Cerebral Malaria In Children

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Introduction:
Cerebral malaria is a severe complication of Plasmodium falciparum infection which may account for 80% deaths of patients admitted to the hospitals. Cerebral malaria may be gradual in onset, but it is commonly sudden, a progressive headache, may be followed by a coma, uncontrollable rise in temperature to above 108 °F. and psychotic symptoms or convulsions, specially in children. Death may be certain in a matter of hours. In diagnosis based on symptoms alone, Malaria cannot be distinguished from other febrile illness, and the species of Plasmodium causing the fever, if any, cannot be identified. Five to six hundred millions of people throughout the world, suffer from malaria and more than one million die each year as a consequence. In about 20-30% of pts who died because of malaria suffered CM as a complication.

Cerebral malaria is endemic in various parts of Africa. Although malaria is still not an endemic disease in Libya, its incidence is difficult to be estimated as Libyan nationals are migrating to endemic areas and there is a continuous influx of foreign workers in the country. Many of them are currently parasite carriers. Moreover, existence of the foci of few species of Anopheles in South-West region (Fazan) continue to maintain malaria transmission in the country. During the period from April 2001 to November 2003, only 14 cases of malaria had been reported in Sebha, Fazan. 10 of these cases were positive for P. falciparum. No mortality was reported among those patients. All positive cases for malaria were Libyans and had never been abroad. Occurrence of malaria in those patients remains a matter of controversy. How did they get infected? Epidemiological surveys are needed to confirm whether malaria is present among Libyans or is it introduced by infected Anopheles or transmitted from emigrant carriers. In Kenya, at least 1.300-7,800 children have neurologic sequelae following cerebral malaria in stable endemic areas per year. The figure is likely to be considerably higher, since these estimates do not include neurocognitive impairment following non-cerebral malaria in children or adults in stable endemic areas, or populations in low stable or epidemic areas. The incidence in Niger is 469 cases per 100.000 people, while Mali 454 Angola 354 and Sierra Leone. Children suffer the worst effects of the disease. This is especially true in Africa, where a child dies every 30-40 seconds due to malaria. In some areas of sustained transmission, malaria accounts for about 25% of mortalities in children aged 0 to 4 years. In Sudan, among the 2488 diagnosed malaria patients, 4.4% fulfilled the WHO criteria for severe malaria.

In Nigeria, 46% of deaths were attributed to cerebral malaria(12). A gradual increase in incidence of cerebral malaria (CM) was reported during the period between 1988 and 1991. Recently, six hundred and four out of 3.868 patients (15.6%) had neurologic morbidity, and cerebral malaria was found in 28.0% of these patients. The clinico-epidemiological pattern of severe malaria varies considerably from that of hyperendemic regions in sub-Saharan Africa, and there is considerable variation between the individual complications of severe malaria. Mortality of 10 % was observed only in P. falciparum malaria. In Uganda, the mortality was 7% of children with cerebral malaria. Cerebral malaria and meningitis accounted for all the deaths.

Causative organism
Cerebral malaria is caused by P. falciparum because erythrocytic schizogony of the parasite completed in the capillaries of deep organs of the body, especially in the brain capillaries. Cerebral malaria is a serious complication of severe falciparum malaria and is seen in approximately 32% of P. falciparum positive cases. Although P. vivax usually causes benign uncomplicated malaria, it can

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occasionally result in severe disease with life-threatening, end-organ involvement, generally seen with falciparum malaria. Kochar and his group reported cases of cerebral malaria with P. vivax. Peripheral blood microscopy, parasite antigen-based, assays, and parasite 18s rRNA gene-based polymerase chain reaction PCR showed the presence of P. vivax and absence of P. falciparum. The PCR test yielded highly concordant results with microscopic examination, with the only exception of a mixed (P. falciparum plus P. vivax) infection case, which was diagnosed as a single infection of P. falciparum by microscopy. Bruce et al (2000) described the dynamics of co-infections of Plasmodium falciparum and P. vivax in 28 asymptomatic children by genotyping these species using the polymorphic loci Msp2 and Msp3alpha, respectively. It has been noticed that the dynamics of P. falciparum and P. vivax genotypes varied greatly both within and amongst children. These major fluctuations in the density of genotypes over time, as the result of the mechanism of antigenic variation, thought to be present in these Plasmodium species.

A case of cerebral malaria has been described in Ceara, a non-endemic zone. P. vivax was the probable cause. They observed the existence of mixed infection and the potential dissemination with the presence of the sand fly transmitter.

**Pathogenesis**
P. falciparum malaria is the most important parasitic disease infecting the central nervous system of humans worldwide. The pathogenesis of the neurological complications of falciparum malaria remains unclear. Despite many studies, the pathophysiology of cerebral malaria is not understood, especially concerning the intricacy and respective roles of the various mechanisms identified: sequestration of parasitized red cells in microvessels, cytokine secretion, changes in the T lymphocyte repertoire, host genetic factors driving sensitivity pathogenic factors from Plasmodium.

Sequestration of parasitized red blood cells by P. falciparum in cerebral micro-vessels is significantly higher in the brain of patients with CM compared with those with non-cerebral malaria in all parts of the brain (cerebrum, cerebellum, and medulla oblongata). There is more hierarchy of sequestration in the cerebrum and cerebellum than the brain stem. There were 26.6 times more parasitis than the peripheral blood. The sequestration index was found to be significantly higher in cerebral malaria patients than in non-cerebral malaria ones. The degree of sequestration of P. falciparum-infected erythrocytes in cerebral microvessels is quantitatively associated with pre-mortem coma.

In the high-sequestration group (n 8), the mean percentage of cerebral microvessels that showed parasitized red blood cell (PRBC) sequestration was 71.2± 8.1% in the cortex and 84.0± 6.7% in the white matter. The difference in the PRBC sequestration rate between cortex and white matter was statistically significant. Perivascular and ring hemorrhages were seen more frequently in the white matter than in the cortex. Deposition of IgG and P. falciparum antigen in the cerebral microvessels was highly significant in the white matter than in the cortex. It has been demonstrated that the localized concentration of PRBC sequestration in the brain correlated with the marked immunohistologic differences in the microvessels of cortex and white matter.

Parasite sequestration in the brain, metabolic disturbances, and host immune responses all play a role. Experimental studies revealed the potential role for host cells, especially platelets, in the pathogenesis of cerebral malaria. Urokinase plasminogen activator receptor deficiency attenuates the severity of CM, most likely by its important role in platelet kinetics and trapping. Platelets may provide an adhesion receptor to microvascular beds originally devoid of it. It has been found that the surface of platelet accumulation and the proportion of vessels filled with platelets were significantly higher in patients who died of CM than in those who died of other causes. This novel mechanism of cytoadhesion may reorient the sequestration of different parasite phenotypes and play an important role in the pathogenesis of severe malaria.

Immunofluorescent studies demonstrated intense deposition of P. falciparum antigen, IgG, and fibrin in cerebral vessels associated with the histopathologic finding of hemorrhage in the white matter of cerebrum and cerebellum regardless of the presence of parasitized erythrocytes in the cerebral vessels.
In the cerebellum, the percentage of microvessels with PRBC sequestration was higher than that in the cerebrum. The difference in sequestration rates between cerebrum and cerebellum is statistically significant. There is a higher degree of vascularity in the cerebellum (7 vessels/mm²) than in the cerebrum (5 vessels/mm²), and the difference is also statistically significant. Perivascular hemorrhages also occur more frequently in the cerebellum than in the cerebrum.²⁴

Nitric oxide (NO) is known to play a protective role against clinical malaria, but is also suggested to have a pathogenic role in cerebral malaria.²⁵

Asymptomatic malaria-exposed children have high production of nitric oxide (NO) and universal expression of leukocyte NO synthase type 2 (NOS2), which may protect against disease. Elevated production of NO in both infants and older children may be related to age per se and malaria infection respectively.²⁶ One of the mechanisms of parasite-related anemia in such children may be through the adverse hematologic effects of parasite-induced NO production.²⁷ Protection from severe malaria in African children has been found associated with polymorphisms of the NOS-II promoter. However, a pathogenic role of endogenous NO has been documented in cerebral malaria.²⁸ The relationship between reactive nitrogen intermediates concentrations and the spleen suggest that nitric oxide may have a regulating role in the complex physiology of the spleen during malaria.²⁹

It has been suggested that the IgG2-binding Fc gamma RIIa-His/His131 genotype is associated with enhanced susceptibility to P. malariae in HIV-positive women but not in HIV-negative ones.³⁰

At least, theoretically, the molecular pathogenesis of human cerebral malaria revealed that a diverse receptor molecules on the endothelial cell CD36, thrombospondin (TSP), intercellular adhesion molecule 1(ICAM-1), vascular cell adhesion molecule 1(VCAM-1), endothelial leukocyte adhesion molecule 1(ELAM-1) and chondroitin sulfate A (CSA) might be the molecular basis for the pathogenesis of cerebral malaria.³¹

Anticardiolipin antibodies (aCL) had been studied in patients with chronic malaria. IgG aCLg were found to be higher in asymptomatic P. falciparum carriers than in patients with uncomplicated acute or cerebral malaria. IgM aCLg were found to be higher in the cerebral malaria group than in groups with uncomplicated acute malaria patients or asymptomatic individuals. It has been suggested that using a serum co-factor independent, sensitive ELISA, aCL are commonly detected during malarial infections and related to malarial infection status.³²

In particular, how do asexual parasites confined to the vascular space of the brain cause neuronal impairment? The evidence for a breakdown in the blood-brain barrier (BBB) is conflicting. There is evidence of breakdown of the BBB in some animal models of malaria, but the data from humans suggests the BBB is mildly impaired only, with few morphological changes. Whether these changes in the BBB are sufficient to account for the neurological complications remain to be determined.³³

In cerebral malaria, microvascular activation accompanies blood-brain barrier dysfunction which in turn represents the pathophysiological basis of neurological impairments in affected patients. Deininger et al (2003)³³ analyzed localization of proangiogenic vascular endothelial growth factor (VEGF), its receptor vascular endothelial growth factor receptor-1 (VEGFR-1, Flt-1), of downstream VEGF effectors matrix-metalloproteinase-1 (MMP-1) and connective tissue growth factor (CTGF), and of VEGF-interacting antiangiogenic thrombospondin-1 and -independent angiostatin in brains of patients who died with CM and controls by immunohistochemistry and Western blotting experiments.

Most prominently, Deininger et al (2003)(33) detected more VEGF( t) astrocytes in CM patients and deposition of Flt-1 in Durck's granulomas. MMP-1 and thrombospondin-1 accumulated in macrophages/microglial cells in Durck's granulomas. In one CM patient, massive amounts of CTGF were detected as perivascular paracellular deposits. Angiostatin was observed in the serum of 2/7 control but in no CM patients. This data demonstrates the activation of the proangiogenic VEGF signaling cascade in patients with CM, probably reflecting compensatory mechanisms of general and focal brain hypoxia observed in these patients.³³
The genetic role of cerebral malaria

Persons who carry the (heterozygotes for the abnormal hemoglobin gene HbS) will be relatively protected against severe disease and death caused by *Plasmodium falciparum* malaria. In general, the prevalence of hemoglobin-related disorders and other blood cell dyscrasias, such as Hemoglobin C, the thalassemias and G6PD deficiency, are more prevalent in malaria endemic areas and are thought to provide protection from malarial disease. Deficiency of G6PD in human RBCs gives protection against *Plasmodium* spp, because this enzyme is required for the metabolism of the parasites. Another example of a genetic factor involves persons who do not have the Duffy blood on their erythrocytes. These Duffy blood group negative antigens (Fy/Fy) individuals have red blood cells act as carriers for merozoites of *Plasmodium* spp that are refractory to infection by *P. vivax*. Most of the people in West Africa and much of East Africa do not have this receptor and they are protected from *P. vivax* infection.

The role of cytokines

Malaria is fundamentally a systemic inflammatory state. Inflammatory cytokines play an important role in human immune responses to malarial disease.

Cerebral malaria is associated with significantly elevated levels of IL-6 and IL-10 compared to severe malaria cases without cerebral manifestations. Hyperparasitemia is associated with significantly lower levels of IL-6. These results illustrate the complex relationship between inflammatory cytokines and disease in *P. falciparum* malaria. It has been suggested that IL-4 and/or IgE play a regulatory role in the pathogenesis of severe or complicated malaria. Gyan et al (2004) found a significantly higher frequency of IL-4 intron-3 B1B1 genotype in the cerebral malaria.

Furthermore, carriers of IL-4 +33T/-590T with cerebral malaria have elevated total IgE compared to non-carriers (36). High mobility group box 1 (HMGB1) protein, a DNA-binding protein that can also act as a pro-inflammatory cytokine if released from cells, is an important amplification signal in various forms of inflammation. The concentration of HMGB1 in serum taken at admission was increased in falciparum malaria in sixteen African children, more in fatal cases than in those who subsequently recovered. Serum from both non-fatal and fatal cases contained significantly more circulating HMGB1 than did serum from healthy Caucasian adults. In keeping with its developing role in sepsis, HMGB1 may enhance and prolong the inflammatory processes, and thus illness, in malaria.  

The level of tumor necrosis factor is frequently increased in patients with severe falciparum malaria, particularly in those with cerebral malaria or hypoglycemia. It has been concluded that increased TNF production is a normal host response to *P. falciparum* infection, but that excessive levels of production may predispose to cerebral malaria and a fatal outcome. Serum level of TNF-alpha is increased in *Plasmodium* falciparum malarial infections. The serum TNF-alpha measured by avidin-biotin sandwich ELISA, was found to be significantly raised in *P. falciparum* and more in fatal infections. It has been observed that the serum concentration of TNF-alpha correlated well with severity of malaria, and these values could be used as an important prognostic marker of the disease.

Symptomatology of cerebral malaria

Coma

Common causes of coma in falciparum malaria are cerebral malaria, hypoglycaemia and electrolyte disturbances. Focal deficits due to arterial infarcts may sometimes occur in children, but are rare in adults. Three adults with falciparum malaria who had fever, altered consciousness and focal neurological deficits (one of whom also had seizures) are being reported here. CT scan of the brain revealed haemorrhagic infarction of the cerebral cortex and subcortical white matter with surrounding oedema suggestive of venous infarction in all three patients. The diagnosis of cerebral venous thrombosis was missed in the first patient, and was detected only at autopsy. In the next two patients, superior sagittal sinus thrombosis was confirmed angiographically. Only one patient survived; the other two died of increased intracranial pressure. Two of the three patients also had *P. vivax* co-infection. A hypercoagulable state resulting from severe malaria that can be responsible for this rare and potentially fatal complication. Cerebral malaria may be associated with raised intracranial pressure due to cerebral edema. Cerebral venous thrombosis may worsen this and adversely affect outcome. This diagnosis should be suspected in patients with severe
malaria who develop focal neurological deficits and confirmed by appropriate imaging; judicious use of local thrombolytic therapy may help improve outcome.41

**Convulsions**

Falciparum malaria is the most common cause of convulsions in children admitted to hospitals in malaria endemic areas. About the third of acute seizures in children with cerebral malaria, do not manifest as convulsions, but as changes in eye deviation. salivation and/or eye deviation.42 However, the cause of seizures in children with falciparum malaria is unclear. In malaria endemic areas, children who develop severe falciparum malaria with seizures may have a higher genetically risk of epilepsy or febrile seizures.43

Koibuchi et al (2003)(44) diagnosed acute disseminated encephalomyelitis (ADHM) following P. vivax malaria from the clinical course and MR images. ADEM should be regarded as one of the neurological complications after malarial infection. The presenting symptoms are febrile convolution which is the most common neurologic morbidity seen (35.1%), followed by cerebral malaria (28.0%) and then meningitis (27.0%).13 Patients infected with P vivax exhibited cerebral malaria, renal failure, circulatory collapse, severe anemia, hemoglobinurea, abnormal bleeding, acute respiratory distress syndrome, and jaundice.16

A prospective study done in 216 children with complicated falciparum malaria, showed hepatopathy in 33.5% of cases with a higher incidence in children aged above five. Bilirubin and alanine aminotransferase were moderately raised in most cases. No significant association with other common complications and no higher risk of mortality was observed.35 P. falciparum malaria, hyperbilirubinemia is not a severe complication itself, and only appears to be linked with mortality when associated with at least one other complication.40

**Age:**

Age appears to influence not only the acquisition of clinical immunity to malaria, but also the susceptibility to and clinical manifestations of severe malaria.26-27 The mean ages of patients with cerebral malaria (14.1 years).11 Most children presenting with severe falciparum malaria were less than 5 years (92.3% of 583 cases). Cerebral malaria usually occurs in children over 18 months old.37 The highest death rate was recorded in the age group of 1-5 years, with a peak in the 2nd and 3rd year.12 Children five years of age and less were 466 (77.2%), and modal age group was 1-2 years.13 Malaria transmission intensity in Africa varies over several log orders, from less than one infecting bite per year to more than one thousand. In this review, we examine the consequences in terms of age pattern, clinical spectrum and overall burden of disease and discuss the possible implications for interventions that reduce exposure to infecting bites.48 The risks of severe disease in childhood are lowest among populations with the highest transmission intensities, and the highest disease risks are observed among populations exposed to low-to-moderate intensities of transmission.49 Age and level of exposure independently influence the clinical presentation of severe malaria. The median age of patients was 1 year in high transmission, 3 years in moderate transmission, and 5 years in low transmission areas. The odds of severe malarial anemia (hemoglobin <5 g/dL) peaked at 1 year of age at high transmission and at 2 years at moderate and low transmission intensities and then decreased with age. Odds were highest in infants and high transmission intensity areas The odds of cerebral malaria were significantly higher in low transmission intensity areas and with the age of 5 older.50

**Sex:**

Both sexes are usually affected with P. falciparum infection.12 In a series studied by Kamble, Raut and Hussain (2002)(3) the M:F ratio was 2:1.

**The prognostic indicators:**

The prognostic indicators with the highest case fatality rates were coma/seizures, hyperlactataemia and hypoglycaemia, and the highest case fatality rate was in children with all three of these features.47 It has been noticed that the serum concentration of TNF-alpha correlated well with severity of malaria, and these values could be used as an important prognostic marker of the disease.48 Independent predictors of mortality were found to be respiratory distress, circulatory failure, generalized hyporeflexia and parasite density > or =500,000/microl. Circulatory failure could be predicted by a combination of hypothermia,
cold peripheries and dehydration. Death occurred within 12 hours of admission only in children with these predictors, and the risk of death increased with the number of risk factors.15

**Seasonal variations**

Malaria continue to be a major problem in tropical countries14 Ofovwe et al (2005)13 reported an increased incidence of cases during the rainy season.

**CNS manifestations of cerebral malaria**

Several neurological complications are associated with complicated and severe falciparum malaria. Cerebral malaria is one of the most dreaded complication. Children are particularly more vulnerable to have this complication.51

**Acute cerebellar ataxia**

In 1976, Illangasekera and De Sylva52 described a case of cerebellar ataxia occurred during an attack of falcibarum malaria. Onifade and Dancsi (2004)53 reported 5 patients with cerebellar ataxia (CA) following proven/presumed acute falciparum malaria. Two of them were children. The youngest was a 7-year-old girl and, as far as we know, was the youngest child in which the syndrome has been reported. The mode of presentation is similar to that of patients previously reported with the syndrome from other parts of the world. The minimum duration of ataxia was 2 weeks, while the maximum duration was 6 weeks.53 In comparison with cerebral malaria, this neurological complication of falciparum malaria has a good prognosis, resolving completely in virtually all cases. Therefore, there is the need to be on the look out for it in order to appropriately counsel of patients.

**Pseudobulbar palsy**

Demyelination may be a pathogenic mechanism of post-malarial neurological sequelae. It can cause pseudobulbar palsy, which has not been recorded earlier. Two cases had been reported of pseudobulbar palsy after cerebral malaria with evidence of demyelination.54

**Neurocognitive impairments**

After severe malaria, some children have neurocognitive impairments that are evident as long as nine years later. Impairments may become more evident as children progress and face more complex cognitive and linguistic demands, socially and educationally. Furthermore, cerebral malaria CM and malaria with complicated seizures M/S are associated with developmental impairments. If these impairments persist, this may have implications on at least 250,000 children in Sub-Saharan Africa each year. Active epilepsy significantly increases the risk of cognitive and behavioral problems in children with a history of severe malaria.55

This highlights the importance of follow up for children with severe malaria and the involvement of therapists and educators in the provision of services for this population.56

**Retinopathy:**

A characteristic retinopathy associated with a poor prognosis has previously been described in African children with established cerebral malaria. This has been described in 106 Gambian children admitted consecutively to hospital with severe malaria, including six with established cerebral malaria.57

**Diagnosis**

**CT scan and MRI of the brain**

This may reveal haemorrhagic infarction of the cerebral cortex and subcortical white matter with surrounding oedema suggestive of venous infarction in patients with focal deficit. Angiography may confirm the diagnosis of cerebral venous thrombosis, e.g. superior sagittal sinus thrombosis.41 MRI is the examination of choice when cerebral venous thrombosis is suspected.41 In the case of post infection by P. vivax, magnetic resonance, (MR) images of the brain showed multiple high- intensity spotty lesions in the left cerebral cortex and subcortex.44

**PCR techniques**

The golden standard is the Giemsa-stained thick and thin blood films.59 However, this method lacks insufficient sensitivity and requires considerable expertise.60 Zhang et al (1993) described a new malaria diagnostic method based on the detection of malaria parasite DNA by PCR-ELISA. The thresholds of parasite density for the detection of Plasmodium falciparum and Plasmodium vivax by this test were noticed to be as low as 4 and 10 parasites per microliter of blood respectively, and no cross reaction was seen in the detection of falciparum and vivax malaria parasites.61 The sensitivity of PCR for the
detection of P. vivax and P. falciparum malaria was higher than that of microscopy. Real-time PCR with species-specific probes detected one plasmid copy of P. falciparum, P. vivax, P. malariae, and P. ovale specifically. The same sensitivity is achieved for all species with real-time PCR with the 188 screening probe.

The ParaSight F test was developed as a pioneer industry effort in the large-scale, process-controlled production of a device for the rapid diagnosis of malaria. The sensitivity of the device was 100% for P. falciparum densities of >500 parasites/μl, with a sensitivity of 83% for parasite densities of <500/μl. The specificity for the exclusion of P. falciparum was 93%. These findings indicate that assays for rapid diagnosis have the potential to enhance diagnostic capabilities in those instances in which skilled microscopy is not readily available.

Prevention and Prophylaxis
Effective malaria control and prevention of meningitis can reduce the incidence of neurologic morbidities and, if this is associated with health education of the populace on the importance of attending health facility early, mortality from these causes would be greatly reduced.

References
Cerebral Malaria In Children ….. Kamal Salih, et al.


