

NEUROLOGICAL MANIFESTATIONS OF MALARIA

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SUMMARY — The involvement of the nervous system in malaria is reviewed in this paper. 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 cells causing sludging in the capillary circulation is one hypothesis to explain its pathogenesis. The other is a humoral hypothesis which proposes nonspecific, immune-mediated, inflammatory responses 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 remains unexplored, but offers excellent perspectives for research at a clinical as well as experimental level.

KEY WORDS: malaria, *Plasmodium falciparum*, nervous system.

Manifestações neurológicas da malária

RESUMO — O envolvimento do sistema nervoso central pela malária é revisto neste artigo. Malária cerebral, a encefalopatia que complica exclusivamente a infecção pelo *Plasmodium falciparum*, atinge essencialmente crianças e adolescentes em áreas hiperendêmicas. Uma das hipóteses para a sua patogênese consiste no desvio da circulação capilar por obstrução de capilares e vênulas cerebrais por eritrócitos parasitados. Outra, a teoria humoral, propõe que a resposta inflamatória, imunomediada e inespecífica, liberta substâncias vasoativas capazes de produzir alterações endoteliais e de permeabilidade. Malária cerebral tem taxa de mortalidade até 50% e também considerável morbidade a longo prazo, particularmente em crianças. A sintomatologia cerebral pode ser complicada por hipoglicemia, principalmente em doentes tratados com quinino. Outras manifestações incluem hemorragia intracraniana, oclusão arterial cerebral e sintomatologia transitória extrapiramidal e neuropsiquiátrica. Em Sri Lanka, alguns doentes em recuperação têm mostrado ataxia cerebelar, autolimitada, provavelmente devida a mecanismos imunes. Malária é causa frequente de convulsões febris nos trópicos e contribui para o desenvolvimento posterior de epilepsia. Envolvimento medular e dos nervos periféricos também têm sido descritos. Durante episódios febris, alguns doentes têm apresentado paralisia transitória semelhante à paralisia periódica. A patogênese das manifestações neurológicas na malária continua por ser esclarecida e oferece excelentes perspectivas de investigação tanto clínica como experimental.

PALAVRAS CHAVE: malária, *Plasmodium falciparum*, sistema nervoso.

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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 manifestations.

CEREBRAL MALARIA

Cerebral malaria is an acute encephalopathy that complicates exclusively the infection by *Plasmodium falciparum*. Reported frequencies of cerebral malaria in malarial infections vary from 0.01% to 16%²⁴. 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 concern that acquired immune deficiency syndrome (AIDS) may predispose to cerebral malaria in the tropics.

Pathophysiology — Macroscopically, the most striking findings are moderate cerebral edema and diffuse petechial hemorrhages preferentially involving the white matter of brain³⁵. Some degree of slate-grey discoloration of the cerebral cortex due to malarial pigment (hemozoin) is present. Microscopically, these petechial hemorrhages 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 microthrombosis³⁶. Perivascular demyelination and intravascular aggregates of parasitized erythrocytes and thrombosis of capillaries have also been reported¹.

The pathogenesis of cerebral malaria remains an unsolved riddle³⁰. Observations 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 have provided the basis for a «mechanical» hypothesis. This cytoadherence is mediated by knobs which protrude from the surface of parasitized red cells. Attachment of knobs on endothelial cells surface receptors is probably mediated by host molecules such as OKM5 and thrombospondin²⁹. Lack of response to corticoids has been interpreted either as an indication that damage of the blood-brain barrier with vasogenic edema is not a major pathogenic element, or that the role of inflammation mediated by cytokines or free oxygen radicals is limited and unaffected by dexamethasone treatment³⁸. 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 parasitemia¹⁹. Serum TNF concentrations are significantly increased in children dying with cerebral malaria¹³. The recent findings of early lesions of endothelial cells, basal lamina, and astrocytes resulting in damage of blood-brain barrier in the murine model, probably due to TNF effect, further confirm the importance of vascular lesions in cerebral malaria²⁷. 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.

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 that resembles acute alcohol intoxication or an acute psychotic episode.

Diagnosis — Cerebral malaria must be differentiated from other causes of stupor and coma in the tropics. A lumbar puncture should be done to exclude conditions such as meningitis. In cerebral malaria, the cerebrospinal fluid (CSF) is generally under normal pressure, with a few lymphocytes and a slight increase in protein content in half the patients. A presumptive diagnosis can be made by demonstrating malarial parasites in peripheral blood. The degree of invasion of the peripheral red cells by falciparum trophozoites 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. The recommended treatment is chloroquine 5 mg/kg diluted in 10 ml/kg isotonic fluid by i.v. infusion over 4-6 hr every 12 hr to a total dose of 25 mg/kg. In chloroquine resistance, treatment should be started with quinine, with a loading of dose 16.7 mg/kg diluted in 10 ml/kg isotonic fluid by i.v. infusion over 4 hr, then 8.4 mg/kg over 4 hr, 8 hourly until patients can swallow. Then quinine tablets approximately 8.4 mg/kg 8 hourly is given to complete 7 days of treatment⁵. Deep intramuscular injections may be given if intravenous treatment is impossible. 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 mortality³⁹. Lowering intracranial pressure by lumbar puncture or by osmotic agents such as urea or mannitol may be beneficial²². 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 i.m. injection of phenobarbitone (3.5 mg/kg) is effective in preventing seizures in cerebral malaria⁴⁰. Gram-negative sepsis is common in patients with severe malaria, and appropriate antibiotic therapy should be considered. Treatment with qinghaosu from *Artemisia annual L.* appears promising¹⁵.

Prognosis — Mortality rates of cerebral malaria in children, reported mainly from African countries, vary from 6% to over 50%²⁰. It also causes considerable longterm morbidity, particularly in children, up to 21% of patients reported to having neurological sequelae⁶. 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 anaemia. The possibility of some of the children who made a good recovery having subtle neurological defects such as intellectual impairment cannot be discounted⁶.

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 hemorrhages has been described in a rodent model of malaria¹². 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 hemorrhages²¹. Retinal hemorrhages are an important sign of prognostic significance in cerebral malaria.

Cerebral arterial occlusion — Some of the focal neurological signs complicating cerebral malaria have been shown to be due to arterial occlusion⁶. 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 cortex³⁷.

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 convalescence³⁷. 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 weeks². There is also a report of a patient who developed opsoclonus and hand tremor during the course of *P. falciparum* infection²⁸.

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 hypertension²³.

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 described³⁷. 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 weeks¹¹. Although there is no evidence of a specific malarial psychosis, the organic nature of the malarial psychoses has been well established. The occurrence of schizophrenia-like conditions may indicate malaria triggering off a latent endogenous psychosis³⁷.

HYPOGLYCEMIA

Some patients with falciparum malaria develop hypoglycemia, causing coma, decerebrate posturing and seizures. Up to 52% of African children⁴¹ and about half the pregnant women with falciparum malaria treated with quinine¹⁸ 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 utero²⁵. The hypoglycemia may develop hours, or even days after admission³⁴. In the pathogenesis, quinine-induced hyperinsulinemia is probably the principal mechanism⁴². Consumption of glucose by the parasite, and increased peripheral utilization of glucose may be contributory²⁵.

Clinical features characteristic of hypoglycemia, such as tremulousness, sweating, mydriasis, and tachycardia may not be present²⁵. 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 difficulty³⁴. In quinine-treated adults, hyperinsulinemia may cause recurrent hypoglycemia despite continuous infusion of dextrose. A somatostatin analogue SMS 201/995 has proved effective in Thailand²⁶.

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^{8,17}. A syndrome of isolated cerebellar ataxia following falciparum malaria has been recognized in Sri Lanka in otherwise well, conscious patients, with no features 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 2nd or the 3rd 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 cerebellar 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 is usually takes a few weeks or up to 4 months³². This condition has later been reported from other parts of Sri Lanka⁹, and from different parts of the world^{7,10}. The selective involvement of the cerebellar system, the delay in onset of the ataxia, and the favorable response in some patients treated with prednisolone³²,

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 TNF α , interleukin 6 and interleukin 2, and elevated CSF cytokine in these patients (HJ de Silva, personal communication) providing further evidence for an immunological basis for the neurological symptoms.

EPILEPSY

Epilepsy has long been recognized as a late sequel of cerebral malaria. Generalized tonic-clonic seizures as well as partial motor seizures have been recorded³⁷. Pathological examination of the brain in fatal cases, in late stages, have shown the malaric granuloma of Durck formed by astroglial reaction³⁶. 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 seizures³³. 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 group⁴. 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 infections²⁴.

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, e.g. spastic gait, tremor, and occasionally nystagmus and speech disorders. On treatment with quinine these symptoms are reported to regress³⁷.

PERIPHERAL NEUROPATHY

Early literature refers to cases of neuritis, polyneuritis, Landry's paralysis, and cranial nerve palsies in association with malarial infections³⁷. «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 reported¹⁶. More recent cases include Guillain-Barre type polyneuropathy developing 2 to 3 weeks following vivax or falciparum malaria^{3,14}.

PERIODIC PARALYSIS

Transient muscular paralysis resembling periodic paralysis has been observed during febrile episodes of malaria in 3 Sri Lankan patients³¹. 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 hr, and the recovery was complete in 8 to 10 hr, 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 make only some individuals susceptible, may explain the general rarity of the phenomenon.

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 unexplored, but offers excellent perspectives for research at clinical as well as experimental level.

REFERENCES

1. Aikawa M. Human cerebral malaria. *Am J Trop Med Hyg* 1988, 39:3-10.
2. Arya TVS, Awasthi R, Bhutani J. Extraparaventricular syndrome in falciparum malaria. *J Assoc Physicians India* 1989, 37:393-394.
3. Avasthi G, Aggarwal SP. Plasmodium falciparum malaria associated with Guillain-Barre syndrome. *J Indian Med Assoc* 1985, 83:360-363.
4. Bittencourt PRM, Gracia CM, Lorenzana P. Epilepsy and parasitosis of the central nervous system. In Pedley TA, Meldrum BS (eds): *Recent Advances in Epilepsy*, vol 4. Edinburgh: Churchill Livingstone, 1988, p 123-159.
5. Bradley DJ, Newbold CI, Warrell DA. In Weatherall DJ, Ledingham JGG, Warrell DA (eds): *Oxford Textbook of Medicine*. Oxford: University Press, 1987, p 5474-5502.
6. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990, 336:1039-1043.
7. Chine P, Woimant F, Corabianu O, Fayada C, Haguenu M. Isolated cerebellar syndrome: an atypical form of cerebral malaria. *J Neurol Neurosurg Psychiatry* 1991, 54:655.
8. Chitkara AJ, Anand NK, Saini L. Cerebellar syndrome in malaria. *Indian Pediatr* 1984, 21:908-910.
9. De Silva HJ, Gamage R, Herath HK, Peiris JB, Abeysekera DT. A self-limiting midline cerebellar syndrome. Is falciparum malaria the cause? *Trop Doct* 1988, 18:5-6.
10. Girard PM, de Broucker T, Fryer DG, Netter JM, Saimot AG, Coulaud JP. Cerebellar syndrome in mild Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg* 1988, 82:204.
11. Gopinathan VP, Thampi UR, Ganguly SB. Neuropsychiatric manifestations of falciparum malaria. *J Indian Med Assoc* 1982, 78:155-157.
12. Grau GE, Fajardo LF, Puiguet PF, Allet B, Lambert PH, Vassalli P. Tumor necrosis factor (cachectin) as an essential mediator in murine cerebral malaria. *Science* 1987, 237:1210-1212.
13. Grau GE, Taylor TE, Molyneux ME, Wirima JJ, Vassalli P, Honamel M, Lambert PH. Tumor necrosis factor and disease severity in children with falciparum malaria. *N Engl J Med* 1989, 320:1586-1591.
14. Guerreiro CAM, Facure NO, Gonçalves FL Jr, Da Silva LJ, Ramos MC, Pedro R De J. Polirradiculoneurite e malaria. *Arq Neuropsiquiatr* 1985, 43:214-216.
15. Guoqiao L, Kingbo G, Rui J, Zicai W, Xuaxiang J, Ziyang L. Clinical studies on treatment of cerebral malaria with qinghaosu and its derivatives. *J Tradit Chi Med* 1982, 2:125-130.
16. Harvey AM. A type of neuritis associated with malarial fever. *Bull Johns Hopkins Hosp* 1944, 75:225-231.
17. Illangasekera VL, De Sylva S. Acute cerebellar syndrome in falciparum malaria. *Ceylon Med J* 1976, 21:130-132.
18. Looareesuwan S, Phillips RE, White NJ, Silamut A, Phillips RE, Warrell DA. Quinine and severe falciparum malaria in late pregnancy. *Acta Leiden* 1987, 55:139-149.
19. Maegraith B, Fletcher A. The pathogenesis of mammalian malaria. *Adv Parasitol* 1972, 10:49-75.
20. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989, 71:441-459.
21. Murugavel K, Saravanapavanathan S, Anpalahan A, James RF. Subarachnoid haemorrhage in Plasmodium falciparum malaria. *Postgrad Med J* 1989, 65:236-237.
22. Newton CRJC, Kirkham FJ, Winstanley PA, Pasvol G, Peshu N, Warrell DA, Marsh K. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991, 337:573-576.
23. Okelo GBA. Benign intracranial hypertension associated with resistant Plasmodium falciparum malaria infection: a case report. *E Afr Med J* 1985, 62:363-364.

24. Osuntokun BO. Malaria and the nervous system. *Afr J Med Sci* 1983, 12:165-172.
25. Phillips RE. Hypoglycaemia is an important complication of falciparum malaria. *Q J Med* 1989, 266:477-483.
26. Phillips RE, Warrell DA, Looareesuwan S, Turner RC, Bloom SR, Quantrill D, Moore AR. Effectiveness of SMS 201-995, a synthetic long-acting somatostatin analogue, in treatment of quinine induced hyperinsulinaemia. *Lancet* 1986, 1:713-716.
27. Polder TW, Eling WMC, Jerusalem CR, Wijers-Rouw M. A cytochemical study of cerebrovascular lesions in mice infected with *Plasmodium berghei*. *J Neurol Sci* 1991, 101:24-34.
28. Pongvarin N, Praditsuwan R. Opsoclonus in malaria: the first report in the literature. *J Med Assoc Thai* 1990, 73:462-466.
29. Roberts DD, Scherwood JA, Spitalnik SL, Panton LJ, Howard RJ, Dixit VM, Frazier WA, Miller LH, Ginsburg V. Thrombospondin binds falciparum malaria parasitized erythrocytes and may mediate cytoadherence. *Nature* 1985, 318:64-66.
30. Roman GC. Cerebral malaria: the unsolved riddle. *J Neurol Sci* 1991, 101:1-6.
31. Senanayake N, Wimalawansa SJ. Periodic paralysis complicating malaria. *Postgrad Med J* 1981, 57:273-274.
32. Senanayake N. Delayed cerebellar ataxia: a new complication of falciparum malaria? *Br Med J* 1987, 294:1253-1254.
33. Senga P, Mayanda HF, Nzingoula S. Profile of seizures in infants and young children in Brazzaville (Congo). *Ann Pediatr* 1985, 32:477-480.
34. Taylor TE, Molyneux ME, Wirima JJ, Fletcher KA, Morris K. Blood glucose concentrations in Malawian children before and during parenteral quinine treatment for severe falciparum malaria. *N Engl J Med* 1988, 319:1040-1047.
35. Toro G, Román G, de Roman LN. Paludismo. In Toro G, Román G, de Román LN (eds): *Neurología Tropical: Aspectos Neuropatológicos de la Medicina Tropical*. Bogotá: Editorial Printer Colombiana, 1983, p 106-113.
36. Toro G, Román GC. Cerebral malaria: a disseminated vasculomyelinopathy. *Arch Neurol* 1978, 35:271-275.
37. Vietze G. Malaria and other protozoal diseases. In Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology*, vol 35. Amsterdam: North-Holland, 1978, p 143-160.
38. Warrell DA, Looareesuwan S, Phillips RE, White MJ, Warrell MJ, Chapel H, Areekul M, Tharavanij S. Function of the blood-cerebrospinal fluid barrier in human cerebral malaria: rejection of the permeability hypothesis. *Am J Trop Med Hyg* 1986, 35:882-889.
39. Warrell DA, Looareesuwan S, Warrell MJ, Kasemsam P, Intrapasert R, Bunnag D, Harinasuta T. Dexamethasone proves deleterious in cerebral malaria: a double-blind trial in 100 comatose patients. *N Engl J Med* 1982, 306:313-319.
40. White NJ, Looareesuwan S, Phillips RE, Chanthavanich P, Warrell DA. Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet* 1988, 2:64-66.
41. White NJ, Miller KD, Marsh K, Berry CD, Turner RC, Williamson DH, Brown J. Hypoglycaemia in African children with severe malaria. *Lancet* 1987, 1:708-711.
42. White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983, 309:61-66.