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Neuro Psychiatric Manifestation Of “Malaria.

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INTRODUCTION

Despite intensive efforts over the last century to understand and control malaria, it remains a leading cause of morbidity and mortality in humans; An estimated 300-500 million people contract malaria each year, resulting in 1.5-2.7 million deaths annually.¹⁻² Malaria is caused by intraerythrocytic protozoa of the genus Plasmodium, with humans being infected by one or more of the following species: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi. Plasmodia are primarily transmitted by the bite of an infected female Anopheles mosquito. Infections can also occur

through exposure to infected blood products and by congenital transmission.² P. falciparum is responsible for the majority of severe and fatal malaria.³ As the term 'benign tertian malaria' implies, vivax malaria is usually an uncomplicated disease that runs a benign course and is rarely fatal.⁴ This clinical paradigm has been challenged recently by numerous reports of symptoms and signs of severe disease, and even deaths due to P. vivax mono-infections.⁴⁻¹⁰

The classic presentation of malaria consists of paroxysms of fever alternating with periods of fatigue but otherwise relative wellness. Symptoms associated with febrile paroxysms include high fever, rigors, sweats, and headache,

as well as myalgia, back pain, abdominal pain, nausea, vomiting, diarrhea, pallor, and jaundice.² However, classical presentation is seen in only 50%-70% of the cases with the rest having ; atypical manifestations. In endemic regions, malaria can present with unusual features due to .development of immunity, increasing resistance to antimalarial drugs, and the indiscriminate use of antimalarial drugs.¹¹ As a result of lack of awareness of atypical manifestations, it is not uncommon for malaria to get diagnosed late or even remain unrecognized, resulting in severe illness or death. We briefly review the atypical manifestations of malaria.

Path physiology in Malaria (Over view)

The development of severe malaria probably results from a combination of parasite-specific factors, such as adhesion and sequestration in the vasculature and the release of bio-active molecules, together with host inflammatory responses. The sequestration of red cells containing mature forms of the parasite (trophozoites and meronts) in the microvasculature is believed to cause the major complications of falciparum malaria, particularly cerebral malaria.¹² The sequestration of parasitized red blood cells (PRBCs) in the relatively hypoxic venous beds allows optimal parasite growth and prevents the PRBCs from being destroyed by the spleen. Sequestration is believed to be a specific interaction between

PRBCs and the vascular endothelium. The adhesion of the PRBCs to the vascular endothelium (cytoadherence) reduces the microvascular blood flow, which may explain organ and tissue dysfunction such as coma. The adherence of nonparasitized RBCs (NPRBCs) to PRBCs (resetting) and PRBGs to PRBCs (agglutination) have also been implicated in the pathogenesis of cerebral malaria. As the parasite grows .within the RBCs, the erythrocyte becomes less deformable and may contribute to the RBC destruction and impair the microcirculatory flow. The reduction in red cell deform-ability occurs not only in PRBCs, but also in the NPRBCs. The NPRBCs have to undergo considerable deformation as they squeeze through the sequestered microcirculation. Microvascular perfusion in severe falciparum malaria is, therefore, limited by mechanical obstruction, adherence of other RBCs, and the stiffness of the nonadherent RBCs. Blood concentrations of proinflammatory cytokines are raised in cerebral malaria, as in many severe infections in which inflannosome is involved. Tumor necrosis factor, a (TNF- α) upregulates endothelial cytoadherence receptors and can cause hypoglycemia and dyserythropoiesis, which are features of severe disease.¹²⁻¹⁷ Compared to the pathophysiology of falciparum malaria, there are large gaps in knowledge for vivax malaria. Because *P. vivax* preferentially infects young RBCs, parasitemias rarely exceed 2% of circulating RBCs, and high

parasite burdens are not a feature of severe disease. Because all stages of *P. vivax* are visible in peripheral blood, *P. vivax* is not believed to sequester or cause end-organ dysfunction. However, cytokine production during *P. vivax* infections is higher than *P. falciparum* infections of similar parasite biomass.¹⁴

Atypical neurological manifestations of malaria

Cerebral malaria

Cerebral malaria is one of the most common and potentially life-threatening complications of *P. falciparum* malaria and is characterized by unarousable coma.¹⁸ However, coma associated with *P. vivax* is rare, and its etiology is the least characterized of the syndromes associated with *P. vivax*. Cytoadherence phenomena are believed to be central to the etiology in *falciparum* malaria, but their role in *P. vivax* malaria remains unclear. Potential factors suggested are the presence of concurrent infections, mixed plasmodium infections, reversible local changes in the microvasculature, endothelial activation, and injury and microvascular thrombo-inflammatory responses.¹⁴ Convulsions are common, especially in children.¹⁸⁻²¹ Most seizures seem to be generalized, but electroencephalogram identifies a focal origin in many patients.¹⁸⁻²¹ Malarial encephalopathy is usually symmetric with localizing signs being noted infrequently. Neurological signs include depressed sensorium,

convulsions, passive resistance to neck flexion with divergent gaze, sixth nerve palsy, absence of abdominal reflexes, extensor plantars with variable tone, and deep tendon reflexes.^{18,20,21} Generalized hypertonia and opisthotonus may be observed in severe cases, suggesting brain stem dysfunction. Some signs (used in prognostic calculation) in children predict poor outcome. These include deep coma, decerebration, absence of corneal reflexes, convulsions on admission, and age < 3 years.²⁰

A variety of neuro-ophthalmological signs may be noted. Dysconjugate gaze is a common finding.²¹ Corneal and conjunctival reflexes are usually intact with symmetric pupils reacting normally to light. Papiiledema, although rare, is a poor prognostic sign.¹⁸ Retinal hemorrhages and unusual retinal 'whitening' may be observed.²¹ The prognosis of cerebral malaria worsens considerably with coexistent renal failure, severe jaundice, or metabolic acidosis.¹⁸

Subarachnoid hemorrhages have been described in patients with cerebral malaria. They usually occur due to the rupture of small vessels which get plugged by red cells in combination with severe thrombocytopenia and associated disseminated intravascular coagulation.^{24,25}

Other reported atypical neurological manifestations associated with cerebral malaria include central pontine myelinosis (CPM) and spontaneous subdural empyema.^{24,25} CPM occurs

in cerebral malaria as a result of ischemia and the toxic effects of the PRBCs in the cerebral microvasculature leading to capillary occlusion and damage.²⁵

Psychiatric manifestations

Psychiatric manifestations have been described as part of cerebral malaria or after recovery from coma.^{16,18,21} Confusional states, delirium with hallucinations and j transient amnesia, dementia, personality disturbances, and schizophrenia have been described. Agitation and confusion may develop after patient has recovered from coma. Psychiatric manifestations may be a presenting feature in patients with uncomplicated malaria in association with hyperpyrexia. Neuropsychiatric manifestations may also be caused by antimalarial drugs.²⁹⁻³⁰

Cerebellar ataxia

Cerebellar ataxia occurs in malaria due to extensive damage to the Purkinje cells of the cerebellum associated with hemorrhages, small infarction, and microglial infiltration. The prognosis is generally good without neurological deficit on follow-up.³¹⁻³³

Postmalaria neurological syndrome

Postmalaria neurological syndrome (PMNS) is defined as the acute onset of confusion, epileptic seizures, or any other neurological or psychiatric sign occurring with a latency of several days to weeks (generally within 2 months) after an episode of successfully treated

P. falciparum malaria.³⁴ Schnorf and others have divided PMNS into three subtypes: a mild and localized encephalopathy affecting the cerebellum and causing delayed cerebellar ataxia, a diffuse but not severe encephalopathy causing confusion with or without epileptic seizures, and a severe generalized encephalopathy resembling an acute disseminated encephalomyelitis, with usually a good response to steroid therapy.¹⁵⁻¹⁶ The pathogenesis of PMNS is unknown. It could be mediated immunologically as steroids are effective in some patients, but in mild cases, symptomatic treatment can result in spontaneous and favorable evolution, but in severe cases, corticosteroids are required to limit brain inflammation.³⁵⁻³⁷

Guillain-Barré syndrome

Guillain-Barre syndrome (GBS) associated with malarial infection has been reported.^{38,39} The exact pathogenesis of GBS following malaria infection is not known, but it is likely to be immunological. Another mechanism suggested for the development of polyneuropathy includes parasitic emboli obstructing vasa nervosum and causing anoxic stagnation, leading to temporary demyelination. Complete recovery after disappearance of parasitemia and establishment of normal blood flow in vasa nervosum have been reported. Release of neurotoxins, associated metabolic and nutritional disturbance, immune-mediated capillary damage, and release of free

radicals and TNF may also be responsible for the pathogenesis of GBS after *Rfalcipantm* infection.^{16, 38-40}

Isolated hemiparesis

Kochar et al have described a case of isolated hemiparesis in a 15-year-old female patient with *falciparum* malaria.⁴¹ The patient was conscious; hence, the hemiparesis was not associated with cerebral malaria. Computed tomography (CT) scan of the brain was suggestive of nonenhancing hypodense area in left frontoparietal region suggestive of infarction or vasogenic edema. The patient improved within / 2 months with no neurological sequelae.

Neurological sequelae

Despite adequate treatment, 3%-29% of survivors of cerebral malaria develop neurological sequelae in the form of psychosis, ataxia, hemiplegia, cortical blindness aphasia, pseudobulbar palsy, hearing defects, and extrapyramidal syndrome.¹⁸⁻²¹ These sequelae are more common in children. Some are transient, whereas others often improve over months, although they may not completely resolve.²¹ Van Hensbroek et al observed sequelae in 23.3% of children at discharge, which decreased to 4.4% at follow-up 6 months later. Cognitive and behavioral abnormalities were observed in 2% of survivors when assessed at 1 month. Depth and duration of coma and multiple convulsions were independent risk factors for these sequelae."

Kochar et al in their study of 441 patients with cerebral malaria noted the following neurological sequelae in survivors: psychosis (5.06%), cerebellar ataxia (4.72%), hemiplegia (1.68%), extrapyramidal rigidity (1.35%): peripheral neuropathy (1.01%), EPR with trismus (0.33%), and isolated sixth nerve palsy (0.33%). All patients showed complete recovery on follow-up.⁴³ Epilepsy can occur as a late complication of cerebral malaria.^{18,21,44,45} Generalized tonic-clonic seizures as well as partial motor seizures have been reported. Several pathogenic mechanisms have been proposed: vascular/ischemic mechanism, neurotoxic effects, 'malaric granulomas of Durck', genetic mechanisms, and antibodies against voltage-gated channels.⁴⁴⁻⁴⁵

Cerebral venous thrombosis

Cerebral venous sinus thrombosis has been reported in those with severe *P. falciparum* malaria. The mechanism of thrombosis is still unclear and may be multifactorial. Altered phospholipid in malaria-infected red cells causes increased von Willebrand factor and other coagulation factors. In addition, endothelial damage by malaria-infected red cells releases tissue factor and other cytokines, resulting in a hypercoagulable state.^{46,47}

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