Chapter 86

Epilepsy Associated with Malaria

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Introduction

There are now five recognised species of *Plasmodium* that naturally infect humans, but only *P. falciparum* is associated with epilepsy, although seizures are reported during *P. vivax* infections. Falciparum malaria is the most severe form of malaria and is responsible for most of the neurological complications, since the infected erythrocytes adhere to the endothelium of the brain.

Epidemiology of Malaria

It is estimated that over 1 billion persons live in areas with exposure to malaria-carrying mosquitoes. The World Health Organization estimated that in 2015 there were 214 million clinical episodes of malaria, with about 438 000 deaths [1]. The incidence fell by 37% from 2000 to 2015, with 88% of cases occurring in Africa, mainly in young children living in sub-Saharan Africa. There are differences in the clinical presentation between African children and non-immune individuals, i.e. people not living in endemic areas, although the age at which children present with cerebral malaria (CM) in endemic areas has increased [2].

Pathogenesis of Malaria

The erythrocyte stages of *P. falciparum* are responsible for the acute symptoms including the neurological symptoms and the development of epilepsy. *P. falciparum* is different from the other species of malaria in that the late stages of the erythrocytic cycle, i.e. schizonts, sequester within the vascular beds of the internal organs, with a particular propensity for the brain. The infected erythrocytes adhere to the post capillary venules via parasite-derived proteins exported to the erythrocyte surface that attach to ligands upregulated in the endothelium. This sequestration stimulates mediators such as cytokines and nitric oxide, causing microvascular obstruction leading to a reduction in the perfusion of brain tissue. However, frank ischaemia is rarely documented in falciparum malaria, since most patients recover without any evident sequelae.

Manifestations of Falciparum Malaria

The manifestations of severe falciparum malaria include coma, seizures, severe anaemia, metabolic acidosis, and, in non-immune individuals, renal impairment and pulmonary oedema. CM is the most severe neurological complication. It is a diffuse encephalopathy, characterised by coma, decorticate or decerebrate posturing, and occasionally brain-stem signs. Malaria retinopathy is a pathognomonic feature in African children [3], and is documented in non-immune individuals. The brains of people dying with CM are often swollen (particularly African children) and grey (from haemozoin, the pigment produced by the breakdown of haemoglobin by the parasite), and the cut surfaces reveal petechial haemorrhages throughout the brain. Microscopically, the pathological hallmark is sequestration of the infected erythrocytes within the venules of the brain (Figure 86.1). There are two types of haemorrhages, petechial and ring haemorrhages. The petechial haemorrhages consist of normal erythrocytes surrounding a ruptured cerebral vessel, appear more common in the white matter, and are associated with sequestration. The ring haemorrhage is unique to malaria, since it consists of infected erythrocytes, pigment, and monocytes surrounding a layer of uninfected erythrocytes and gliosis, encircling a central thrombosed vessel. Durck's granulomata are seen in patients (particularly adults) who have died following a prolonged illness. These are circumscribed cellular reactions scattered throughout the brain, and may represent the residue of ring haemorrhages.

Seizures are common during the acute infection in children, and can occur in association with CM or in non-comatose patients. They are less common in adults. Over

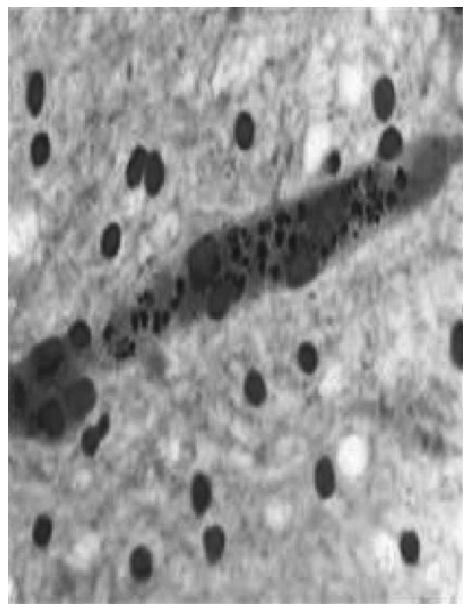

Figure 86.1 Histological section of the brain of a patient who died of cerebral malaria, showing sequestration of the parasitised erythrocytes in a cerebral venule.

https://doi.org/10.1017/9781108355209.088 Published online by Cambridge University Press

80% of African children with CM present with a history of seizures, and about 60% have seizures during the admission. Status epilepticus occurs in about 28% of children with CM and this is associated with neurological sequelae [4]. The cause of acute seizures in falciparum malaria is unclear. Since falciparum malaria is the most common cause of fever in children aged between 6 months and 6 years in endemic areas, the seizures are often classified as febrile seizures. However, in contrast to febrile seizures not associated with malaria, the seizures associated with malaria tend to be repetitive, focal, and often prolonged [5].

Epilepsy and Malaria

Although a case series of malaria and epilepsy was first reported in the 1940s [6], only recently have epidemiological studies demonstrated the association between falciparum malaria and the development of epilepsy. The first study that reported an association was conducted in Kenyan children who had had CM or malaria with complicated seizures [7]. Of the children who had CM or complicated seizures during their acute illness, 9% and 12% had developed epilepsy 2–9 years later, i.e. there was a significantly increased risk of developing epilepsy following CM (9.2%; OR 4.4, 95% CI 1.4–13.7) or malaria + seizures (11.5%; OR 6.1, 95% CI 2.0–18.3) compared with the unexposed group (2.2%), respectively. These initial observations have been confirmed in four subsequent studies of African children in: (i) Mali, the incidence of epilepsy was 17.0 per 1000 person-years following CM, with a relative risk 14.3 (95% CI 1.6–132.0), after adjusting for age and duration of follow-up [8]; (ii) Gabon, the OR of epilepsy was 3.9 (95% CI 1.7–8.9) in children with a history of CM [9]; (iii) Uganda, where 16.2% developed epilepsy during a 2-year follow-up period [10]; and (iv) Malawi, where 12 of 132 CM survivors followed up for a median of 17 months developed epilepsy compared with none of the controls (OR undefined; $p < 0.0001$) [11]. In a meta-analysis of these studies, CM was associated with an increased risk of epilepsy (OR 4.68, 95% CI 2.52–8.70) [12].

In a multi-centre study of active convulsive epilepsy conducted in five African countries, high titres of antibodies to malaria schizonts were associated with active convulsive epilepsy (OR 1.27, 95% CI 1.04–1.56) on the univariate analysis, but not when the analysis was adjusted for age, sex, study site, education (none, primary, or secondary and above), employment, and marital status [13]. However, the combination of the presence of antibodies to *P. falciparum* and *Toxoplasma gondii* (OR 11.66, 95% CI 1.48–91.53), *Toxacara canis* (OR 3.63, 95% CI 1.14–11.47), and *Onchoceria volvulus* (OR 3.81, 95% CI 1.29–11.17) was associated with active convulsive epilepsy in this study, further confirming the epileptogenic role of *P. falciparum.*

The epilepsy documented in these epidemiological studies and case series are characterised by both generalised and focal seizures. In the seizures that occur following recovery from CM, 40 to 66% are generalised seizures, with the remainder focal or partial with secondary generalisation. Complex partial seizures are infrequently reported from series of African children, but this may be caused by difficulties in describing the semiology in this patient group. Complex partial seizures have been reported in case reports of epilepsy following CM in non-immune travellers [14].

The seizures may start from a month after the episode of CM, but there is a wide time interval [7–9,11] and the cumulative incidence is likely to increase with longer follow-up [10]. The frequency of seizures in the African studies varied considerably from one per week to less than one in the last 2 years. Most of the children with epilepsy in these studies were not on treatment at the time of assessment [7–9,11]. There are no comparable studies following adults exposed to CM.

EEG abnormalities occur in about a third of the African children with epilepsy following CM [7–9,11]. Focal features, e.g. slowing, are the most common, with only a quarter having epileptiform abnormalities. Discharges over the temporal lobe are recorded in only a few patients.

In most of the African children who develop epilepsy following falciparum malaria, there are few reports of the neuroimaging findings. CT identified cerebral atrophy in some patients [15]. Magnetic resonance imaging demonstrated hippocampal sclerosis in one adult [14], but studies in patients with epilepsy have not been reported.

The epilepsy in Kenyan children, particularly the active epilepsy, was associated with other neurological deficits such as hemiparesis and quadriparesis. Behavioural problems, e.g. attention deficit disorder and cognitive impairment, appear to be more common in children with active epilepsy.

Epileptogenesis of Falciparum Malaria

The cause of epilepsy following falciparum malaria is unknown. Since complicated seizures during the acute episode have similar features to complex febrile seizures, the mechanisms by which these cause epilepsy may be similar. In particular, hippocampal damage following seizures associated with high body temperature in children, particularly if prolonged, may be important.

Several interacting mechanisms could be responsible. The most likely are vascular or ischaemic damage, secondary to microvascular obstruction [16], although ischaemic lesions are detected in only a few adults with severe malaria [17,18]. Family history of seizure disorders is more common in children who develop seizures during acute malaria than those who do not have seizures, suggesting that genetic predisposition may contribute to the epilepsy [19]. An increase in excitotoxins, particularly quinolinic acid and glutamate, have been measured in the cerebrospinal fluid of patients during the acute illness [20,21]. Antibodies against voltage-gated channels are increased during the acute infection and this may lead to epilepsy [22].

Management of Epilepsy

Most patients who develop epilepsy following severe malaria respond to first-line AEDs, such as phenobarbital, phenytoin, and carbamazepine; these are the AEDs most commonly used in resource-poor countries. During the acute illness, the control of

https://doi.org/10.1017/9781108355209.088 Published online by Cambridge University Press

seizures appears to be relatively resistant to benzodiazepines, perhaps because falciparum malaria down-regulates the GABA receptors [23]. However, this latter finding is unlikely to affect the control of seizures in patients with epilepsy following severe malaria. The epilepsy following malaria is often associated with considerable co-morbidity, particularly behavioural and neurocognitive impairment in children [7,11]. The epilepsy appears relatively easy to treat with standard AEDs, although a few patients may require more aggressive treatment, including surgery. In an adult who developed mesial temporal lobe epilepsy following CM, anteromedial temporal lobe resection with amygdalohippocampectomy stopped the seizures for at least 3 years postoperatively [14].

Antimalarial Drugs and Epilepsy

Antimalarial drugs are used to prevent and treat malaria. There are many case reports and case series that have suggested that antimalarial drugs are associated with increasing seizure frequency in patients with epilepsy or with precipitating seizures in those without epilepsy [24]. However, there are not any carefully conducted studies reported to establish the association.

The aminoquinolones, such as chloroquine and mefloquine, are contraindicated in patients with epilepsy, based upon a number of case reports. Mefloquine is used as chemoprophylaxis but has been reported to increase seizure frequency in people with epilepsy as well as precipitate seizures in people without epilepsy or predisposing neurological conditions [24,25].

The safest and most effective chemoprophylaxis for people with epilepsy is the atovaquone/proguanil combination [24], although for travellers, the suitability of this combination for the area of travel should be checked with an authoritative source. Doxycycline (100 mg daily), which is often prescribed as an alternative chemoprophylactic agent, is less efficacious than atovaquone/proguanil. Furthermore, since AEDs such as carbamazepine, phenytoin, and phenobarbital may increase the metabolism of doxycycline, the dose should be doubled (100 mg bd) for patients on one of these AEDs. Other drugs such as proguanil alone or pyrimethamine/dapsone are less effective in preventing malaria, but may be useful in some areas. Prevention of being bitten by infected mosquitoes with bed nets and suitable clothing in the evening reduces the risk considerably.

Falciparum malaria is likely to be a major cause of epilepsy in Africa and Asia, but the contribution of other species of malaria, e.g. *P. vivax*, is undetermined. The pathogenesis remains unclear, although it is likely to arise from different mechanisms interacting with genetic susceptibility. Further neuroimaging studies may provide insights. Prevention of seizures during the acute illness may prevent the onset of epilepsy. The epilepsy associated with falciparum malaria is easily controlled on standard AEDs, and the choice of antimalarials in people with epilepsy needs careful consideration.

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https://doi.org/10.1017/9781108355209.088 Published online by Cambridge University Press

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