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Children with Retinopathy-Negative Cerebral Malaria : A Pathophysiological Puzzle

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Abstract

Background—Cerebral malaria, defined as otherwise unexplained coma in a patient with circulating parasitemia, is a common disease in the developing world. The clinical diagnosis lacks specificity and children with other underlying causes of coma might be misdiagnosed as having cerebral malaria. The presence of malarial retinopathy can be used to differentiate children whose comas are caused by *Plasmodium falciparum* and its attendant pathophysiologies from those with other reasons for their abnormal mental status. Children with cerebral malaria who lack malarial retinopathy have not previously been described.

Methods—All patients admitted to Queen Elizabeth Central Hospital in Blantyre, Malawi, during a twelve month period with a clinical diagnosis of cerebral malaria were evaluated for the presence of malarial retinopathy. Thirty-two patients lacked retinopathy findings. Clinical, laboratory, and radiologic information data were collected.

Results—Thirty-two cases of retinopathy-negative cerebral malaria are presented.

Conclusions—Children with retinopathy-negative cerebral malaria share a common clinical phenotype with lower rates of mortality compared with those who have malarial retinopathy. There are at least four possible pathophysiologic explanations for this common condition.

Keywords

Malaria; Cerebral; Pediatrics; Neurology; Malawi

Introduction

Cerebral malaria (CM) is clinically defined by the World Health Organization (WHO) as an otherwise unexplained coma occurring in a patient with circulating *Plasmodium* parasitemia (1). Although five species of malaria parasites are infective for man, it is *Plasmodium falciparum* that is responsible for the large majority of cases of CM. Approximately 500,000 people per year develop this disease, the vast majority of them being children less than five years old living in sub-Saharan Africa (2).

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Although the organism does not directly invade the cerebral parenchyma, it sets in motion a cascade of pathophysiological processes than induce coma (3). These include sequestration of circulating infected erythrocytes (4), abnormalities in cytokines and inducible nitric oxide synthase (5), and increased permeability of the blood brain barrier (6). Of the three, many authors believe that sequestration is the most important. *P. falciparum*, the infectious agent in the vast majority of cases of CM, is the only one of the five parasite species that causes sequestration. A clinical-pathological correlation study has revealed that approximately 23% of African children who fulfill WHO diagnostic case criteria for CM and have autopsy examinations lack evidence of sequestration (7). The comatose state in this sizable minority, though attributed to CM, was found to be due to another cause. In this autopsy study, children whose brains lacked evidence of sequestration had features compatible with a diversity of causes for coma including pneumonia, Reye's syndrome, and head trauma.

In geographic areas of high malaria transmission, people may be bitten by multiple infective mosquitoes each day. In humans repeatedly exposed to this infective challenge a state of partial immunity, termed premunity, may be established. Patients with premunity are not completely protected against developing systemic symptoms of malaria, but are at greatly decreased risk of developing severe and complicated malaria, including CM. In those living in areas of high malaria transmission, this partial immune state commonly occurs in children who have survived to age 5 years (8). Thus, the majority of CM cases occur in children less than this age. Interestingly, in areas of high transmission, a large percentage of the population may have circulating parasitemia but lack any clinical manifestations. The population prevalence of asymptomatic parasitemia may be up to 50% (9). This may explain the lack of pathological findings typical of CM in a large percentage of children who fulfill WHO diagnostic case criteria for this diagnosis. These children may have lapsed into coma for a reason other than CM, yet the presence of circulating parasites has triggered a diagnosis of the condition.

A cerebral malaria-specific retinopathy has been described (10) and well characterized (11). Evaluated by direct and indirect ophthalmoscopy, these retinal abnormalities are 90% sensitive and 95% specific for detecting African children who have CM caused by *Plasmodium falciparum* (12). Retinopathy positive patients have eye findings that confirm CM's pathophysiological processes as responsible for their comatose state. If ophthalmoscopy is unavailable to assess the presence of retinopathy, all comatose patients with circulating parasitemia and no other clearly evident etiology for coma are diagnosed with CM and treated as if *Plasmodium falciparum* was the sole cause of their abnormal mental status. Even when a child is determined to be retinopathy negative, only limited resources for diagnostic investigations into other causes of their coma may be available.

Clinical characteristics of patients with malarial retinopathy have been well described (13). Children who fulfill WHO case criteria but lack malaria retinopathy have not previously been well characterized clinically. This group is the subject of our case series.

Five hundred thousand children per year are diagnosed with CM using WHO clinical criteria. In a previous case series in Malawi, twenty-three percent of them lack retinopathy (7). If these figures are generalized to other African countries, there may be 100,000 cases per year of this previously undescribed entity. If a large percentage of this group has an underlying etiology for their coma that is amenable to either a primary prevention strategy (vaccination, environmental changes) or a therapeutic intervention (antivirals, immunosuppression) then the mortality and neurologic morbidity attributed to CM (retinopathy negative or WHO case defined) could fall.

Materials and Methods

We studied pediatric cases of WHO clinically defined CM who lacked evidence of malarial retinopathy. These children presented over twelve non-consecutive months (January 9 to June 21, 2009, and January 4 to June 18, 2010) to Queen Elizabeth Central Hospital, a tertiary referral center and teaching hospital in Blantyre, Malawi. Patients were enrolled during the rainy season, the time of annual peak incidence of CM.

All children who fulfilled WHO case criteria for CM were admitted to the Pediatric Research Ward, a section of the pediatric department specially suited for investigations and intensive care required for these comatose children. Enrollment in this observational study required explicit written consent from the parent or guardian. Our study was approved by the University of Malawi College of Medicine Research Ethics Committee and Michigan State University Biomedical Institutional Review Board. As required by the WHO case definition of CM, all children had circulating *Plasmodium falciparum* parasitemia, a Blantyre Coma Scale less than or equal to 2, and no other cause of coma evident either by history or physical examination. The Blantyre Coma scale evaluates patient neurological response by assigning subscores in three domains: motor, verbal, and visual fixation and following. Motor response is graded as localization to pain (+2), generalized non-localized response (+1), or no motor response to pain (0). Verbal response to pain is graded as normal (+2), groaning (+1), or none (0). Visual fixation and following are graded as present (+1) or absent (0). The total of the three subscores equals the Blantyre Coma Score.

Indirect ophthalmoscopy was performed by a single ophthalmologist well versed in the findings typical of malarial retinopathy. Laboratory testing on admission included: thick and thin blood films to assess circulating parasitemia; full blood count; whole blood lactate and blood glucose; and HIV status. Blood cultures were performed. A lumbar puncture was done immediately if the patient was deemed stable enough to tolerate the procedure and no clinical signs of increased intracranial pressure were present. Cerebrospinal fluid (CSF) was evaluated for cell count and Gram stain, and was cultured. If patients were thought stable enough to temporarily leave the Research Ward, a brain MRI scan using a GE Signa Ovation Excite 0.35T magnet was obtained during admission. Attempts were made to repeat scanning every 24 hours during hospitalization while the child remained comatose. Those whose coma resolved before imaging could be repeated were not sedated for repeat scanning. MRIs were interpreted by a neuroradiologist blinded to the patient's retinopathy status. All children were treated with intravenous quinine as standard antimalarial therapy. If admission lumbar puncture could not be performed, intravenous antibiotics (ceftriaxone 100 mg/kg given once per day, maximum 5 days) were administered until the patient was deemed clinically stable and the procedure could be accomplished.

At discharge children who fulfilled the WHO clinical case definition for CM were classified as having retinopathy negative CM. Those who had an admission hematocrit less than or equal to 15 or who warranted a blood transfusion on clinical grounds were diagnosed as retinopathy negative CM plus anemia. If coma resolved rapidly (within two hours) after diagnosis, the patient was diagnosed with uncomplicated malaria. Surviving patients were seen as outpatients one month after hospital discharge date. At this appointment, parents were asked if the child had returned to normal in the areas of movement, personality, behavior, and learning. If parents answered affirmatively and the neurological examination was normal, the child was classified as Alive and Normal. If parents answered that the child had some neurologic abnormality at the time of follow-up or there was evidence of abnormality on neurological examination, the child was classified as being Alive with Neurological Sequelae. Children old enough to hold still without use of sedation were scheduled for a follow up outpatient MRI scan with this follow-up visit.

Results

During the study period, 164 children were admitted who fulfilled WHO case criteria for CM. Thirty two of these patients (19.5%) had no evidence of malaria retinopathy on examination. Clinical, laboratory, and radiologic findings for these children are shown (see Tables, Supplemental Digital Content 1 and 2).

Patients ranged in age from 8 to 114 months and two-thirds were female. All children had a history of fever before admission. Families had often sought medical care before hospital presentation and antimalarials (usually intramuscular) had been given in slightly greater than one half of cases. Paracetamol had been administered before admission in twenty-two children (data not shown). No child received aspirin before or during their hospitalization. On admission examination, hepatomegaly or splenomegaly was seen in nine children and three patients had both findings. Palpable lymphadenopathy was present in six.

Admission laboratory evaluation did not reveal hypoglycemia in any patient. White blood cell counts were usually normal or mildly elevated, but three children had counts greater than 20,000/ μ L. Severe anemia (hematocrit less than 15) was documented in two and thrombocytopenia (platelet count less than or equal to 20,000/ μ L) in five children. The mean parasite count was 139859 per microliter (range 308 to 755420/ μ L). In 26 patients, cerebrospinal fluid analysis showed no pleocytosis or organisms, though 6 children had no lumbar puncture performed during admission due to their clinical condition. All blood and CSF cultures were negative. Four of 30 children tested were HIV positive. Two other families refused testing.

Nineteen children had brain MRIs that did not reveal any acute abnormalities. Two of these children had preexisting neuroanatomic abnormalities first diagnosed when these imaging studies were performed; patient 24 was found to have a previously unknown lobar holoprosencephaly and patient 28 had diffuse mild cerebral atrophy. Of the 32 children in this series, 2 died and four were left with neurologic sequelae at hospital discharge and at one month follow-up. Acute imaging of the two children who subsequently died revealed severe bilateral diffuse cerebral edema. The four children who survived but had neurologic sequelae (Patients 3, 4, 9, and 20) had either focal cerebral abnormalities (pontine infarction or focal abnormalities in the occipital lobes and peritrigonal white matter) or signs of cerebellar tonsillar herniation that subsequently resolved (2 patients).

With IV antimalarial administration, circulating parasites were rapidly cleared. Intravenous antibiotics were concurrently administered with antimalarials in seventeen of the children.

Patients 2 and 7 were the only deaths in our studied group. These children did not differ demographically from others in the series. Neither child defervesced nor recovered consciousness before succumbing to their illness. Our patient group's rates of 6.25% mortality and 12.5% with neurologic sequelae contrast with rates of 17% and 11%, respectively, in the retinopathy positive patients admitted during this time.

Discussion

This case series of children with retinopathy negative cerebral malaria shows a stereotyped patient presentation of a short febrile prodrome lasting hours to a few days, a rapid deterioration in mental status, few abnormalities on laboratory evaluation, rapid recovery, and a relatively low mortality rate.

In an autopsy case series, CM retinopathy was found to be 90% sensitive and 85% specific that the underlying cerebral pathology typically associated with *P. falciparum* was present,

indicating that the parasite is likely responsible for the patient's coma and illness(7). This implies that 10% of children who lack malarial retinopathy but fulfill WHO case criteria for CM are false negatives and have CM with its attendant pathophysiologies responsible for their comatose state. We thus assume that at least three of the children in our series had "true" CM. The etiologic diagnoses in the others are unknown.

There are at least four possible pathophysiologic explanations for the clinical findings in our patient group. It is possible that parasitemia in children with retinopathy negative CM is truly incidental, reflecting residence in an area of high malaria transmission. In this scenario, our patients should be considered as having an acute febrile encephalopathy of unknown origin. A second possibility is that the presence of circulating malarial parasites is not an incidental finding. The presence of underlying host factors (immunity or genetic constitution) may change the child's reaction to acute malarial infection. Possibly, depending on the presence or absence of a yet identified factor (alone or in combination), a patient infected with *Plasmodium falciparum* would be more likely to develop retinopathy positive CM, retinopathy negative CM, severe malarial anemia, uncomplicated malaria, or no illness. A third and fourth explanation for retinopathy negative CM is that coinfection is changing the host's response to a pathogen or other exposure. A previous established infection could be changing a patient's response to *P. falciparum* infection. Conversely, circulating malaria parasites, though not symptomatic alone, could be changing the host's response to a different infectious or environmental challenge. Exposures (infectious, post-infectious, or environmental) would have different clinical effects depending on whether or not malarial parasitemia was present when that exposure occurred.

We will discuss these four possibilities in turn.

What if malarial parasitemia is an incidental finding in children with retinopathy negative CM?

If it is assumed that the parasitemia seen in our patients only reflects residence in an area of high malarial transmission then these children have an unexplained encephalopathy accompanied by fever. This symptom complex has been termed acute febrile encephalopathy (AFE). It is defined as fever and an abnormal level of consciousness with or without seizures and is a common presentation of pediatric patients to tertiary care facilities in the developing world (14). In its common usage, the descriptive "Acute Febrile Encephalopathy" implies nothing about etiology. Previously published case series of this symptom complex revealed a diversity of identified causes, almost all infectious. In these series, patients with retinopathy negative CM were diagnosed as having "cerebral malaria", as ophthalmoscopy was not available. Few case series of AFE in pediatric patients have been published (14-16). No previous study has excluded patients whose diagnoses were evident by examination or laboratory evaluation. Therefore, rather heterogeneous patient groups were presented. In contrast to these previous reports, our patients all had malarial parasitemia and no other clear etiology for their AFE. In previous studies retinoscopy of patients with *Plasmodium falciparum* parasitemia was not performed. All of our patient group would have been classified as having CM.

In our patient group, antimalarials quickly cleared circulating parasites. It is unclear whether their administration had any effect on clinical outcome. If the circulating parasites are truly an incidental finding, administration of antimalarials may not change mortality or morbidity in most retinopathy negative CM patients. Proof of this conjecture is not ethically possible.

What if malarial parasitemia is not an incidental finding in children with retinopathy negative CM?

Possibly, the presence or absence of retinopathy in a patient with CM is genetically determined or a consequence of previous exposures (and partial immunity) to the organism. Clearly, host immunity is important in changing an individual's risk of developing CM upon infection with *P. falciparum*. Children who have attained premunity are not protected from developing systemic malaria, but are at greatly decreased risk of developing severe malarial disease, including CM. Additionally, susceptibility to developing CM may be at least partially genetically determined (3). The situation is likely complex and obvious candidates for genetic susceptibility are either negative or show conflicting results. A recent study of ICAM1, an important endothelial receptor for parasite-infected erythrocytes in CM, has shown that single nucleotide polymorphisms within the gene encoding this protein had no influence on a patient's odds of developing CM (17). On the other hand, combinations of nematodes and *Plasmodium* species that are highly lethal with simultaneous infection may become less so if the animal model is bred to be unable to form certain inflammatory cytokines (18).

Two other possibilities for retinopathy negative CM involve coinfection. A coinfecting organism may be changing the host's response to malaria infection or the converse may be occurring.

It is known that a host's clinical response to *Plasmodium* infection may vary based on coinfection with other organisms. This has been clearly demonstrated in murine models. In mice, protective immunity to the blood stage of non-*falciparum* malaria is impaired by previous or concurrent intestinal nematode infection (19). In humans, the change of host response to helminth-malaria coinfection is less clear (20, 21). A case-control study in adults in Thailand revealed that simultaneous infection with *Ascaris lumbricoides* decreased the odds of developing CM in patients with acute systemic malaria (22). No similar study in pediatric patients has been performed.

In diseases other than malaria, modulation of immune responses to viral, bacterial, and protozoal pathogens by concurrent parasite infection has been observed in both animal models and human epidemiological studies (19). Antibody response to tetanus vaccination is impaired in those infected with *Onchocerca volvulus*, a filarial parasite (23). In an animal model, infection with *Schistosoma* decreases host immune response to injected *vaccinia* virus (24). Following antigenic challenge from a *Plasmodium falciparum* candidate vaccine, children coinfecting with schistosomiasis had lower acquired specific immune responses compared to those not infected (25).

It is clear that coinfection may change a host's response to malaria. What is not clear is whether a preexisting protozoal, viral, or bacterial agent may be modifying the pediatric patient's response to malaria infection, changing it from a different clinical picture (anything from asymptomatic carriage to CM) to the phenotype of retinopathy negative CM.

Conversely, an otherwise asymptomatic carrier state of *Plasmodium falciparum* may be changing the host's response to an intercurrent protozoal, viral, or bacterial agent, or even an intoxication or post-infectious process.

Conclusions

If retinopathy negative cerebral malaria is a variant of AFE in a patient with otherwise asymptomatic circulating parasitemia then a search for a causative infectious, post-infectious, or other etiology is warranted. If only a few etiologies are found responsible for

this syndrome, this may have significant public health impact, including vaccine and environmental changes that could decrease disease incidence. In this setting, development of a successful malaria vaccine will not change the incidence of idiopathic AFE in Malawian children. Treatment of the parasitemia will not change outcomes. But if retinopathy negative CM is a novel disease phenotype produced by genetic susceptibility, a partial immunity, or coinfection with *Plasmodium falciparum* and another infectious agent, then treatment (or prevention) of the malaria parasite is necessary. In the case of a coinfection, treatment of either malaria or the coinfectious agent could be successful in the therapy of retinopathy negative CM. However, treatment of the non-malarial coinfection could be detrimental if this second infectious agent is partially protecting the host against developing more severe CM symptoms.

Our series of 32 children with WHO case defined CM but without malarial retinopathy reveals a unique patient group with relatively little variation in presentation, laboratory parameters, and clinical course. We believe it possible that a substantial majority of these children have a unified pathophysiology responsible for their fever and encephalopathy. In patients with the diagnosis of “retinopathy negative cerebral malaria” is the parasite an innocent bystander? Or is *Plasmodium falciparum* causative but with a clinical expression modified by underlying host factors, either immune or genetic? Is the parasite a coinfectious agent with clinical expression of malaria being modified by another infectious agent? Or is the circulating parasitemia asymptomatic but modifying the host’s response to another exposure, either infectious or non-infectious? Further studies to establish underlying diagnoses in these children are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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