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CEREBRAL MALARIA IN AN EMERGENCY PAEDIATRICS UNIT OF A DEVELOPING COUNTRY - A CASE REPORT WITH A REVIEW OF THE LITERATURE

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ABSTRACT
Malaria continues to be an important global health issue with significant prevalence in Sub-Saharan Africa. Cerebral Malaria is a severe manifestation of Plasmodium falciparum infection. Cerebral malaria is defined as the presence of coma in a child with *P. falciparum* parasitaemia and an absence of other reasons for coma. It carries with it significant mortality as well as debilitating sequelae for its survivors such as sensorineural deafness and cortical blindness. We present below a 14year old girl who presented with 6days of high-grade fever, headache, vomiting, multiple convulsions and subsequent loss of consciousness. Examination findings showed that she had features of raised intracranial pressure at admission. Investigation results revealed asexual forms of Plasmodium falciparum in the peripheral blood film and absence of evidence of a concomitant infection. She was managed as a case of Cerebral Malaria and was treated with intravenous Artesunate, Mannitol, Diazepam and Phenobarbitone. She however succumbed to the illness within 6hours of admission. Autopsy findings were significant for a slaty grey enlarged spleen as well as an enlarged and oedematous brain with pinpoint hemorrhages. This report is aimed at re-emphasizing the significant fatality rate of cerebral malaria, as well as, to remind clinicians working in malaria-endemic regions about the need for early diagnosis and prompt treatment.

KEYWORDS: Cerebral malaria, convulsions, coma, Plasmodium falciparum, Benue, Nigeria.

INTRODUCTION
Malaria is a parasitic infection affecting over 1.6billion people worldwide[1] with developing countries being the most affected. Most cases are said to occur in the African region. WHO estimated that the region accounted for 93% of all malaria deaths in 2017.[1] Nigeria, which is home to about 193 million people[2], was estimated to have contributed to about 25% of all malaria cases globally in 2017.[1]

Malaria is caused by the intracellular Plasmodium protozoa with 5 distinct species known to cause disease in humans. These include P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi.[3] These organisms are mainly transmitted following bites of adult female Anopheles mosquitoes (Figure 1) but other routes of transmission include blood transfusion, transplacentally from an infected mother to a child and through use of contaminated needles. The organism leads a complex life cycle – a sexual form in the vector (i.e. mosquito) and an asexual form in the primary host (i.e. humans).

Malaria infection mainly occurs in 2 principal forms – an acute uncomplicated symptomatic form and a severe life-threatening form.[4] The acute uncomplicated form can affect anyone who is infected with the parasite. However, the severe form predominantly affects select groups of individuals who are at a higher risk compared to the general population and they include children (especially under 5 years) growing up in endemic regions, pregnant women, patients with HIV/AIDS, non-immune migrants, mobile populations and travelers.[5] This is because these groups of individuals have little to no immunity against the parasite. It is generally expected that older children, adolescents and adults living in malaria-endemic regions of the world possess passive immunity against the Plasmodium parasite and are such immune against severe forms of Malaria.

The aim of reporting this is to re-emphasize the significant fatality of cerebral malaria as well as to remind clinicians working in malaria-endemic region about the need for early diagnosis and prompt treatment.

The index case occurred in Makurdi, capital city of Benue state, which is located in North-central Nigeria.[6] Benue state was reported to have a malaria parasitaemia prevalence of 36-45% among children aged 6-59months.[7] This figure is the second highest in the country and is thus expected that older children, adolescents and adults living in this particular region will have acquired some form of passive immunity against severe forms of malaria due to this high parasite load.

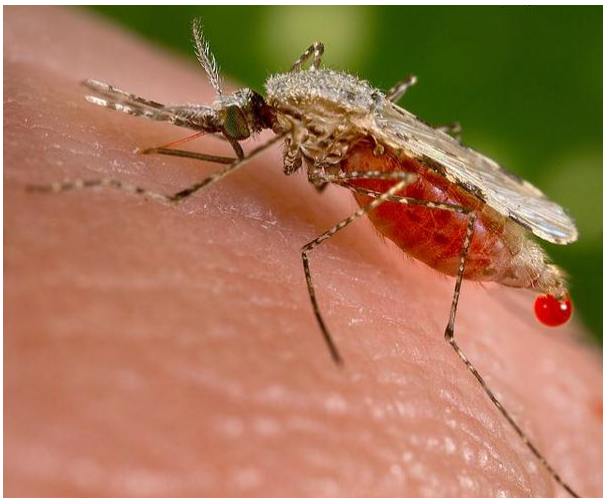

Figure 1: Showing adult Anopheles mosquito. (Source: Wikipedia).

CASE REPORT

A 14year old girl presented to the Emergency Paediatrics Unit of Benue State University Teaching Hospital following a referral from a private hospital with complaints of 6days history of headache and fever, 3days history of vomiting and 5hours history of repetitive multiple convulsions with subsequent loss of consciousness.

Referral note had indicated 3+ of Plasmodium falciparum was noted on the blood film and that oral Artemisinin-based Combination Therapy was administered. She was referred to our facility following onset of repetitive sustained convulsions and accompanying loss of consciousness. Examination findings at presentation revealed an actively convulsing child (duration of current episode of convulsion had lasted over 30minutes prior to presentation) with axillary temperature of 40.8^0C. She was unconscious with a Glasgow Coma Score of 6/15; pupils were normal-sized but sluggishly reactive to light bilaterally and there was global hypertonia and exaggerated deep tendon reflexes. She was in severe dyspnea with Kussmaul's breathing, and had a respiratory rate of 48 breaths per minute. Her pulse rate was 206 beats per minute, blood pressure was 128/70mmHg and heart sounds were 1st & 2nd only.

Blood film showed trophozoites of Plasmodium falciparum at 4+ which corresponds to >10parasites per thick field (actual parasite count was 267cells/µl); serum electrolyte was significant for acidosis with a bicarbonate level of 16mmol/L and a serum creatinine level of 249µmol/l. Haemoglobin concentration was 10.6g/dl while total leukocyte count was 5000cells/mm^3 with a normal differential count. Random blood glucose was 5.9mmol/l. Lumbar puncture was deferred in view of the hemodynamic instability of the child. A Brain CT Scan was ordered for but could not be done before the demise of the patient.

A diagnosis of Cerebral Malaria with status epilepticus and raised intracranial pressure was made. Convulsions were aborted with intravenous Diazepam and Phenobarbitone. She was commenced on intravenous Artesunate and Mannitol. She was also commenced on intravenous Ceftriaxone empirically. Seizures were controlled 45mins into admission after 2 repeated doses of Diazepam and a loading dose of Phenobarbitone. She was also commenced on intranasal oxygen therapy as well as intravenous fluids 8% Dextrose in 0.18 Saline at 2/3rd of her daily maintenance.

Clinical condition, however, deteriorated progressively as the GCS dropped to 3/15 and respiratory pattern changed from Kussmaul's breathing to Cheyne-Stokes breathing. She succumbed to the illness 6hours into admission.

Pertinent findings at autopsy revealed slaty grey and enlarged spleen. Other findings were those of an oedematous and congested brain with tonsillar herniation. Cut section of the brain revealed multiple pinpoint hemorrhages.

DISCUSSION

Cerebral malaria is one of the clinical syndromes associated with the severe form of malaria. Historically, it represents a loose term often used to describe any disturbance in the central nervous system as a result of malaria infection. It is sometimes regarded as the most common non-traumatic encephalopathy in the world.[8] It is the most serious complication of falciparum malaria in endemic areas with higher prevalence among well-nourished children than malnourished children.[9] It is defined as the presence of coma in a child with P. falciparum parasitaemia and an absence of other reasons for coma.[3]

Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15-20% and is associated with long-term cognitive impairment in children.[3]

The exact pathophysiological mechanism responsible for Cerebral Malaria is unknown. There are however several hypotheses that have been proposed and documented as being responsible for the manifestations of cerebral

malaria. The pathophysiological processes involved include:

i. **Sequestration** of parasitized erythrocytes containing matured forms of the parasites (i.e. trophozoites and meronts) in deep microvascular beds including the brain prevents the destruction of the parasitized erythrocytes by the spleen and also allows optimal growth of the parasites. It is these sequestered parasites that cause the pathological features of cerebral malaria and the prognosis is related to the biomass of the sequestered parasites. The ability of the sequestered parasites to evade splenic sequestration explains why patients with cerebral malaria may not be anaemic.[10-14]

ii. **Cytoadherence** is the interaction between sequestered parasitized erythrocytes and the vascular endothelium which is mediated by plasmodium derived proteins on the surface of the parasitized erythrocytes (such as Plasmodium falciparum erythrocyte membrane protein-1) as well as ligands found on the endothelial cells (such as intracellular adhesion molecule-1). The cytoadherence of parasitized erythrocytes in cerebral vessels cause reduction in microvascular blood flow which thus leads to organ dysfunction from the consequent cerebral hypoxia. The parasitized erythrocytes also compete with the host tissue for substrates such as glucose and also produce toxins that interfere with host metabolism.[15-17]

iii. The adherence of non-parasitized erythrocytes to parasitized erythrocytes (**rosetting**) and parasitized erythrocytes to parasitized erythrocytes (**agglutination**) have also been shown to be involved in the pathogenesis of cerebral malaria.[18]

iv. Blood levels of pro-inflammatory cytokines are known to be elevated in cerebral malaria. Tumor necrosis factor-α (TNF- α) causes endothelial cytoadherence receptors and cause hypoglycemia and dyserythropoiesis which are all features of severe malaria.[19,20] Prognosis of disease is said to be worse with rising levels of cytokines. TNF- α concentration levels >98pg/ml in patients with falciparum malaria is highly associated with disease severity including hypoglycaemia, coma and death.[21]

Cerebral malaria tends to occur after the patient has been ill for several days but may also develop precipitously. It commonly starts with typical symptoms of malaria infection which include fever, chills & rigors, headache, anorexia, myalgia, malaise and vomiting. Cerebral malaria is however typically characterized by fever, convulsions and loss of consciousness. These three symptoms tend to be the most consistent features from various studies.[22] Cerebral malaria is typically characterized by a diffuse encephalopathy with unarousable coma. It is often heralded by generalized seizures and subsequent impairment of consciousness. Convulsions are noted more in paediatric cases (50%) compared to adults (15%).[23] The index patient in this report had an illness duration lasting for 6days. It was heralded by fever, headache and vomiting. Convulsions and loss of consciousness were noted 11hours before her demise.

Raised intracranial pressure (ICP) is common in cerebral malaria. Almost all children with cerebral malaria who have lumbar puncture have elevated cerebrospinal fluid opening pressure.[24,25] ICP monitoring in 23 Kenyan children with cerebral malaria found that all had raised ICP.[26] Typical features of raised ICP include a combination of headache, vomiting and papilloedema. Progressive deterioration in consciousness, sluggishly reactive pupils or anisocoria, and intractable seizures level are also indicative of a rising ICP. Other signs such as pupillary dilatation, respiratory irregularity and bilateral ptosis are related to a tentorial or tonsillar herniation rather than an absolute level of ICP.[27] The index case had clinical features which were in-keeping with a raised ICP and these included her presenting complaints of headache and vomiting, sluggishly reactive pupils, abnormal breathing pattern and progressive deterioration of her consciousness level. Autopsy findings later confirmed the clinical suspicion of raised ICP and tonsillar herniation.

Clinically, cerebral malaria is diagnosed following demonstration of asexual forms of Plasmodium falciparum in the blood of a patient with unarousable coma lasting more than 30mintues for whom no other cause of the coma can be identified[28]. WHO, however, updated its diagnosis to be Blantyre Coma Score of <3/5 in young children who cannot speak or Glasgow Coma Score of <11/15 in older children and adults with demonstrable forms of asexual P. falciparum parasitaemia in their blood irrespective of the duration of the impaired consciousness.[29] Asexual forms of P. falciparum are demonstrated via examination of a Giemsa-stained peripheral blood smear which was done in this patient. A high index of suspicion is necessary to make prompt diagnosis of cerebral malaria. Hypoglycaemia which is also a feature of severe malaria must be ruled out and corrected if present. Meningitis, particularly in the tropics, must also be excluded. Thus, a cerebrospinal fluid analysis via lumbar puncture should be done. The reported case had numerous trophozites of P. falciparum found in her blood film both at the referral centre as well as at our facility. Her admitting random blood glucose level was normal. An attempt to analyse her cerebrospinal fluid was deferred due to her haemodynamic instability as at the time of presentation.

Autopsy can further confirm the diagnosis of cerebral malaria by demonstrating cerebral vessels that are clogged with parasitized erythrocytes and around the vessels are ring hemorrhages.[30,31] Upon cross sectioning of the brain in the index case, pinpoint hemorrhages which are consistent with ring hemorrhages were seen grossly. Durck granulations which are small focal inflammatory reactions may also be seen on histology.

The specific treatment for cerebral malaria and other forms of severe malaria is parenteral Artesunate (specifically intravenous Artesunate). Other options include injectable Quinine and Artemether. Artesunate belongs to the Artemisinin class which act on both mature and immature forms of P. falciparum. It also clears parasites faster and resolves symptoms quicker than Quinine.[32-34] A dose of 2.4mg/kg of parenteral Artesunate is given at admission, followed by same dose after 12 hours, 24 hours and hen daily until the patient is able to take oral medications.

Supportive treatments include anticonvulsant therapy, blood transfusion, fluid and calorie management as well as general management of unconscious patients. Despite obvious presence of raised ICP in cerebral malaria, administration of Mannitol has been shown not to have any significant effect on clinical outcome of patients and this appears to also be the case in our index patient.[35]

The index patient had a dose each of IV Artesunate, IV antibiotics, IV Mannitol and IV Phenobarbitone before her demise. She was also on intravenous fluids to cater for both her caloric and fluids needs as well as intranasal oxygen.

Death among hospitalized children with cerebral malaria is often due to respiratory arrest and brainstem signs with most deaths occurring within 24hours of presentation.[36] Fatality rate from cerebral malaria varies from reported cases in Nigeria. Jiya et al[37] reported that Cerebral Malaria constituted 8% of admissions into its Emergency Paediatric Unit in a prospective study with a case fatality rate of 26%. Poor prognostic factors highlighted from the study include age less than 3 years, acidotic (Kussmaul's) respiration, hypoglycemia and raised plasma urea concentration. Oninla et al[38] also reported a case fatality of 5% among patients managed for Cerebral Malaria although the study population reported was quite small. The case fatality rate was however similar to those of Elusiyan et al[39] which also reported a mortality of 5.2% among 154 patients managed as case of Cerebral Malaria in a retrospective study spanning a 5year period. Lesi et al[40] however reported a mortality rate of 17.8% among 107 patients managed as a case of Cerebral malaria in a cross-sectional descriptive study.

Respiratory distress or altered consciousness predicted 84.4% of 64 deaths among 1844 Kenyan children admitted for malaria in a study conducted by Marsh et al in 1995.[41] The study also revealed that various combination of coma, respiratory distress and anaemia carry a worse prognosis than any of the features on their own.[41] The index patient in this report had acidotic respiration which is poor prognostic factor as reported by Jiya et al.[37] She also had a combination of respiratory distress and coma which also carry a poor prognosis as reported by Marsh et al.

Survivors of cerebral malaria often come down with neurological sequelae which are commonly hemiplegia, cortical blindness, aphasia, sensorineural deafness and cerebellar ataxia.[42-44]

CONCLUSION

This report revealed the possibility of severe forms of malaria in older children and adolescents living in malaria-endemic regions who are otherwise assumed to be free of severe forms of malaria due to their acquired passive immunity. It also serves as a timely reminder to clinicians in malaria-endemic regions that malaria still has a potentially lethal outcome if not diagnosed early and promptly treated.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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