Cerebral Malaria in African Children: Clinical Features, Treatment and Pathogenesis
Malawi
Plasmodium falciparum: Life cycle
Sequestration
Infection
Illness
  Uncomplicated malaria
  Severe malarial anemia
  Acidosis
  Cerebral malaria
Clinical management
Fatal malaria
  Risk factors
  Post mortem studies
Age distribution of *P. falciparum* parasitemia in asymptomatic Senegalese

![Age distribution chart](chart.png)

Severe Malaria in African Children:
Clinical Features and Pathogenesis

- Infection
- Illness:
  - Uncomplicated malaria
  - Severe malarial anemia
  - Acidosis
  - Cerebral malaria
- Fatal malaria
  - Risk factors
  - Post mortem studies
Age distribution of *P. falciparum* parasitemias and clinical attacks in Senegal.

Infection

Illness

- Uncomplicated malaria
- Severe malarial anemia
  \( (HIV\text{ seroprevalence}: 35\%)^* \)
- Acidosis
- Cerebral malaria
  \( (HIV\text{ seroprevalence}: 21.3\%)^* \)

Clinical management

Fatal malaria
- Risk factors
- Post mortem studies

\(^*HIV\text{ seroprevalence for non-malarial coma}: 23.9\%\)
Severe malarial anemia

Acidosis

Cerebral malaria

Uncomplicated malaria

Severe malarial anemia

ACIDOSIS: Clinical features

- Deep breathing (Kussmaul respirations)
- Low pH
- Low plasma bicarbonate
- Hyperlactatemia
- No obvious lung pathology
- +/- cerebral malaria, anemia


SEVERE ANEMIA:

Clinical features

- May develop rapidly
  - Exacerbated by fever (increased metabolic demand)
- Pallor
- High output CHF
  - Rales
  - Gallop rhythm
  - Enlarging liver
- Confusion, obtundation
ANEMIA:

- Hemolysis of PRBCs
- Hematopoietic suppression
- Circulatory insufficiency
- Exacerbated by fever
- Blood transfusion
  - Inherent dangers
  - Risk of HIV transmission
CEREBRAL MALARIA:
Clinical features

Rapid onset: fever < 1 day, immediate coma
CEREBRAL MALARIA:
Clinical features

Wide variety of neurological findings:
cerebral cortex → brain stem
CEREBRAL MALARIA:
Unique funduscopic features
CEREBRAL MALARIA:
Clinical features

- Rapid recovery
- Reversible neurological deficits
- Death or recovery generally within 72 hours
- 10% neurological sequelae
- 15-20% mortality rate
CEREBRAL MALARIA: Time course

- Fever Clearance Time
- Parasite Clearance Time
- Coma Resolution Time
SEVERE MALARIA:
Clinical management

• Immediately:
  – Identify and Rx hypoglycemia
  – Identify and Rx convulsions
  – Identify and Rx life-threatening anemia
  – Administer antimalarial drugs
SEVERE MALARIA: Clinical management

• Assess Blantyre Coma Score
• Begin serial observations
  – MPs
  – PCV
  – Glucose
  – Coma Score
• Respond to changes in clinical condition
FATAL MALARIA:
Who dies of severe malaria, and why?

- Infection
- Illness
  - Uncomplicated malaria
  - Severe malarial anemia
  - Cerebral malaria
- Fatal malaria
  - Risk factors
  - Post mortem studies
FATAL MALARIA:
Depth of coma

- Blantyre Coma Score
- Best motor response (0-2)
- Best verbal response (0-2)
- Eye movement (0-1)

FATAL CEREBRAL MALARIA: Hypoglycemia

- Pre-treatment
- Associated with quinine treatment
- *Not* starvation
- *Not* hyperinsulinemia
- ? parasite consumption/focal
- ? impaired gluconeogenesis

FATAL MALARIA:
Funduscopic features

- **Hemorrhages**
  - 35-40% of children with CM
  - *NOT* associated with a poor outcome

- **Papilledema**
  - 8-10% of children with CM
  - RR (death): 7 (95% CI 3-17)

- **Retinal whitening**
  - 50% of children with CM
  - RR of death: 3 (95% CI 1-8)

- **Retinal vessel abnormalities**
  - Seen in 25% of children with CM
  - RR of death: 3 (1-10)
FATAL MALARIA: Interventions

• Hyperimmune serum
  – No impact

• Anti-TNF antibodies
  – Decreased fever only

• Anticonvulsants
  – Increased mortality
And then...even with the introduction of more rapidly acting antimalarials (the artemisinin drugs), mortality rates of patients admitted to hospital with clinically defined cerebral malaria did not decrease.
FATAL CEREBRAL MALARIA: Pathogenesis

- Infection
- Illness
  - Uncomplicated malaria
  - Severe malarial anemia
  - Cerebral malaria
- Fatal malaria
  - Risk factors
  - Post mortem studies
The Team

• Directors
  – Terrie Taylor
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    Liverpool School of Tropical Medicine (Wellcome Trust)

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  George Liomba
  Sebastian Lucas
  Dan Milner
  Charles Mackenzie
  Charles Richert
  Val White
  Rich Whitten
  Katerina Zis

• Mortuary Attendants
  Davis Kotokwa
  James Mbewe
  Wales Namanya
Plasmodium falciparum: Life cycle
Clinicopathological Correlates of Cerebral Malaria

Aim
• Improve understanding of pathogenesis
  – decrease malaria mortality

Primary Hypothesis
• Sequestration causes cerebral malaria
Clinicopathological correlates of fatal malaria: 1996-2000

- Patients admitted: 1073
- Deaths: 183
- Autopsies requested: 140
- Autopsies done: 45
### Standardized Autopsy

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<th>LM BMP</th>
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**Notes:**
- LM: Light Microscopy
- BMP: Bright Field
- GECN: Gomori’s Epithelial Cell
- IC: Immunocytochemistry
- OR: Orderly Reticulum
- CM: Cytological Microscopy
- SMEAR X: Smear Examination
- TOUCH X: Touch Preparation
- SR X: Special Staining
- SPAC X: Special Staining
- GT: Giant Tissue
Comparing sequestration: clinical definitions

### Cases: n=31
- Clinically defined cerebral malaria
  - Blantyre Coma Score \(< 2\)
  - *P. falciparum* parasitemia
- No other obvious cause of coma
  - Meningitis
  - Hypoglycemia
  - Post-ictal state

### Controls: n=11
- Non-malaria comas (10)
  - Bacterial meningitis (4)
  - TB meningitis (1)
  - Reye’s Syndrome (2)
  - Septicemia (2)
  - Renal papillary necrosis (1)
- Comatose patients with incidental parasitemia (1)
  - Organophosphate toxicity

*Excluding 3 cases of severe malarial anemia*
Clinicopathological correlates of fatal malaria – the first 42 cases*

Cerebral malaria (clinically defined): 31

Non-malarial comas: 11

* Excluding 3 non-comatose patients with SMA
Sequestration...in some cases
Intra- and peri-vascular pathology in some cases (always with sequestration)

- Accumulations of pigmented white blood cells
- Hemorrhages
- Widespread deposition of fibrin thrombi
Comparing sequestration: pathological classes

Using semiquantitative assessments, two pathologists agreed on three different patterns of pathology:

- **Class I (n=6):** Sequestration only
- **Class II (n=18):** Sequestration + intra/perivascular pathology
- **Class III (n=18):** Little/no sequestration, no intra/perivascular pathology
Comparing sequestration: Quantitative data on parasites

- Capillaries in cross-section were identified
- Contents of >100 were counted
  - Presence/absence of parasitized erythrocytes:
    - % vessels parasitized
  - Unpigmented parasites/100 vessels
  - Pigmented parasites/100 vessels
  - Extra-erythrocytic pigment/100 vessels
Comparing sequestration: Quantitative data on parasites

• Capillaries in cross-section were identified
• Contents of ≥100 were counted
  – Presence/absence of parasitized erythrocytes: % vessels parasitized
  – **Unpigmented parasites/100 vessels**
  – Pigmented parasites/100 vessels
  – Extra-erythrocytic pigment/100 vessels
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  - Pigmented parasites/100 vessels
  - Extra-erythrocytic pigment/100 vessels
Statistical ‘sorting’ approach – CART (Classification and Regression Tree):

What is the relationship between parasite elements in cerebral capillaries and cerebral pathology?

All cases

Sequestration

No sequestration (Class III)

SQ only (Class I)

SQ plus intra- & peri-vascular pathology (Class II)
The parasitology predicts the pathology--

All cases

- % vessels parasitized (cutoff: 23%)
  - Sequestration
  - No sequestration (Class III)

- Free pigment/100 capillaries (cut off: 55)
  - SQ only (Class I)
  - SQ plus intra- & peri-vascular pathology (Class II)
Sequestration: pathological/parasitological classes vs clinical diagnosis (cases & controls)

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<thead>
<tr>
<th>Pathological/parasitological classes</th>
<th>Cases vs. controls</th>
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<tbody>
<tr>
<td>Class I (n=6): Sequestration only</td>
<td>Cerebral malaria (clinically defined): n</td>
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<td>Class II (n=18): Sequestration + intra/perivascular pathology</td>
<td>Non-malarial comas: n = 11</td>
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<td>Class III (n=18): Little/no sequestration, no intra/perivascular pathology</td>
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“No sequestration” (Class III): 11/11 controls + 7/31 with clinically defined CM

Alternative causes of death were found in all 7 “CM” cases:
- Reye’s Syndrome
- Ruptured AVM
- Hepatic necrosis
- S. pneumoniae pneumonia (2)
- Viral pneumonitis (2)

• Implications:
  - Inappropriate treatment?
  - Underpowered clinical trials?
  - Phenotypic imprecision?
Sequestration with and without intra/peri-vascular pathology (Classes I and II): all clinically CM

- CM 1
  - Sequestration only

- CM 2
  - Sequestration + intra/peri/vascular pathology

Different mechanisms? Different timing?

Implication: A single “silver bullet” may be unlikely

Pathological Categories

- Neuropathology
  - Inflammation
  - Hypoxia
  - Excitotoxicity

Clinical Manifestations

- Eye Findings
- Coagulopathies
- Metabolic Abnormalities
Safunsa anadya phula....

Pali funso?