Seizures and intracranial dynamics in Kenyan children with acute non-traumatic encephalopathies
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CHAPTER 9

SUMMARY

Childhood acute non-traumatic encephalopathies present a major challenge in clinical practice for health workers in sub-Saharan Africa (SSA). At presentation, the aetiology is often unclear and intensive care management is often non-existent in health facilities in SSA. These encephalopathies are mostly attributed to Cerebral Malaria (CM), Acute Bacterial Meningitis (ABM), and viral encephalitides, and are associated with high mortality and significant occurrence of neuro-cognitive sequelae among survivors [1-5]. Multiple seizures, raised intracranial pressure (ICP) and shock have consistently been shown to be associated with such poor outcome, presenting potential targets for interventions. Indeed, intensive monitoring and management of these risk factors has been associated with better outcome [6]. However, tools for intensive care monitoring are invasive, require expertise that is non-existent in most health facilities in SSA, and are resource intensive. Development of simple solutions for diagnosis and brain monitoring would improve management and provide greater insight on the pathophysiology of these encephalopathies in SSA. In the absence of appropriate tools and supporting expertise for diagnosis and intensive care monitoring, simple empirical interventions may improve the outcome.

Recent studies have revealed significant mis-diagnosis of childhood encephalopathies, suggesting inaccurate estimates of burden, inappropriate understanding of pathophysiology, and erroneous clinical outcomes in previous studies [7]. Understanding the aetiology of childhood acute coma in SSA is therefore an important first step in investigating risk factors and interventions to improve outcome. This thesis outlines studies conducted between the years 2004 and 2010 on children with acute non-traumatic coma: i) examining the trends in
the aetiology and outcome of childhood coma, ii) outlining the incidence of seizures in childhood illnesses, iii) describing their electro-encephalographic (EEG) seizure profile, iv) investigating the efficacy of the antiepileptic drug (AED), fosphenytoin, for preventing seizures and improving outcome, v) exploring the utility of a non-invasive tool for monitoring ICP, vi) reviewing the use of osmotic agents for managing ICP, and vii) investigating the efficacy of a gelatin based colloid, gelofusine, in managing shock.

Changing Trends in Incidence and Aetiology of Childhood Acute Non-Traumatic Coma

Over the last seven years, we observed a significant reduction in malaria transmission on the rural coast of Kenya, and a decrease in the incidence of malarial disease presenting to our district hospital [8]. This epidemiological development was associated with reduction of up to 75% in severe disease and deaths from malaria [8]. We expected a proportionate reduction in the incidence of CM and overall, of childhood coma presentations over this period. We therefore analysed prospectively collected data to examine the trends in incidence, aetiology, clinical characteristics, mortality and risk factors for death in childhood non-traumatic coma over this period. Indeed, we observed a significant decline in the incidence of childhood coma, from 93/100,000 children in 2004, to 44/100,000 children in 2009. There was a 64% reduction in annual malaria-positive coma admissions and an almost three-fold increase in annual admissions of children with encephalopathies of unknown cause over this study period. Clearly, malaria played a significant role in the aetiology of childhood coma in Kilifi. However, the apparent dramatic increase in the number of children with undetermined aetiology was unexpected. Whilst it is possible that another aetiological agent or condition is increasing in this region, it is more likely that the coma of undetermined aetiology represents a condition previously masked by coincidental malaria
parasitaemia. Our study was on children who have previously been well and have had normal growth and development, suggesting a greater possibility of an acquired infectious aetiology, perhaps viral. In fact, we have previously demonstrated significant occurrence of *Herpes simplex* type 1 virus in the cerebrospinal fluid (CSF) of children diagnosed with CM[9]. However, it is also possible that a proportion of these children may represent presentation of previously unrecognised inborn errors of metabolism or cerebro-vascular anomalies.

The aetiology of childhood coma differs across Africa. Thus, metabolic diseases play a prominent role in Egypt where socio-cultural practices like consanguineous marriages are common, malaria has a significant role in East and West Africa where it is endemic, and in Equatorial Guinea, bacterial meningitis plays a greater role, perhaps due to lack of vaccines, and unique geographical characteristics[1-3]. However, in comparing studies from the different regions, we need to consider that studies conducted in tertiary or secondary level facilities may not be representative of the actual burden of the different aetiologies. The definition of coma may also not be consistent across the different studies. Whatever the situation, many children die before reaching health facilities in Africa and these studies under-estimate the actual burden of childhood encephalopathies.

My colleagues and I are not aware of any studies that have examined the aetiology of childhood coma in SSA over a prolonged period of time. The changing malaria transmission and introductions of vaccines are likely to alter the aetiology and outcome of childhood coma in SSA. Such changes call for a re-examination of public health interventions, clinical management protocols, and research priorities.
The Incidence, Aetiology and Outcome of Childhood Acute Seizures

Acute seizures are a common neurological symptom in childhood illness. They are a major risk factor for poor outcome, and frequently are a harbinger for coma onset, perhaps due to neuronal insult or metabolic drain on an already compromised physiology [10-13]. However, there is little data on the burden, risk factors and outcome of childhood acute seizures in sub-Saharan Africa. Most published studies report on rates in hospital and are limited to the diagnoses associated with the seizure-events [14-16].

My colleagues and I conducted a study to determine incidence, aetiology and outcome of incident seizures among children aged between 0 and 13 years in Kilifi. We found an incidence of 425 per 100,000 per year and of status epilepticus of 46 per 100,000 per year. Younger children were at a higher risk; the incidence of acute seizures in children younger than 5 years was 879 per 100,000 per year and of that of non-epilepsy associated status epilepticus was 95 per 100,000 per year. Malaria and neonatal sepsis were the major aetiological factors for acute seizures and malaria for status epilepticus. Mortality was 3.1% while 1.3% of the surviving children had gross neurological deficits at the time of discharge from hospital.

Clearly, children living in Kilifi at the time of our study experienced a very high burden of acute seizure disorders associated with infectious diseases. Our estimates of seizures related to malaria are higher than that reported from west Africa [15]. We have since documented significant decline in malaria transmission in coastal Kenya [8]. We hypothesised that the reduction in malaria transmission would lead to decreased burden of childhood seizures with consequent reduction in neurological disabilities. Indeed, we have since observed decrease in the incidence of all childhood acute symptomatic seizures in congruence with
predicted decline estimated by malaria-attributable fractions [17]. Such declining burden of seizures may also mean less impact on outcome by prophylactic AEDs and other neuro-protective adjuvant therapies in childhood encephalopathy.

**Continuous Electroencephalographic Monitoring in Acute Non-Traumatic Coma**

Significant occurrence of clinically subtle and electrographic seizures has been well described in encephalopathic children in developed countries [18]. There are very few similar studies in SSA and there is little information on the burden of electrographic seizures in childhood encephalopathy. It is not clear how these types of seizures impact on outcome and whether their treatment is useful in clinical management. We made continuous EEG observations on children presenting to our hospital in coma. We observed significant occurrence of electrographic seizures; 66% of all the seizures observed, and the only type of seizure observed in 20% of the children. Among children with electro-clinical seizures, we observed significant incongruence between clinical and EEG observations; the majority (63%) of the electro-clinical seizures had focal clinical features but appeared as generalized (79%) or focal with secondary generalization (14%) on EEG.

Our study demonstrated significant occurrence of electrographic seizures in childhood encephalopathies. However, standard EEG machines are unavailable for routine use in most health facilities in Africa. Cheaper devices like the Cerebral Function Analyser Monitor (CFAM) that have 1, 2 or 4 EEG channels and are relatively easy to use and interpret, may have a role in facilitating optimal care in such resource-poor setups. Indeed we were able to demonstrate that 93% of all the seizures detected by the EEG machines would have been
detected with the standard placement leads used for the 2-channel CFAM (F3, F4, P3 and P4). Empirical use of effective prophylactic AEDs administered at admission may help in preventing seizure occurrence in the first place and improving outcome.

We were not able to clarify the effect of electrographic seizures on outcome because of the small numbers and inability to carry out prolonged follow-ups and cognitive tests. Experimental evidence indicates that prolonged electrographic seizures may result in memory and behavioural problems [19]. It is possible that cognitive tests and prolonged follow-up in larger studies may reveal neuro-cognitive deficits in patients with electrographic seizures.

**Fosphenytoin for Preventing Seizures and Improving Outcome in Childhood Acute Non-Traumatic Coma**

Seizures may be a cause or consequence of brain damage in acute encephalopathies. If they cause poor outcome, their prevention may help reduce the mortality and neuro-cognitive sequelae. A placebo controlled trial of phenobarbital (a single intramuscular (IM) injection of 20mg/Kg) as a prophylactic AED in children with CM showed more than 50% reduction in the incidence of seizures in those who received phenobarbital, with a trend towards decreased neurological sequelae[20]. However, mortality was more than double in those given phenobarbital due to respiratory depression in the unventilated children. With this initial experience with phenobarbital, it appeared feasible to improve outcome using an AED with minimal cardio-respiratory depression profile. Fosphenytoin was an attractive choice since it is already in use in neurosurgery patients [21], has minimal cardio-respiratory depression,
and could be administered intramuscularly (IM), an appropriate characteristic for resource-poor regions. We conducted a trial to examine the effectiveness of a single IM injection of fosphenytoin (20 phenytoin equivalents/Kg) to prevent seizures and improve outcome in children with acute non-traumatic encephalopathies. We did not observe any benefit in use of fosphenytoin for preventing seizures in comparison to placebo despite achieving adequate drug levels. Although, we did not achieve the desired sample size because of a very slow recruitment rate, it was clear that it was futile to proceed with the study during assessment at interim analysis. There was no indication of a trend in benefit that needed to be confirmed by a larger sample size.

The use of prophylactic AED in paediatric traumatic brain injury (TBI) is well established [22]. There is a clearer understanding of the pathophysiology of TBI and the ability to determine the time of neurological insult and thus administer the intervention during an appropriate window of opportunity. Thus, although we have demonstrated that fosphenytoin did not prevent seizures or reduce neurological deficits in the Kenyan children, this finding may need to be confirmed by larger studies that are appropriately powered to allow for examination of the different aetiologies of childhood encephalopathies, time of administration of the prophylactic AED relative to the time of onset of illness, and the potential effect on other risk factors like raised ICP.

**Tympanic Membrane Displacement Measurements in Childhood Encephalopathy**

Clinical manifestations of raised ICP are not as dramatic as that of seizures. Intensive monitoring and management of ICP dynamics may be important to improve outcome. In
health facilities in SSA, monitoring of ICP is limited by the fact that tools for monitoring ICP are invasive and require technical proficiency to maintain accuracy [23]. Non-invasive tools for monitoring ICP could be of great use in such settings, guiding management and providing greater insights in the pathophysiology of childhood encephalopathies. The utility of one such tool, the tympanic membrane displacement (TMD) analyser, has been explored among children with idiopathic intracranial hypertension (IIH) and hydrocephalus, indicating significant correlation with direct ICP measurements [24]. Two types of measurements are possible using the TMD analyser; baseline TMD pressure measurements achievable by acoustic stimulation of the stapedial reflex, and intracranial cardiac and respiratory pulse pressure measurements, being measurements of spontaneous physiological variations in ICP. The latter mode of measurement has been little studied.

We conducted a study to examine the utility of TMD pulse pressure measurements in monitoring children with acute non-traumatic coma. We observed that children with clinical features of raised ICP had higher cardiac and respiratory intracranial pulse pressure amplitudes in the semi-recumbent position compared to those without. Children who died had significantly higher cardiac pulse amplitudes in both the semi-recumbent and recumbent positions, and higher semi-recumbent respiratory pulse amplitudes, compared to those who survived. However, we did not demonstrate significant relationship between lumbar puncture (LP) manometry and TMD measurements. LP manometry is not an appropriate technique for validating a non-invasive tool for monitoring ICP in an intensive care setting as this would require prolonged monitoring to be able to make adequate comparisons of the pulsatile pressure variations [23]. Where ICP is not uniform throughout the CSF
compartment as could occur in infectious encephalopathies, it is not an accurate measure of ICP dynamics. Thus, our study was inadequately designed to confirm the utility of the TMD pulse pressure measurements in monitoring ICP. Even so, our study suggests a potential role for TMD pulse pressure measurements in detecting and monitoring ICP dynamics, and in predicting clinical outcome in childhood encephalopathy. However, such utility would need to be confirmed with studies that allow for direct ICP monitoring in intensive care settings and incorporate intracranial imaging. Incidentally, we also observed a significant association between abnormal tympanometry and mortality. Investigators in Russia (Boris, Personal Communication) have observed a significant relationship between tympanometry and ICP measurements. In the absence of direct ICP measurements in our study, we can only speculate on the possibility of a similar relationship in our children. Potentially, tympanometry may provide a cheaper and simpler technique for diagnosing altered ICP dynamics and prognosticating children with acute encephalopathy.

An accurate non-invasive tool for monitoring ICP will be useful in promoting the understanding of the pathophysiology of childhood encephalopathies and allow for better clinical care management in resource-poor settings.

The Role of Osmotic Agents in Children with Acute Encephalopathies: A Systematic Review

Besides developing simple tools for brain monitoring, it appears useful to explore simple and effective interventions that can be used empirically to improve outcome in childhood encephalopathies. Osmotic agents offer attractive possibilities for management of childhood encephalopathy in SSA, being cheap and widely available. Unfortunately, guidelines for use of osmotic agents have been developed from Traumatic Brain Injury (TBI) studies, mostly in
adults, and have been adapted for use in children with minimal evidence obtained directly from children with acute non-traumatic encephalopathies.

We conducted a systematic review to determine the best available evidence on the efficacy and effectiveness of various osmotic agents and their effect on resolution of coma and outcome (neurological sequelae and mortality) in children with acute encephalopathies. The results of our review supported the use of oral glycerol in children with ABM and the use of hypertonic saline in acute traumatic and non-traumatic encephalopathies. The two agents have their own individual advantages for use in resource-poor settings.

Hypertonic saline achieved greater and more sustained reduction in ICP, particularly when administered as a continuous infusion, compared to mannitol, normal saline and ringer’s lactate. It is cheap, easily available, and improves volume deficit, a common complication of childhood encephalopathies and one of the main disadvantages of using mannitol which reduces volume load. On the other hand, glycerol can be administered orally via naso-gastric tube, a useful characteristic in health facilities with limited resources. However, the studies that we reviewed were not sufficient to change or modify the guidelines. There is need for well designed studies to determine the optimal concentrations, doses and modes of administration of the various osmotic agents to provide satisfactory guidance on use in childhood encephalopathies.

**Volume expansion with albumin compared to gelofusine in children with severe malaria**

In childhood encephalopathic illnesses where the integrity of the blood brain barrier may be impaired, therapy aimed at correcting volume deficits and improving tissue perfusion carries
the risk of cerebral oedema. Volume resuscitation with colloids might be safer than crystalloid solutions, as the latter freely equilibrate throughout the extracellular compartment and thus have the potential risk of aggravating intracranial pressure. This possibility was initially supported by a randomised trial on children with severe malaria that demonstrated that volume expansion with 4.5% human albumin solution was associated with a significantly lower mortality (4%) than saline (18%) in children with acidosis, especially amongst those admitted in coma (5% versus 46% respectively)[25]. Unfortunately, Albumin is too expensive for most health facilities in resource poor SSA and it seems appropriate to establish whether a similar survival benefit can be achieved using cheaper non-albumin colloidal solutions.

We carried out a randomised controlled trial to compare the safety and efficacy of gelofusine, a modified gelatin, to albumin, in children with severe malaria complicated by volume deficit. Both interventions safely corrected the features of shock. We observed lower mortality in children receiving albumin compared to those who received gelofusine. There was no difference in occurrence of neurological deficits between the two groups.

Modified gelatins like gelofusine are attractive alternatives to albumin for volume resuscitation of encephalopathic children as they are cheap, widely available and have been shown to have similar efficacy to albumin and other colloids for correcting shock [26-28]. That we did not demonstrate a similar mortality benefit in our children with gelofusine compared to albumin may suggest a neuro-protective effect for albumin that cannot be replicated by the former. A larger multicentre clinical trial on fluid boluses in severely ill African children has since demonstrated greater mortality with saline and albumin bolus fluid administration compared to no fluid bolus administration [29]. However, the criteria
for volume deficit in this study were not optimal and it is likely that a significant number of
children receiving fluid boluses did not warrant the intervention [30]. Children with coma
were not specifically examined for differences in neurological sequelae or mortality in this
study. Thus, without studies that would provide appropriate guidance, normal saline
remains the fluid of choice for resuscitation of encephalopathic children. It may be that
hypertonic saline is useful for volume resuscitation children considering that it boosts
volume load and is useful in the prevention and treatment of raised ICP.

Future Studies
There is still a great lack of knowledge on the aetiology, pathophysiology, risk factors,
outcomes and appropriate interventions for childhood acute encephalopathies in SSA.
Understanding the aetiology of childhood acute non-traumatic coma in Africa is necessary in
defining the directions in research and is part of my post-doctoral research agenda. I
envisage a prospective observational study in malaria and non-malaria endemic areas that
incorporates viral and bacterial studies, imaging, and detailed clinical observations. If
previously unappreciated infectious agents are found to be responsible for a significant
proportion of the childhood encephalopathies, it makes sense to extend these studies by
investigating useful biomarkers that would aid in developing simple techniques, like rapid
diagnostic kits, that would allow for widespread and accurate diagnoses even in resource-
poor settings.

I am also keen on investigating the utility of the TMD analytical and tympanometry in
monitoring ICP dynamics in these encephalopathies. I plan to do this by conducting a study
in an intensive care setting that would allow for concurrent direct ICP monitoring, intensive
physiological measurements, and imaging, to enable the clear determination of the relationship between ICP dynamics, intra-aural pressure waves, intracranial anatomical configurations, and outcome. If the TMD analyser is found to be useful, it could be used for routine clinical management, and may provide an opportunity to study osmotic agents for managing ICP and improving outcome through clinical trials. This is important because trials to determine the efficacy and effectiveness of osmotic agents in improving outcome require large samples sizes that can only be achieved through multi-centre studies which may be in settings where the resources and expertise for invasive ICP monitoring are not available. Guided by our review, it seems of priority to determine the concentration and rate of administration of hypertonic saline that is optimal for managing ICP, and whether the efficacy of the various osmotic agents serves for the various aetiologies of childhood encephalopathies.

**Conclusion**

Over the next decade of research, significant victory against childhood morbidity and mortality in Africa will be achieved if there is concerted effort to better understand the aetiology of childhood encephalopathy, develop simple tools and techniques for diagnosis and brain monitoring, and better and simplify interventions to optimise management, prevent complications and improve outcomes.
REFERENCES


Samenvatting

Acute, niet traumatische hersenaandoeningen bij kinderen zijn een belangrijk probleem in Afrika ten zuiden van de Sahara (sub-Sahara Afrika, sS Afrika). Deze hersenaandoeningen worden meestal toegeschreven aan malaria (cerebrale malaria), aan acute bacteriële meningitis (ABM) en virale hersenontstekingen. Zij gaan gepaard met hoge sterfte en met neurologische en cognitieve restverschijnselen bij degenen die overleven [1-5]. Er is een duidelijk verband tussen de slechte afloop en het voorkomen van meerdere toevallen, verhoogde intracraniële druk (verhoogde druk binnen de schedel) en shock. Het aanpakken van deze factoren bleek te leiden tot een betere afloop [6]. Dit vereist meerdere voorzieningen voor intensieve zorg die er vaak niet zijn terwijl de middelen en methoden voor intensieve zorg invasief zijn en ervaring vereisen die in de meeste instellingen ontbreekt. Ontwikkeling van eenvoudige methoden voor het stellen van een diagnose en voor het bewaken van de hersenfunctie zou de zorg voor deze patiënten verbeteren en meer inzicht kunnen geven in de achterliggende oorzaken van de aandoeningen. In afwezigheid van de juiste middelen, van voldoende kennis en van mogelijkheden van intensieve zorg, zouden eenvoudige empirische interventies mogelijk de afloop kunnen verbeteren. Recent onderzoek heeft aangetoond dat vaak een verkeerde diagnose wordt gesteld betreffende hersenaandoeningen bij kinderen hetgeen aannemelijk maakt dat verkeerde schattingen zijn gemaakt van de ziektelast door bepaalde aandoeningen, dat onjuiste ideeën zijn ontstaan over pathofysiologie en verkeerde conclusies zijn getrokken over het klinische eindresultaat [7]. Kennis van de oorzaak van acuut coma bij kinderen in sS Afrika is dan ook een belangrijke eerste stap bij het bestuderen van de risicofactoren en interventies om de afloop te verbeteren.

In dit proefschrift worden de volgende studies beschreven die tussen 2004 en 2010 werden verricht bij kinderen met acuut, niet traumatisch coma:

1. onderzoek betreffende de veranderingen van oorzaak en afloop in de loop der tijd;
2. beschrijving van het voorkomen van toevallen tijdens kinderziekten;
3. beschrijving van het electro-encefalografisch patroon (EEG);
4. onderzoek naar de effectiviteit van het anti-epilepticum fosphenytoine voor de preventie van toevallen en ter verbetering van de afloop;
5. onderzoek van een niet invasieve methode om intracraniële druk te meten;
6. bespreking van het gebruik van middelen voor het beïnvloeden van de intracraniële druk;
7. onderzoek naar het nut van gelofusine, een op gelatine gebaseerde vloeistof bij het bestrijden van shock.