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NEUROLOGICAL COMPLICATIONS: CHANCES OF SURVIVAL IN CEREBRAL MALARIA

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ABSTRACT
Cerebral malaria is one of the most common non-traumatic encephalopathy in the world. The pathogenesis and neurological complications are often leads to multisystem dysfunction. The clinical presentation differs between adults and children. Cerebral malaria is a common cause of neurological sequelae and death among children. Current studies show that the molecular mechanisms of pathogenesis and raised possible interventions. Antimalarial drugs, however, remain the main intervention to bring effective outcome, although increasing resistance to the established antimalarial drugs is of serious concern. Artemisinin derivatives have shown an immense impact in reference to treatment, but other drugs are required to bring into the limelight. With appropriate antimalarial drugs, the prognosis of cerebral malaria often depends on the management of other complications—for example, seizures, renal failure, acidosis. Research on the pathogenesis of coma and neurological damage shows increasing effect on human life especially children and the immediate invention of treatment is required. Cerebral malaria is the most severe neurological presentation of acute falciparum malaria. The clinical hallmark of cerebral malaria is the comatous stage.

INTRODUCTION
Malaria is the most common parasitic diseases in human being and its neurological complication. Cerebral malaria is one of the most common non-traumatic encephalopathies in the world. Malaria affects about 5% of the world's population at any time and causes somewhere between 0.5 and 2.5 million deaths each year. There are four species causing human malaria. *Plasmodium falciparum* causes nearly all the deaths and neurological complications. Plasmodium falciparum is the most common cause of malaria worldwide. It is responsible for almost all the mortality from malaria and affects the central nervous system causing neurological deficits and cognitive sequelae. The social and economic burden of malaria in malaria-endemic countries is immense.

Severe malaria occurs predominantly in patients with little or no background immunity—that is, children growing up in areas where malaria is rare or travelers or migrants who come from areas without malaria, but are exposed to malaria later in life. Severe malaria leads to multi-system dysfunction. The outcome often depends on the degree of vital organ dysfunction.

The manifestations of severe malaria differ depending on the age of the patient and previous exposure. In the first 2 years of life severe anemia is a common presenting feature of severe malaria. In older children seizures and cerebral malaria predominate; whereas in adults acute renal failure, acute pulmonary edema, liver dysfunction, and cerebral malaria may all occur. Metabolic acidosis, mainly a lactic acidosis, is common at all ages.

P falciparum is transmitted by female Anopheles mosquitoes. In humans, although the parasite undergoes development in the liver, it is the erythrocytic cycle that is responsible for disease. The merozoites released by the liver invade the erythrocyte, and during a period of 48 hours, pass through morphologically distinct stages, before the meronts (schizonts) rupture the erythrocyte. Ring stages are seen in the peripheral blood, but trophozoites are usually absent, as they are sequestered within the deep vascular beds.

DEFINITION OF CEREBRAL MALARIA
"Cerebral malaria" is any disturbance of the CNS due malarial infection. In the case reports of the cerebral involvement caused by *P vivax*, other causes of an encephalopathy or mixed infections with *P falciparum* is often observed. In falciparum malaria, disturbances of consciousness can be caused by systemic complications—such as fever, hypoglycemia, hyponatremia, and uremia. It is defined as a deep level of unconsciousness (inability to localize a painful stimulus) in the presence of a *P falciparum* asexual parasitemia. In

adults, coma was required for more than 6 hours after a generalized convulsion to seizures (which rarely lasts more than 1 hour), although in children this was reduced to 1 hour. In children, the diagnosis of cerebral malaria is supported by finding cerebral capillaries and venules packed with PRBCs. These features may be absent if the patient dies after several days of treatment, and are not specific for cerebral malaria. In clinical practice any impairment of consciousness or other sign of cerebral dysfunction is an indication for parenteral treatment and intensive care management.

Cerebral malaria in adults

CLINICAL FEATURES

Diffuse encephalopathy in which focal neurological signs are rare in Cerebral malaria.. The patient is febrile and unconscious with passive resistance to neck flexion, but associated with meningitis. Absence of rash, and no lymphadenopathy. As cerebral malaria often leads to multi-system dysfunction, anemia, jaundice and, most importantly, the presence of acidotic (Kussmaul's) breathing is essential. The prognosis of cerebral malaria become threatening when it is accompanied by renal failure, severe jaundice, or metabolic acidosis. The metabolic acidosis is caused by either an acute renal failure, or a lactic acidosis, or a combination of both. Even acute pulmonary edema can occur.

SEIZURES

The incidence of seizures in adults with cerebral malaria varies. In the early 1980s studies conducted in Thailand and Vietnam, 50% of adults with cerebral malaria had generalized seizures, whereas in these countries in the 1990s the incidence was less than 10%. The reason for this difference is not specified. Possible explanations include differences in parasite virulence characteristics, or possibly the decrease in the excessive use of chloroquine as pre-treatment.. The level of consciousness after a seizure is usually lower than that preceding it. More than one seizure is common in Cerebral Malaria.

OUTCOME

Mortality depends on the associated vital organ dysfunction. Mortality of adults varies every year. Mortality also depends on the availability of intensive care facilities. In patients with cerebral malaria with no other evidence of vital organ dysfunction. The mortality rate is 8%, whereas it increases upto 50% risk of acute renal failure and metabolic acidosis.. In some cases patient may die from a sudden acute respiratory arrest, with a normal blood pressure. Other patients may die from shock, hypoxia and hypotension secondary to acute pulmonary edema or some cases aspiration pneumonia. Most deaths occur within 48 hours of admission.

Cerebral malaria in African children

In African children growing up in malaria prone areas, severe falciparum malaria usually manifests as seizures, impaired consciousness, metabolic acidosis resulting in respiratory distress or severe anemia. Children have a higher incidence of seizures compared to adults.The incidence and pattern of neurological sequelae are different. Patients often die with features of brain death. African children rarely develop renal failure or pulmonary edema. In older children, cerebral malaria can be defined as in adults. The Blantyre coma scale, was device to assess young children with severe malaria and a summated score$\leqslant$2 is used to define cerebral malaria in many studies. The Blantyre coma scale has similar components to the Glasgow coma scale, but measures different responses. African children with cerebral malaria are older (40–45 months of age), than children are commonly with other complications of the disease, but cerebral malaria is rarely detected after the age of 10 years in people exposed to *P falciparum* since birth. Cerebral malaria presents usually with a 1–4 day history of fever and convulsions, the second often precipitates coma. Convulsions are the most clinically detected seizures, but sub-clinical seizures detected with Electroencephalography (EEG) are also common. In some children, the level of consciousness improves with the administration of anticonvulsant drugs, suggesting that seizures contribute to the coma. Seizures get prolonged with poor outcome.

Most African children with cerebral malaria survive with appropriate treatment, regaining consciousness within 48–72 hours of starting treatment. Most deaths occur within 24 hours of starting treatment, accompanied by brainstem signs, respiratory arrest, or overwhelming acidosis.

BRAIN SWELLING

Most African children with cerebral malaria evident brain swelling on CT and at postmortem. Many children die with cerebral malaria and its clinical signs. Some cases children had sonographic features of progressive intracranial hypertension. Those children who develop severe intracranial hypertension either died or survived with severe neurological sequelae. During the initial stages of cerebral malaria there is a raise of ICP resulting in an increase of cerebral blood volume. Cerebral blood volume could be increased by the sequestration of PRBCs in the vascular compartment, by obstructing venous outflow. An increased cerebral blood flow is another main complication of cerebral malaria, such as seizures, hyperthermia, and anemia. Severe neurological sequelae have evidence of edema during recovery that may contribute to the severe intracranial hypertension.

Mannitol is considered to be effective medication in lowering the ICP and prevent children with mild intracranial hypertension that develops from neurological sequelae, but it did not prevent the development of intracranial hypertension in those children with a poor outcome result and severe.

DISCUSSION

Neurologic sequelae were defined as impairment of neurologic or cognitive function. Specifically they

include: impairment or loss of function in musculoskeletal system, these includes paralysis or paresis manifesting as inability to walk, staggering, monoparesis, hemiparesis, quadriparesis; memory impairment (unusual forgetfulness of recent events), hyperactivity (excessive activity on the part of the child), seizure disorder (two or more seizures after discharge from hospital, unprovoked by fever), speech Impairment (difficulty in verbal expression), hearing impairment (inability to hear, or turn toward sound), and visual impairment (inability to visually follow brightly colored objects or pick such objects with open eyes). Neurological sequelae are accompanied with seizures, prolonged and deep coma, hypoglycemia, and severe anemia in some studies, but not in others. Some neurological deficits are transient and whereas others hemiparesis and cortical blindness. It often improves over months, although they may not completely resolve. African children with severe neurological sequelae usually die within a few months of discharge. More subtle deficits—for example, cognitive difficulties, language and behavioural problems—are increasingly recognized. As the seizures that occur during the acute illness are often focal, repetitive, or prolonged.

The causes of the sequelae are largely unknown. Severe neurological sequelae are accompanied with severe intracranial hypertension. Half of the children with hemiparesis have stenosis or occlusion of the basal cerebral arteries demonstrated by angiography or transcranial Doppler. The cause of large vessel disease is unknown. Some children with hemiparesis have the CT appearances of hemiconvulsion- hemiparesis syndrome. Blindness is usually cortical, often follows seizures, and is usually associated by evidence of more diffuse damage, although it can occur in isolation. Brain damage could be caused by a mismatch between the delivery of oxygen (anemia, decreased microcirculatory flow) and glucose (hypoglycemia), in the presence of increased demand (seizures, fever).

Seizures and malaria

Seizures are the other common neurological manifestation of falciparum malaria. *P falciparum is* the most common cause of seizures in children admitted to an African hospital. Although fever may precipitate some seizures, most seizures occur when the rectal temperatures are less than 38.0^{o}C. The seizures in malaria are often recurrent and 84% of the seizures are complex, most often with a focal nature. The seizures may be caused by intracranial sequestration of metabolically active parasites.

Management of patients with suspected cerebral malaria

Cerebral malaria is a medical emergency demanding urgent clinical assessment and treatment. Impairment of consciousness, convulsions, and other neurological features are possible complications of cerebral malaria in any person who have been exposed to this infection during the previous year. Most cases occur within 3 months of exposure. In such patients the high level of care is required where an appropriate antimalarial drug should be administered as soon as possible, through the parenteral route. Complications of cerebral malaria, such as convulsions, hypoglycemia, and hyperpyrexia, should be detected as early as possible. Relevant treatment and preventive measures should be taken as soon as possible. Fluid, electrolyte and acid-base balance may need correction. Skilled nursing care of the unconscious patient is crucial. Ancillary treatments should be avoided unless they have proved safe and effective.

The management of cerebral malaria is similar to that of any serious unconscious patient. Intensive care with rehydration and thereafter careful fluid balance management are necessary to navigate the narrow division between underhydration, worsening renal impairment and lactic acidosis, and overhydration and pulmonary oedema. Children are less likely to develop pulmonary oedema and more likely than adults to be hypovolemic and underperfusion. Many require rapid restoration of an adequate circulating blood volume.[81] Adults with severe malaria are particularly likely to develop the adult respiratory distress syndrome, more than patients with bacterial septicemia, so management is aided considerably by monitoring of central venous pressure, and if necessary, pulmonary artery occlusion pressure. Blood transfusion is indicated when the packed cell volume falls below 20%, and may be beneficial above this threshold. The blood glucose must be checked often and hypoglycemia must be corrected. The stomach should be drained via a nasogastric tube. If ventilation is required, an experienced operator should perform intubation. A lumbar puncture should be performed to exclude meningitis. In patients with acute renal failure or severe acidosis, hemofiltration should be started early if available.

Specific parenteral antimalarial treatment is the only intervention that unequivocally affects the outcome of cerebral malaria. Resistance has meant that chloroquine can no longer be relied on in most tropical countries. The Cinchona alkaloid quinine (in the United States its diastereomer quinidine) remains the mainstay of antimalarial treatment of severe malaria. There has been controversy over many years over the optimum dosage and methods of administering quinine in severe malaria. Quinine must be given with an adequate loading dose (20 mg/kg of the dihydrochloride salt infused over 4 hours) to ensure that parasiticidal concentrations are reached in blood as soon as possible in the disease. In Zambian children a loading dose was associated with a shorter duration of coma and faster parasite clearance and resolution of fever. Thereafter 30 mg/kg/day is given for 7 days, usually in 2–4 hour infusions of 10 mg/kg every 8 hours. Infusion rates must be monitored and these drugs must not be given by manual intravenous injection. The dose of quinine is reduced by 30–50% after 48 hours. Oral treatment should be substituted when the patient can

swallow reliably. Quinine is a powerful stimulant of pancreatic insulin secretion and may cause iatrogenic hypoglycaemia particularly in pregnant women.

Antimalarial treatment of cerebral malaria

Artemisinin derivatives of the plant *Artemisia annua* have been used extensively in the treatment of cerebral and other forms of severe falciparum malaria. In uncomplicated malaria, these compounds clear parasitemia and fever faster than the cinchona alkaloids, but although in recent large randomized controlled trials of intramuscular Artemether and quinine in African children, and Vietnamese adults, there was no improvement in the mortality. These trials had only limited power to detect mortality reductions; none were powered to detect a reduction of <30%. An analysis of these and other randomized trials indicates that in adults Artemether did reduce mortality (by about one fifth), but there was no convincing difference in children. Nevertheless, because of their safety and simplicity in administration. There was a great decline in usage of quinine as compare to artesunate. However in pregnant women still the quinine is preferred choice. Suppository formulations of Artemisinin and Artesunate have proved effective in cerebral and severe falciparum malaria. Although concerns about neurotoxicity have arisen from animal studies, no significant side effects have been documented in humans and there is not an increased incidence of neurological sequelae. In many parts of the world, complete cure requires the addition of a course of oral sulfadoxine/pyrimethamine or tetracycline/doxycycline for 7 days (clindamycin in pregnant women and children), which is started as soon as the patient is able to swallow tablets.

ANCILLARY TREATMENT

Phenobarbital (3.5 mg intramuscularly) reduced the frequency of convulsions in adults, but higher doses are needed to prevent convulsions in children. In a recent double blind controlled trial in Kenyan children, phenobarbital (20 mg/kg) reduced seizures by 50%, but doubled the mortality. There seemed to be an interaction with diazepam in these unventilated children. There was not a reduction in long term neurological sequelae. Brain swelling should be excluded by imaging in patients who show a deteriorating level of consciousness and appearance of neurological abnormalities in the absence of hypoglycemia. If there is evidence of cerebral swelling, 20% mannitol solution should be infused. In adults, corticosteroids did not benefit patients with cerebral malaria; consciousness was prolonged, and there was an increased incidence of infection and gastrointestinal bleeding in the corticosteroid treated group.

There are numerous numbers of reports and cases published over the years for severe falciparum malaria, but no adequate randomized control data are available yet. On empirical grounds, this intervention is probably justified when peripheral parasitemia exceeds 10% of circulating erythrocytes in a presumed non-immune patient who has deteriorated on optimal conventional treatment.

CONCLUSION

Cerebral malaria is common and should be considered in any patient with impairment of consciousness. Urgent treatment with appropriate antimalarial drugs are required, but the prognosis often depends on the management of other complications—for example, renal failure, acidosis. Therapies that interfere with underlying pathophysiological processes—for example, reduced red cell deformability and cytoadherence—require further investigation. Further research on the pathogenesis of coma and neurological damage is required to develop other ancillary treatments.

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