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

Acute non-traumatic encephalopathies are an important cause of paediatric morbidity in sub-Saharan Africa. Cerebral malaria (CM), acute bacterial meningitis (ABM) and viral encephalitides are the most common causes [1-3]. These three diseases are responsible for most of the deaths from childhood encephalopathies, with up to 33% case fatality [1,3,4]. They also result in significant persistent gross neurological and cognitive impairments among survivors [5,6]. The latter sequelae are more subtle but have a significant deleterious effect on a child’s social and educational functioning[6]. Indeed, childhood CM is associated with impaired attention and specific everyday memory [7,8]. Significant occurrence of deafness in children who survive ABM is likely to have consequences on their cognitive development [9,10]. The impact of these encephalopathies on child survival in Africa is therefore far much greater than is apparent from health facilities’ statistics.

AETIOLOGY OF CHILDHOOD NON-TRAUMATIC ENCEPHALOPATHY

Understanding the aetiology of childhood non-traumatic encephalopathy is a crucial first step towards comprehending the burden and exploring interventions to improve outcome. There is considerable overlap in the clinical presentation of CM, ABM, viral encephalitides, and other non-traumatic encephalopathies [11]. In malaria endemic areas, as many as 80% of the children in the communities may be parasitaemic and asymptomatic [12]. Thus, even where reliable and timely malaria microscopy exists, encephalopathic illness in a parasitaemic child may not always be caused by malaria. In Malawi, an autopsy study of 31 children with positive malaria microscopy who fulfilled the WHO’s definition of CM revealed misdiagnosis in 23% of the deaths
[13]. In another study in Kenya, 9% of children with WHO defined CM were found to have Herpes simplex type 1 in cerebrospinal fluid (CSF) [14]. Such diagnostic conundrums are complicated by the fact that even in the most optimal of circumstances in this setting, microbial cultures are not sensitive and facilities for viral diagnosis are almost non-existent [11]. The consequences of the potential mis-diagnoses are that clinical presentation, pathophysiological mechanisms, and outcomes are attributed to the wrong diseases, and life-threatening encephalopathic illnesses are sub-optimally managed. Clearly, there is need to determine the aetiology of childhood encephalopathies in Africa to have a better understanding of the risk factors for poor outcome and points for intervention.

**RECOGNISING AND MANAGING RISK FACTORS FOR POOR OUTCOME: SEIZURES, RAISED ICP AND SHOCK**

Multiple seizures, shock and raised intracranial pressure (ICP) have consistently been shown to be associated with increased risk of poor outcome in childhood encephalopathy irrespective of the aetiology [3 ,5 ,15 ,16]. These features are associated with ischaemic neuronal damage due to altered cerebral auto-regulation, diminished cerebral blood flow and intracranial herniation[17 ,18]. These complications also represent ideal targets for simple and practical interventions to improve outcome. However, the clinical signs are often difficult to detect and occur late during the illness. For example, papilloedema is a late sign of raised ICP and is associated with significant inter-observer variability among clinicians [19]. Low blood pressure occurs late in shock and is not a reliable indicator of childhood haemodynamic deficit in severely
ill children [20]. Significant occurrence of subtle and electrographic seizures have been demonstrated among children with CM [21].

In better resourced settings, intensive, often invasive, monitoring to detect raised ICP, seizures and hypovolaemia allows for early recognition and better management for improved outcome. In sub-Saharan Africa, the challenge is that of limited resources and access to expertise to facilitate optimal management. In this context, there is need to explore simple and inexpensive diagnostic solutions, investigate the use of non-invasive tools for brain monitoring, and examine simple interventions to improve outcome.

**Seizures**

Seizures are a frequent feature of childhood acute encephalopathies. Over eighty percent of children presenting to hospital with CM have a history of seizures and sixty percent have clinical seizures after admission [22]. Multiple and prolonged seizures after admission are associated with increased mortality and neurological deficits [3, 4, 16]. Such poor outcome is likely due to neuronal damage by excitotoxins released by repeated neuronal firing, inadequate cerebral blood flow for metabolic demand (particularly in the context of impaired cerebral-vascular auto-regulation), abnormal respiration and aspiration of gastric contents during seizure episodes, and aggravated intracranial hypertension [17, 23]. The types of seizures vary considerably. Many are not detected clinically either because they are subtle or do not have any clinical manifestations and can only be detected on electroencephalography (EEG); electrographic seizures [21]. The latter type of seizures have been described in intensive care
settings in developed countries but there is little data on their prevalence in African children with acute non-traumatic encephalopathies. Their association with outcome is not clear. Continuous EEG monitoring may allow for a better description of childhood seizures in encephalopathic African children, enable us to investigate their association with outcome, and facilitate better management. However, standard EEG monitoring equipment is inaccessible to most African hospitals. Simple tools for EEG monitoring like the Cerebral Function Analyser Monitor (CFAM) are cheaper and easier to use and may have a place in routine clinical care in tertiary health facilities.

In lower level health facilities, empirical prophylactic anti-epileptic drug (AED) use may have a role in preventing seizure occurrence. An initial placebo controlled study exploring the use of a single intramuscular (IM) injection of phenobarbital (20mg/Kg) in children with CM showed more than fifty percent reduction in the incidence of seizures in the active arm and a trend towards decrease in neurological sequelae[24]. However, fatal respiratory depression was more than double in the active arm compared to the placebo arm. This finding provides grounds to explore the efficacy and effectiveness of other suitable AEDs with less cardio-respiratory depression, in preventing seizures and improving outcome. Improved strategies for better seizure management may improve other risk factors for poor outcome like raised ICP and better outcomes.
Raised ICP

Several studies have documented the role of raised ICP as an important determinant of poor outcome in childhood encephalopathies [25,26]. Raised ICP may compromise cerebral perfusion leading to global ischaemia with subsequent parenchymal damage or may lead to death directly by brainstem compression due to intracranial herniation [18]. Intensive monitoring and management of raised ICP may improve outcome [27]. However, tools for monitoring ICP are invasive, require technical expertise and intensive care set-ups [18]. Most health facilities in rural Africa do not have capacity to support such monitoring and thus ICP monitoring in these settings is virtually non-existent. Non-invasive tools for monitoring ICP could circumvent these limitations in capacity, allowing for better monitoring and management of ICP, and facilitating greater understanding of the pathophysiology of these encephalopathies. One such promising tool for non-invasive monitoring of ICP is the Tympanic Membrane Displacement (TMD) analyser. The TMD analyser makes use of the communication between the subarachnoid space and the inner ear, allowing for transmission of ICP to the perilymphatic fluid and resulting in detectable movements of the tympanic membrane [28]. Potentially, the TMD analyser could help in describing ICP patterns in African children with non-traumatic encephalopathies, provide better understanding of the pathophysiology of these encephalopathies and allow for trials of simple interventions for management of raised ICP.

Osmotic agents like hypertonic saline, glycerol and mannitol are an example of such simple interventions and have potential for routine use in preventing or treating raised ICP in childhood encephalopathies in SSA [29]. They are cheap and widely available but are of differing efficacy,
safety and practical utility in children with non-traumatic encephalopathies. Current protocols on their use are mostly guided by studies on adults with traumatic brain injury, are not consistent on dosage and concentrations, and do not envisage resource-poor circumstances. Thus, it is critical that we improve our understanding of the utility of these agents in childhood encephalopathy, particularly in resource-poor settings.

**Shock**

The association between shock and poor outcome in childhood illness is well established. The overall haemodynamic deficit in shock impacts negatively on cerebral perfusion and in encephalopathic illness, likely aggravates the effect of multiple seizures and raised ICP. However, interventions to correct shock may aggravate raised ICP in childhood encephalopathy. Thus an intricate balance is necessary to achieve a beneficial rather than deleterious effect on clinical outcome. Intensive haemodynamic and ICP monitoring may guide in achieving such a balance in severely ill encephalopathic children but is not practical in low-resource settings. Cautious empirical interventions need to be tested. Current protocols advise on use of normal saline for correction of shock in African children with or without encephalopathy. In reality, these protocols are mainly based on expert opinion and consensus and are guided by very few studies in severely ill children in resource-poor settings [30]. An initial study at our hospital demonstrated an apparently greater benefit in using albumin (4.5%) over normal saline for volume resuscitation of children with CM [31]. Although this was a small study, it nevertheless called for the exploration of the use of other cheaper and more widely available colloids for use in resuscitation of severely ill children.
HYPOTHESES

In this thesis, I have examined the following hypotheses:

1. The incidence and aetiology of acute non-traumatic encephalopathies has been altered by change in malaria transmission in a malaria endemic area at the rural coast of Kenya;

2. Seizures are a common feature of childhood illness in rural Kenya and are mostly attributable to malaria and other preventable causes;

3. Electrographic seizures are common in acute non-traumatic encephalopathies;

4. A single intramuscular injection of fosphenytoin (20 PE/Kg) prevents seizures and improves outcome in children with acute non-traumatic encephalopathies;

5. Tympanic Membrane Displacement analyser intracranial pulse pressure measurements have potential utility in non-invasive monitoring of ICP and may help predict outcome;

6. Osmotic agents have a role in the management of children with raised ICP in non-traumatic encephalopathies;

7. Gelofusine, a relatively cheaper colloid, is similarly safe and efficacious as albumin in resuscitation of children with severe malaria complicated with metabolic acidosis.

To examine these hypotheses, I conducted studies between the years 2004 and 2010 at Kilifi District Hospital, a first-level referral health facility in Kilifi District on the coast of Kenya. Kilifi District is a malaria endemic area. It is subdivided into 36 administrative units known as locations. Two-thirds of the population lives in fourteen locations surrounding Kilifi District
Hospital from which eighty percent of paediatric admissions come. These fourteen locations have been incorporated into the Kilifi demographic surveillance site (Figure 1).

**Figure 1: The Kilifi Demographic Surveillance Site**

![Map of the Kilifi Demographic Surveillance Site]

**Summary of subsequent chapters**

I have summarised these studies in the subsequent chapters. In chapter 2, I examine the trends in aetiology and outcome of acute non-traumatic coma in the study area over a period of documented change in malaria transmission; from the year 2004 to 2009. In chapter 3, I provide a description of the incidence and aetiological risk factors for acute seizures in the demographic surveillance area. In Chapter 4, I describe and discuss the electroencephalographic features of children who present to the hospital with acute non-traumatic coma. In chapter 5, I report on a randomised double-blind placebo-controlled trial examining the efficacy of a single
intramuscular injection of fosphenytoin in preventing seizures and improving outcome in children with acute non-traumatic encephalopathy. In chapter 6 and 7, I explore the utility of a non-invasive tool, the tympanic membrane displacement analyser, for monitoring intracranial pressure in children with acute coma. In chapter 8, I review published literature on the efficacy and effectiveness of osmotic agents for managing raised intracranial pressure and improving outcome among children with non-traumatic coma. In chapter 9, I examine the efficacy of gelofusine, a gelatin-based colloid, in treating shock, as compared to albumin. In chapter 10, I provide a summary and discussion of all these studies and explore the possibilities in future studies in consideration of my findings.
REFERENCES