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A Literature Review of Clinical Characteristics of Cerebral Malaria

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ABSTRACT

Malaria is a disease transmitted by the bite of the female Anopheles mosquito and caused by protozoa of the genus Plasmodium. Malaria infection has several manifestations with cerebral malaria (CM) being the most severe neurological complication and a leading cause of malaria death. Cerebral malaria is characterized by a coma at least 1 hour after a seizure or a hypoglycemia, asexual forms of Plasmodium falciparum on peripheral blood smears, with the absence of any other causes of coma. This definition is quite vague in practice, thus making an accurate identification of clinical characteristics of cerebral malaria necessary in diagnosis to help reducing malaria deaths. This article is to summarize the medical literature to clarify the clinical characteristics of cerebral malaria.

Keywords: cerebral malaria; severe malaria; clinical characteristic; *Plasmodium falciparum*

INTRODUCTION

Malaria is a disease transmitted by the bite of the female Anopheles mosquito and is caused by protozoa of the genus Plasmodium [1]. Malaria in humans is generally caused by four species of Plasmodium, namely: Plasmodium malariae, Plasmodium vivax, Plasmodium ovale, and Plasmodium falciparum [2]. Infection from P. falciparum is the biggest contributor to malaria deaths (99%) compared to other Plasmodium species [3].

P. falciparum infection has several manifestations, with cerebral malaria (CM) being the most severe neurological complication and a leading cause of malaria death [4]. CM is responsible for almost 20% of adult deaths and 15% of childhood deaths [5]. Children with CM, roughly 11% of them display neurological deficits upon discharge which indicates a long-term damage of cerebral malaria [6].

According to World Health Organization, CM is characterized by a coma at least 1 hour after a seizure or a hypoglycemia, asexual forms of P. falciparum on peripheral blood smears, with the absence of any other causes of the coma [7]. This definition is quite vague in practice since it may include patients whose other encephalopathies are the cause of their coma or those with previously undetected neurological problems with incidental parasitemia (quite common in malaria endemic areas) [8]. Identifying the clinical characteristics of CM is necessary for diagnosis, thus can help reducing malarial deaths. This review aims to summarize the medical literature to clarify the clinical characteristics of CM.

IMPAIRED CONSCIOUSNESS

CM is characterized by sequestration of P. falciparum infected red blood cells (iRBCs), which engorge cerebral capillaries and post-capillary venules, thus triggers an inflammatory cytokine response, and results in vascular leakage [9]. Thus sequestration, inflammation, and endothelial dysfunction in the microvasculature of the brain are the main risk factors that eventually induce brain hypoxia in individuals with the severe form of malaria [10]. These individuals may experience reduced levels of consciousness that can range from delirium, seizure, to coma that lasts 4 days on average but can be longer [11].

Sequestration is the accumulation of iRBCs in the brain and visceral organs (kidney, liver lung) and is a unique characteristic of P. falciparum infection in humans. This phenomenon occurred through the ligan-receptor binding mechanism using P. falciparum Erythrocyte Membrane Protein 1 (PfEMP1) and the host's receptors such as CD36 and ICAM-1 expressed on endothelium surface, and chondroitin sulphate A (CSA) and hyaluronic acid expressed on synctitiotrophoblast of the placenta [12, 13]. The result of iRBCs sequestration is likely a patchy impairment of microvascular blood flow on different vital organs, ranging from partial occlusion to total obstruction [14]. Sequestration of iRBCs in the brain alters the structural and functional properties of cerebral endothelial cells [15, 16], activating them, altering the blood-brain barrier permeability, and causing secondary neuropathological events such as cerebral edema and axonal damage [17].

Inflammation from the rupture of iRBC plays an important role in the pathogenesis of malaria, including sequestration in P. falciparum infection which is a consequence of the pro-inflammatory cytokines release. From various studies for more than ten years, it has been widely proven that pro-inflammatory cytokines, especially TNF as the most studied cytokine, increase the expression of surface molecules of the endothelial cells like ICAM-1 where erythrocytes adhere to [18, 19, 20].

A decrease in endothelial dysfunction and an increasing in its permeability is caused by three mechanisms: transcellular leak, paracellular leak and leak due to endothelial cells death with the last two being the focus investigation in many recent literatures. [21]. In paracellular leak, tight junctions between brain endothelial are the key role in maintaining an effective barrier. This is shown in an experiment where a decrease of mRNA transcripts for tight junction proteins is shown in endothelial monolayers co-cultured with parasitized-erythrocytes from CM patients, and in another experiment where there is also a decrease in trans-endothelial electrical resistance of human brain endothelial cell monolayers on direct contact with PEs or *P. falciparum* culture supernatant [22, 23].

The first clinical requirement in cerebral malaria is impaired consciousness defined as a coma with Glasgow Coma Scale (GCS) score < 11 in adults and a Blantyre score < 3 in children [24]. There have been explanations that argue there are four separate groups of cerebral malaria rather than one single, homogenous syndrome: a prolonged post-ictal state, covert status epilepticus, severe metabolic derangement and a primary neurological syndrome [25].

In patients with prolonged post-ictal state, they have coma after a seizure, regain consciousness after 6 hours and show a good neurological recovery. The seizure is different to simple febrile seizure, but maybe both have similar risk factor. On the other hand, CM patients with convert status epilepticus present following prolonged seizures. Since the physical symptoms of seizure activity are commonly minimal, they might not be noticed. These patients are hypoxic and hyper carbic from hypoventilation and at danger of aspiration, so failing to recognize the condition can be disastrous. The length of the seizures will affect the neuro-cognitive outcome [4].

After resuscitation, patients with severe metabolic derangements may regain consciousness after a few hours. Extended periods of either acidosis or hypoglycemia may result in neuronal malfunction or death, and among survivors, prognosis may depend on exposure duration. Patients with primary neurological syndromes have the lowest neuro-cognitive outcomes and frequently present with seizures without substantial metabolic changes. They are not severely anemic and intracranial hypertension is common. The coma lasts for at least 24-48 hours after the end of the seizure. It could be a main consequence of intracranial sequestration of the parasites [4].

RETINOPATHY

Confirmed-malaria-specific retinopathy is an important diagnostic consideration in patients with CM. When malarial retinopathy is detected, diagnostic accuracy in fatal cases is significantly increased compared to standard clinical case definition [26]. When appropriately assessed, retinopathy has a 90% sensitivity and 95% specificity for the identification of cerebral malaria in African children caused by *P. falciparum* [27]. Malarial retinopathy consists of three elements: hemorrhages, vascular alterations that appear as orange or white discoloration, and retinal whitening [28].

Retinal whitening manifests as discrete areas of pale discoloration of the retina that correspond to areas of capillary non-perfusion visible on a fluorescein angiogram. Retinal whitening and capillary non-perfusion appear to occur first and most severely in watershed areas such as the foveal avascular zone margin, horizontal raphe, and retinal periphery [29]. Microcirculatory obstruction and the resulting hypoxia are to blame for retinal whitening. They discovered impaired perfusion and occlusion of retinal vessels in CM patients using fundus photography and fluorescein angiography of the retina [30]. They also discovered a link between non-perfusion areas and retinal whitening. Other possible mechanisms include parasitic metabolic steal and occlusion caused by microthrombi [29].

Vascular alterations are characterized by vascular discoloration, primarily at the capillary level, which is more common in peripheral areas of the retina. The most common retinal hemorrhages of malarial retinopathy have a white central area that corresponds to the presence of fibrinoid matter. The number of hemorrhages is related not only to the severity of the underlying disease, but also to the patient's anemia and the number of brain hemorrhages [31]. Additionally, observed are papilledema and disc hyperemia, two retinal disorders that are not specific to CM. The ophthalmologist evaluates all these retinopathy abnormalities in each eye using direct and indirect ophthalmoscope [26].

POST CM SEQUELAE

Up to 25% of pediatric survivors experience chronic neurologic sequelae after CM, including cognitive impairment, motor skills, visual coordination, and seizures [32, 33, 34, 35, 36].

In prospective research, 25% of child patients were shown to have long-term cognitive impairment after recovering and 11.8% of them show language impairment especially in vocabulary, receptive, and expressive speech, word finding, and phonology [37, 38]. Another indicator of the neurocognitive issues that pediatric CM survivors experience post-recovery is the degree of retinopathy [39]. A study suggests that dysregulation of the LIMK-1/cofilin-1 pathway could alter neuronal morphology and may be the cause of cognitive deficits in CM survivors [40]. It has also been suggested that CM child patients may develop neurocognitive impairment due to dysregulation of synaptic pruning brought on by high levels of complement activation during malaria infection [41]. Cognitive impairments are more commonly found on CM child survivors compared to adults, this may be explained with astrocytes immaturity on CM child patients [32, 39].

Sequalae on discharge, CM patients may also experience motor and movement disorders such as spasticity (hemiplegia, quadriparesis, or quadriplegia), cranial nerve palsies, central hypotonia, ataxia, tremors, and dystonia. On long term after discharge, central hypotonia, ataxia, and tremors mostly resolve [4]. Before discharge, the most common neurological feature was symmetrical upper motor neuron lesion that is shown as bilateral plantar extension and exaggerated tendon reflexes which could help in diagnosing CM. These patients have features of meningeal irritation but with absence of neck rigidity, kerning's sign, and photophobia therefore the possibility of meningitis could be excluded [42].

More than 80% of pediatric patients with cerebral malaria require hospitalization due to seizures. After treatment, these seizures recur in more than 60% of cases. Recurrent awakenings or seizures worsen the prognosis and raise the risk of neurologic sequelae. In cerebral malaria, seizures may be brought on by cerebral hypoxia, fever, hypoglycemia, or lactic acidosis [43]. Since *P. falciparum* is an epileptogenic parasite, hyperparasitemia of this parasite raises the risk of seizures. In cerebral malaria, generalized seizures are more common than partial seizures. Antiepileptic medication is typically more ineffective at controlling seizures, which can progress to either a convulsive or nonconvulsive status epilepticus [44]. Drugs used to treat malaria can also trigger [43].

CONCLUSION

Cerebral malaria (CM) is a severe neurological complication of *Plasmodium falciparum* infection. It is characterized by a coma at least 1 hour after a seizure or a hypoglycemia, asexual forms of *P. falciparum* on peripheral blood smears, with the absence of any other causes of the coma. CM patients may experience reduced levels of consciousness that can range from delirium, seizure, to coma as a result of brain hypoxia. Another important clinical characteristic in CM patients is malarial retinopathy. When malarial retinopathy is detected, diagnostic accuracy in fatal cases is significantly increased compared to standard clinical case definition. CM pediatric survivors may also experience neurologic sequelae including cognitive impairment, motor skills, visual coordination, and seizures. These neurological sequelae occurred on up to 25% of pediatric survivors.

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