175/93

4 yr old boy presented with a 2 day history of seizures



Monitoring started
6 hrs post admission

Time of Mx (hrs)	Admission	0	4	12	20	24	31	36
ACS	8	7	7	6	6	8	8	10
Brain stem	N	N	Y	Y	N	N	N	N
Posture	N	N	N	N	N	N	N	N
Parasitaemia	4293	77430	57312	328000	-	174760	7182	6800
Hb	48	37	-	-	-	-	-	-
pH	-	-	7.43	7.41	-	-	-	-
pCO2	-	-	3.34	3.4	-	-	-	-
BE	-	-	-6.6	-7.1	-	-	-	-
Glucose	4.3	6.3	-	2.4	-	-	-	-
Sodium	135	127	-	135	-	-	-	

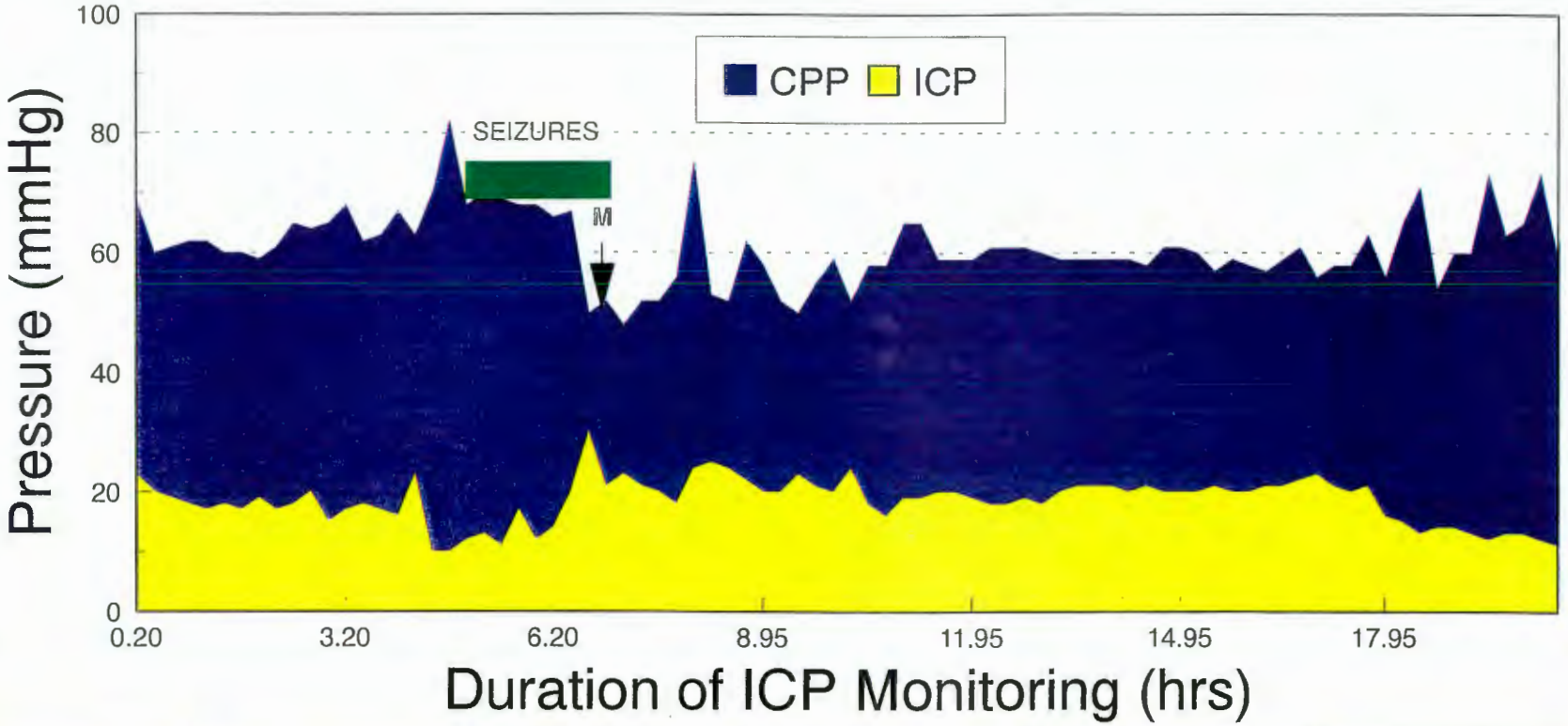
Patient No. 185/93

A 7 year old boy who presented with status epilepticus, which was initially controlled with IV diazepam. ICP monitor was inserted 2 hours after admission. For the first 10 hours of monitoring the child had frequent seizures (green rectangle) which precipitated spikes of RICP and episodes of decerebrate posturing. The seizures were controlled with phenytoin, the ICP dropped in response to mannitol. The bolt was removed when the ICP had been below 20 mmHg for more than 6 hours and the child was becoming more rousable.

185/93

7 yr old boy
Presents with
1 day history of
fever & seizures

Monitoring
started 2 hrs
post admission



Time (hrs)	Admission	0	5	11	17	20
ACS	7	7	6	-	-	10
Brain stem	Y	N	N	Y	N	N
Posture	N	N	N	N	N	N
Parasitaemia	9500	-	400	616	528	0
Hb	76	-	82	76	-	76
pH	7.30	-	7.4	-	-	-
pCO2	2.56	-	5.2	-	-	-
BE	-13.4	-	+2.4	-	-	-
Glucose	-	-	4.3	-	-	-
Sodium	-	-	131	-	-	-

Patient No. 210/93

A 6 year old boy who presented with status epilepticus.

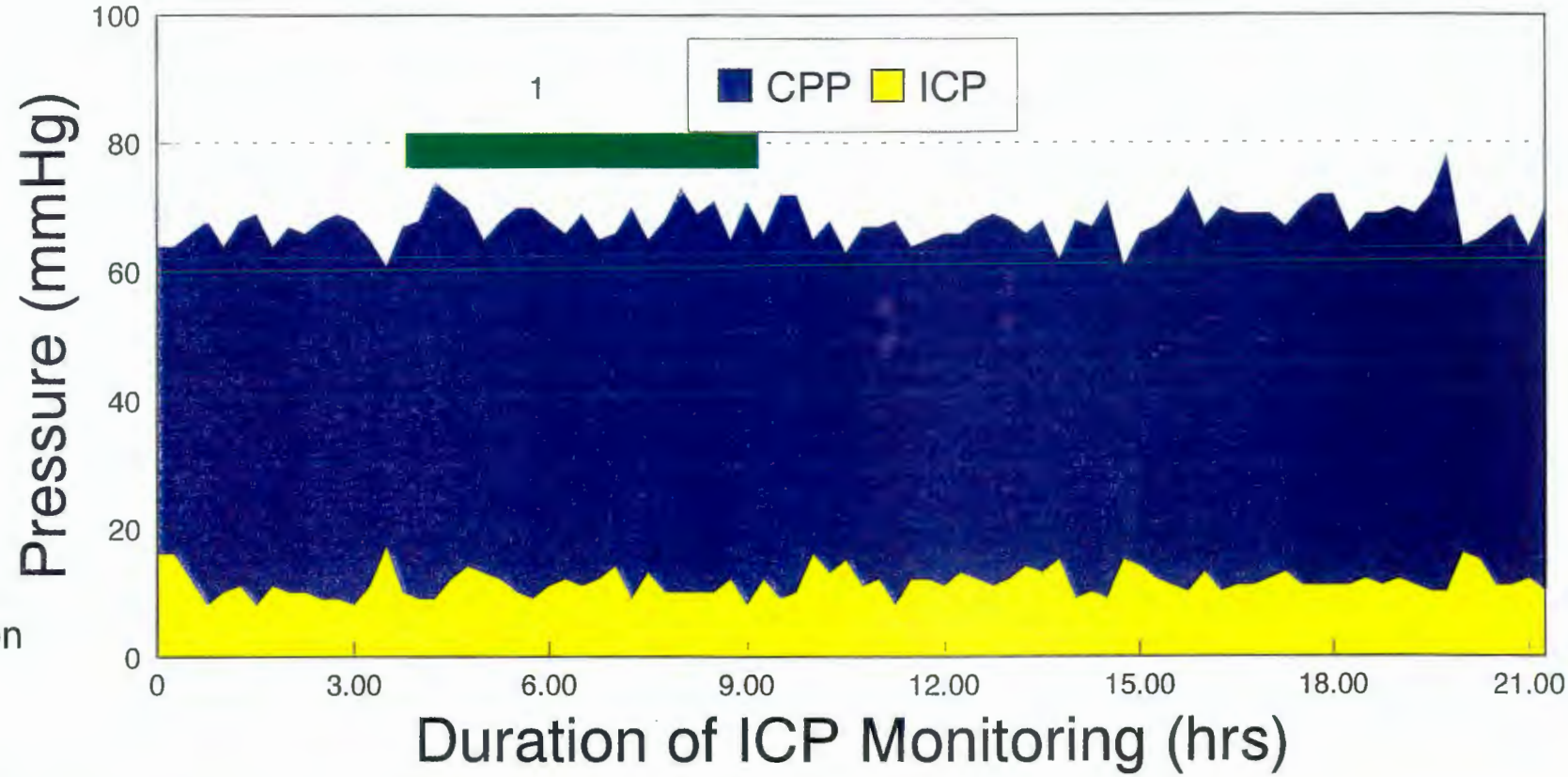
1. Frequent twitching of his hands (green rectangle), not associated with a significant rise in ICP.

Survived without any sequelae.

210/93

6 yr old boy
status epilepticus
given mannitol
prior to monitoring

Monitoring started
32hrs post admission



Time (hrs)	Admission	0	4	10	14
ACS	8	3	5	6	7
Brain stem	N	N	N	N	N
Posture	N	N	N	N	N
Parasiaemiat	38480	79000	300	240	120
Hb	60	50	-	-	43
pH	-	-	-	7.42	-
pCO2	-	-	-	3.7	-
BE	-	-	-	-5.0	-
Glucose	5.6	6.0	-	5.0	4.2
Sodium	135	137	-	139	139

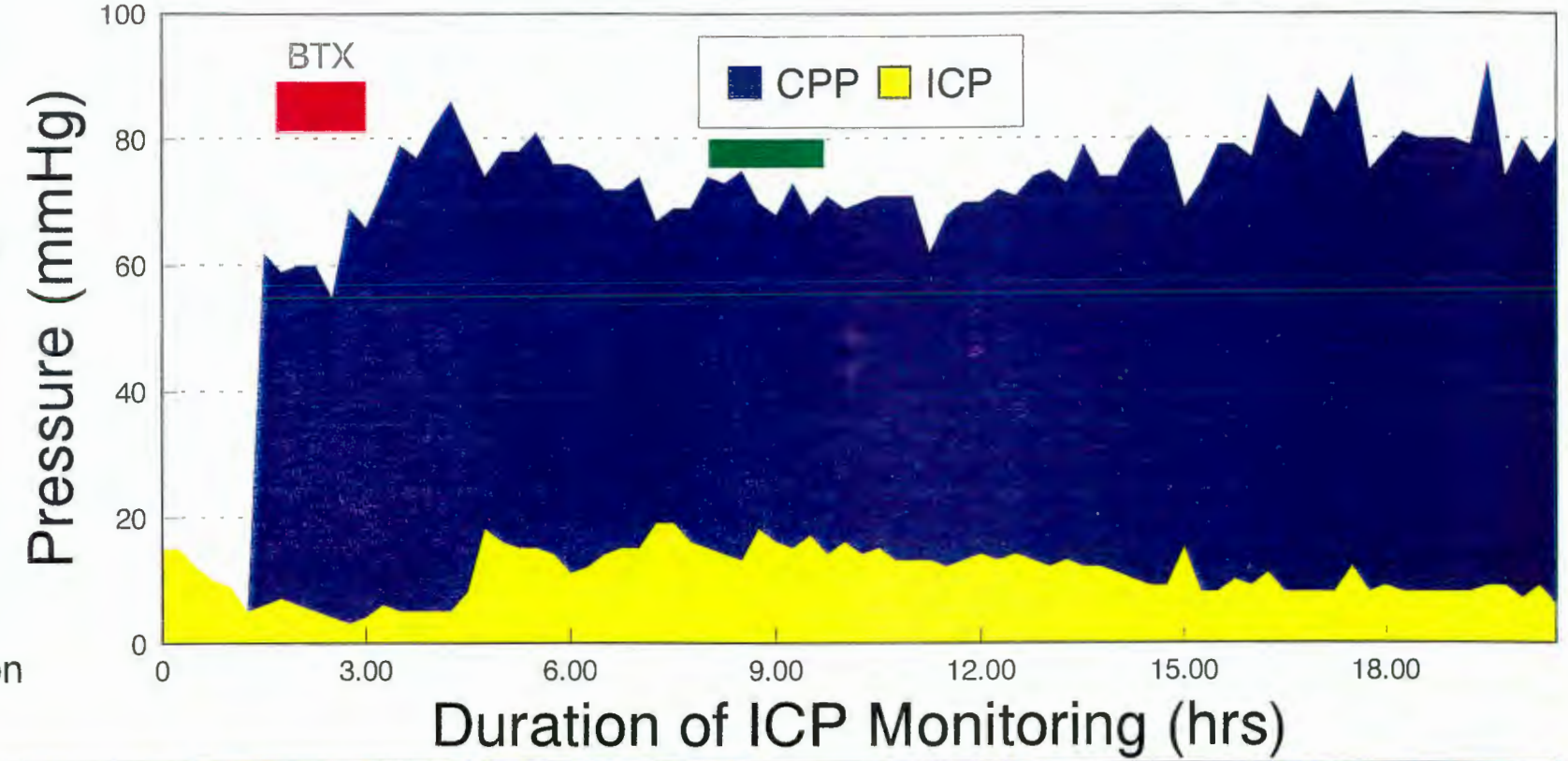
Patient No. 214/93

21 month old girl who did not have any seizures prior to admission/

A blood transfusion (BTX) improved the CPP and partial motor seizures were associated with a rise in ICP, but not higher to fulfil the criteria for giving mannitol.

214/93

21 month old girl
no seizures
found unconscious
on the morning of
admission



Monitoring started
2 hrs post admission

Time (hrs)	Admission	0	3	12	18	22
ACS	9	7	6	6	7	7
Brain stem	N	N	N	N	N	N
Posture	N	N	N	N	N	N
Parasitaemia	49742	-	54500	45800	17850	1026
Hb	49	-	-	-	-	83
pH	7.27	-	7.39	7.45	-	7.47
pCO2	1.98	-	1.45	2.8	-	3.59
BE	-17.2	-	-13.7	-5.5	-	-1.9
Glucose	5.4	-	5.9	6.4	-	5.8
Sodium	150	-	151	151	-	130

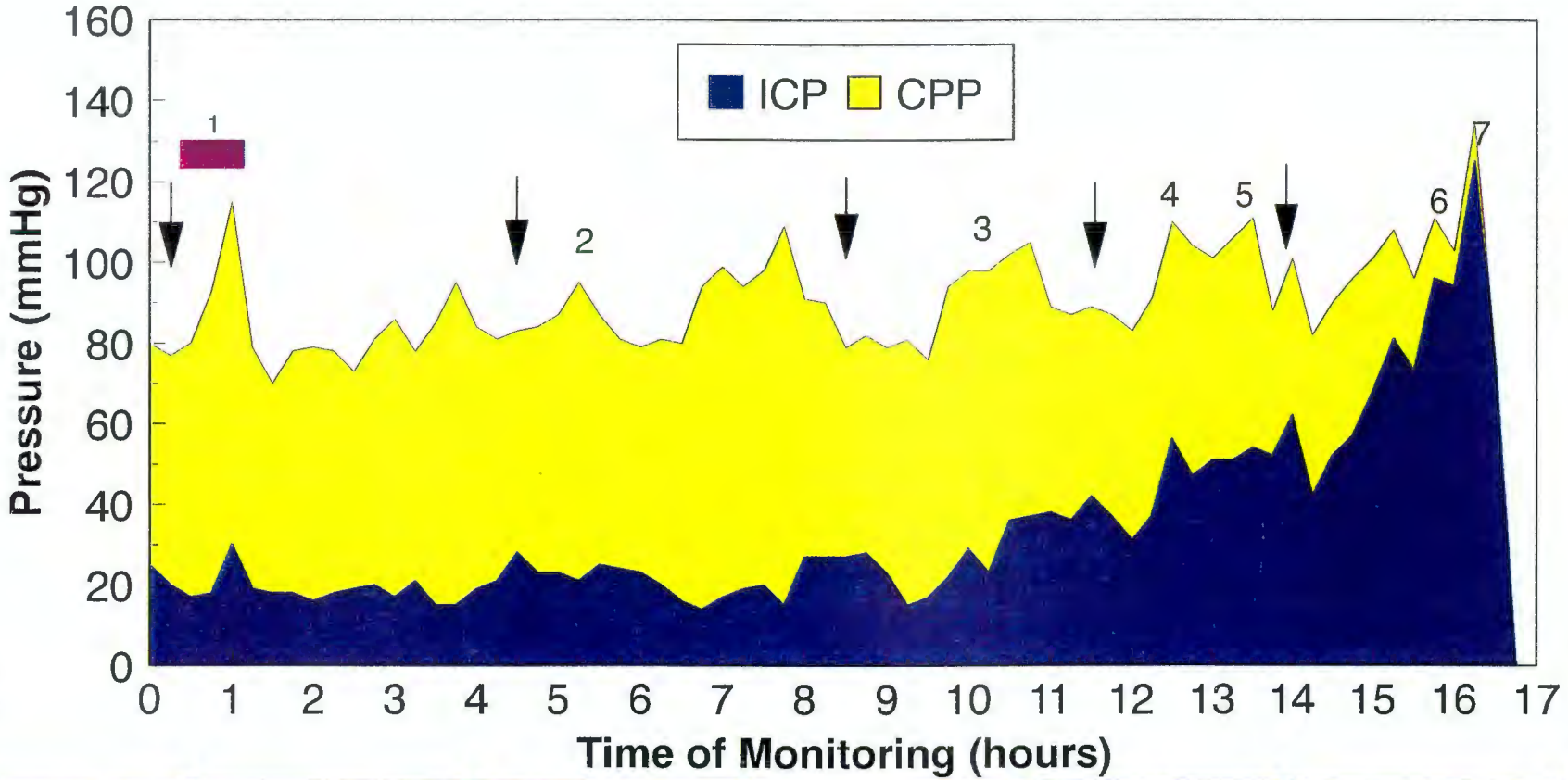
Patient No. 094/94

3 year old girl who presented with coma and opisthotonic posturing.

1. Opisthotonic posturing associated with a significant rise in ICP (37 mmHg).
2. Increase in ICP associated with agitation
3. Became agitated again
4. Agitation, developed respiratory abnormalities
5. R pupil larger than L, both sluggish to light.
6. R pupil dilated and unreactive, L pupil midpoint but sluggish. Respiration irregular
7. Irregular respiration, both pupils fixed and dilated. Thereafter had a respiratory arrest.

094/94

3 yr old girl unconscious 6hrs prior to admission, with opisthtonic posturing



Monitoring started
9 hrs after admission

Time (hrs)	Admission	0	2	9	14	16.5
ACS	6	-	-	-	-	Died
Brain stem	N	N	N	N	Y	-
Posture	Y	Y	N	N	Y	-
Parasitaemia	310200	1200	-	19000	534000	-
Hb	54	-	-	70	-	-
pH	7.22	7.44	-	7.40	7.48	-
pCO2	3.4	2.4	-	2.0	2.2	-
BE	-15.2	-9.9	-	-10.4	-9.2	-
Glucose	3.4	3.8	-	3.2	-	-
Sodium	140	138		132	-	-

APPENDIX VII:

Brain swelling and iscahaemia in Kenyans with cerebral malaria

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Brain swelling and ischaemia in Kenyans with cerebral malaria

C R J C Newton, N Peshu, B Kendall, F J Kirkham, A Sowunmi, C Waruiru, I Mwangi, S A Murphy, K Marsh

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.

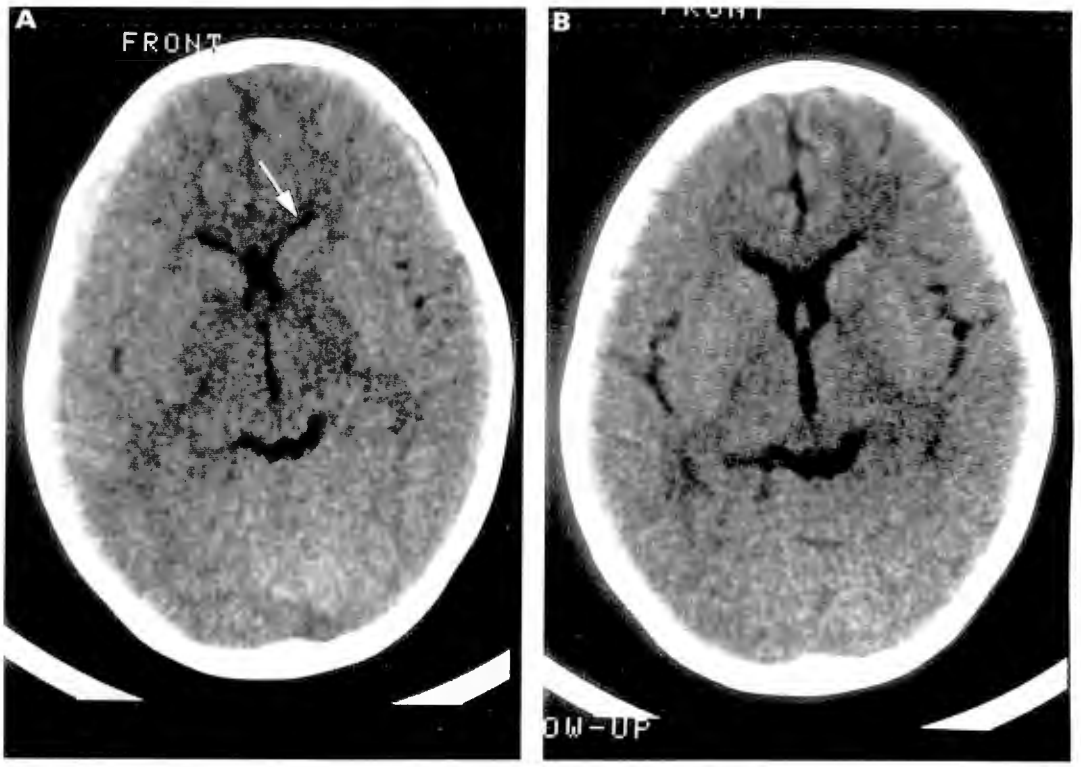

Figure 1 Patient 10. (A) Acute scan: diffuse brain swelling with loss of sulci and compression of ventricles (arrow). (B) Convalescent scan: resolution of brain swelling, with increase in the sulci and ventricles but without atrophy.

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.

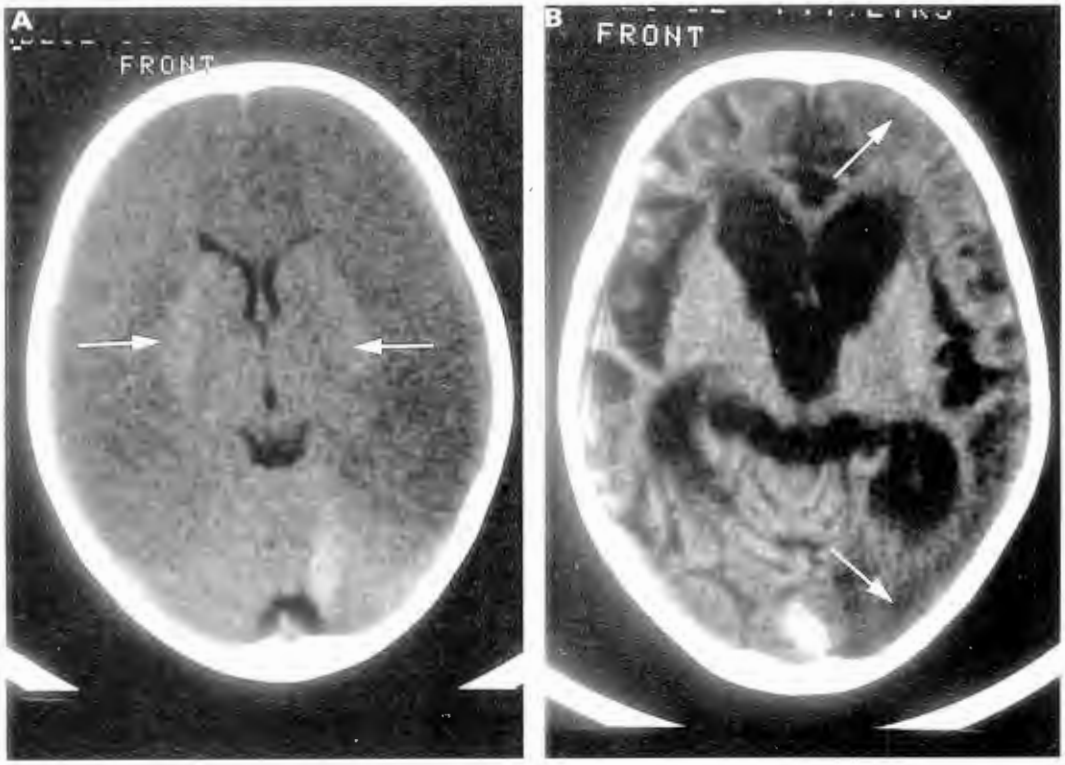

Figure 2 Patient 13. (A) Acute scan: brain swelling with diffuse hypodensity sparing the basal ganglia (arrows). (B) Convalescent scan: cerebral atrophy with infarction (arrows) of right frontal and parietal regions.

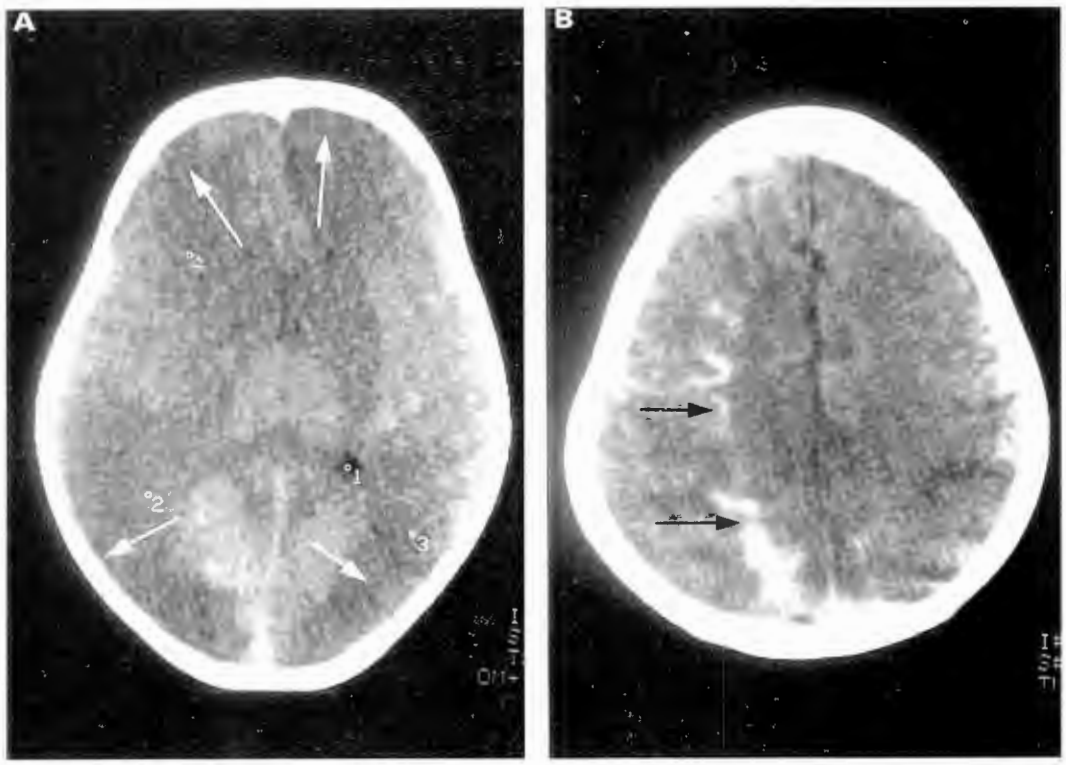

Figure 3 Patient 11. (A) Acute scan: diffuse brain swelling with extensive hypodensity of the superficial watershed areas (arrows) and the basal ganglia. (B) Convalescent scan: contrast scan showing enhancement of the border zone (arrows) between the left middle and posterior cerebral artery areas.

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,

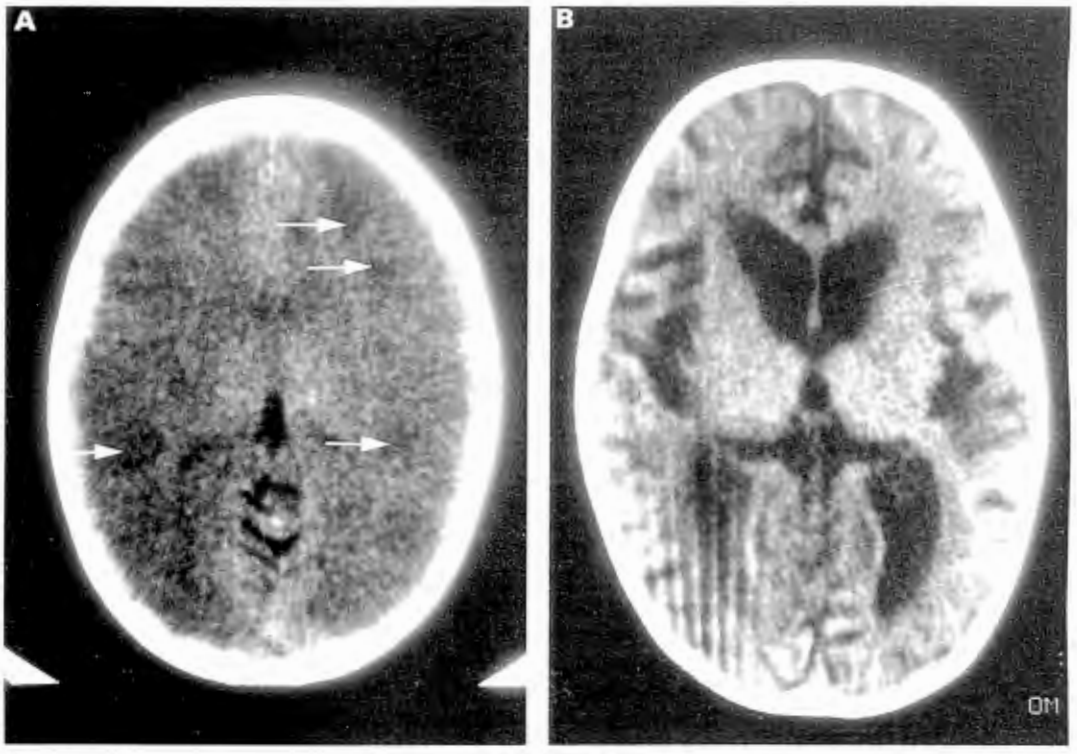

Figure 4 Patient 14. (A) Acute scan: diffuse brain swelling with scattered areas of hypodensity (arrows) throughout including the basal ganglia. (B) Convalescent scan: cerebral atrophy.

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.

ARCHIVIST