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Clinical aspects of malarial retinopathy: a critical review

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ABSTRACT

This review will provide a better understanding of a set of signs known as malarial retinopathy. The discovery of this retinopathy in association with cerebral malaria is important because it best distinguishes patients with true cerebral malaria from those with coma due to other causes and incidental *Plasmodium falciparum* parasitemia. Identifying a comatose patient with malarial retinopathy increases the likelihood of an accurate severe or cerebral malaria diagnosis. As the World Health Organization does not specify that malarial retinopathy is one of the factors included in determining a cerebral malaria diagnosis, there are significant false-positive diagnoses of cerebral malaria. Once a cerebral malaria diagnosis is assigned, other possibilities and treatments are often excluded making an incorrect diagnosis of cerebral malaria potentially fatal. However, *Plasmodium falciparum* may also contribute to coma in some children with retinopathy-negative cerebral malaria, as this group is still not clinically well characterized, so all children with the WHO definition of cerebral malaria should be treated for severe malaria. Nevertheless, by raising awareness about malarial retinopathy, there could be a greater potential to accurately diagnose cerebral malaria and thus achieve more positive patient outcomes in the future. This literary review aims to raise awareness of the retinopathy by defining what it is to non-experts, explaining its pathology, clarifying the techniques needed to accurately diagnose malarial retinopathy, as well as the barriers that prevent clinicians from providing a proper diagnosis in malaria-endemic regions; and finally, discuss future directions to continue the study of malarial retinopathy.

KEYWORDS

Cerebral malaria; malarial retinopathy; retina; fundoscopy; macular whitening; vessel discoloration

Introduction

Malaria is a deadly infection caused by the parasitic protozoan *Plasmodium* and is transmitted by the mosquito genus *Anopheles*, which is commonly encountered in tropical regions of the world. With almost half of the global population susceptible to infection, malaria has had one of the strongest selective pressures on humanity in our history, bringing about various mutations in malaria-endemic regions such as sickle cell disease, thalassemia, and G6PD enzyme deficiency, among others. During 2020, there were an estimated 241 million malaria cases globally [1]. There are five different species of the *Plasmodium* parasite that can infect humans, of which *Plasmodium falciparum* is the deadliest, accounting for almost all cases in Sub-Saharan Africa. Of the 627,000 mortalities worldwide in 2020, approximately 96% of all deaths occurred on the African continent. Young children, infants, and pregnant women are some of the most vulnerable population groups to the *Plasmodium* parasite and account for the vast majority of mortalities [2]. While there are various anti-malarial treatments for the disease such as artemisinin-based combination therapies (ACT) and its derivatives which are used to treat severe malaria cases, there is a growing resistance to such treatments in regions of the world such as South-East Asia [3]. As ACT is considered one of the last lines of defense against severe malaria, if such resistance were to become widespread on the African continent, the results would be devastating as most severe malaria cases occur in Sub-Saharan Africa. As such, not only is there a need for continued investment in novel antimalarial therapies, but also in bettering our understanding of the severe malaria pathology, and our means of diagnosing cerebral malaria.

Some of the complications of severe malaria include severe anemia, metabolic acidosis, respiratory distress, and cerebral malaria, which is considered the most extreme form of severe malaria. While cerebral malaria (CM) is a rare condition affecting less than 1% of malaria cases, it is one of the deadliest complications with a mortality rate of 15–20% of those treated with ACT and an almost 100% fatality rate without treatment. Children under 5 years of age are some of the most vulnerable to cerebral malaria. CM is an incompletely understood complication and the exact pathogenic mechanisms are still unknown. The current understanding of the pathology hypothesizes that infected red blood cells (iRBC) adhere to endothelium cells in the brain and retina where they remain

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sequestered in the microvasculature. The iRBC are attached to the endothelium mediated by proteins such as *Plasmodium falciparum* erythrocyte membrane protein-1 [4]. This can lead to complications including obstruction of blood vessels, reduced perfusion, hypoxia and ischemia, inflammation due to increased expression of inflammatory cytokines, among other immune system agents, and increased brain volume and intracranial pressure [5–7]. Findings further suggest that such an increase in intracranial pressure is associated with brain swelling and are strong predictors of death [5].

The World Health Organization (WHO) defines cerebral malaria as a patient with *Plasmodium falciparum*, coma (Blantyre scale <3) for longer than a half-hour following a seizure, and exclusion of other possible coma-causing diseases [8]. As impaired consciousness is one of the hallmarks of CM and can be generalized to a variety of other diseases, this definition may lack specificity in malaria-endemic regions. There is a wide range of reasons that could be responsible for coma in an individual with malaria parasitemia such as pneumonia, meningitis, hypoglycemia, or head trauma. Estimates of populations in malaria-endemic regions asymptomatically infected with malaria range anywhere up to 40–70% [9,10]. Based on these facts, even with accurate identification of malaria infection, demonstrating coma and evidence of *Plasmodium falciparum* may not be sufficient to conclude that a comatose patient has cerebral malaria.

Introduction to malarial retinopathy

There are thought to be frequent misdiagnoses of cerebral malaria in comatose patients only incidentally infected with malaria who die from non-malarial causes. An autopsy study performed on children diagnosed with cerebral malaria found that approximately 23% died of other illnesses [11]. In recent decades, many studies have verified retinal changes that are found in children with cerebral and severe malaria. Both the retina and brain tissues have similar networks of vessels, maintain high metabolic demand, and may be vulnerable to sequestration and non-perfusion [12]. The current evidence suggests that the severity of malarial retinopathy mirrors the cerebral malaria evolution in the neurovasculature [13]. As the retina is an integral part of the central nervous system (CNS) and is easily accessible via noninvasive fundoscopy exams, the examination of these retinal changes is demonstrated to be the best predictor of accurately diagnosing CM and extrapolating the inflammatory and obstructive processes that could be occurring in the brain. These retinal signs in comatose patients are described as malarial retinopathy (MR) with more severe retinal signs related to poorer outcomes such as extended length of time in coma and death [14]. There are four general signs present, that by themselves or in combination describe malarial retinopathy, two of which are exclusive to MR: retinal whitening, and discoloration of retinal vessels. When retinal hemorrhages are found in the setting of coma and parasitemia, there is a strong indication that the patient has developed CM. Papilledema is also frequently present in MR and if either found alone or in conjunction with the other signs indicates a much more severe prognosis, but it is not exclusive to CM [15,16]. The MR pathology shows insights into the causes of cerebral malaria as there are analogous structures between the blood-retinal barrier and the blood-brain barrier (BBB) found in the central nervous system. The first study to demonstrate that signs in the retina can serve as a prognosis specifically for CM was published in 1993. Before this, previous reports documented occasional hemorrhages, pupils were not dilated, or only direct fundoscopy was utilized. The researchers found that patients with papilledema were five times more likely to have a poor outcome than children without papilledema. For the first time, fundus findings were found to be useful predictors of outcome in children thought to have developed CM [17]. A follow-up long-term study by the same researchers in 1996 determined that retinal whitening is unique to CM patients as it was not present in children infected with other diseases [16]. During this four-year study the researchers also came to a similar conclusion that extramacular edema in patients diagnosed with CM is strongly associated with death. Currently, malarial retinopathy is seen as the best predictor in accurately diagnosing a comatose patient with CM or severe malaria.

Description of retinal signs in CM patients

There are three components to MR that if present, definitively indicate cerebral malaria. The first is retinal whitening (edema), in which opacification is seen in the macula (Figure 1a) and around the fovea (perifoveal). When such whitening occurs in the periphery of the eye it is termed peripheral whitening (Figure 1b). This is the result of vessel obstruction and hypoxia. The second unique component is termed vessel discoloration in which the retinal vessels become discolored with an orange tinge or white appearance. Capillary discoloration (Figure 2) occurs when the retinal capillaries turn from a red to orange or white color and are visible in contrast to the choroidal background. This is due to mature parasites within sequestered dehemoglobinized iRBC. Within larger vessels tramlining, or a narrowed blood column within the vessel, are visible. When a patient is in a comatose state and with parasitemia, white-centered hemorrhages are indicative of CM and are the easiest of the retinal signs to identify among clinicians without experience in this

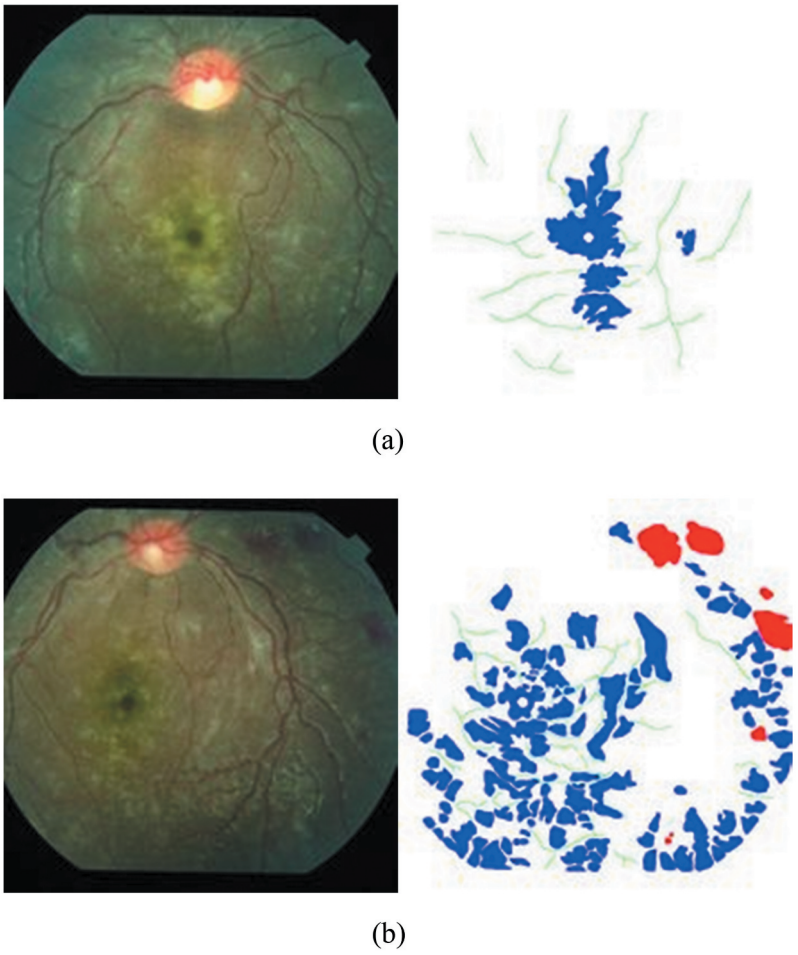

Figure 1. A. Retinal whitening in the macula and cotton wool spots are observed B. Retinal whitening in the macula and periphery, cotton wool spots observed as well (cotton wool spots are considered a nonspecific feature of malarial retinopathy). (Left) Topcon 50-EX desktop camera image. (Right) Ground truth annotation with blue represents whitening and hemorrhages in red.

area [18]. While retinal hemorrhages are not exclusive to cerebral malaria, in the setting of coma and parasitemia retinal hemorrhages and white-centered retinal hemorrhages are strongly suggestive of malarial retinopathy (Figure 3). In MR, these hemorrhages are predominantly white-centered and either occur in isolation or small clusters. Papilledema (Figure 4) is the last component and is a nonspecific sign of raised intracranial pressure. Papilledema can be found in conjunction with the first three signs, but if it appears alone does not necessarily indicate cerebral malaria. When seen together with retinal whitening and vessel discoloration, it indicates a higher risk of death in the patient [19]. However if seen alone, while also predictive of a poor outcome, the clinician should keep in mind other diseases that could potentially cause similar signs.

Images were obtained by an ophthalmologist. The patients were lying on a bed sideways with the camera standing next to the bed and the lens set in front of the patient's eyes. These images and ground truth annotations are generated manually by a certified retinal reader who graded the images either by annotation of lesions on each image (hemorrhages, whitening, vessel discoloration) or binary grading of the image as 'hemorrhage present/absent', 'whitening present/absent', and 'discoloration present/absent'. Images provided courtesy of VisionQuest Biomedical, Inc, Dr. Nicholas Beare, and the University of Liverpool Department of Eye and Vision Science, Blantyre Malaria Project in Queen Elizabeth Central Hospital

Pathogenesis of malarial retinopathy and outcome

Retinal whitening

The extent of retinal perfusion has been analyzed in children with cerebral malaria via fluorescein angiography. Retinal angiography facilitates our understanding of the infected CNS microvasculature by studying the retinopathy *in vivo*. The standardization of fluorescein angiogram practice patterns further improves the capabilities of researchers to analyze and compare various patient groups with MR signs and pediatric cerebral malaria [20]. Researchers observed that impaired retinal perfusion was recognized in 82% of patients with CM. Capillary nonperfusion (CNP) affected 76% of

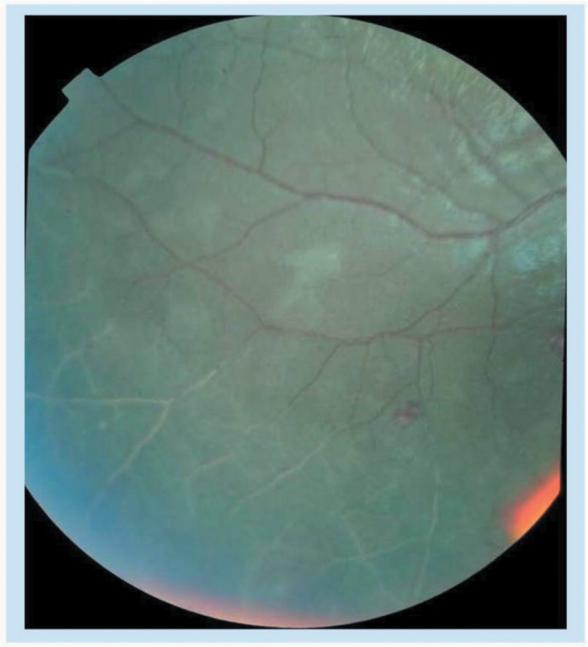

Figure 2. Capillary discoloration in the lower part of the image. Image source: Dr. Nicholas Beare, Retinal Vessel Whitening, Redefining Cerebral Malaria by Including Malarial Retinopathy, Future Medicine Ltd original publisher (reuse not permitted).

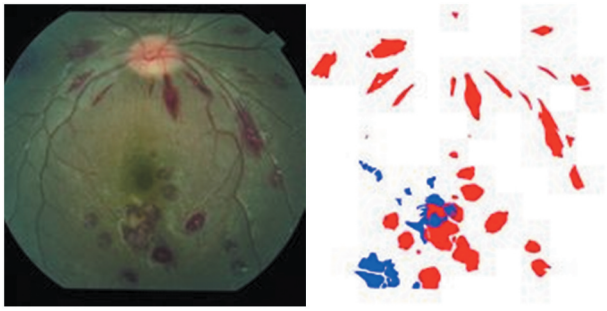

Figure 3. Retinal hemorrhages and white-centered retinal hemorrhages. (Left) Topcon 50-EX desktop camera image. (Right) Ground truth annotation with blue represents whitening and hemorrhages in red.

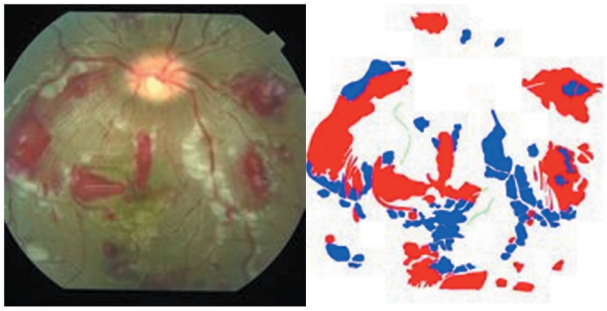

Figure 4. Papilledema. (Left) Topcon 50-EX desktop camera image. (Right) Ground truth annotation with blue represents whitening and hemorrhages in red.

patients, in both the macula and retinal periphery where zones of CNP matched retinal whitening [6]. Thus, the researchers concluded that the majority of children with malarial retinopathy had vessel obstructions in capillary vessels that matched with areas of retinal whitening seen in MR. The adherence of sequestered iRBC to the endothelium of the retinal vessels is suspected to be responsible for vessel tramlining [15]. CNP and retinal whitening are useful predictors in diagnosing malarial retinopathy and cerebral malaria. Ischemia found in zones of capillary non-perfusion suggests a model of cerebral hypoxia. Immunohistochemistry data on MR-positive patients found that the hypoxia marker VEGFR1 and intracellular edema marker AQP4 have increased expression in glial cells that were situated in areas of retinal whitening [21]. This data has led researchers to surmise that if the pattern of abnormalities seen in retinal angiography mirror the brain, it is likely that there are numerous regions in the CNS with reduced perfusion that lead to hypoxia and ischemia responsible for the severe signs seen in the CM pathogenesis. Furthermore, MR and specifically retinal whitening in the macula do not seem to have any impact on the vision of the patients at one-month post-CM infection [22]. This further strengthens the proposition that macular whitening in malarial retinopathy is reversible due to temporary hypoxia, caused by iRBC.

Hemorrhages

Pericytes play a role in controlling capillary blood flow, the permeability of the BBB, and the regulation of immune system agents. Damaged or destroyed pericyte cells may lead to BBB damage, vasculature rupture, and hemorrhaging [23]. Immunostaining evidence has found a reduction in a key protein marker, SMA, and signaling molecule, PDGRFβ, in MR-positive patients indicating significant dysfunction in pericyte cells in the retinal tissue of MR patients [21]. As pericytes are susceptible to hypoxia damage and there is an especially high concentration of pericyte cells in the retina and CNS tissues, it is suspected that when pericytes become damaged or dysfunctional due to hypoxia, hemorrhaging may result. Furthermore, provided that retinal hemorrhages are linked to cerebral hemorrhages, there is evidence that the speed and extent of cerebral hemorrhages may be a source of fatal brain swelling in CM [24].

Additionally, perivascular glial cells such as astrocytes and Muller cells that were affected by iRBC in MR-positive patients had statistically significant increases in the markers astrocyte intercellular adhesion molecule 1 (ICAM-1) and Muller cell cytoskeletal glial

fibrillary acidic protein (GFAP). ICAM-1 is normally present in low concentrations and when activated leads to increased expression and allows for leukocyte binding while the GFAP marker is primarily used to demonstrate glial cell activity. No MR-negative patients demonstrated ICAM or GFAP positive immunostains indicating that the malaria parasite in the retina has a greater influence on glial cells than previously thought [21]. Additional research is still needed in this area.

Hemorrhages and white-centered hemorrhages are considered common features found in malarial retinopathy. Capillary damage and the development of platelet-fibrin thrombus causes white-centered hemorrhages, which present a clear, white lesion in the center of the hemorrhage [25]. While noted that a portion of CM cases do not show signs of hemorrhages, in a malaria-endemic region, white-centered hemorrhages are a strong indicator of CM. In one study, 70% of fatal cerebral malaria cases displayed the presence of retinal hemorrhages [18]. Furthermore, the usage of direct fundoscopy exams, without dilation, even by inexperienced clinicians can identify hemorrhages. This evaluation can increase confidence in a clinician's diagnosis of MR and cerebral malaria.

Vessel discoloration

A study compiling the data of 817 children with malarial retinopathy (angiographic image analysis n = 260) determined that the sequestration of iRBC, seen primarily in discolored orange vessels, is coupled with a 2.71-fold increase in death [21]. Sequestered iRBC in the microvasculature of the brain found in autopsies contain little hemoglobin, the pigment responsible for the normal red color, which explains why the discoloration of blood vessels is uniquely found in severe malaria cases. This data provides evidence that the presence of discolored orange vessels not only indicates cerebral malaria but also a poor outcome [21].

Outcome

Malarial retinopathy in patients with CM is significantly associated with poor outcomes. The risk of death is 3.7 times greater in CM patients with MR as opposed to those without MR [14]. There is evidence that retinopathy-negative CM patients may have an asymptomatic malaria parasitemia and their illness is the result of another infection. For example, researchers examined seasonal differences in malarial retinopathy positive (MR (+)) and malarial retinopathy negative (MR (-)) CM cases. The researchers assumed that if the cause of MR (-) CM cases was not related to acute malaria infection and remained constant throughout the year, then the ratio of MR (+) cases and MR (-) cases should vary with the rainy and dry season. The study found that when the rate of malaria infection was highest, so was the ratio of MR (+) CM cases in comparison to MR (-) CM. The researchers thus presented evidence that patients in a coma with MR (-) CM might have a distinct etiology from those with MR (+) CM [26]. Other studies comparing both retinopathy positive and negative CM cases show evidence that malaria parasitemia does contribute to the pathogenesis of retinopathy negative CM patients [27–29]. Some children may have a genetic predisposition or a preexisting neurodevelopmental condition that could increase their probability of entering into a comatose state when infected with malaria. One MRI study found that 22% of children with MR (-) CM had preexisting neuroradiologic anomalies [30]. Evidence indicates that malarial retinopathy positive CM patients have more severe clinical signs than malarial retinopathy negative CM patients and that a spectrum of signs may exist in CM patients [28]. Malarial retinopathy negative CM patients may have an earlier presentation of CM than malarial retinopathy positive CM patients, which have more severe clinical signs and symptoms. While the presence of MR strongly suggests cerebral or severe malaria, the absence of it does not necessarily exclude CM as one of the possible diagnoses. However, it must be noted that MR negative CM remains a topic for discussion amongst researchers and its validity as a genuine form of CM is still in question.

Diagnostic practice patterns

There exists a certain subjectivity to malaria retinopathy exams. In many situations, MR is not observed during initial tests but may appear in follow-up exams. Conversely, although less frequent, MR seen on an initial exam is sometimes not seen on a second exam. As such, one recommendation is that clinicians perform examinations every 24 hours while the patient is comatose to possibly detect MR on later attempts. Otherwise, if such an examination is only performed once by a non-ophthalmologist, objectively determining if a patient is MR positive or negative may become considerably more difficult. In the future, newer technologies and cameras that can obtain images across the full fundus and determine if MR is present will require minimal skill by the operator and could make MR examinations more objective. One study utilized three general fundoscopic classifications to diagnose a suspected CM patient: Normal fundus, papilledema only, and retinopathy [31]. The normal and papilledema-only groups alert the clinician that other coinfections could be playing a role. After the fundus classification is determined three clinically defined pathologies fit the WHO definition of CM: MR (+) CM, MR (-) cases with another cause for coma, and MR (-) CM in which *P. falciparum* is still thought to have led to

coma [29]. MR (+) CM has sequestered iRBC within the blood vessels of the retina with the severity of malarial retinopathy signs generally mirroring the severity of cerebral malaria signs and symptoms. In MR (-) cases, there are not enough iRBC within the microvasculature or key MR signs (retinal whitening, hemorrhages, and vessel discoloration) to diagnose the patient with MR. In MR (-) cases with another cause for coma, the malaria parasite is not responsible for coma and another infection is involved. However, in cases of MR (-) CM in which *P. falciparum* is still thought to have led to coma, it is hypothesized that the patient may have a predisposition to enter a comatose state when infected with acute malaria, or the parasite could act in combination with another disease resulting in coma and MR (-) CM. Our understanding of MR (-) CM is highly limited, and the incidence of MR (-) cases with another cause for coma and MR (-) CM cases in which *P. falciparum* is still thought to have led to coma is still unknown. When MR signs are present, the clinician can diagnose the patient with MR (+) CM. But when the clinician cannot find MR signs, at that moment, the patient may present MR (-) CM signs, or another disease may be responsible for the coma. When the patient is thought to be malarial retinopathy negative, the clinician should continue to verify if the patient is MR (-) or if MR signs appear at a later moment during the infection.

Fundoscopy (Ophthalmoscopy) tests are a routine part of inspections that health professionals use in any complete eye examination to assess the fundus of the eye. There exist two means of performing a fundoscopy exam: direct and indirect fundoscopy (Figure 5). The fundoscopic technique used is important as signs like retinal whitening and vessel discoloration may be in the periphery of the retina and thus out of the scope of a direct fundoscopy examination. The best practice patterns when identifying malarial retinopathy involve dilating the pupils and using indirect fundoscopy techniques to achieve a wider angle of the fundus and identify specific signs of MR such as peripheral whitening and vessel discoloration. Although seen as more reliable, as it can analyze the periphery of the retina, indirect fundoscopy is a more technically challenging tool requiring expensive equipment, and training [19]. However, while direct fundoscopy (Figure 6) is a cheaper, more accessible option, it may be better suited for diagnosing papilledema and retinal hemorrhages as this technique captures a smaller field of view. Trained clinicians using indirect fundoscopy exams (Figure 7) should be the standard but there are not enough trained ophthalmologists and fundoscopic equipment in Africa to complete these tests. While direct fundoscopy may be limited in its scope, it is still an important diagnostic tool that can diagnose patients with MR, and by extension, cerebral and severe malaria. For example, in adult MR studies in Bangladesh, there was no significant difference found when diagnosing a patient with MR using direct or indirect methodologies [32]. The use of indirect and direct fundoscopy exams should be frequently done when diagnosing comatose patients with CM in Africa and around the world as they are crucial in determining the health of the patient and the status of the retinopathy. However, a 2018 survey of clinicians in malaria-endemic regions revealed that about 20% of international clinicians in malaria-endemic regions were not aware of malarial retinopathy practices, and 50% never examined the eye in cases of suspected CM. Some of the barriers to

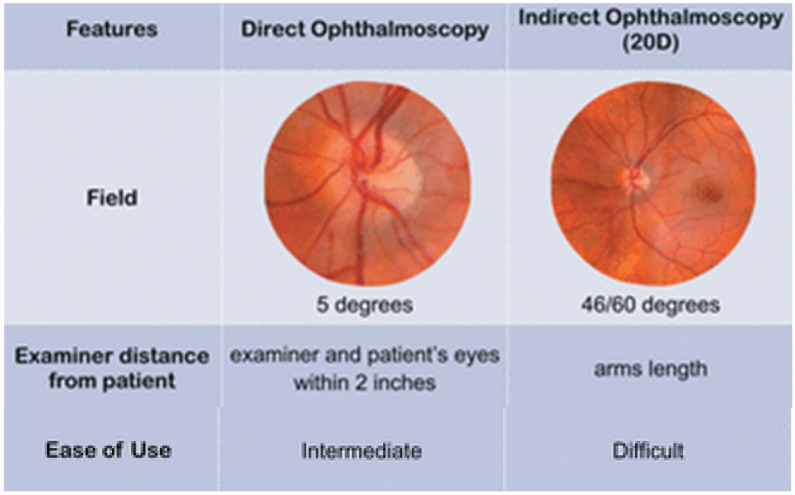

Figure 5. Direct ophthalmoscopy has a narrower field of view, generally does not use dilation drops, and would be best in identifying hemorrhages or white-centered hemorrhages. The equipment required is more accessible, an important factor in resource-poor countries where malaria is endemic. Indirect ophthalmoscopy uses a wider field of view that can better detect peripheral signs specific to malarial retinopathy: retinal whitening (macular and periphery), vessel discoloration, and hemorrhages. The disadvantage is the apparatus itself requires more financial resources and a higher degree of training to utilize. Note: Image Source: Livingstone I, Bastawrous A, Giardini ME, Jordan S, Peek Collaboration. Peek: Portable Eye Examination Kit. The Smartphone Ophthalmoscope. *Invest Ophthalmol Vis Sci*. 2014;55:ARVO E-Abstract 1612. The Association for Research in Vision and Ophthalmology is the copyright holder of Figure 5.

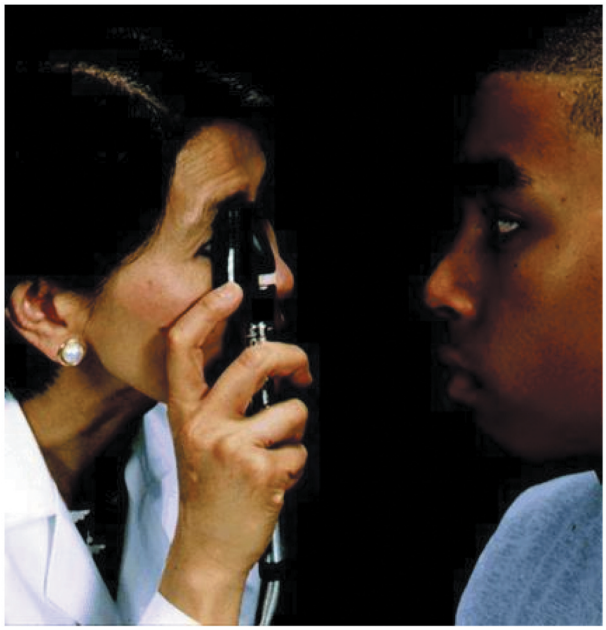

Figure 6. Direct fundoscopy exam. This clinician will move within a few centimeters of the eye to examine the patient's fundus. Note: Image Source: National Eye Institute, National Institutes of Health (NEI/NIH)

proceeding with the exam are an absence of a working fundoscope/no fundoscope (46%), the assumption that a fundoscopy test would not help diagnose CM (17%), unease performing retinal examinations (25%), and lack of dilating eye drops (17%) [33].

Grading scale

The current grading scale to measure the severity of MR signs was developed to standardize how clinicians and ophthalmologists would determine if MR is present, and the extent of the severity to better diagnose the comatose patient [34]. The four most prominent signs are graded beginning with the most identifiable: hemorrhages and white-centered hemorrhages. This aspect of the grading test quantifies the number of hemorrhages found as well as the percentage that are white-centered. If papilledema and macular whitening are confirmed, then their severities are also evaluated as mild, moderate, or severe. Peripheral whitening is determined by dividing the peripheral regions into four quadrants: superior, inferior, nasal, and temporal (Figure 8), and determining the severity of each quadrant is also graded as mild [+1], moderate [+2], or severe [+3]. The peripheral whitening score is determined as such:

$$\textit{Peripheral Whitening Score} = \frac{\textit{Sum of Score of Each Quadrant}}{\textit{Number of Quadrants Seen}}$$

Vessel changes can occur in venules, arterioles, and capillaries to varying degrees. This can include tramlining and discoloration of vessels to orange or white. These alterations are graded using a similar parameter to peripheral whitening as it is not always possible to examine every quadrant in the periphery:

$$\textit{Vessel Change Score} = \frac{\textit{Number of Affected Quadrants}}{\textit{Number of Quadrants Seen}}$$

However, the presence of vessel changes to any degree is seen as a sign of malarial retinopathy and therefore cerebral malaria. As such, the occurrence of vessel changes has greater importance than the severity of overall changes. If papilledema is found in the absence of white-centered hemorrhages, retinal whitening, or vessel changes, the clinician should consider other potential coma-causing diseases as well. The creation of a standardized grading chart facilitates quantifiable and reproducible analyses of MR scores between independent observers [35].

Figure 7. Indirect fundoscopy exam. Images demonstrate clinicians performing an indirect fundoscopy examination on patients at arm's length. The patient can be in a sitting or reclined position. Note the additional headgear required for the indirect fundoscopy exam. Image Sources: National Eye Institute, National Institutes of Health (NEI/NIH) (Left Image). Beare NA, Taylor TE, Harding SP, Lewallen S, Molyneux ME. Malarial retinopathy: a newly established diagnostic sign in severe malaria. Am J Trop Med Hyg. 2006 Nov;75(5):790-7. PMID: 17123967; PMCID: PMC2367432. (Right Image).

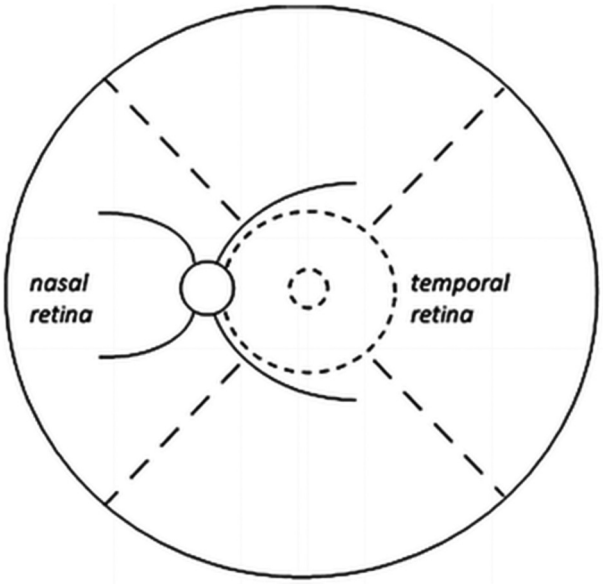

Figure 8. Center dotted circle of the image represents the fovea. The larger dotted circle encompasses the macular region. The solid circle adjacent represents the optic disc. The four quadrants are divided into superior, inferior, nasal, and temporal. Note: Image source: 10.1007_978-1-4614–8757-9_85-1

Difficulty diagnosing cerebral malaria

The World Health Organization (WHO) defines severe *P. falciparum* malaria as a positive malaria blood test indicating *P. falciparum* parasitemia, a measure of severe disease such as impaired consciousness or severe anemia, and exclusion of other diseases to diagnose a patient with CM [8]. However, consistently excluding other diseases while accurately testing parasitemia is generally difficult to achieve. A large study in Tanzania showed that 54% of patients treated for severe malaria had no parasitemia; likely because the blood films were inaccurate or ignored [36]. Such confirmation tests can often be inaccurate, likely due to a lack of resources and training.

Further complicating matters is that in malaria-endemic regions it is estimated that anywhere up to 40–70% of the population can be asymptomatically infected with malaria [9,10]. This means that patients are infected with malaria but through partial immunity or other unexplained mechanisms, they do not exhibit symptoms. Comatose patients may be asymptomatically infected with malaria, which is only incidental to another coinfectious disease causing the coma. For these reasons, even with reliable blood film tests and RDTs, definitively excluding other possible diseases is exceedingly difficult as neither of the principal signs of CM, i.e. coma and a positive malaria blood test, can definitively diagnose CM. Additionally, a study on Ghanaian children with severe malaria found that 50–75% of patients demonstrate malarial retinopathy with a high frequency in CM and non-CM severe malaria cases [37]. This may be a limit to the clinician's capacity to distinguish with a greater degree of certainty between the various types of severe malaria (severe anemia, metabolic acidosis, cerebral malaria, etc.). Even so, there is still a tremendous need to perform fundoscopy exams to determine if patients have malarial retinopathy as it is the only set of signs until now seen to be largely exclusive to CM and severe malaria patients. Three decades of evidence point to the inclusion of fundoscopy exams in the assessment of patients in a coma to determine if they have CM. The inclusion of a fundoscopy exam can only improve the diagnosis of CM and does not need to modify any other aspect of current WHO criteria in CM diagnosis. Current limitations in determining if a patient has MR and therefore evidence of a possible cerebral or severe malaria diagnosis include a lack of knowledge of its existence, financial constraints, limited resources, and too few ophthalmologists or trained clinicians to perform fundoscopy exams in endemic regions.

Potential for improved CM diagnosis

Based on the current WHO criteria, there are a significant number of false-positive diagnoses of cerebral malaria. Once a CM diagnosis is confirmed, other possibilities and treatments will be excluded making an incorrect diagnosis of CM potentially fatal. In one study in Malawi, ophthalmologists confirmed malarial retinopathy in fatal cases of CM with a sensitivity and specificity of 95% and 90% respectively when using the detection of MR to diagnose CM in fatal cases of comatose patients. In contrast, there is 61% specificity when using WHO criteria alone to diagnose CM cases in patients [11,15]. However, fundoscopy exams require expensive equipment and ophthalmologists, or properly trained technicians, which are rarely available in under-resourced malaria-endemic regions. Recent advances in technology have created new opportunities to take on such challenges. There are a variety of retinal cameras (desktop, portable, iPhone-based) being tested and compared to capture photos of the fundus in comatose children [38]. Automated software capable of analyzing the digital fundus images of patients and confirming the presence or absence of MR with high accuracy has also been developed. This software program was the first designed to detect retinal whitening, vessel discoloration, and white-spotted hemorrhages, and to identify the patient with a high degree of accuracy as MR positive or non-MR (specificity of 100% at a sensitivity of 95%) [39]. While patients determined to be non-MR would continue to receive anti-malarial treatment, this would advise clinicians to continue to look for other potential causes of coma beyond CM. This image processing technique can aid cerebral malaria diagnoses and improve outcomes for non-CM comatose patients by diminishing the rate of false-positive CM diagnosis

that frequently occurs when following general WHO guidelines for cerebral malaria diagnosis. While researchers are still struggling to integrate this software system with low-cost, portable cameras, the current results demonstrate that malarial retinopathy detection is attainable in actual situations outside of ideal conditions established in a laboratory [40]. Another recent study has provided evidence that hand-held optical coherence tomography (HH-OCT) is a noninvasive approach that images the microvasculature of neural tissue and can be used in suspected CM patients. The retinal signs observed in optical coherence tomography were specific to CM patients with MR. This study has demonstrated an additional noninvasive mechanism that can create avenues to provide better clinical care through the use of HH-OCT and distinguish between patients in which *P. falciparum* is still thought to have led to coma and cases in which another disease is the cause for coma [41]. If such software programs and HH-OCT methods could be integrated into routine use by clinicians in malaria-endemic areas that lack proper training and resources to perform indirect fundoscopy exams, there could be a significant increase in accurate CM diagnoses and a decline in false-positive diagnoses.

Areas for future study

Malarial retinopathy in adult patients

Adult malarial retinopathy has not been extensively studied. This may be due in part to the greater focus on pediatric MR, but researchers are still trying to determine if malarial retinopathy is the same in adult CM as in pediatric CM. There have been reports indicating *Plasmodium vivax* manifests MR in adult patients with severe malaria [42]. An observational study on adults with cerebral and severe malaria in Bangladesh found that 63% (17/27) of adults with severe malaria and 70% (14/20) of adults with CM had MR [43]. While other adult studies did not find rates of MR as high as in this study, the researchers stressed that the type of fundoscopic test is important and their results may be because of their use of indirect fundoscopy they found higher rates of MR in adults than in other studies that utilized direct fundoscopy approaches. Additionally, this specific study observed that retinal whitening was commonly found although vessel discoloration was not observed. They concluded that adult MR is commonplace even though not all the signs were the same as in pediatric MR. A follow-up study of adult patients in Bangladesh with cerebral and severe malaria determined that there was no statistical difference between non-ophthalmologist clinicians using direct and non-direct ophthalmoscopy examinations. This group of researchers also determined that adult MR is commonplace as they found approximately one-third of their patients with MR using indirect fundoscopy as their baseline. Furthermore, they noted that as they are non-experts the frequency of adult MR observed in this study is likely an underestimate [32]. Another adult MR inquiry found a singular adult with severe MR but in relatively good condition who showed all the usual descriptions of MR: retinal whitening, discoloration of vessels, and retinal hemorrhages [44]. This study also found the signs are similar to those in pediatric MR except for the deterioration in visual acuity. Researchers hypothesized that because adult patients may have been continuously exposed to the parasite in endemic areas, they have gained some sort of partial resistance to malaria. This may explain why the condition of the patient was stable even with severe MR. Another study evidenced that the appearance of retinal signs in adults observed with cerebral malaria is identical to the signs and symptoms in children that develop CM [45]. The evidence is still unclear if MR is the same in adults as it is in children and further observational studies with larger sample sizes should be performed to determine what similarities and differences exist. Nevertheless, if cerebral malaria is a suspected cause of coma the retina should be examined to determine if the patient has malarial retinopathy regardless of age.

Malarial retinopathy and neurocognitive deficits

Cerebral and severe malaria are both linked to long-term internalizing and externalizing behavioral issues in a significant portion of pediatric CM survivors [46]. While the vast majority of CM research studies focus on the pathophysiology and treatment of CM patients, there are few studies with a primary objective to monitor and test for neurocognitive deficits in survivors after recovery from cerebral malaria. With an annual incidence of cerebral malaria estimated in the hundreds of thousands, there is thought to be a large under-reported population of pediatric CM survivors who suffer from moderate to severe developmental delays, consequently placing a burden on families and communities who care for these survivors. Various investigations have determined that a significant percentage of children post CM have deficits in all cognitive fields including the following: memory, language, executive functions, and attention [47,48]. Cerebral malaria is the leading cause of neurological impairment in Sub-Saharan Africa, with varying estimates of cognitive or neurological deficits with most ranging between 14–26% of CM survivors depending on how the definition of deficit was defined [48,49]. 12 months post-recovery survivors of CM performed significantly worse in all domains in comparison to community controls demonstrating how these deficits remain for the long term [50]. Socioeconomic status factors were also taken into consideration by

using community control children from the same family, or extended family of the CM survivors. By utilizing neurocognitive exams, researchers could further learn valuable information about the pathophysiology of brain injury. Due to concerns that many developmental tests formulated in the United States and other countries would provide inaccurate data due to cultural differences, culturally specific tests, such as MDAT (Malawi Development Assessment Tool), were created to examine developmental delays in pediatric CM survivors specifically in rural Malawi. MDAT results in preschool children between MR positive CM survivors and comparison children from the hospital that did not develop CM or have a malarial infection determined that MR positive CM survivors suffered from significant delays, particularly in language development [51].

If malarial retinopathy signs are proportional to the severity of cerebral malaria, additional emphasis should also be placed on MR signs and their association with long-term neurocognitive sequela and behavioral changes. As malarial retinopathy is a part of the CM pathophysiology, it has been hypothesized that there exists an association between MR and future behavioral issues/neurocognitive deficits [52]. A preliminary study found that children surviving MR (+) or MR (-) CM are both at a higher risk of negative neurologic results [53]. A prospective study found that preschool MR (+) CM survivors with developmental problems are at a significantly higher risk of impaired development at school age, particularly in memory and executive function in comparison to non-malaria control [54]. Additional studies that compare MR (+) and MR (-) CM survivors could be beneficial in determining the role of a MR diagnosis and its association with behavioral alterations and neurocognitive deficits in survivors. Future emphasis on early identification of developmental delays, proper effective rehabilitative interventions, and clinical follow-ups should be sought out to maximize a positive developmental outcome in CM survivors. This should include additional research and resources allocated to discovering novel, potential neuroprotective interventions, educating families and teachers on proper rehabilitation techniques, and/or special education to help reduce the burden of developmental delays and neurocognitive deficits on families [55].

Concluding remarks

Malarial retinopathy can evidence a spectrum of malaria infection cases in patients that develop severe and cerebral malaria. To date, it is the only feature that distinguishes a cerebral malaria diagnosis from other causes of coma in malaria-endemic regions. The WHO should include a malarial retinopathy provision in the diagnosis of CM as its usage can only increase a clinician's accuracy in diagnosing CM/severe malaria and exclusion of other tropical diseases. Detection of malarial retinopathy should be included as a widespread practice in the diagnosis of suspected cerebral malaria patients. There is a dire need to raise awareness about this diagnostic practice among clinicians in malaria-endemic regions and to further seek out various avenues to increase the resources and training opportunities among health care facilities in these areas. A lack of awareness, training, and resources continues to be some of the key barriers impeding clinicians from performing indirect and direct fundoscopy examinations to identify malarial retinopathy and more accurately diagnose cerebral malaria. Utilizing potential novel technologies such as computer algorithms to identify MR in digital images could be a possible future path to better diagnose patients with CM. This tool could analyze cellphone images of the fundus in the near future and provide accurate predictions of MR in resource-scarce regions without properly trained clinicians and help diminish false cerebral malaria diagnoses. The underlying pathological mechanisms are still not completely understood and should be studied in further detail through continued pediatric and adult studies to better combat cerebral and severe malaria in the coming years.

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