Neurological sequelae of pediatric *Plasmodium falciparum* cerebral malaria in sub-Saharan Africa: A brief overview

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Abstract

Cerebral malaria, characterized by multiple seizures, coma, and other neurological abnormalities, is a particularly devastating complication of *Plasmodium falciparum* malaria. Children in sub-Saharan Africa comprise the most susceptible group to cerebral malaria worldwide, with more than 575,000 cases each year. Long-term neurological deficits – including motor impairments, language regression, cognitive deficits, behavioural abnormalities, and epilepsy – occur in approximately 25% of child survivors of cerebral malaria, which is now recognized as the leading cause of childhood neurodisability in sub-Saharan Africa. These neurological sequelae generate an enormous economic and social burden as child survivors' impaired intellectual function and learning abilities have a substantial impact on their prospects for education and future employment. The aim of this article is to provide a brief overview of the current literature on the neurological sequelae of pediatric cerebral malaria, as well as offer suggestions for future research. While the current understanding of risk factors, disease mechanisms, and treatments for these neurological deficits is lacking, recent studies have shown great promise in revolutionizing the way that cerebral malaria is diagnosed and treated. It is speculated that an inflammatory response to malarial antigens in neural blood vessels triggers a cascade of events that ultimately results in cerebral tissue damage, high intracranial pressure, and hemorrhaging into the brain, resulting in long-term brain damage. Potential risk factors for neurological deficits include the duration of coma, the occurrence of multiple seizures, and high fever. Malaria retinopathy, angiopoietin-1 and -2, and EEG patterns are being investigated as potential biomarkers to improve the definitive diagnosis of cerebral malaria. New drug therapies that endeavor to prevent long-term neurological deficits after cerebral malaria include erythropoietin and statins, as well as cognitive rehabilitation and physical and speech therapy, the latter having been shown to be successful among survivors.

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Introduction

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium* that are transmitted by Anopheles mosquitoes. In 2017, an estimated 219 million people were infected with malaria worldwide, the vast majority of whom (92%) were located in sub-Saharan Africa,[1] where it is one of the leading causes of death.[2] Each year, *Plasmodium falciparum* malaria – the most lethal form of the disease – causes 435,000 deaths in this region.[1] This form of malaria often produces fever, jaundice, anemia, hypoglycemia, metabolic acidosis, and multi-organ failure, and has the potential to develop into cerebral malaria. This particularly life-threatening complication occurs when parasitized red blood cells break through the blood-brain barrier and sequester in the neural microvasculature. Cerebral malaria is characterized by multiple seizures and coma, among other neurological signs.[3] More than 575,000 cases of cerebral malaria occur in children in sub-Saharan Africa each year, meaning that they comprise the most susceptible group to the disease worldwide.[4]

Cerebral malaria has been linked to long-term neurological deficits in child survivors of the disease since the early 1970s, when British researchers working in Uganda observed a connection between the onset of pediatric neurological disorders and a history of "catastrophic, feverish illness", such as that observed in cerebral malaria.[5] The first comprehensive evaluation of the neurological effects of pediatric cerebral malaria was conducted in Ghana in 1995.[6] It was determined that poor performance in memory, attention, and sensory processing tasks were correlated with a previous episode of cerebral malaria. Since then, however, only a small number of studies have focused on the association between cerebral malaria and neurological sequelae. In fact, a 2006 systematic review of the effect of *Plasmodium falciparum* malaria on cognition, which analyzed all relevant research that had been published at the time, included only eighteen studies.[7]

Recently, however, substantial interest has been generated on this topic, with the publication of the first series of comprehensive, controlled prospective studies examining the neurological sequelae following pediatric cerebral malaria[8,9] as well as the publication of the first study to investigate the possibility of cognitive rehabilitation in these patients.[10] It has been determined that approximately 25% of child survivors of cerebral malaria exhibit long-term neurological deficits, including motor deficits, language regression, cognitive impairment, and behavioural abnormalities for at least six months following an episode of cerebral malaria, and 10% develop epilepsy.[4] If these results can be generalized, then it is hypothesized that neurological impairment

due to cerebral malaria may occur annually in 36,000 children between the ages of five to nine years old in sub-Saharan Africa.[8] To exacerbate this problem, a 2008 review of retrospective studies has suggested that these cognitive deficits may persist for as long as three to nine years after recovery from the original episode of cerebral malaria.[9] As a result, cerebral malaria is now recognized as the leading cause of childhood neurodisability in sub-Saharan Africa.[11]

Finally, in addition to inducing significant morbidity and mortality in children, cerebral malaria and its consequent neurological sequelae also generate an enormous economic and social burden in sub-Saharan Africa. Primary school students in Kenya miss an average of 11% of school days per year as a result of malaria.[12] This absenteeism increases failure rates, repetition of school years, and drop-out rates, thus resulting in a notable loss of educational attainment that students may otherwise have achieved. Even more alarming is the reality that fully one quarter of survivors of cerebral malaria experience long-term neurological sequelae, including behavioural disorders, impaired intellectual function and learning ability, and diminished ability to perform executive functions. Undoubtedly, this cascades into a negative impact on the survivors' prospects for education and future employment.[12]

It is clear that the study of the neurological deficits observed in survivors of pediatric cerebral malaria is of immense public health significance. The aim of this article is to provide a brief overview of the symptoms and diagnosis, risk factors, pathogenesis, and treatment of the neurological sequelae of cerebral malaria, as well as to offer suggestions for future research.

Symptoms and Diagnosis

Symptomatology and Diagnostic Criteria

The clinical manifestation of *Plasmodium falciparum* malaria differs depending on the severity of the disease. Clinicians often distinguish between uncomplicated malaria, severe (non-cerebral) malaria, and cerebral malaria when treating patients and estimating their prospects for recovery.[13] This clinical distinction between different positions on the disease spectrum is important, as each is associated with a different prognosis, and only the patients suffering from cerebral malaria will develop neurological deficits.

The symptoms of the least severe form of malaria, uncomplicated malaria, consist of fever, chills, sweats, headache, nausea, vomiting, and general malaise. It is diagnosed by the detection of malaria parasites in the blood via microscopy and has excellent survival prospects assuming that treatment is provided.[13] Severe non-cerebral malaria, while demonstrating no neurological involvement, is a medical emergency, wherein patients often suffer from severe anemia, acute respiratory distress syndrome, hypotension, multi-organ failure, hyperparasitemia, metabolic acidosis, and hypoglycemia.[13]

By definition, cerebral malaria is diagnosed when a patient in a malaria-endemic region exhibits: (i) impaired consciousness at least one hour after a seizure, (ii) positive peripheral blood smears for asexual forms of malaria parasites, and (iii) other causes for encephalopathy are excluded.[14] Since older children and adults in sub-Saharan Africa tend to develop immunity to malaria, the majority of cases of severe and cerebral malaria occur in children under the age of five.[4] The case fatality rate of cerebral malaria is estimated to be 15%. Among those who survive, more than 20% will exhibit neurological deficits.[11]

Generally, the neurological sequelae observed in survivors of cerebral malaria immediately after the malaria episode include cortical blindness, deafness, severe cerebral palsy, hemiplegia, hemiparesis, ataxia, spasticity, speech problems, cognitive impairment, and epilepsy.[15] However, some of these symptoms resolve automatically. For instance, it has been shown that blindness generally disappears completely after 6 months[16] and gross motor deficits (hemiplegia, diplegia, quadriparesis, dystonia, and ataxia) disappear within several weeks.[11] On the other hand, no improvement has been shown in either speech problems (aphasia and dysarthria), as assessed at the 6 month post-episode mark,[16] nor subtle cognitive deficits.[8] A 2008 study determined that at two years after release from hospital, children who had experienced cerebral malaria had a 3.76-fold increased risk for a cognitive deficit (specifically in the area of attention) compared with age-matched controls,[9] while a 2001 study determined that when compared to controls, children who had experienced cerebral malaria exhibited significantly impaired attentiveness, behaviour, and language development at 42 months after hospital release.[15] More recently, a 2019 exposure-control study examining 85 survivors of cerebral malaria established that half of these survivors were neurodevelopmentally impaired at one year after hospital discharge, which is 4.5 times greater than for age-matched controls.[16] Furthermore, patients who develop severe epilepsy as a result of cerebral malaria generally do not improve over time, and a minority of those with multiple seizure types (experiencing more than 10 seizures a day) are not responsive to medication.[17] In a 2007 retrospective study assessing neurological deficits in 7,281 survivors of cerebral malaria, behavioural problems were observed in approximately 11% of patients, including hyperactivity, violent and impulsive behaviour, hallucinations, excessive eating, and fear or anxiety. These behavioural symptoms commenced several months after the patients were discharged from hospital.[18] Clearly, the neurological sequelae of cerebral malaria can be devastating for patients and their families.

Screening

There exists a relative ambiguity in the current diagnostic criteria for cerebral malaria due to the high rates of asymptomatic parasitemia.[19] At present, definitively diagnosing cerebral malaria is quite challenging. According to an autopsy study, 23% of children who had met the diagnostic criteria for cerebral malaria actually had a non-malarial cause of coma and death.[11] This aforementioned ambiguity is further exacerbated in sub-Saharan Africa by the paucity of neurodiagnostic resources. Therefore, considering the significance of the disease's long-term neurological consequences, it would be beneficial to develop a biomarker that could instantly determine the presence and severity of the disease, or the likelihood of the disease progressing further.

There are several cerebral malaria biomarker candidates currently being researched. Malaria retinopathy appears to be one of the most promising candidates given that in cases of cerebral malaria, examination of the ocular fundus by ophthalmoscopy reveals hemorrhaging, retinal whitening, vessel abnormalities,

and papilledema.[20] With regard to the pathophysiologic mechanisms of these findings, papilledema is caused by raised intracranial pressure resulting from brain swelling, retinal whitening is a result of local tissue hypoxia, and abnormal retinal vessels are caused by the sequestration of parasitized red blood cells.[21] The combination of these aforementioned retinopathy characteristics is unique to cerebral malaria and when used as a diagnostic tool, it has been found to be 95% sensitive.[11]

Two other encouraging biomarker candidates are angiopoietin-1 and angiopoietin-2, which are vascular growth factors involved in endothelial activation and integrity. Elevated plasma or serum levels of these two factors are correlated with malaria of varying severity, and allow for the differentiation between uncomplicated, severe, and cerebral malaria.[22] Compared to uncomplicated malaria, there are significantly lower levels of angiopoietin-1 and higher levels of angiopoietin-2 detected in patients with severe malaria or cerebral malaria. Further, in patients with severe malaria, there are significantly lower levels of angiopoietin-1 levels when compared to patients with cerebral malaria.[23]

Recently, electroencephalography (EEG) has begun to be investigated as a potential prognostic tool. A 2018 study of 281 children with cerebral malaria in Uganda and Malawi determined that specific EEG findings on admission – namely lower average voltage, lower maximum voltage, slower dominant frequencies, focal slowing, and a lack of reactivity – were able to predict neurological morbidity and mortality.[24]

Given the multitude of biomarkers currently in development, it is hoped that they will soon serve an important role in the rapid and accurate diagnosis of cerebral malaria in children throughout sub-Saharan Africa.

Risk Factors

In light of the fact that 25% of child survivors of cerebral malaria develop some form of neurological deficit, there is significant utility in determining not only which specific risk factors are associated with the development of neurological sequelae, but also why 75% of patients do not develop long-term symptoms.[4] Precise knowledge of the factors involved would allow physicians to target specific components of the disease in in order to prevent unnecessary brain damage from occurring.

Numerous studies have examined the potential risk factors that correlate with subsequent development of neurological sequelae; however, they report conflicting results. Some studies maintain that the depth and duration of coma as well as the occurrence of multiple seizures in the context of cerebral malaria are risk factors for neurological deficits,[25] while others report that only the number of seizures before hospital admission and the duration of coma are relevant.[8] Additional studies have implicated intracranial hypertension and hypoglycemia,[4] as well as duration of fever.[16] Finally, one cohort study has reported that a higher maximum temperature during fever is correlated with epilepsy and behavioural disorders, acute seizures during admission are associated with the development of epilepsy, and male sex is a risk factor for the development of general neurodisability.[11] A detailed 2006 retrospective analysis of hospital records of 143 children aged 6-9 years also made several associative claims: (i) multiple convulsions were linked with motor impairment, (ii) age younger than 3 years, severe malnutrition, intracranial hypertension, and hypoglycemia with language impairments, and (iii) prolonged coma, severe malnutrition, and hypoglycemia with other cognitive deficits.[26] In summary, it can be concluded that the development of neurological sequelae is associated with a more severe presentation of cerebral malaria.

Pathogenesis

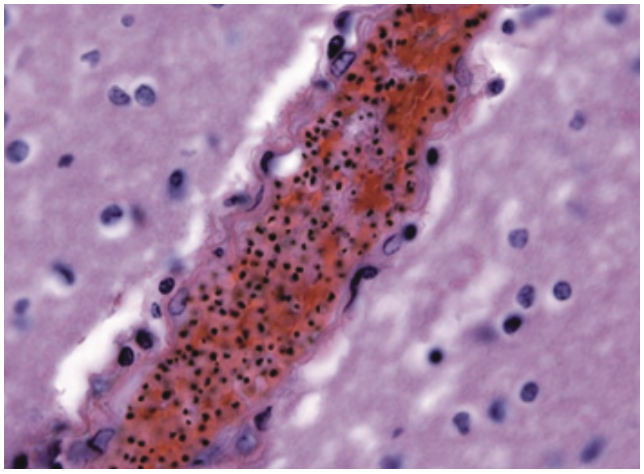

Figure 1. A photo of a section of the brain of a patient with pediatric cerebral malaria, depicting a collection of parasitized erythrocytes in the microvasculature of the brain.[27]

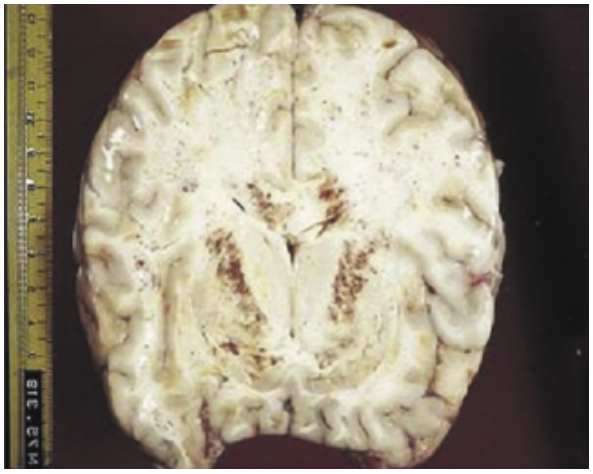

Figure 2. A photo of a section of brain from a fatal case of cerebral malaria, showing petechial hemorrhages in white matter, particularly in the subcortical rim and corpus callosum.[14]

Despite the recent increase in interest in the long-term deleterious neurological effects of cerebral malaria, researchers have not yet determined its precise pathogenic mechanisms. Generally, it is speculated that an inflammatory response to malarial antigens in the neural microvasculature during an acute episode of cerebral malaria triggers a cascade of events that ultimately results in cerebral tissue damage and neurological deficits.[4]

At the beginning of an episode of cerebral malaria, several platelet molecules such as Toll-like receptors are thought to bind to antigenic molecules derived from malaria parasites in the bloodstream, thus activating the pathogenic inflammatory response and the patient's own immune response.[28] Proinflamma-

tory cytokines are then generated, which increase the expression of cell adhesion molecules on the endothelium, causing parasitized red blood cells to sequester in blood vessels (see Figure 1) and leukocytes and platelets to adhere to the endothelium.[29] The sequestration of parasitized erythrocytes into rosette formations obstructs tissue perfusion, causes local endothelial apoptosis, and results in local inflammation, which in concert reduce the integrity of the brain microvasculature and can cause vascular leaks or hemorrhage into the brain (see Figure 2).[30] Reduction of tissue perfusion impairs the delivery of nutrients and oxygen to the brain, which can cause hypoxic neural injury and may in turn precipitate coma, seizures and further brain injury.[4] High intracranial pressure – indicative of ischemic damage – and cerebral edema have also been observed in severe cases of cerebral malaria and their subsequent neurological deficits.[30]

The flagship study on in vivo magnetic resonance imaging in the context of cerebral malaria confirmed several theories of cerebral malaria pathogenesis: mice infected with *Plasmodium berghei* ANKA exhibited blood-brain barrier disruption and hemorrhages caused by inflammatory processes, the generation of major edema which exacerbated severe ischemia, and reduced brain perfusion.[31] Subsequent MRI studies involving human patients have demonstrated the concurrent involvement of vasogenic edema, likely caused by damage to the blood-brain barrier, as well as venous congestion, caused by parasitized red blood cell sequestration, in different parts of the brain, supporting the hypothesis that both endothelial dysfunction and microvascular obstruction by infected erythrocytes contribute to the pathogenesis of cerebral malaria.[32]

The mechanisms of specific neurological sequelae have also been investigated. Increased levels of central nervous system tumour necrosis factor (TNF) correlate with long-term cognitive impairment and language deficits, and are thought to be caused by either global cerebral injury or damage to specific language centers in the brain.[17] In addition, epilepsy is associated with focal ischemic injury in border-zone regions of cerebral circulation.[17] MRI scans performed one year after hospital discharge have shown a direct association between the severity of brain atrophy and/or multifocal lesions on imaging and the severity of subsequent developmental and cognitive deficits.[16]

Treatment and Rehabilitation

Acute cerebral malaria is treated parenterally with either cinchona alkaloids (quinine or quinidine), or an artemisinin derivative such as intravenous artesunate.[27] These antimalarial drugs effectively kill and clear *Plasmodium falciparum* parasitemia from the body.[33] Mannitol has proven to be an effective treatment in cases of cerebral malaria with evidence of increased intracranial pressure, and benzodiazepines show similar promise in limiting brain damage in patients suffering from seizures, if provided quickly.[27]

Several new drug therapies presently under development are also directed at preventing long-term neurological deficits after cerebral malaria . For instance, a 2010 murine model study compared the neurological outcomes of C57BL/6 mice, infected with *Plasmodium berghei* ANKA and treated with either just the antimalarial drug chloroquine or a combination of chloroquine and antioxidants.[34] Strikingly, the mice that were given the combined treatment showed no long-term cognitive impairment, while those that were solely given chloroquine still exhibited cognitive impairment in measurements taken 30 days after the initial malaria infection.[34] These results indicate that reactive oxygen species may play a significant role in the development of neurological injury during cerebral malaria.[34]

Another treatment candidate, a low-molecular weight thiol called pantethine, has shown great promise as an upstream therapy to prevent the development of cerebral malaria and maintain the integrity of the blood-brain barrier: pantethine appears to down-regulate platelet reactivity, which is thought to preclude the previously described cascade of events that ultimately results in neural damage.[31]

Erythropoietin, a cytokine with anti-apoptotic and anti-inflammatory effects, has also been targeted as a potential new treatment for cerebral malaria. This cytokine provides neuroprotection, increases blood flow, and reduces apoptosis of endothelium cells: in a murine model study, high doses of erythropoietin reduced mortality by 40-90% in mice suffering from cerebral malaria, and in a subsequent study involving children infected with cerebral malaria, it was shown that the drug was associated with 80% reduced risk of developing neurological deficits.[35] A phase I study of the effects of erythropoietin in children with cerebral malaria was successfully concluded in 2009.[36]

Finally, in a more recent study, statins (HMG-CoA reductase inhibitors) were tested in mice to determine whether or not they could prevent neurological sequelae after cerebral malaria, given that they are already known to prevent neuroinflammation. Mice in the study were either given chloroquine or both chloroquine and lovastatin, and treatment with lovastatin correlated with a complete absence of cognitive dysfunction in measurements 15 days after infection with *Plasmodium berghei* malaria.[37]

While none of these promising new drugs are currently in clinical use yet, it is also valuable to recognize that current treatments of cerebral malaria such as intravenous artesunate can be effective at reducing neurological sequelae if applied early and aggressively.[8] In addition, patients who already exhibit neurological deficits as a result of past cerebral malaria can reduce their symptoms through rehabilitation therapy. Although research on this topic is still lacking, it has been shown that physical therapy and speech therapy can eliminate motor and speech impairment and generally ameliorate brain function, and traditional cognitive rehabilitation can teach survivors cognitive strategies to enhance attention, concentration, and executive functioning.[10] A landmark 2009 study also introduced the idea of computer-based cognitive rehabilitation: children trained with a cognitive rehabilitation computer program post-infection were shown to improve significantly in visuomotor processing speed, working memory, and learning, compared to controls.[38] This idea was expanded in a 2019 randomized controlled trial in Uganda, which demonstrated that pediatric cerebral malaria survivors who completed two months of computerized cognitive rehabilitation training (CCRT) scored better on evaluations of mental processing than survivors who did not undergo the training, although these benefits did not typically extend to one-year follow-up.[39]

Future Directions

While recent progress has been made in the development of new diagnostic tools and treatment options for cerebral malaria

and its subsequent neurological sequelae, it is clear that there is still significant room for improvement when it comes to understanding and treating this disease.

First of all, the diagnostic criteria for cerebral malaria ought to be redefined more specifically so as to eliminate misdiagnoses and uncertainty with relation to the current severity or potential progression of the disease. Easily accessible and accurate biomarkers for cerebral malaria should be identified and incorporated into official diagnostic guidelines, in order to provide physicians in resource-poor areas of sub-Saharan Africa with a more definitive means of diagnosis for this disease.

More research needs to be completed regarding the risk factors for the development of specific neurological sequelae and the mechanisms involved in the pathogenesis. In particular, there is extremely limited current knowledge about the development of behavioural impairments, and why they tend to occur several months after infection with malaria. Once more specific risk factors are determined, physicians will need to work aggressively to reduce or prevent these risk factors from occurring, in order to minimize neural damage during an episode of cerebral malaria. In addition, once the mechanisms of cerebral malaria and its neurological sequelae are better understood, more effective treatments, and perhaps vaccines, will be able to be developed.

Despite the large number of children and adults living with neurological deficits caused by cerebral malaria, there is only a small number of studies examining the benefits of rehabilitation for these patients. More research needs to be conducted to determine the most efficacious methods of improving the cognitive and motor symptoms of neurological sequelae. It would also be helpful to locate a source of funding for large-scale rehabilitation programs in sub-Saharan Africa, as those who would benefit most from rehabilitation are unlikely to be able to afford it.

Perhaps most importantly, a greater effort should be made to eradicate malaria worldwide by targeting the *Anopheles* mosquito vector. There has been an increase in the worldwide burden of malaria in recent years, due to increases in population in malarious regions, the building of dams, the resistance to antimalarial drugs and insecticides, and the reduction in funding of public health programs in many sub-Saharan African countries. Further, there is speculation that with global warming, the number of countries endemic for malaria will increase.[12]

Conclusion

In summary, long-term neurological deficits occur in approximately 25% of child survivors of cerebral malaria, which is now recognized as the leading cause of childhood neurodisability in sub-Saharan Africa.[11] While current understanding of risk factors, disease mechanisms, and treatments for these neurological sequelae are lacking, recent studies have shown great promise in revolutionizing the way that cerebral malaria is diagnosed and treated.

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