Cerebral Malaria Insights: Pathogenesis, Host Parasite Interactions including Host Resistance

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Case Study

A 3-year-old African-American boy was brought to the emergency department by his mother in a small town in Ethiopia. The child complained of a persistent headache for a few days. He eventually developed coughing, lethargy, generalized joint pain, nausea, vomiting and a high fever which came and went with shaking chills. The physician examined the patient, and he noted splenomegaly under left costal margin and upper left quadrant along with bilateral retinal hemorrhages on funduscopic exam. The patient was immediately admitted to the pediatric floor as the physician suspected malaria, a common disease in the local area. Blood work was drawn to measure the boy's CBC, electrolytes, urea, creatinine, haptoglobin, lactic dehydrogenase and reticulocyte count. A lumbar puncture was done along with blood, urine, and sputum cultures plus a test for HIV. Dipstick tests for *P falciparum* histidine-rich protein-2 (PfHRP-2) antigen were positive. Following admission to the floor, the patient suffered a tonic clonic seizure which developed into status epilepticus. The boy was sedated and ventilated. He had a Blantyre coma score of 1, and he died hours later from septic shock.

Clinical Presentation of Cerebral Malaria

> TNF-alpha → Fever

> Fever → Increased Metabolic Demand → Hypoglycemia → Cerebral Neuron Cell Damage/Death

> Adherence of pRBC to ICAM → Blood coagulation → Decreased Cerebral Blood Flow → Hypoxia

> Hypoxia → Irritated Neurons → Seizures

****Clinical Hallmark:** Decreased Consciousness (Obtunded, Stuporous)

> Coma 1 hour after seizure termination or 1 hour after hypoglycemia

Clinical Presentation of Cerebral Malaria Continued

> Blood coagulation in Retinal Vessels → Retinal Hemorrhage → Vision Loss
    > Occurs in 15% of Cerebral Malaria Patients

> Blood coagulation in Cerebral Vessels → Increased Intracranial Pressure → Passive Resistance to Neck Flexion (pain), Decreased Arousal

Multi-organ System Dysfunction

> Anemia, Jaundice, Kussmaul Breathing

> Worsening prognosis with coexistent renal failure

> Acute pulmonary edema

> Rapid pulse

> Normal blood pressure

> Hypoglycemia: plasma glucose < 2.2 mmol/L
    Occurring in 8% of adults and 20% of kids with cerebral malaria

WHO Definition

- Cerebral malaria is a clinical syndrome characterized by a coma lasting at least 1 hour after termination of a seizure or correction of hypoglycemia, asexual forms of *Plasmodium falciparum* parasites on peripheral blood smears and no other cause to explain the coma

Cerebral Malaria

- Cerebral Malaria is the most severe neurological complication due to *Plasmodium falciparum* infection
- Cerebral malaria is an example of the a virulence factors causing a host response to infection
- 575,000 cases annually
- Kids in sub-Saharan Africa are most affected.
- Patients recovering from Cerebral Malaria have an increased risk of neurological and cognitive deficits

Epidemiology

- In Africa, between 17% and 50% of hospital admissions for severe malaria are attributed to cerebral malaria
- More common in areas of low or unstable transmission than in areas of high transmission
- Over the past 5 years, 1,620 comatosed patients of both sexes aged 1-75 years were screened for cerebral malaria. Of these, 505 (31.2%) were positive for Plasmodium falciparum. During this period frequency of malaria increased from 22.1% in 1991 to 44.4% in 1995
- 64% of cerebral malaria cases were seen in children and 36% in adults.
- Mortality was also higher, 41% in children, than in adults, 25%
- Most deaths occur within 3 days of admission

Pathology

- Plasmodium Species
  - Eukaryotic Parasites
  - Transferred via mosquito
    - Sporozoites are transferred from the mosquito gland into blood
  - Different stages
    - Merozoite stage, found in RBC and circulation
    - Throphozoite stage, feeding
      - Feed on hemoglobin
    - Gametocytes for reproduction
    - Shizonts, asexual reproduction

Pathology

- Reproduction
  - Migrate to liver, multiply, released into blood as Merozoites
  - Form gametocytes as well as stage V cells within the RBC, repeat cycle
    - Gametocytes appear as crescent shapes, found in RBC
    - Combine when a mosquito has a blood meal
      - Creates zygote in mosquito
      - Becomes ookinate, oocyst, then ruptures into sporozoites, which begin the infectious cycle after biting host

Cytoadherence

- Mediated by PfEMP-1 (*P. falciparum* erythrocyte membrane protein-1) on pRBCs
  - Adherence is highly effective in the second half of *P. falciparium* life cycle
  - Late stage parasite (trophozoites and schizonts) are sequestered to organs
- Main receptor for cytoadherence is ICAM-1
  - Upregulated by proinflammatory cytokines TNF-α, IFN-γ and IL-1
  - Regulated by NFκB which increases transcription of cytokines and chemokines

Sequestration

- Pathogenesis of fatal cerebral malaria is associated with sequestration of pRBCs
- Occurs during the second half of intra-erythrocytic phase following cytoadherence
- Accumulates in the Central Nervous System
  - Cerebellum
  - Cerebrum
  - Medulla Oblongata
- Forms a mechanical obstruction resulting in:
  - Decreased tissue perfusion
  - Hypoxia
  - Decreased removal of waste products like lactic acid

Red cell deformability, rosetting and autoagglutination

- Maturation of parasites inside RBCs decreases their ability to deform by inducing changes in cytoskeleton which increases the stiffness of the RBC membrane

- **Adherence**
  - Rosetting — non-pRBCs with pRBC
  - Agglutination — pRBC with pRBC

- Comprises microcirculation that leads to impaired tissue perfusion, hypoxia and creates a toxic local environment

Diagnosis - Must act fast!

- Diagnosis is made based on clinical assessment and parasite findings.
- Parasite-based confirmation should be carried out as soon malaria is suspected.
- Testing for malaria can be done through: light microscopy (visualization of parasites in stained blood samples), rapid diagnostic tests (detecting antigen or antibody), and molecular techniques which detect parasite genetic material.
- Detection of parasites on Giemsa-stained blood smears by light microscopy is the standard tool for diagnosis of malaria; it allows identification of the *Plasmodium* species as well as quantification of parasitemia.
- Microscope examination is *not* always reliable in detecting very low parasitemia (<5 to 10 parasites/mcL).
- Rapid diagnostic tests for detection of malaria parasite antigens are becoming increasingly important diagnostic tools. This is very important in resource-limited areas as they have high accuracy, ease of use, and rapid results.
- RDTs detect one or more of the following antigens: histidine-rich protein 2 (HRP2), *Plasmodium* lactate dehydrogenase (pLDH), and aldolase.

Diagnosis - other tests

- CT/MRI
- Routine bloodwork CBC, Electrolytes, Urea, Creatinine, LFTs, blood glucose levels, coagulation studies
- Urine, blood, and stool cultures
- G6PD activity - prior to giving primaquine

Evidenced Based Treatment

- Initial treatment of severe malaria consists of parenteral therapy with drugs such as Artesunate rather than intravenous quinine if possible, and then to an oral regimen. Artemisinin combination therapy regimen (three-day course) recommended. Quinine or quinidine may be used if artemisinins are not available in conjunction with an additional agent (clindamycin, doxycycline, or tetracycline).
- Supportive care is critical for patients with severe malaria as death can occur within hours of arrival to the clinical setting.
- Emergent assessment and initiation of antimalarial therapy is crucial with supportive care to manage life-threatening complications of the disease.
- Treatment of the pulmonary complications of severe malaria with is with supplementary oxygen to mechanical ventilation.

Evidenced Based Treatment

- Treatment of the neurological complications requires a clinical evaluation with a full physical examination, calculation of Blantyre coma score, funduscopic exam, and lumbar puncture. Seizures should be managed pharmacologically.
- Hematologic complications may require transfusion
- Hypoglycemia should be suspected in any patient who deteriorates suddenly and be treated with an initial bolus of dextrose and then IV solutions with 10% dextrose. Blood glucose measurement should be consistently monitored until stabilized.
- Hypovolemia with each patient. Adults with malaria are further prone to fluid overload than children. Their is a narrow threshold between underhydration (and risk of renal impairment) and overhydration (and risk of pulmonary and cerebral edema).

Prevention

- In areas where malaria is endemic, infants are protected from severe malaria during the first 3 to 6 months of life by passive immunity from maternal antibodies, but as this immunity wanes, they succumb to severe malarial anemia and cerebral malaria.

- In endemic areas, the main method of prevention is mosquito nets, insect repellents and insecticides. The biggest problem with preventing malaria in these areas is cost and accessibility of proper health care.There are preventative drugs, and a new vaccine currently under clinical trials available for travellers There are also some conditions that offer resistance to malaria.

Conclusion

- Cerebral malaria deaths most commonly occur in children of sub-Saharan Africa due to the parasite *Plasmodium falciparum*.
- Pathogenesis of fatal cerebral malaria is associated with sequestration of pRBCs and occurs during the second half of intra-erythrocytic phase following cytoadherence
- It then accumulates in brain tissue forming mechanical obstruction resulting in decreased tissue perfusion, hypoxia, and decreased removal of waste products like lactic acid.
- Prompt diagnosis and treatment is imperative in treating patients suffering from the condition.
- Prevention when possible is essential to attempt to prevent the spread of the parasite and therefore cases of cerebral malaria.

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