Perspective

Cerebral Malaria: A New Way Forward with Magnetic Resonance Imaging (MRI)

Sornchai Looareesuwan,† Jiraporn Laathamatas, Truman R. Brown, and Gary M. Brittenham*
Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Faculty of Tropical Medicine, and
Department of Radiology, Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok, Thailand;
Departments of Radiology and Biomedical Engineering and of Pediatrics and Medicine,
College of Physicians and Surgeons, Columbia University, New York, New York

Abstract. Magnetic resonance studies offer a new way through the impasse that now seems to block further progress in disentangling the pathogenesis and improving the treatment of cerebral malaria, a catastrophic neurologic complication of infection with Plasmodium falciparum. The underlying mechanisms responsible for coma in cerebral malaria are still unknown and the relative contributions of the microvascular sequestration of infected erythrocytes, the inflammatory response to P. falciparum, disordered hemostasis, and other factors remain controversial. For more than a century, neuropathologic studies have provided the basis for concepts of causation of cerebral malaria. Magnetic resonance techniques now offer non-invasive means of determining essential anatomic, metabolic, biochemical, and functional features of the brain in patients with cerebral malaria during life that could transform our understanding of the pathogenesis of cerebral malaria and lead to the development of new neuroprotective treatments.

Magnetic resonance studies offer a new way through the impasse that now seems to block further progress in disentangling the pathogenesis and improving the treatment of cerebral malaria, a catastrophic neurologic complication of infection with Plasmodium falciparum. In many parts of the world, this complex syndrome of potentially reversible encephalopathy with coma is the most common clinical presentation and cause of death in patients with falciparum malaria. In those who survive, persistent neurocognitive defects are now recognized, affecting up to one in four children in sub-Saharan Africa who recover from the acute episode. The underlying mechanisms responsible for coma in cerebral malaria are still unknown and the relative contributions of the microvascular sequestration of infected erythrocytes, the inflammatory response to P. falciparum, disordered hemostasis, and other factors remain controversial. Treatment continues to consist only of administration of antimalarials with emergency supportive care, including management of hypoxemia, hypoglycemia, hypervolemia, shock, anemia, metabolic acidosis, and seizures; no specific or neuroprotective therapy is available.

For more than a century, neuropathologic studies have provided the basis for concepts of causation of cerebral malaria. The studies examine only patients who die, typically after antimalarial treatment, using tissue specimens obtained at various times after death. Their findings provide information about the end result rather than the course of the disease. Although comparisons have been made between fatal and surviving cases using biochemical, immunologic and pathologic examinations of tissue obtained by biopsy or of cerebrospinal fluid, blood, urine, or other body fluids, the resulting data are generally indirect. In addition, their interpretation is subject to limitations arising both from the details of metabolism and clearance of the disease indicator studied and from the specific assays used. Genetic approaches and observations in experimental systems in vitro have made important contributions but their interpretation and application are also problematic. In some circumstances, animal “models” provide alternative means of examining the biologic origins of a disorder. Rodents and primates may be infected with natural species of malaria but the manifestations and progression of these animal malarias differ from those of P. falciparum. In particular, the histopathologic hallmark of human cerebral malaria—sequestration of infected erythrocytes within the cerebral microvasculature—is absent. Magnetic resonance techniques offer a non-invasive means of determining essential anatomic, metabolic, biochemical, and functional features of the brain in patients with cerebral malaria during life. Magnetic resonance imaging (MRI) can provide sensitive detection of structural lesions, edema, hemorrhage, and thrombosis. Time of flight magnetic resonance angiography (TOF-MRA) can detect macroscopic vascular stenosis and, together with diffusion-weighted (DWI) images, identify effects on distal cerebral perfusion, such as diffusion-perfusion mismatch. Measurement of cerebral blood flow using arterial spin labeling (ASL) techniques can provide information about regional tissue perfusion on a scale of millimeters. Functional magnetic resonance studies (fMRI) are methodologically complex, in part because the coupling between neural activity and local cerebral blood flow almost certainly is different in patients with cerebral malaria and in healthy controls. Despite these difficulties, fMRI studies have the potential to provide information on the regional distribution of neural activity during coma and recovery that could help determine whether the severe neurologic dysfunction of cerebral malaria has its origin in specific regions of the brain or is the product of a global, diffuse process. Proton magnetic resonance spectroscopy (1H MRS) can measure lactate, a key indicator of the severity of the pathologic processes responsible for cerebral malaria and an important independent predictor of poor outcome. In addition, 1H MRS can determine N-acetylaspartate, an index of axonal integrity, providing a means of detecting diffuse axonal damage. Moreover, 1H MRS can quantify total creatine (an indicator of intact energy metabolism), myo-inositol (potentially, an astrocyte marker), glutamate (the principal excitatory neurotransmitter), glutamine (the amination product of glutamine in astrocytes), and choline compounds (involved in membrane turnover). 13P magnetic resonance spectroscopy (31P MRS)
permits assessment of brain bioenergetics by measurement of adenosine $5'$-triphosphate, phosphocreatine, inorganic phosphate, and intracellular pH. Magnetic resonance examinations of mice infected with *Plasmodium berghei* ANKA have documented the applicability of most of these techniques in vivo. No magnetic resonance method has been developed to detect microvascular sequestration of infected erythrocytes but perfusion maps derived from ASL, fractional anisotropy maps from diffusion tensor imaging (DTI), and diffusional kurtosis imaging (DKI) offer promising approaches. In the future, other imaging methods, such as positron emission tomography (PET), may also become feasible in malaria-endemic areas.

Magnetic resonance examinations of patients infected with *P. falciparum* could transform our understanding of the pathogenesis of cerebral malaria. Until now, almost all MRI studies have involved unsystematic examinations of single or small series of patients who developed cerebral malaria after travel to an endemic area. The first (and still only) MRI study of a series of malaria patients living in an endemic area—more than a decade ago, using a 0.2 Tesla scanner—showed that cerebral edema is not consistently found in living patients with cerebral malaria and consequently cannot always be the cause of their coma. The current generation of clinical magnetic resonance instrumentation now operates at 3.0 Tesla and the methods listed above have been refined or developed substantially in the years since this first study. Clinical MRI units are now available in or near some endemic areas and reports of single cases and small numbers of patients with cerebral malaria are beginning to appear. Despite an array of technical and logistic challenges, these clinical MRI facilities can be adapted for investigational use. We now need research teams and resources to overcome the challenges of using magnetic resonance techniques for the study of cerebral malaria. Over the past 30 years, billions of dollars have been invested in the development of magnetic resonance methods for studies of disorders affecting the developed world. Application of these methods to the study of malaria could provide enormous dividends in advancing our understanding of this scourge of the developing world and lead to the development of new neuroprotective treatments.

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Authors’ addresses: Jiraporn Laothamatas, Advanced Diagnostic Imaging and Image-guided Minimally Invasive Therapy Center, Siririk Medical Building, Ramathibodi Hospital, Mahidol University, Rama VI Road, Ratchawat, Bangkok 10400, Thailand, Tel: +66-2-246-0024, Fax: +66-2-354-7233, E-mail: laothamatas@gmail.com. Truman R. Brown, Columbus University College of Physicians and Surgeons, Hatch Magnetic Resonance Research Center, 710 West 168th Street, New York, NY 10032, Tel: 212-305-1864, Fax: 212-342-5773, E-mail: trb11@columbus.edu. Gary M. Brittenham, Columbus University College of Physicians and Surgeons, Children’s Hospital of New York, Room CHN 10-08, 3959 Broadway, New York, NY 10032, Tel: 212-305-7005, Fax: 212-305-8428, E-mail: gm351@columbia.edu.

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