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

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Chapter 1

General introduction
GENERAL INTRODUCTION

Epidemiology

Malaria is a major public health problem in many tropical countries. Of the four species that cause malaria in man, *Plasmodium falciparum*, which is transmitted by female anopheles mosquitoes, causes the most severe illness. Recent estimates indicate that worldwide, over 2 billion people are at risk of contracting malaria annually and in 2002, there were 515 million clinical episodes of acute falciparum malaria. The majority (70%) of these clinical events occurred in sub-Saharan Africa. South East Asia contributed 25% of the cases[1].

Although Africa accounts for the majority of cases of falciparum malaria, the distribution of malaria in this region is not uniform. The pattern is greatly influenced by the annual entomological inoculation rate (the number of infected mosquito bites per person per year)[2] which in turn is influenced by climatic factors[3] and land use[4]. About 75% of the population in sub-Saharan Africa lives in areas with stable malaria transmission where children under the age of 5 years are most at risk and 18% live in areas where transmission is seasonal and unstable such that all age groups are vulnerable to infection and disease. Such areas are prone to malaria epidemics.

Severe malaria

The majority of clinical episodes of falciparum malaria are uncomplicated. In African children under the age of 5 years, 1 out of every 100 clinical episodes may progress to severe and complicated disease often, within 48 hours of fever onset[5] such that between 25–40% of paediatric admissions to hospitals in malaria endemic areas are due to malaria. Children with severe malaria may present with life threatening complications such as impaired consciousness, severe anaemia or severe metabolic acidosis. Other features include repeated seizures, prostration, hypoglycaemia and shock (table I).[6] Children with these severe features have a mortality >5%. It is estimated that at least one million deaths occurring in children living in sub-Saharan Africa are a result of the direct effects of falciparum malaria. Deaths are particularly common among children who develop impaired consciousness, respiratory distress, shock or hypoglycaemia[6].

Among survivors, gross neurological deficits have been observed in those admitted with recurrent and prolonged seizures, repeated episodes of hypoglycaemia or prolonged and deep coma[8, 9]. More recently, severe malaria in children has been associated with deficits in cognition (memory, attention, executive functions, speech and language), behavioural disorders[10-13] and subsequent epilepsy[14, 15].
The manifestations of severe malaria in children in endemic areas is dependent on age and transmission intensity[16]. In areas of intense transmission, infection and clinical disease are rare until about 6 months. Symptoms are mild as a result of the passive immunity offered by maternal antibodies. The highest disease burden is borne by children in their first two years of life and by four years, they experience few clinical episodes. In areas with less intense transmission, the peak incidence of severe disease falls at a later age[17]. Repeated infections over several years provide protection against disease. Immunity is effective but partial and declines in the absence of continuous exposure.

Neurological involvement in falciparum malaria

Falciparum malaria appears to have a particular propensity to involve the brain in children. Many children are brought to hospital with seizures, confusion, prostration, impaired consciousness and/or coma. Seizures are the most frequent manifestation of central nervous system (CNS) involvement[18]. In those with cerebral malaria, seizures may manifest as convulsions, have subtle features like noisy breathing or only be detected by electroencephalographic monitoring[19]. Brainstem signs and abnormalities of posture, tone and reflexes are also observed[20, 21]. However, apart from cerebral malaria, the features of CNS involvement in acute falciparum malaria have not been systematically described. It is also not known why some children develop CNS disease and others do not.

Risk factors and precipitants of seizures in falciparum malaria

Up to 20% of children admitted to some district hospitals in sub-Saharan Africa may have a history of seizures. Infection with falciparum malaria is an important cause

<table>
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<td><strong>Clinical manifestations and laboratory findings</strong></td>
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(Adapted from WHO 2000)[7]
of admission to hospitals and malaria is thought to be the primary diagnosis in the majority of children admitted with seizures[22-24]. Although most children who present to hospital with seizures have *P. falciparum* parasitaemia, in an endemic area where asymptomatic parasitaemia is common, it is unclear if malaria causes these seizures or there are other factors that precipitate them. A greater proportion of seizures are complex (focal, prolonged or multiple) when compared to simple febrile seizures despite occurring in the context of a febrile illness[24]. Parasite and host factors may be important underlying risk factors. Specific alleles, mutations and polymorphisms may be risk factors. It is possible that seizures are precipitated by co-infection with viral infections[25] and the seizure-threshold and frequency modulated by specific micronutrient deficiencies[26].

**Outcome of seizures, mechanisms of neuronal damage and neuro-protective therapy**

Earlier studies suggested that recovery from cerebral malaria is almost complete[27] but recent data suggest otherwise. Multiple and prolonged seizures are associated with increased mortality and neurological and cognitive deficits. Neurological assessments performed after discharge have indicated that most deficits thought to arise from mild degrees of ischaemia like blindness, ataxia and paresis may be transient and resolve over a 6-month period[8] but long-term neurological and cognitive impairments are common. These include spasticity, epilepsy, hearing, language, memory, and learning impairments. It is estimated that, over 20% of children who survive cerebral malaria may have persistent impairments. These deficits are not only limited to cerebral malaria but also follow other features of CNS involvement such as malaria with multiple seizures[12]. The risk factors for such persistent impairments are unknown yet identifying them may allow early initiation of interventions for patients at risk. This is particularly critical in centres across Africa where assessments to detect neuro-cognitive impairments are either poorly developed or non-existent.

The mechanisms by which neuronal damage develops are also poorly understood. Studies that have examined the role of neuro-protection[28] and adjuvant therapies[29, 30] aimed at improving outcome have been disappointing. There is need for a clearer understanding of the pathogenesis of neuronal damage and for a study of other adjuvant and neuro-protective therapies.
Hypotheses
In this thesis, I have examined the following hypotheses:
1. Seizures are the most common feature of central nervous system involvement in children with acute falciparum malaria.
2. Seizures in children with acute falciparum malaria are associated with specific haptoglobin genotypes and deletions in the α-globin gene (α-thalassaemia).
3. Seizures in cerebral malaria may manifest as convulsions, tonic posturing or only be detected by continuous electroencephalographic monitoring.
5. Erythropoietin may be associated with an improved neurological outcome of children with cerebral malaria.

Studies conducted
To answer these questions, I undertook a series of studies at the Kenya Medical Research Institute/Wellcome Trust - Centre for Geographic Medicine Research – Coast in Kilifi, Kenya. The patients described in the thesis attended Kilifi District Hospital and came from the hospital’s catchment area – a well mapped area that undergoes regular census and has a population of about 230,000[31], (figure 1).

Figure 1  Kilifi Demographic Surveillance study (DSS) area

A map of the study area (marked DSS) in Kilifi District, Kenya
The results of these studies are presented in chapters 2 to 10. Chapter 2 provides the incidence and a description of the aetiological risk factors for acute seizures in the Kilifi demographic surveillance area. In chapter 3, I examined the relationship between common host polymorphisms in malaria endemic areas and acute seizures. Chapter 4 is an estimate of the burden and a description of the features of CNS involvement in children with acute falciparum malaria. Chapter 5 examines the relationship between abnormal motor posturing and seizures in children with cerebral malaria while chapter 6 describes electroencephalographic features of cerebral malaria on continuous monitoring. In chapter 7, we review the published literature of the clinical presentation, pathogenesis and neurological outcome of cerebral malaria. In chapter 8, I examined the risk factors for long-term deficits following cerebral malaria and in chapter 9, some of the mechanisms involved. Chapter 10 describes the potential of erythropoietin as a neuro-protective therapy for cerebral malaria. Lastly, I summarised the findings and suggested further studies, some of which my colleagues and I have started.

REFERENCES


