REVIEW

NEUROLOGICAL COMPLICATIONS OF MALARIA

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Abstract. This paper reviews the neurological complications of malaria. Cerebral malaria, the acute encephalopathy which complicates exclusively the infection by *Plasmodium falciparum* commonly affects children and adolescents in hyperendemic areas. Plugging of cerebral capillaries and venules by clumped, parasitized red blood cells causing blood sludging in the capillary circulation is one hypothesis to explain its pathogenesis. The other is a humoral hypothesis which proposes a nonspecific, immune-mediated, inflammatory response with release of vasoactive substances capable of producing endothelial damage and alterations of permeability. Cerebral malaria has a mortality rate up to 50%, and also a considerable longterm morbidity, particularly in children. Hypoglycemia, largely in patients treated with quinine, may complicate the cerebral symptomatology. Other central nervous manifestations of malaria include intracranial hemorrhage, cerebral arterial occlusion, and transient extrapyramidal and neuropsychiatric manifestations. A self-limiting, isolated cerebellar ataxia, presumably caused by immunological mechanisms, in patients recovering from falciparum malaria has been recognized in Sri Lanka. Malaria is a common cause of febrile seizures in the tropics, and it also contributes to the development of epilepsy in later life. Several reports of spinal cord and peripheral nerve involvement are also available. A transient muscle paralysis resembling periodic paralysis during febrile episodes of malaria has been described in some patients. The pathogenesis of these neurological manifestations in malaria remains unexplored, but offers excellent perspectives for research at clinical as well as experimental level.

INTRODUCTION

Malaria is rising again as the most important parasitic disease in the world. Several factors have been responsible for this resurgence: first, resistance of the parasite to antimalarial drugs and of the arthropod vectors to insecticides; second, socio-economic factors which have resulted in migration, irrigation, deforestation, and also violence and warfare which have forced populations into new areas and have prevented the implementation of malaria control campaigns. Malaria can be a life-threatening disease with involvement of many organs and systems. In this review, however, we focus on the neurological complications.

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CEREBRAL MALARIA

Cerebral malaria is an acute encephalopathy that complicates exlusively the infection by *Plasmodium falciparum*. Reported frequencies of cerebral malaria in malarial infections vary from 0.01% to 16% (Osuntokun, 1983). It affects children and young adults in hyperendemic areas, and also nonimmune adults traveling from non-endemic areas, commonly when preventive treatment is interrupted. Pregnant women are at risk because of the decreased immunity during pregnancy. There is serious concern that acquired immune deficiency syndrome (AIDS) may predispose to cerebral malaria in the tropics (Smith *et al*, 1988), although in a recent study in Zaire malaria was not more frequent or more severe in children with progressive human immunodeficiency virus type I (HIV-I) infection (Greenberg *et al*, 1991).

Pathophysiology

Macroscopically, the most striking findings are moderate cerebral edema and diffuse petechial hemorrhages preferentially involving the white matter of brain at autopsy (Toro *et al,* 1983). Some degree of slate-grey discoloration of the cerebral cortex due to malarial pigment (hemozoin) is present. Microscopically, these petechial hemorrhage show the typical appearance of ring hemorrhages occurring predominantly around white matter arterioles, the sine qua non of cerebral malaria. These are most likely the result of an immune mediated vasculopathy leading to alteration of endothelial permeability, perivascular edema, diapedesis of leukocytes and erythrocytes, necrosis of the vessel wall and intravascular microthrombosis (Toro and Roman, 1978). Perivascular demyelination and intravascular aggregates of parasitized erythrocytes and thrombosis of capillaries have also been reported (Aikawa, 1988).

The pathogenesis of cerebral malaria remains an unsolved riddle (Roman, 1991). Observations by Marchiafava and Bignami, nearly a century ago, of plugging of cerebral capillaries and venules by clumped, parasitized red blood cells, as well as demonstration of blood sludging in the capillary circulation in malarial infections (Knisely, 1941) have provided the basis for a "mechanical" hypothesis. Erythrocytes containing mature tropozoites and schizonts tend to be sequestered in deep vascular beds where they stick to endothelial cells. This cytoadherence is associated with knobs which protrude from the surface of parasitized red cells (Trager, 1966; Luse and Miller 1971). The knobs are derived from the parasite plasmalemma and transported to the erythrocyte membrane via clefts in the erythrocyte cytoplasm (Aikawa, 1988). Attachment of knobs on endothelial cells surface receptors is probably mediated by host molecules such as OKM5 and thrombospondin (Roberts *et al,* 1985; Rock *et al,* 1988). Apparent support for the mechanical hypothesis is provided by the demonstration that dexamethasone provides no benefits in terms of outcome in the treatment of cerebral malaria (Warrell *et al,* 1982). Lack of response to corticoids was interpreted either as an indication that damage of the blood-brain barrier with vasogenic edema is not a major pathogenic element (Warrell *et al,* 1986), or that the role of inflammation mediated by cytokines or free oxygen radicals is limited and unaffected by dexamethasone treatment.

The "humoral" hypothesis is based on the fact that most pathogenic mechanisms in mammalian malaria are nonspecific, immune-mediated, inflammatory responses with release of vasoactive substances capable of producing endothelial damage and alterations of permeability. It has been demonstrated that obstruction of cerebral circulation occurs before plugging of the cerebral vessels by high parasitemia (Maegraith and Fletcher, 1972). In a murine model of cerebral malaria, it has been shown that tumor necrosis factor (TNF), a cytokine produced primarily by activated macrophages and T lymphocytes, is essential for development of lesions in mice (Grau *et al,* 1987). Serum TNF concentrations were found to be significantly increased in children dying with cerebral malaria, and as the concentrations of TNF increased, so did the mortality rate. TNF increases were also associated with hypoglycemia, hyperparasitemia, age under 3 years, and more severe illness (Grau *et al,* 1989). Serum TNF concentrations also correlate with malarial parasite density and the patient's temperature (Butcher *et al,* 1990). Early lesions of endothelial cells, basal lamina, and astrocytes resulting in damage of blood-brain barrier, probably due to TNF effect, has recently been described in the murine model (Polder *et al,* 1991a). Morphological changes consistent with pathologic spastic constriction of intracerebral arterioles in clinical and experimental cerebral malaria further support a central role of the arteriole in the pathogenesis of cerebral malaria (Polder *et al,* 1991b). Neither mechanical obstruction nor isolated immune responses by themselves are capable of explaining the pathogenesis of cerebral malaria; the answer, very likely, will be found in the interaction of these elements.

A study of Kenyan children with cerebral malaria which demonstrated raised cerebrospinal fluid (CSF) pressure at lumbar puncture has recently drawn attention to the importance of intracranial hypertension in the pathophysiology of cerebral malaria (Newton *et al,* 1991b). Increased blood volume due to sequestration of large numbers of malaria-infected erythrocytes in the cerebral microvasculature and the vasodilatory effect of lactate produced by the parasites, rather than cerebral edema, has been suggested as the cause of

the raised CSF pressure in these children (Newton *et al,* 1991a). A computed tomography study of the brain in 10 Thai patients with severe cerebral malaria showing evidence of cerebral edema in only 2 fatal cases (Looareesuwan *et al,* 1983b) would also be in keeping with the argument that cerebral edema is unlikely to be the cause of the intracranial hypertension in these patients. But, there are contrary views. Any increased blood volume in cerebral malaria would be generalized-involving the entire brain, including the brain-stem - and would not result in uncal herniation. Thus a much more likely cause of the intracranial hypertension would be cerebral edema (Poser and Roman, 1991), consequent to alteration in the blood-brain barrier (Toro and Roman, 1978). The magnetic resonance appearance of the brain in cerebral malaria has not yet been published. On the basis of pathological changes, however, it is likely that increased areas of signal intensity of T2 weighted images will confirm the alteration of the blood-brain barrier and the presence of edema of cerebral white matter (Poser and Roman, 1991).

Clinical manifestations

Cerebral malaria may present abruptly or develop as a late complication in the progressive worsening of falciparum malaria with multisystem involvement. Typically, the patient presents with fever, severe headache, and delirium progressing to an acute febrile stupor, with hyperthermia reaching 40°C to 42°C. There is rapid worsening from stupor to coma with fluctuations.

Decerebrate and decorticate rigidity may occur. Fundi may show retinal hemorrhages. Generalized seizures occur in about 40% of adult patients and in most children. Partial seizures may occur, and transient focal neurological signs are occasionally seen. Tendon reflexes and muscle tone are variable; brisk reflexes, extensor plantar responses, and ankle clonus may be elicited in half the patients; areflexia is a poor prognostic sign. Cutaneous and abdominal reflexes are usually absent. Neck rigidity is frequent, and the Kernig's sign may be positive. Other forms of presentation of cerebral malaria include a clinical picture of psychomotor agitation and delirium which may resemble acute alcohol intoxication, Wernicke encephalopathy or an acute psychotic episode.

Diagnosis

Cerebral malaria must be differentiated from other causes of stupor and coma in the tropica. A lumbar puncture should be done to exclude conditions such as meningitis (Kwiatkowski *et al,* 1991; Greenwood, 1991), but the potential risks and benefits of lumbar puncture should be considered carefully (Newton *et al,* 1991a,b). If lumbar puncture is delayed, the possibility of pyogenic meningitis must be covered by giving an appropriate broad-spectrum antibiotic in adequate dosage (Greenwood, 1991). In cerebral malaria, CSF contains a few lymphocytes and a slight increase in protein content in half the patients. The opening pressure may be normal or increased, higher pressures being observed in severe and fatal cases (Newton *et al,* 1991a,b; Kwiatkowski *et al,* 1991). A presumptive diagnosis can be made by demonstrating malarial parasites in peripheral blood. The degree of invasion of the peripheral red cells by falciparum tropozoites cannot always be correlated with the severity of the cerebral involvement. Therefore, it is important to treat the patient on clinical suspicion alone.

Treatment

Treatment should be started as soon as possible, since there is a highly significant correlation between delayed chemotherapy and mortality. In localities such as Sri Lanka chloroquine resistance is not common, iv chloroquine may be used, and the regimen recommended for adults is: (i) a loading dose of chloroquine 10 mg base/kg diluted in approximately 500 ml of isotonic saline or 5% dextrose infused at a constant rate over at least 4 hours, and (ii) maintenance dose of 5 mg base/kg infused over 2 to 4 hours at 12-hour intervals to a total dose of 25 mg base/kg (WHO Malaria Action Programme, 1986). In chloroquine resistance, treatment should be started with iv quinine with a loading dose of 20 mg quinine dihydrochloride (16.7 mg base)/kg diluted in about 500 ml of isotonic saline or 5% dextrose, infused at a constant rate over 4 hours. If the patient has taken quinine within the previous 2 days, a loading dose should not be given but 10 mg of the quinine salt (8.3 mg base)/kg should be diluted in about 500 ml of isotonic saline or 5% dextrose, infused at a constant rate over 4 hours.

The subsequent maintenance dose is 10 mg salt/kg given 8 hourly until patients can swallow tablets. At least 7 days treatment should be completed with quinine tablets (approximately 8.4 mg/kg 8 hourly) (WHO Malaria Action Programme, 1986). Deep intramuscular injections may be given if intravenous treatment is impossible. Quinidine may prove as a useful alternative where quinine is not available. Intravenous amodiaquine is a potentially valuable drug for the treatment of severe chloroquine-resistant falciparum malaria. Mefloquine, another antimalarial, is too irritant to be given by injection, and nasogastric administration cannot be recommended in severe disease if parenteral formulations of other quinoline antimalarials to which the parasites are sensitive are available (WHO Malaria Action Programme, 1986). Treatment with artemesinine dervatives from *Artemisia annua L.* appears promising in reducing the mortality of severe falciparum malaria because of their speed of action (Guoqiao *et al,* 1982).

The patient must be in bed to avoid postural hypotension. Hypoglycemia should be corrected and monitored frequently. Corticosteroids cannot be recommended because their use is accompanied by increased mortality (Warrell *et al,* 1982). Fever should be controlled with acetaminophen and physical means. Aspirin should not be used because of its antiplatelet effects. Anemia should be corrected with packed red cells. Appropriate fluid and electrolyte balance is mandatory. Metabolic acidosis due to hypotension and shock should be corrected. A single intramuscular injection of phenobarbitone (3.5 mg/kg) is effective in preventing seizures in cerebral malaria (White *et al,* 1988). Gram-negative sepsis is common in patients with severe malaria, and appropriate antibiotic therapy should be considered (Bradley, 1987).

Prognosis

Mortality rates of cerebral malaria in children, reported mainly from African countries, vary from 6% to over 50% (Molyneux *et al,* 1989). It also causes considerable longterm morbidity, particularly in children, up to 21% of patients reported to having neurological sequelae (Brewster *et al,* 1990). In a study of 308 Gambian children, the mortality rate was 14%. Of those who survived, 32 (12%) had residual neurological deficits, the commonest being hemiplegia (23 cases), cortical blindness (11), aphasia (9), and cerebellar ataxia (6). Factors predisposing to sequelae included prolonged coma, protracted convulsions, and severe anemia. The possibility of some of the children who made a good recovery having subtle neurological defects such as intellectual impairment cannot be discounted (Brewster *et al,* 1990).

OTHER CEREBRAL MANIFESTATIONS

Intracranial hemorrhages

Cerebral hemorrhages causing focal neurological signs such as hemiplegia and aphasia are known to occur in association with malaria. Paralysis associated with cerebral hemorrhage has been described in a rodent model of malaria (Grau *et al,* 1987). In this model the mechanism is immunopathological, and TNF seems to be a critical mediator. A single case of subarachnoid hemorrhage has been reported. He also had numerous retinal hemorrhages (Murugavel *et al,* 1989). Retinal hemorrhages are an important sign of prognostic significance in cerebral malaria (Looareesuwan *et al,* 1983a).

Cerebral arterial occlusion

Some of the focal neurological signs complicating cerebral malaria have been shown to be due to arterial occlusion (Brewster *et al,* 1990). In an unusual case of malaria which presented like a cerebral tumor, the postmortem examination revealed thrombosis of individual brainstem vessels and perivascular hemorrhages in the cerebellar cortex (Vietze, 1978).

Extrapyramidal manifestations

Extrapyramidal manifestations may be seen in association with cerebral malaria, some as late sequelae. Clinical syndromes reported include tonic-dyskinetic posturing, myoclonia, chorea, and athetoid movements. Even Parkinson's syndrome with its typical posture, facies and tremor has been observed during convalescence (Vietze, 1978). Three patients with falciparum malaria reported from India developed cog-wheel rigidity, coarse tremor at rest, and slowness of movements. The signs disappeared completely in 1 to 2 weeks

(Arya *et al,* 1989). In Sri Lanka, 2 patients, one aged 3 months and the other 45 years, presented with fever and choreoathetoid movements. Both had ring stages of *P. falciparum* in the peripheral blood. The baby recovered completely following antimalarial therapy, while the other developed cerebral malaria (Wijesundere, 1988).

Opsoclonus - a spontaneous chaotic multivectorial conjugate saccadic eye movement disorder– and hand tremor have been reported in a patient during the course of *P. falciparum* infection (Poungvarin and Praditsuwan, 1990). Opsoclonus is due to dysfunction of the pause cells in the pons as a result of cerebellar or brainstem disease, the most frequent causes being viral or postviral encephalitis, as well as toxic, metabolic, and paraneoplastic disorders (Lavin, 1991).

Benign intracranial hypertension

A report is available of a young African woman with resistant malaria who presented with typical features of raised intracranial pressure including bilateral florid papilledema, diagnosed as benign intracranial hypertension (Okelo, 1985).

Neuropsychiatric manifestations

In cerebral malaria, acute psychiatric disturbances including schizophrenic-like and manic syndromes, depression of the exogenous or endogenous types, acute malignant anxiety, amok and confusional states, hallucinatory delirium, amnesia, twilight states, have been described (Vietze, 1978). In 6 Indian patients who presented with acute personality disorders, some of the manifestations were disorientation, hysterical features, paranoid ideas, hallucinations, aggressive behavior, and depression. All the patients had *P. falciparum* in the peripheral blood which was treated with antimalarial drugs. The psychiatric features completely resolved in about 4 weeks (Gopinathan *et al,* 1982). In Sri Lanka, 2 patients aged 14 and 55 years, 1 week after recovery from *P. falciparum* infection developed acute psychotic manifestations including hyperactivity, insomnia, mania, depression, and anxiety. The older patient responded to chlorpromazine, benzhexol, diazepam, and imipramine. The other patient was thought to have chloroquine psychosis (Wijesundere, 1988). Although there is no evidence of a specific malarial psychosis, the organic nature of the malarial psychoses has been well established. The occurence of schizophrenia-like conditions may indicate malaria triggering off a latent endogenous psychosis (Vietze, 1978).

HYPOGLYCEMIA

Some patients with falciparum malaria develop hypoglycemia, causing coma, decerebrate posturing and seizures. Up to 52% of African children (White *et al,* 1987) and about half the pregnant women with falciparum malaria treated with quinine (Looareesuwan *et al,* 1985) have been found to have hypoglycemia. Pregnant women with mild malarial infections can become hypoglycemic without symptoms, but have severe fetal distress or even death in utero (Phillips, 1989). The hypoglycemia may develop hours, or even days after admission (Taylor *et al,* 1988). In the pathogenesis, quinine-induced hyperinsulinemia is probably the principal mechanism (White *et al,* 1983). Consumption of glucose by the parasite, and increased peripheral utilization of glucose may be contributory (Phillips, 1989).

Clinical features characteristic of hypoglycemia, such as tremulousness, sweating, mydriasis, and tachycardia may not be present (Phillips, 1989). Hypoglycemia must be suspected and specifically excluded by performing a blood glucose estimation in any patient who has fits, impaired consciousness or unexplained neurological symptoms or signs. Intravenous dextrose corrects hypoglycemia in children without difficulty (Taylor *et al,* 1988). In quinine-treated adults, hyperinsulinemia may cause recurrent hypoglycemia despite continuous infusion of dextrose. A somatostatin analog SMS201/995 has proved effective in Thailand (Phillips *et al,* 1986).

DELAYED CEREBELLAR ATAXIA

Cerebellar involvement is a known but rare feature in malaria which has generally been considered a part of a global encephalopathy associated with cerebral malaria (Illangasekera and De Silva, 1976; Chitkara *et al,* 1984). A syndrome of isolated cerebellar ataxia following falciparum malaria has been recongized in Sri Lanka in otherwise well, conscious patients, with no featu-

res of cerebral malaria. The ataxia occurs as the fever subsides, usually after an afebrile period of 2 to 4 days. The delay between onset of fever and the ataxia is 3 to 4 weeks. Unsteadiness on walking is the first and the most noticeable symptom. The disability is maximum on the second or the third day, but in some cases the symptoms progress up to 2 weeks. Some patients may be bedridden because of the ataxia. On examination, abnormal heel-to-toe walking is a constant feature. Other cerebella signs may be present to a varying degree. CSF examination, electroencephalogram, and computed tomographic brain scan are normal. Treatment consists of antimalarial drugs to clear any parasitemia, symptomatic drugs, and physiotherapy. Complete recovery usually takes a few weeks or up to 4 months (Senanayake, 1987). This condition has later been reported from other parts of Sri Lanka (De Silva *et al,* 1988b; Wijesundere, 1988), and from different parts of the world (Girard *et al,* 1988; Chaine *et al,*1991). Of all cases of malaria admitted to a base hospital in an endemic area in Sri Lanka in 1986, the cerebellar syndrome was the commonest neurological complication (Wijesundere, 1988).

The selective involvement of the cerebellar system, the delay in onset of the ataxia, and the favorable response in some patients treated with prednisolone (Senanayake, 1987), favor an immune mechanism in the pathogenesis. The self-limiting course with full recovery suggests a demyelinating process, similar to those described following certain viral infections. A recent investigation has shown significantly high serum concentrations of TNFa, interleukin 6 and interleukin 2, and elevated CSF cytokine in these patients (De Silva *et al,* 1992) providing further evidence for an immunological basis for the neurological symptoms.

EPILEPSY

Cerebral malaria is a recognized cause of seizure disorders (Bittencourt *et al,* 1988). Generalized tonic-clonic seizures as well as partial motor seizures have been recorded (Vietze, 1978). Pathological examinaition of the brain in fatal cases, in late stages, have shown the malaric granuloma of Durck formed by astroglial reaction (Toro and Roman, 1978). It is conceivable that these lesions may act as epileptogenic foci in those who survive, giving rise to chronic epileptic seizures.

FEBRILE SEIZURES

Malaria is a common cause of febrile seizures in children in the tropics. A study in Congo showed that 9.6% of all children admitted to Brazzaville General Hospital between 1981-1983 presented with seizures (Senga *et al,* 1985). Status epilepticus occurred 13.6% of the cases, and 67% of these were related to benign malaria. Febrile seizures occurred in 73.5% of all cases, and 81% of them were related to malaria. Approximately 60% of all seizure disorders between 1 month and 6 years of age in a large general hospital were related to benign or malignant forms of malaria, and seizures were the reason for admission in 10% of all children in that age group (Bittencourt *et al,* 1988). In Nigeria, 50% of cases of febrile convulsions are due to malaria. Even in the adult Nigerian, the commonest trigger of epileptic seizure is chloroquine-responsive febrile illness, due to malarial infections (Osuntokun, 1983).

SPINAL CORD DISORDERS

Spinal syndromes of malaria are thought to resemble those of amyotrophic lateral sclerosis, funicular myelosis, spastic spinal paralysis and tabes dorsalis; in part they have been interpreted as late sequelae. In contrast to true tabes dorsalis, the typical Argyll-Robertson pupil is not seen. In cases of simultaneous cerebral and spinal disease, the clinical condition may resemble disseminated encephalomyelitis, *eg* spastic gait, tremor, and occasionally nystagmus and speech disorders. On treatment with quinine these symptoms are reported to regress (Vietze, 1978).

PERIPHERAL NEUROPATHY

Early literature refers to cases of neuritis, polyneuritis, Landry's paralysis, and cranial nerve palsies in association with malarial infections (Vietze, 1978). "Irritative" phenomena with sharp or stinging pain in the distribution of a peripheral nerve, followed by a sensation of "drawing" in the

muscles with muscle contraction, intense hyperalgesia, and increased sweating have been reported (Harvey, 1944). More recent cases include Guillain-Barre type polyneuropathy developing a few days or weeks after vivax or falciparum malaria (Avasthi and Aggarwal, 1985; Guerreiro *et al,* 1985; Wijesundere, 1988, 1992).

PERIODIC PARALYSIS

Transient muscular paralysis resembling periodic paralysis has been observed during febrile episodes of malaria in 3 Sri Lankan patients (Senanayake and Wimalawansa, 1981). Following a rigor, the weakness first appeared in the lower limbs, and soon spread to the rest of the body causing paralysis affecting the entire body except for the respiratory muscles. The patients remained conscious during the attack. Signs of improvement appeared in 4 to 6 hours, and the recovery was complete in 8 to 10 hours, the muscles which were affected first being the last to recover. Two of the patients showed a mixed infection of *P. vivax* and *P. falciparum* in the peripheral blood films, while the other had only *P. vivax*. The transient rise of serum potassium concentration due to lysis of red cells and intense muscular contraction during rigors, and the muscular exertion itself caused by the rigor during the febrile episodes of malaria were suggested as the mechanism underlying the muscle paralysis. A genetic predisposition which makes only some individuals susceptible, may explain the general rarity of the phenomenon.

MYOPATHY

Two Sri Lankan males, aged 51 and 57 years, with falciparum malaria developed marked weakness of shoulder and pelvic girdle muscles suggestive of a myopathy. They had a slow but complete recovery in about 4 weeks (Wijesundere, 1988). Skeletal muscle necrosis has been reported in a case of severe falciparum malaria, causing myoglobinuria and acute renal failure (De Silva *et al,* 1988a).

CONCLUSIONS

Involvement of the nervous system in malaria is a complex phenomenon ranging from the lethal encephalopathy to the relatively mild forms of cerebellar involvement. Some of the manifestations, for instance the spinal syndromes and the neuritides, would be difficult to justify as being causally related to plasmodial infections, unless the symptoms disappear or are significantly ameliorated by antimalarial therapy when other causes are excluded. The pathogenesis of the nervous system involvement in malaria remains underexplored, but offers excellent perspectives for research at clinical as well as experimental level.

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