Seizures in children with acute falciparum malaria: risk factors, mechanisms of neuronal damage and neuro-protection
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Summary
SUMMARY

Malaria is a leading cause of ill health in tropical countries. Infection with \textit{Plasmodium falciparum} is the most severe and mainly affects children <5 years in sub-Saharan Africa. In this age group, falciparum malaria may be complicated by severe anaemia, prostration, impaired consciousness, hypoglycaemia, metabolic acidosis and seizures, with cerebral malaria the most severe neurological presentation\cite{1}.

Worldwide, febrile seizures are the commonest seizure disorder. In susceptible children, most are induced by infections such as respiratory tract and ear infections or gastroenteritis. The majority are short-lived single seizures that rarely progress to status epilepticus. The outcome is good. In tropical countries however, acute symptomatic seizures may be more common and falciparum malaria is an important cause of acute symptomatic seizures. Infection with \textit{Plasmodium falciparum} has been associated with over 50% of seizures in children admitted to hospital. Although malaria-related seizures also occur in the context of a febrile illness, unlike simple febrile seizures, the pattern and outcomes are different. Mortality is higher and neuronal damage manifesting as neurological deficits at discharge, epilepsy or long-term neurological and cognitive impairments has been described in up to 24% of exposed children. These poor outcomes are not limited to cerebral malaria, but extend to other less severe forms such as malaria with multiple or complicated seizures\cite{2}. Chapter 1 is a summary of the clinical features of falciparum malaria in African children and studies of malaria related seizures.

The risk factors and precipitants of seizures in acute falciparum malaria, the public health burden and the mechanisms by which neuronal damage develops are poorly understood. In this thesis, I estimated the contribution of falciparum malaria to the burden of acute seizures in children living in a well-defined area in Kilifi in coastal Kenya. I examined some of the risk factors for seizures and long-term neurological and cognitive impairments, and looked at possible mechanisms by which neuronal damage develops. Lastly, I examined the possibility of offering neuro-protection to prevent the development of neuronal damage.

Incidence of acute seizures and malaria related seizures in children

To determine the incidence of acute seizures in the study area, we recruited all children aged 0-13 years presenting with incident admissions and acute seizures to Kilifi district hospital over a 2-year period. The population denominator was estimated from the census data of the study area. Seizures were reported in 900/4,921 (18.3%) children and at least 98 had status epilepticus. The incidence of acute seizures in children 0-13 years was 425/100,000/year and was 879/100,000/year in children <5 years. Over 80% of the
seizures were associated with infections. Neonatal sepsis (28/43 [65.1%]) and falciparum malaria (476/821 [58.0%]) were the main diseases associated with seizures, in neonates and in children 6 months or older respectively. Falciparum malaria was also the main illness associated with status epilepticus. Other illnesses associated with seizures included pyogenic meningitis, respiratory tract infections and gastroenteritis. The study concluded that malaria is the leading cause of acute seizures in children living in this area and that most of the important causes of the seizures are diseases that are preventable with available public health programs (chapter 2).

Using a retrospective data set of all admissions of children from the study area over a 13-year period from 1992–2004, we estimated that at a minimum, 1,156 children <5 years per 100,000 were exposed to brain insults from malaria annually. Involvement of the central nervous system was mostly characterised by seizures (incidence 911 per 100,000 per year). The incidence was lower in children older than 5 years[3]. This incidence data is an absolute minimum, since it does not account for children from the study area that did not attend Kilifi district hospital during the study period. From previous estimates, two thirds of deaths in children <5 years in this study area occurred outside the hospital. Although not investigated, the difference in incidence between the two studies suggests that there has been a decline in the incidence of acute seizures. This decline may partly be due to a reduction in the number of cases with malaria: although malaria was associated with 66.5% of seizures in Kilifi district hospital in 1996, over the years 2005–6, this had declined to 53.7%.

**Risk factors and precipitants of seizures in children with malaria**

The causes of seizures in children with falciparum malaria are not well understood. Apart from the epileptogenic nature of the parasite, my colleagues and I hypothesized that seizures in children with falciparum malaria occur in those with a genetic susceptibility to seizures and in particular children with either some common genetic traits in the tropics or single nucleotide polymorphisms in ion channels. The seizures may be precipitated by metabolic derangements or if co-infected with viruses and that the threshold for seizures is lowered by micronutrient deficiencies such as iron or zinc.

To examine these hypotheses, I compared the children with seizures described in chapter 2 to those admitted without seizures. In addition I used the large retrospective cohort of children with malaria admitted between 1992-2004 (chapter 4) to examine some risk factors for seizures. Malaria was the most common illness associated with acute seizures in children 6 months or older and was responsible for over 50% of all acute seizures in children. The median number of seizures in children with malaria was twice that in patients with other causes of seizures. In addition, seizures in children infected
with malaria were of a longer duration and status epilepticus was more common. Although seizures were observed even at low parasitaemia, the proportion of patients with seizures increased with parasitaemia. Children with seizures were older and were more likely to have had seizures in the past (chapters 2 and 4).

Genetic susceptibility to seizures is well recognised and a number of polymorphisms have been associated with the development of febrile seizures[4]. There are a number of polymorphisms that are common in tropical countries, which influence the presentation of falciparum malaria[5]. To determine the association between two very common genetic traits in tropical countries and the high incidence of acute seizures in this region, I examined the polymorphisms associated with the haptoglobin and \(\alpha\)-globin genes. The HP2-2 polymorphism of the haptoglobin gene has been associated with epilepsy and individuals with the \(\alpha\)-thalassaemia are thought to have an altered iron metabolism that may increase the risk of seizures. The proportion of cases and controls with the HP2-2 genotype was similar. Similarly, I found no difference between cases and controls in the proportions of children with deletions in the \(\alpha\)-globin gene. Among cases, the HP2-2 polymorphism and deletions in the \(\alpha\)-globin gene were neither associated with a change in the type, number or duration of the seizures nor did they affect the outcome of treatment (chapter 3). This study suggests that, unlike the idiopathic generalized epilepsies in which the HP2-2 genotype may be involved in the inheritance of the chronic seizure disorder, neither the HP2-2 genotype nor \(\alpha\)-thalassaemia are risk factors for acute seizure disorders.

Seizures and abnormal motor posturing in children with cerebral malaria

Cerebral malaria is the most severe neurological complication of falciparum malaria. Posturing is a common feature but the aetiology and pathogenesis of this sign is poorly understood. Raised intracranial pressure (ICP) is a recognized cause of posturing and raised ICP has been described in cerebral malaria in African children[6]. Seizures have also been described in over 60% of patients with acute non-traumatic encephalopathies and posturing. The hypothesis that posturing may be caused by seizures or is a manifestation of a seizure has led to the use of anticonvulsants in their management. There is little evidence to support this management. In chapter 5, we examined records of children with cerebral malaria to determine risk factors for posturing. Posturing was observed in 163(39.1%) patients and was associated with features of raised ICP on fundoscopy. In addition, decerebrate and opisthotonic postures were associated with recurrence of seizures. Among patients who died, the majority of deaths (19/31 [61.3%]) were associated with features suggestive of transtentorial herniation and in survivors, neurological sequelae were more common. The study suggested that raised ICP might
be the primary cause of posturing in children with cerebral malaria and the association with seizures may be due to raised ICP worsening perfusion to areas with already a critically compromised blood flow[7].

Continuous electroencephalographic monitoring and seizures in cerebral malaria
Seizures are a common feature of cerebral malaria in children and multiple seizures are a risk factor for poor outcome. Continuous EEG recordings in comatose patients in intensive care units have demonstrated a high incidence of non-convulsive seizures that may damage neurons. In this study, I examined the electroencephalographic (EEG) characteristics of 52 children with cerebral malaria on continuous EEG monitoring and related specific EEG features to outcome. The background EEG was characterized by very slow generalised high amplitude waves. One hundred and forty nine clinical seizures (40%) and 223 (60%) electrographic seizures were detected in 20 (38.5%) children. The majority had a focal origin. A higher frequency of the background EEG was associated with a shorter duration of coma while an asymmetrical background EEG, rhythmic runs and electrical status epilepticus were associated with death or neurological sequelae. The study concluded that children with cerebral malaria and convulsive status epilepticus experience frequent electrographic seizures and that electrographic status epilepticus is associated with poor outcome. Continuous EEG monitoring is a useful tool for the detection of such seizures and the acue EEG may be of prognostic value. This section ends with chapter 7, a detailed review of the published literature on cerebral malaria examining the clinical features, pathogenesis and neurological outcome.

Risk factors for long-term impairments after cerebral malaria and mechanisms of neuronal damage in malaria
In children who survive cerebral malaria, gross neurological deficits are detectable in 11% on discharge. Persistent neuro-cognitive impairments have been documented in 24% several years after exposure. In chapter 8, I determined the risk factors for these persisting impairments by examining hospital records of 143 exposed children assessed at least 20 months after discharge to detect motor, speech and language, and other cognitive impairments. I found that previous seizures, deep coma on admission, focal neurological signs observed during admission, and neurological deficits on discharge were independently associated with persisting impairments. In addition, multiple seizures were associated with motor impairment, age<3 years, severe malnutrition, features of raised ICP and hypoglycaemia were associated with language impairments while prolonged coma, severe malnutrition and hypoglycaemia were associated with impairments in other cognitive functions[8]. I concluded that although there are overlaps in impaired functions and in the risk factors for such impairments, the differences in risk
factors for specific functions might suggest separate mechanisms for neuronal damage. These factors could form the basis for future preventive strategies.

Biomarkers in cerebrospinal fluid (CSF) have been used to help delineate pathophysiological mechanisms, predict and monitor neurological outcomes and develop and evaluate new therapeutic strategies in human neurological disease. My colleagues and I determined levels of two markers of brain damage, the tau protein (as a marker of axonal injury) and S-100B (a marker of astrocyte injury), in the CSF of 143 Kenyan children with and without malaria and with different levels of consciousness (chapter 9). The level of tau in the CSF was significantly elevated in children with cerebral malaria compared with either malaria with prostration or malaria with seizures but normal consciousness[9]. Median levels of tau in children with cerebral malaria were 3-fold greater than previous reports in adults and may explain the higher prevalence of neurological sequelae in children[10]. Elevated S-100B in children was associated with an increased risk of recurrent seizures suggesting that the recurrent seizures after admission may be a manifestation of brain damage, rather than a cause of brain damage.

**Neuro-protection in children with cerebral malaria**

Although several poor prognostic factors have been identified for cerebral malaria in African children, protective factors are less well defined. Erythropoietin is protective in animal models of brain injury and administration of this compound in a murine model of cerebral malaria reduced mortality by 90%[11]. My colleagues and I hypothesized that the outcome of cerebral malaria is modified by the cytokine response to hypoxia, in particular to erythropoietin and that high plasma and CSF levels of erythropoietin protect children with cerebral malaria from developing neurological sequelae or death. In chapter 10, we retrospectively compared plasma and CSF levels of erythropoietin in 3 groups of children with cerebral malaria: children who died, those who survived with and without neurological deficits (n=124). The median plasma levels of erythropoietin were 123, 184 and 278 U/L respectively. Plasma erythropoietin >200U/L was associated with greater than 80% reduction in the risk of developing neurological sequelae. These data would support further study of erythropoietin as adjuvant therapy for children with cerebral malaria.

**Ongoing and future studies**

Some of our initial hypotheses were not tested and others are in the process of being examined in ongoing studies. I plan to investigate the association between micronutrient deficiencies in particular, iron deficiency and acute seizures in children. I will also investigate if viral co-infection of children with malaria increases the risk of acute seizures. In addition, I also intend to examine the relationship between acute
seizures and single nucleotide polymorphisms in ligand and voltage gated ion channels. Completion of these studies will provide a better understanding of the genetics of acute seizure disorders in the tropics and the interaction between genetics and environmental factors and the risk of acute seizure disorders.

Several observational and retrospective studies have documented recurrent seizures in children with cerebral malaria as a risk factor for neurological sequelae in surviving patients. What is not clear is whether the recurrent seizures cause the neurological damage or both the recurrent seizures and the neurological sequelae are manifestations of neuronal damage in patients with a more severe illness. If indeed it is the recurrent seizures that cause the sequelae, preventing seizure recurrence should reduce the number of children developing neurological sequelae. We hypothesized that a prophylactic dose of fosphenytoin given on admission to children with cerebral malaria will prevent both the recurrence of seizures and prevent neurological and cognitive impairments when compared to placebo. Recruitment into the trial is in progress. This trial has the potential to improve our understanding of the role of seizures in the causation of neuronal damage.

CONCLUSIONS

In conclusion, falciparum malaria is the leading cause of seizures in children living in malaria endemic areas. The characteristics of the seizures differ from simple febrile seizures to complex, focal, prolonged or multiple seizures and they are a major risk factor for neurological and cognitive impairments in children. The risk of seizures increases with parasitaemia but the role of genetic susceptibility in the development of malaria-related seizures is still unclear. Future studies examining the relationship between acute seizures and polymorphisms in ion channels and the role of prophylactic anticonvulsants in the prevention of seizure recurrences and neuro-cognitive impairments will aid our understanding of pathogenesis and the design of intervention strategies. It may also be possible in future to improve outcome with neuro-protective adjuvant therapies with drugs such as erythropoietin or its analogues.

REFERENCES


