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Case Report

Imaging features of fulminant cerebral malaria: A case report ☆,☆☆

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ABSTRACT

Cerebral malaria is associated with high mortality and morbidity in patients infected with Plasmodium Falciparum. The mechanisms of cerebral malaria include sequestration of parasitized red blood cells in brain capillaries, production of cytokines, immune cell/platelet accumulation, and release of microparticles, resulting in disruption of the blood-brain barrier, which caused brain injuries. The severity of this reflects on neurological findings ranging from simple delirium to profound coma. We herein present unique magnetic resonance imaging findings of a case of fulminant cerebral malaria as computed tomography studies usually underestimate the extent of cerebral involvement in malaria.

Introduction

Parasitic diseases of the central nervous system (CNS) are associated with high morbidity and mortality, especially in resource-limited settings. Parasites are a diverse group of organisms that can be broadly classified into single-celled organisms (ie, protozoa) or multicellular helminths (ie, metazoa) [1].

Helminths or protozoa enter the CNS and cause meningitis, encephalitis, ventriculitis, myelitis, ischemic stroke, bleeding, venous thrombosis or cerebral abscess, clinically manifesting as headache, epilepsy, weakness, cognitive decline, impaired consciousness, confusion, coma or focal neurological deficits [2].

In 2011, an estimated 3.3 billion people were at risk of malaria, with Plasmodium Falciparum (PF) species being a major cause of morbidity and mortality worldwide, with a high incidence in many developing countries including certain regions in Southeast Asia and Africa. Cerebral malaria (CM) is a life-threatening complication seen in 2% of malaria cases, particularly due to PF, with an estimated mortality rate of between 15% and 25%. It is traditionally defined as malaria parasitemia, with impaired level of con-

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sciousness (LOC), and no other etiology causing impaired LOC [3].

The WHO definition of severe imported malaria was modeled by the French presentation in 1999 and revised in 2007 and 2017. It defined CM both in adults and children similarly to malaria parasitemia associated with encephalopathy-related symptoms of drowsiness, prostration, confusion, disturbances in consciousness with a GCS score <11, and convulsions [4].

Uncomplicated malaria involves nonspecific findings including fever, chills, headache, myalgia, abdominal pain, diarrhea, and cough, while severe malaria with cerebral involvement includes neurological manifestations ranging from simple delirium to profound coma. In adults, seizures are uncommon compared with children where the incidence is around 30% in endemic areas [5].

The exact pathophysiology of CM is yet to be further elucidated; but is associated with sequestration of parasitized red blood cells in brain capillaries, with local release of inflammatory cytokines, leading to impaired microcirculatory perfusion disturbed blood-brain barrier, and local cytotoxic effect [6]. Fundoscopy of the retina can identify abnormalities specific to the cerebral microcirculation and has been considered an important diagnostic predictor in patients with CM [7].

On brain autopsy the pathologic findings of classic CM include a variable combination of the following findings: swollen edematous brain with or without frank herniation, white matter, cerebral and cerebellar cortices petechial hemorrhages which correspond to ring hemorrhages centered around small capillaries, and usually contain parasite-derived pigment and fibrin thrombi. Evidence of sequestered pigmented parasite-infected erythrocytes within the lumen of small cerebral and cerebellar vessels, presence of macrophages containing parasite pigment granules (ie, hemozoin), and hypertrophied and denuded endothelial cells [5,8].

Case presentation

A 33 years old Brazilian male with no past medical history, worked as an airline crew and had a history of recent travel to South Africa. He presented to the emergency department with a high-grade fever for 5 days, which got worse in the past 24 hours in addition to abdominal pain. On Clinical examination, he was drowsy but had no focal neurological deficit. His laboratory investigations showed high WBC, anemia, thrombocytopenia, lymphocytosis, and other evidence of multiorgan failure. And serology was positive for malaria PF. After a more detailed investigation, it was found that the patient did not receive adequate antimalarial medications before travel. There was also no past family history of Malaria infection. A day later, the patient's level of consciousness and vital signs deteriorated. Therefore, he was intubated and admitted to the intensive care unit (ICU). Head CT scan excluded acute intracranial bleeding.

Further MRI was undertaken because of suspicion for intracranial pathology and showed swelling and heterogeneous hyperintense signal in T2-weighted and Fluid attenuated inversion recovery (FLAIR) sequences in bilateral globus pallidus, and corpus callosum. There were also diffuse microhemorrhagic changes in bilateral basal ganglia, corpus callosum, superficial and deep white matter in susceptibility-weighted images (SWI) (Fig 1) and corresponding diffusion restriction in basal ganglia and corpus callosum as well as hippocampi, and parasagittal frontoparietal gyri (Fig 2). After 2 weeks in the ICU with supportive treatment and antimalarial medications, the patient was tracheostomized. He stayed in the ICU for 1 week and was then discharged for outpatient rehabilitation as he developed quadriparesis.

Discussion

In a French study of 400 adults admitted to the ICU for severe imported malaria, 32% had strictly defined cerebral malaria, and in these patients, mortality was 28%, and sequelae were observed in 21.5% of survivors [15].

Different studies on neuroimaging findings in cerebral malaria were undertaken. Newton et al. performed CT on 14 Kenyan children with CM and disturbed LOC. Eight of them showed diffuse brain swelling, likely due to severe intracranial hypertension (confirmed in 2 in whom intracranial pressure was monitored), with 4 children with latter serious neurological sequelae also showing widespread low-density areas, the pattern of which was suggestive of critical reduction of cerebral perfusion, versus hypoglycemia, or status epilepticus. And suggested that brain injury in cerebral malaria may not be only due to the direct effect of intravascular sequestration but also in part due to secondary systemic and intracranial factors [9].

Potchen et al. [7] described computed tomography (CT) findings in children with retinopathy confirmed cerebral malaria, they reported diffuse cerebral and deep gray matter nuclei edema and cerebral infractions in multiple large vessel territory, children with protracted coma with ultimate fatal outcome had additional CT findings of posterior fossa and brain stem edema, multiple large vessel infarcts, and basal ganglia edema. Among the survivors with neurological sequelae neurological deficit and seizures, focal and multifocal cerebral and cerebellar lesions with consequent atrophy and gliosis on follow-up CT were identified.

Potchen et al. studied acute brain MRI findings in a cohort of 152 children with defined cerebral malaria. The MRI brain abnormalities were most commonly noted in patients with associated CM-related retinopathy and included markedly increased brain volume, abnormal T2 signal intensity, and DWI abnormalities in cortical, and deep gray matter, as well as white matter structures. The most common finding on initial imaging during the acute presentation was abnormal T2 signal intensity (SI) in the basal ganglia ranging from minimal to marked increased T2 SI with swelling and associated mass effect [10]. Cordoliani et al. [11] reported imaging findings in 3 cases with cerebral malaria, including cortical infarct in 1 case, diffuse white matter T2 hyperintensity in 1 case reflecting edema, and multifocal T2 hyperintense white matter lesions which he attributed to ischemia or toxic injury.

Nickerson et al. also reported MRI changes similar to our index case with diffuse petechial hemorrhages throughout the gray-white matter junction, corpus callosum, and inter-

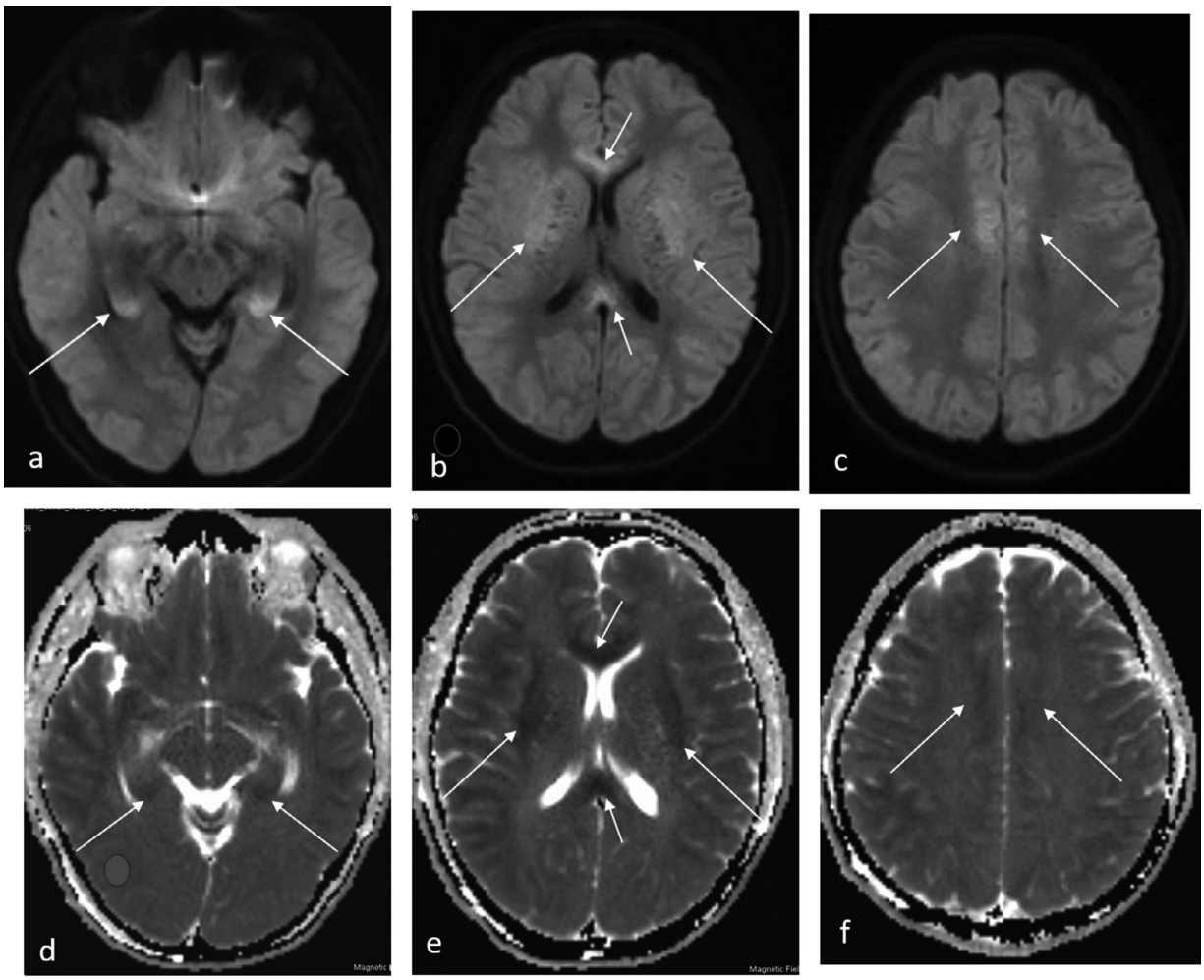

Fig 1 – Axial MRI images, Diffusion weighted images (DWI) long b value (1000), and apparent diffusion coefficient ADC map at the level of temporal lobes (A, D), basal ganglia (B, E), and high convexity (C, F) respectively, showing diffusion restriction with increased DWI signal and low ADC signal in hippocampi (arrows in A, and D), basal ganglia and corpus callosum (long and short arrows respectively in B, and E), and high convexity parasagittal frontal gyri (arrows in C, and F). The diffusion restriction reflects underlying cytotoxic edema or ischemia.

nal capsules on SWI likely representing the histopathological finding of ring microhemorrhages. They also reported edema with multifocal T2 hyperintensities of the corpus callosum and posterior limb of internal capsules likely due to ischemia following microvascular plugging by clumped PF-infected RBCs [12]. This phenomenon of sequestration has been shown to be quantitatively linked to premortem coma in CM patients [13].

Rasalkar et al. described the MRI features in 4 cases of CM all of which revealed bi-thalamic infarctions with or without hemorrhages, in addition to acute hemorrhagic infarctions in the brain stem, cerebellum in 1 patient, cerebral white matter and insular cortex in 2 patients. In this series, the patient with the cerebellum and brain stem involvement died, whereas the remaining 3 survived with antimalarial and supportive treatment, with a follow-up MRI showing resolution of the thalamic infarctions [14].

Yadav et al. [15], in 3 patients with CM, demonstrated MRI findings of multifocal hyperintensities in bilateral periventricular white matter, corpus callosum, occipital subcortex, and bilateral thalami, seen on MRI T2-weighted and FLAIR sequences, with no enhancement on postcontrast T1-weighted images, or restricted diffusion on diffusion-weighted sequence (DWI).

Mohanty et al. in a study of 27 hospitalized Indian patients with CM and reduced LOC. The 11 nonfatal cases (5 adults and 6 children), showed clinical and radiological characteristics with posterior reversible encephalopathy-like (PRES-like) features, with various degrees of cortical and subcortical swelling at baseline MRI with predominate posterior distribution, involving the occipital/parietal and temporal lobes and sparing the frontal lobe, with increased signal intensity on T2-weighted and FLAIR sequences and facilitated diffusion on DWI series consistent with vasogenic edema, with overall rapid recovery seen in 3/5 adults and 5/6 children (reversible on follow up MRI at 48-72 hours). Along with the additional presence of cytotoxic edema in the basal nuclei in 5/11 patients with restricted diffusion on DWI. All 11 patients showed

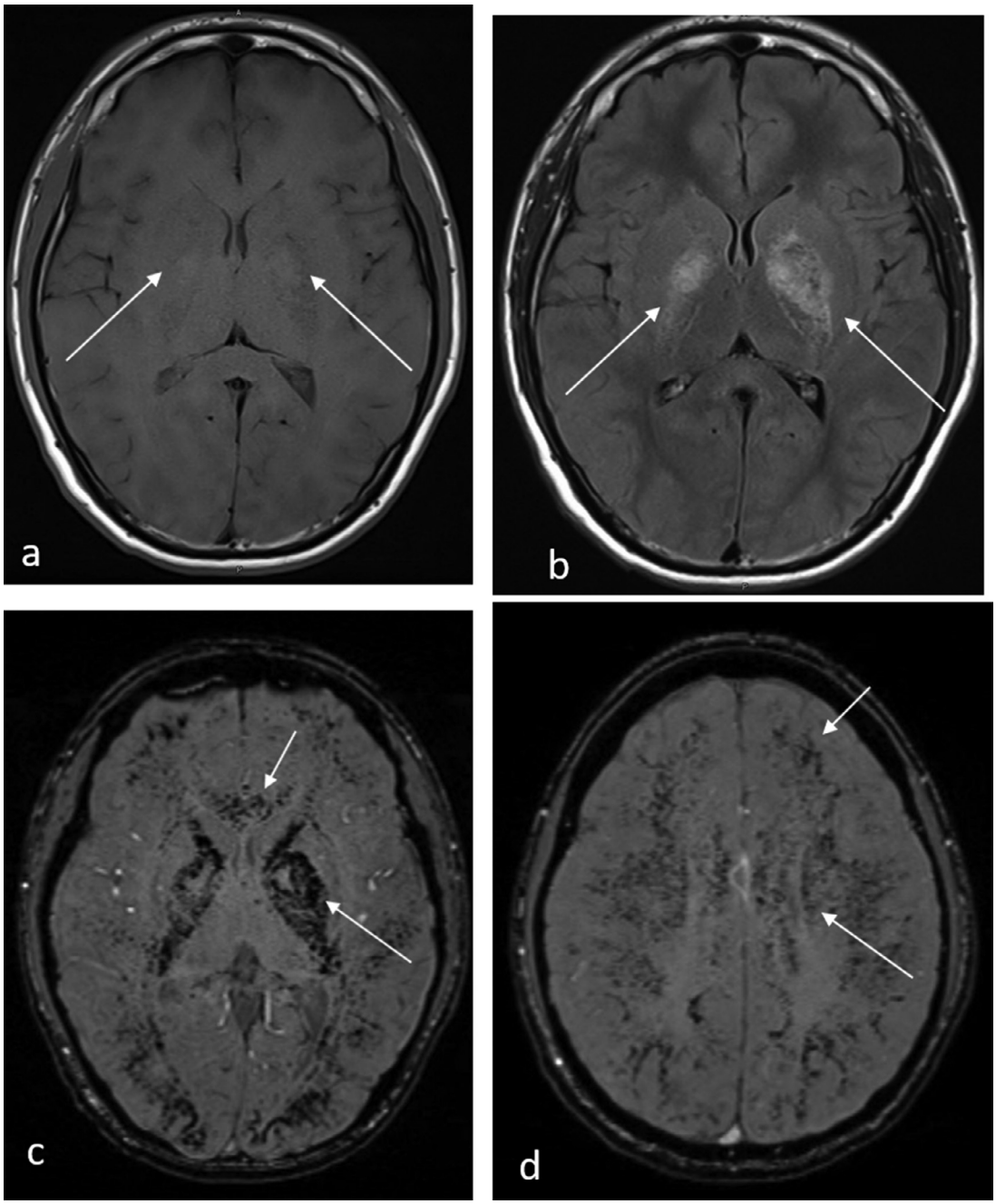

Fig 2 – Axial MRI images, T1WI (A) and FLAIR/T2 (B) at the level of basal ganglia showing subtle low signal on T1WI, and swelling (edema) and bright signal on T2 (arrows in A, and B). Axial susceptibility weighted image at the level of basal ganglia (C), and high convexity (D), showing diffuse punctate blooming foci in basal ganglia and corpus callosum (long and short arrows in c respectively, and centrum semiovale and subcortical white matter (long and short arrows respectively in D). These blooming foci correspond with numerous microhemorrhagic changes. The findings of edema, ischemia, and microhemorrhages in cerebral Malaria are likely related to microcirculatory sequestration and plugging by clumped PF-infected RBCs with disruption of blood-brain barrier.

perfusion parameters (increased cerebral blood volume (CBV), minimally delayed cerebral blood flow (CBF), and slow mean transit time (MTT) consistent with vascular engorgement contributing to parenchymal hypoperfusion, as well as to blood-brain barrier dysfunction. The 11 patients had a complete neurological recovery in 1 month [16].

Saavedra-Lozano et al. [17], reported a case of severe cerebral malaria with preferential cerebellar diffuse cytotoxic edema presenting as diffuse T2 hyperintensity, swelling, and diffusion-weighted restriction, with significant compression of the fourth ventricle, resulting in severe obstructive hydrocephalus. Other rare reported neu-

roimaging findings include central pontine myelinolysis [18].

On the other hand, neuroimaging can be negative showing no abnormalities or subtle increased brain volume, as demonstrated by Looareesuwan et al. [19], in a study of 24 patients with confirmed CM, likely representing less severe CM changes in a retinopathy-negative cohort with less severe micro-circulatory changes and mild vasodilatation, and possibly correlates with the retinopathy negative CM cases with negative MRI findings as described by Potchen et al. [10].

The imaging appearances as in our index case, of diffuse brain swelling and associated extensive foci of cytotoxic edema and/or microbleeds are rather nonspecific, with differential considerations including viral encephalitis (Herpes simplex, nonherpitic, COVID-19), critical illness associated microbleeds, high-altitude exposure acute respiratory distress syndrome, diffuse cerebral fat embolism, disseminated intravascular coagulation, severe diffuse axonal injury, sporadic cerebral amyloid angiopathy, and diffuse minute hemorrhagic cerebral metastases [20].

Critical illness-associated cerebral microbleeds typically diffusely involve the juxtacortical white matter and corpus callosum and spare the deep and periventricular white matter, gray matter, basal ganglia, and thalami. High-altitude exposure to acute respiratory distress syndrome microbleeds have similar appearances and distribution to critical illness–associated microbleeds, suggesting that hypoxia-induced hydrostatic or chemical effects on the blood–brain barrier could potentially account for extravasation of erythrocytes. Sporadic cerebral amyloid angiopathy affects the older age group, and can extensively involve the gray matter and subcortical white matter, typically sparing the deep white and gray matter, and with less extensive corpus callosum involvement [20]. Diffuse microhemorrhagic metastasis, severe diffuse axonal injury, and diffuse type 2C cerebral fat embolism follow specific clinical scenarios.

In the literature, autopsy-based studies of malaria have inherent limitations as data are generated from a single point in time (after death), preventing the assessment of dynamic changes during the process of the pathology. Brain CT scans may not accurately differentiate between vasogenic or cytotoxic edema changes. On the other hand, advanced MRI techniques provide an in-depth assessment of not only structural but also functional changes in the brain in patients with CM, including evaluation of edema, hemorrhage, and ischemia. Yet, there might be discrepancies between studies due to a small number of patients enrolled, a heterogeneous patients population, or the different points at which the MRI scans have been acquired. Also, the brain MRI findings in patients with CM can be related to multiorgan failure rather than "pure'' CM manifestations [21]. Though, brain MRI can provide important information about disease severity and prognosis.

Conclusion

Cerebral malaria is one of the devastating CNS parasitemia, complicating malaria infection, especially with plasmodium falciform. The brain imaging manifestations reflect the severity of brain involvement with microcirculatory sequestration and plugging by clumped PF-infected RBCs with disruption of blood-brain barrier leading to edema, ischemia, and microhemorrhages. In our case, the brain MRI findings included swelling and edema of the bilateral globus pallidus and corpus callosum. There were also cytotoxic edema and diffuse microhemorrhagic changes in bilateral basal ganglia, corpus callosum, superficial and deep white matter. MRI is recommended in such cases because of its sensitivity in demonstrating imaging features, which in the appropriate clinical context helps in establishing the diagnosis, leading to early treatment and improved clinical outcomes.

Patient consent

In this case report, "Imaging Features of Fulminant Cerebral Malaria: A Case Report,", informed consent and permission to publish were obtained from the patient regarding the clinical, ophthalmologic, and radiologic data of the case. However, no personal information or images of patients or any other individuals are used in this publication.

Written consent is retained by the authors, and a copy is available to the journal if needed.

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