Update on pediatric malaria in Malawi: a few more pieces of the puzzle

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Michigan State University

Blantyre Malaria Project
University of Malawi College of Medicine
Malawi
Queen Elizabeth Central Hospital, Blantyre Malawi
Figure 1. Areas Where Malaria Is Endemic.
Data are from the World Health Organization and from the Centers for Disease Control and Prevention.
Malaria infection

~500 billion infections annually

Malaria illness

~200 million malaria illnesses

Severe malaria

~6 million with severe disease

~1 million deaths
Plasmodium falciparum: Life cycle
Our focus has been cerebral malaria

- Blantyre Coma Score $\leq 2$
- *P. falciparum* parasitemia (any density)
- No other obvious cause of coma
  - Hypoglycemia
  - Meningitis
  - Post-ictal state
Basics of clinical care

- Anti-seizure medication
- MPs (thick and thin), PCV, glucose, lactate
- Admission HPI and exam; consent, FBC, blood culture
- Quinine
- Funduscopy, lumbar puncture
- EEG, MRI, fundus photography
- Q6 hr observations: coma score, glucose, lactate, hematocrit, MPs
<table>
<thead>
<tr>
<th>TIME</th>
<th>Day</th>
<th>Date</th>
<th>Day</th>
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</tr>
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<tbody>
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<td>Other times (cross out above line)</td>
<td>6a</td>
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<td>6a</td>
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<td>Hours since admission</td>
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<td>CONVULSIONS</td>
<td>Y/N</td>
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<tr>
<td>COMA SCORE:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MOTOR</td>
<td></td>
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<td>VERBAL</td>
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<tr>
<td>EYE</td>
<td></td>
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<tr>
<td>COMA SCORE: TOTAL</td>
<td></td>
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<tr>
<td>Vomiting/Diarrhoea</td>
<td>Y/N</td>
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<td>Y/N</td>
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<td>Drinking/feeding</td>
<td>Y/N</td>
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<td>Dehydration</td>
<td>(0, +, ++)</td>
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<td>Pallor</td>
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<td>Cyanosis</td>
<td>Y/N</td>
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<td>Y/N</td>
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<td>Passing urine</td>
<td>Y/N</td>
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<td>Y/N</td>
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<tr>
<td>Pulse rate</td>
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<tr>
<td>Respiratory rate</td>
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<tr>
<td>Blood pressure</td>
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<td></td>
<td>systolic / diastolic</td>
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<td>Temperature</td>
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<td>40</td>
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<td>36</td>
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<tr>
<td>Temperature Recorded (Axillary / Rectal)</td>
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<td></td>
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<tr>
<td>Oxygen</td>
<td>Y/N</td>
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<td>Y/N</td>
<td>litres/min</td>
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<tr>
<td>Oxygen saturation</td>
<td>(Without O2)</td>
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<tr>
<td>BLOOD</td>
<td></td>
<td></td>
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<tr>
<td>GLUCOSE</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LACTATE</td>
<td></td>
<td></td>
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<tr>
<td>Lab results:</td>
<td>PCV</td>
<td></td>
<td>PCV</td>
<td></td>
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<tr>
<td>MPa (+, ++, ++++, ++++++, ++++++)</td>
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<tr>
<td>Observer’s Initials</td>
<td></td>
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</tr>
</tbody>
</table>
Clinicians
Karl Seydel
Yamikani Chimalizeni
Rachel Bronzan
Kondwanis Kayira and Kawaza
Lindsay Fox
Emmie Mbale
Elissa Malkin
Madalitso Tembo
Phil Thesing
James Mwenechanya
Paul Pensulo
Alice Muirui Liomba
Ashley Mpakiza
Mac Mallewa
Usual Clinical Course

- 1-3 days of coma (BCS ≤ 5)
- Parasitemia clears within 36-42 hours
- IVF transition to NGT feeds after 24-30 hours
- Anti-seizure medications prn
- Antibiotics occasionally
- Blood transfusions as needed
- Home, fully recovered, Day 3 or 4
- 80 -85% survival
- Follow-up clinical visits: 1 month
Fatal outcomes

- 15-20% die
- Half die within 24 hours
- Most commonly: respiratory failure
- Cardiovascular sparing
Back to the basics

• Studies of association were helpful, but are limited in terms of establishing causality.
• The much-vaulted artemisinins *did* clear parasitemia rapidly, but did not affect overall mortality.
• Interventional studies (with one exception) did not affect overall mortality rates, so….
The Pathology of Fatal Malaria

Dan Milner
Steve Kamiza
Richard Carr
Rich Whitten
Sebastian Lucas

and many volunteer pathologists
Clinicopathological Correlates of Cerebral Malaria: Blantyre, Malawi

- **Case-control Study**
  - Cases (clinically defined cerebral malaria)
    - Blantyre Coma Score ≤ 2, parasitemia, no other cause of coma
  - Controls
    - Non-malaria coma
    - Severe malaria anemia without coma
    - Incidental parasitemia
      - another cause of illness ID during life

- **Dedicated hospital research ward**
- **Standardized protocols**
- **24 hour nursing care and detailed observations**
- **Approach family in the event of a death**
- **Conduct autopsies within 12 hours**
Clinicopathological correlates of fatal cerebral malaria: 1996-2010

2,312 patients admitted
390 deaths
332 autopsy requests
102 autopsies completed
“Faux” Cerebral Malaria

- Patients meet the clinical case definition of cerebral malaria but have two consistent findings at autopsy:
  - 1) No evidence of sequestration or associated pathology in the brain
  - 2) A clear anatomic cause of death
    - Reye’s Syndrome
    - Ruptured AVM
    - Hepatic necrosis
    - *S. pneumo* pneumonia
    - Viral pneumonitis
Sequestration only in the brain. No other anatomic cause of death

CM1

Sequestration and extra- & perivascular pathology in the brain. No other anatomic cause of death

CM2

No evidence of sequestration in the brain. Another anatomic cause of death determined

CM3

Patients Meeting the Clinical Case Definition of Cerebral Malaria

CM1 15%

CM2 57%

CM3 28%
Malaria Retinopathy

Susan Lewallen
Nick Beare
Simons (Harding and Glover)
# Summary of retinopathy vs histopathology

<table>
<thead>
<tr>
<th>Malaria Retinopathy</th>
<th>Sequestration</th>
<th>No Sequestration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>No Retinopathy</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

- **Sensitivity**: 97% (84, 99)
- **Specificity**: 93% (64, 99)
- **Pos predictive value**: 97% (85, 99)
- **Neg predictive value**: 93% (64, 99)
FUNDUS CHANGES

- Hemorrhages
- Retinal whitening
- Retinal vessel color changes

- [Papilledema]
RETINAL HEMORRHAGES

– 35-46% of clinically defined CM
  • 20 % of severe non-cerebral malaria
  • 4% of moderate malaria
  • 2% of uncomplicated malaria
  • As well as being less common they are also less marked in the latter 3 above

– Histologically similar to ring hemorrhages seen in the grain
Retinal angiography in cerebral malaria
Interpreting malaria retinopathy

In patients who meet the standard clinical case definition of cerebral malaria

*Normal ocular fundi (18%):*
less severe malaria, no evidence of sequestration to date, should have no sequestration and a non-malarial cause of death

*Malaria retinopathy (≥ 1 feature, + papilledema) (78%):*
should have sequestration with or without raised intracranial pressure

*Papilledema only (4%):*
parasitemia + another life-threatening, non-malarial illness
Sequestration only in the brain. No other anatomic cause of death

CM1

Sequestration and extra- & perivascular pathology in the brain. No other anatomic cause of death

CM2

No evidence of sequestration in the brain. Another anatomic cause of death determined

CM3

Patients Meeting the Clinical Case Definition of Cerebral Malaria

CM1 15%
CM2 57%
CM3 28%
Neuropathology

Dr. Katerina Zis
University of British Columbia
Brain Weight by Histopathological Category

The diagram shows the brain weight in grams plotted against age in months. Different categories, such as CM1, CM2, CM3, and COC, are represented by distinct symbols. The solid line indicates the Caucasian normal range, while the dashed line represents the prediction 95% CI. The data points for each category are scattered across the graph, illustrating the variation in brain weight with age.
IMMUNOHISTOCHEMISTRY

CM 1  CM2  CM3  COC
(n=7) (n=30) (n=13) (n=18)

Twelve representative samples each from
Cerebral cortex (six from GM, six from WM)
  • frontal, parietal, temporal, occipital lobes and hippocampus
Subcortex
  • caudate and thalamus
Brainstem
  • midbrain, pons, medulla
Cerebellum
  • tonsils, dentate

Axonal injury:  βAPP (mouse MAb; 1:500; Chemicon)
BBB disruption: Fibrinogen (rabbit polyclonal Ab; 1:500; Dako)
Gliosis:  GFAP (rabbit polyclonal Ab; 1:2,000; Dako)
Monocytes:  CD45/CD68 (mouse MAbs; 1:100/1:60; Dako)
Ring Hemorrhages in CM
RH-associated myelin damage in CM
Non-RH associated myelin damage in CM

Median number of non-RH associated areas of myelin damage/10 hpf

Cerebral White Matter
Cortical Gray Matter
Sub-cortex
Brainstem
Cerebellum

CM class within brain area
Axonal injury in CM Associated with RH

Median number of RH-associated axonal lesions/10hpf

- Cerebral White Matter
- Cortical Gray Matter
- Subcortex
- Brainstem
- Cerebellum
RH-associated fibrinogen leakage

Median number of RH-associated areas of fibrinogen leakage/10hpf

CM class within brain area
Non-RH associated fibrinogen leakage

Median number of non-RH associated leaky vessels/10 hpf

CM class within brain area
1. **Ring hemorrhages**:
   a. A feature of CM2 cases
   b. Predominate in the white matter of cerebral hemispheres and cerebellum

2. **Three distinct patterns of axonal injury occur in CM**:
   a. RH-associated: mostly in WM of cerebral hemispheres > cerebellum > brainstem > BG + thalamus
   b. Diffuse:
      - the predominant type, directly related to % vessels parasitized
      - Most prevalent in the cerebral hemispheres > BG + thalamus > cerebellum > brainstem
   c. Adjacent to vascular thrombosis
   d. All three types of axonal injury possibly related to anoxic damage
3. **Diffuse and RH-associated myelin damage**:  
   a. Directly related to % vessels parasitized and the number of RH  
   b. Most prevalent in the cerebral hemispheres > cerebellum > BG + thalamus > brainstem

4. **Increased permeability of the BBB**:  
   a. Directly related to % vessels parasitized, intravascular thrombosis & RH in CM2 cases  
   b. BBB disruption also present in CM1, CM3 and COC patients

5. **Gliosis**: common feature in CM2 and CM1 patients. Not confined to cerebral malaria
6. **Monocyte accumulation in cerebral microvasculature:**
   a. A feature of CM2 cases that may further compromise cerebral blood flow
   b. Not associated with transendothelial migration
   c. Brain invasion by monocytes occurs in areas of RH

7. **Dürck’s granulomas:** not present in pediatric fatal cerebral malaria
Clinical Neurology

Gretchen Birbeck
Mac Mallewa
What is striking?

• Breathing patterns
  – Episodic deep breathing (not continuous Kussmaul)…is this a seizure?
• Posturing…is this a seizure?
• Seizures!!!
• Remarkable, rapid reversibility of deep, unarousable coma
Seizures

• Reported in ~60% of pediatric CM cases
• Frequently prolonged, recurrent and focal
  – All known risk factors for later epilepsy in pediatric populations with febrile seizures
• Difficult to control
  – Paraldehyde x 3, +/- benzodiazepine, then phenobarbital…add phenytoin….and maybe carbamazepine
  – No ventilators. Prophylactic treatment of CM increases mortality from respiratory failure
Contributions of EEG

- Identify subclinical seizures
- Anatomically localize seizures, if focal
- Assess the depth of coma
- Possibly identify regions with structural abnormalities
- Suggest etiologies
  - Triphasic waves = hepatic failure, toxic metabolic abnormalities
  - SSPE
Generalized seizure activity
Partial seizures
PLEDs
Suppression, continuous
Suppression – associated with deep breathing
Other EEG features

- Some preserved features of normal sleep architecture but patient unarousable
  - Vertex sharp waves, K complexes, spindles
  - Asymmetrical spindles (total unilateral absence) associated with poor prognosis
- Often nonreactive
- Arousal pattern is often paradoxical
  - Background slows and flattens
- Unusual spindle coma identified that may be associated with good outcomes
Spindle coma
EEGs in Malawi

Among children with retinopathy-confirmed CM who had no history of a seizure before admission and in whom the examining physician had no suspicion of seizure, 19% had at least one subclinical seizure captured on their admission EEG.
BMPES – Birbeck, et al

- Prospective, exposure-control cohort study of pediatric cerebral malaria survivors
- Matched on age to concurrently admitted children without coma
- Followed prospectively
  - Epilepsy
  - Neurodevelopmental delay
  - ...a disruptive behavioral disorder
- Assessed risk factors for adverse neurologic outcomes
CM Exposed

Year 1

82 CM survivors traditionally defined

1:1 Match

Year 2

58 CM survivors traditionally defined

1:2 Match

Year 3

35 retinopathy positive CM survivors

1:2 Match

175 CM survivors

Omitted 35 CM survivors without retinopathy and 8 CM survivors without eye exams

N = 132 retinopathy positive CM survivors

Unexposed Controls

82 unexposed controls

116 unexposed controls

66 unexposed controls

N = 264 unexposed controls
Year 1

CM Exposed

82 CM survivors traditionally defined

1:1 Match

Year 2

58 CM survivors traditionally defined

1:2 Match

Year 3

35 retinopathy positive CM survivors

1:2 Match

Omitted 35 CM survivors without retinopathy and 8 CM survivors without eye exams

175 CM survivors

N = 132 retinopathy positive CM survivors

Unexposed Controls

82 unexposed controls

116 unexposed controls

66 unexposed controls

N = 264 unexposed controls
...what about the retinopathy-negative patients?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (N = 264)</th>
<th>Retinopathy positive (N = 132)</th>
<th>Retinopathy negative (N = 35)</th>
<th>P value (ANOVA)</th>
<th>Retinopathy negative vs control*</th>
<th>Retinopathy positive vs control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>47.8</td>
<td>47.3</td>
<td>47.9</td>
<td>0.98</td>
<td>P = 0.99</td>
<td>P = 0.85</td>
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<tr>
<td>Sex (% male)</td>
<td>56.1</td>
<td>49.2</td>
<td>40.0</td>
<td>0.13</td>
<td>OR = 0.52</td>
<td>OR = 1.32</td>
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<tr>
<td>Birthweight (kg)</td>
<td>3.2 (N = 173)</td>
<td>3.4 (N = 80)</td>
<td>3.3 (N = 30)</td>
<td>0.67</td>
<td>P = 0.89</td>
<td>P = 0.89</td>
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<tr>
<td>Admit temp (°C)</td>
<td>38.4</td>
<td>38.3</td>
<td>38.2</td>
<td>0.72</td>
<td>P = 0.43</td>
<td>P = 0.68</td>
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<tr>
<td>Body mass index</td>
<td>15.6</td>
<td>15.6</td>
<td>15.4</td>
<td>0.82</td>
<td>P = 0.88</td>
<td>P = 0.99</td>
</tr>
<tr>
<td>Apgar proxy†</td>
<td>8.0 (3.0%)</td>
<td>4.0 (3.1%)</td>
<td>2.0 (5.7%)</td>
<td>0.69</td>
<td>OR = 0.52</td>
<td>OR = 1.01</td>
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<tr>
<td>History of severe malaria‡</td>
<td>12.0 (4.5%)</td>
<td>6.0 (4.5%)</td>
<td>21.0 (2.9%)</td>
<td>0.90</td>
<td>OR = 0.62</td>
<td>OR = 1.00</td>
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<tr>
<td>History of developmental problem(s) (%)§</td>
<td>11.0 (4.2%)</td>
<td>11.0 (8.3%)</td>
<td>7.0 (20.0%)</td>
<td><strong>0.0014</strong></td>
<td>OR = 5.75</td>
<td>OR = 0.48</td>
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<tr>
<td>Family history of epilepsy (%)</td>
<td>12.0 (4.5%)</td>
<td>10.0 (7.6%)</td>
<td>5.0 (14.3%)</td>
<td>0.06</td>
<td>OR = 3.50</td>
<td>OR = 0.58</td>
</tr>
</tbody>
</table>

*χ² test or χ² test used.
†Mother was asked, “Did the child cry immediately after delivery?”
‡Malaria requiring hospitalization per the health passport.
§History of developmental problems assessed per the Ten Question Screen.

## BMPES Admission Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=264)</th>
<th>CM (n=132)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>148 (56.1%)</td>
<td>65 (49.2%)</td>
<td>OR 0.76 (CI 0.50-1.16)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>42.8 (range 7-163)</td>
<td>42.3 (range 9-160)</td>
<td>p=0.85</td>
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<tr>
<td>BMI</td>
<td>15.6</td>
<td>15.6</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Admit temp (°C)</td>
<td>38.4</td>
<td>38.3</td>
<td>p=0.45</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>3.2 (n=173)</td>
<td>3.2 (n=62)</td>
<td>p=0.38</td>
</tr>
<tr>
<td>Problem birth</td>
<td>13 (4.9%)</td>
<td>8 (6.1%)</td>
<td>OR 1.25 (CI 0.50-3.08)</td>
</tr>
<tr>
<td>Hx severe malaria</td>
<td>12 (4.5%)</td>
<td>6 (4.5%)</td>
<td>OR 1.00 (0.37-4.96)</td>
</tr>
<tr>
<td>FH of epilepsy</td>
<td>12 (4.5%)</td>
<td>10 (7.6%)</td>
<td>OR 1.72 (CI 0.72-4.09)</td>
</tr>
</tbody>
</table>
### Head CT findings in CM survivors

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Acute Sxs</th>
<th>Sequelae</th>
<th>Head CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>Left FM seizures</td>
<td>Blind, spastic quad, epilepsy</td>
<td>Severe diffuse atrophy</td>
</tr>
<tr>
<td>26</td>
<td>Multifocal szs</td>
<td>Spastic quad, epi</td>
<td>Mild atrophy including Brain stem</td>
</tr>
<tr>
<td>49</td>
<td>Coma</td>
<td>Motor def, ADHD</td>
<td>Normal</td>
</tr>
<tr>
<td>53</td>
<td>Coma</td>
<td>Right LE def in UMN distribution</td>
<td>Normal</td>
</tr>
<tr>
<td>36</td>
<td>Coma</td>
<td>Motor def, epi</td>
<td>Normal</td>
</tr>
<tr>
<td>50</td>
<td>Right FM szs</td>
<td>Language regress, Right HP</td>
<td>Low attenuation L parietal + vasc malformation</td>
</tr>
<tr>
<td>26</td>
<td>Right FM szs</td>
<td>Motor def</td>
<td>L parietal/R occipital atrophy</td>
</tr>
<tr>
<td>21</td>
<td>Right FM szs</td>
<td>Language regress</td>
<td>L parietal atrophy</td>
</tr>
<tr>
<td>9</td>
<td>Posturing</td>
<td>Motor def</td>
<td>Post fossa atrophy</td>
</tr>
<tr>
<td>17</td>
<td>Multifocal szs</td>
<td>Left LE HP</td>
<td>Bifrontal atrophy</td>
</tr>
<tr>
<td>32</td>
<td>Left FM szs</td>
<td>ADHD</td>
<td>Vermian atrophy</td>
</tr>
</tbody>
</table>
Head CT findings in CM survivors

• Motor deficits corresponded with regions of atrophy which correlated with brain regions affected by recurrent, prolonged seizures as localized acutely.
• Epilepsy was localization related. Seizure semiology and follow-up EEG correlate with brain regions affected by recurrent, prolonged seizures as localized acutely.

# Outcomes: CM vs controls

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=264)</th>
<th>CM Survivor (n=132)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>12 (9.1%)</td>
<td>Undefined 95% CI: Control 0-1.4% Case 4.8-15.3%</td>
</tr>
<tr>
<td>Disruptive behavior</td>
<td>1 (0.4%)</td>
<td>14 (10.6)</td>
<td>31.2 (4.1-240.1)</td>
</tr>
<tr>
<td>New neurodisability</td>
<td>n=253</td>
<td>n=121</td>
<td>37.8 (8.8-161.8)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (1.1%)</td>
<td>6 (4.5%)</td>
<td>4.1 (1.02-16.8)</td>
</tr>
</tbody>
</table>
Kaplan-Meier Curve for Epilepsy Outcome in CM Survivors vs. Controls

- CM survivors
- 95% confidence interval for CM survivors
- Controls
Risk factors for adverse neurological outcomes?
<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (n=12)</th>
<th>ADHD (n=14)</th>
<th>Neurodisability (n=28)</th>
<th>Any (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>41.3 v 42.4</td>
<td>40.3 v 42.5</td>
<td>49.3 v 39.9</td>
<td>43.9 v 41.6</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>58.3 v 48.3</td>
<td>57.1 v 48.3</td>
<td>71.4 v 40.9</td>
<td>63.4 v 42.9</td>
</tr>
<tr>
<td>BMI</td>
<td>17.0 v 15.5</td>
<td>15.8 v 15.6</td>
<td>15.8 v 15.3</td>
<td>15.8 v 15.5</td>
</tr>
<tr>
<td>FH Epilepsy</td>
<td>8.3 v 7.5</td>
<td>7.1 v 7.6</td>
<td>14.3 v 5.4</td>
<td>12.2 v 5.5</td>
</tr>
<tr>
<td>Admit temp</td>
<td>38.2 v 38.9</td>
<td>38.3 v 38.4</td>
<td>38.3 v 38.3</td>
<td>38.2 v 38.4</td>
</tr>
<tr>
<td>Admit BCS</td>
<td>66.7 v 45.0</td>
<td>78.6 v 43.2</td>
<td>63.3 v 42.2</td>
<td>67.4 v 37.1</td>
</tr>
<tr>
<td>Admit PCV</td>
<td>18.2 v 18.2</td>
<td>18.4 v 18.2</td>
<td>18.8 v 18.0</td>
<td>18.6 v 18.0</td>
</tr>
<tr>
<td>Admit WBC</td>
<td>10,718 v 14,010</td>
<td>10,583 v 14,057</td>
<td>14,426 v 13,480</td>
<td>13,146 v 13,935</td>
</tr>
<tr>
<td>Bld cxs +</td>
<td>9.6 v 9.1</td>
<td>9.7 v 8.3</td>
<td>9.1 v 11.1</td>
<td>9.3 v 10.3</td>
</tr>
<tr>
<td>Parasitemia</td>
<td>18,138 v 25,388</td>
<td>21,292 v 10,084</td>
<td>18,491 v 25,345</td>
<td>19,593 v 19,821</td>
</tr>
<tr>
<td>Lactate&gt;5</td>
<td>58.3 v 53.9</td>
<td>38.5 v 52.7</td>
<td>59.3 v 52.7</td>
<td>55.0 v 54.0</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>50.0 v 45.8</td>
<td>46.6 v 42.9</td>
<td>53.3 v 44.1</td>
<td>51.2 v 43.8</td>
</tr>
<tr>
<td>Max temp</td>
<td>39.4 v 38.5</td>
<td>39.2 v 38.6</td>
<td>38.6 v 38.6</td>
<td>38.9 v 38.5</td>
</tr>
<tr>
<td>Seizures</td>
<td>91.7 v 63.3</td>
<td>64.3 v 66.1</td>
<td>71.4 v 61.3</td>
<td>73.2 v 62.6</td>
</tr>
<tr>
<td>Coma duration</td>
<td>46.6 v 53.4</td>
<td>44.7 v 54.0</td>
<td>48.3 v 53.9</td>
<td>46.4 v 55.2</td>
</tr>
<tr>
<td></td>
<td>Epilepsy (n=12)</td>
<td>ADHD (n=14)</td>
<td>Neurodisability (n=28)</td>
<td>Any (n=42)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>58.3 v 48.3</td>
<td>57.1 v 48.3</td>
<td>71.4 v 40.9</td>
<td>63.4 v 42.9</td>
</tr>
<tr>
<td></td>
<td>OR 1.50 CI 0.45-4.98</td>
<td>OR 1.43 CI 0.47-4.37</td>
<td>OR 3.62 CI 1.44-9.06</td>
<td>OR 2.31 CI 1.08-4.94</td>
</tr>
<tr>
<td>Admit BCS</td>
<td>66.7 v 45.0</td>
<td>78.6 v 43.2</td>
<td>63.3 v 42.2</td>
<td>67.4 v 37.1</td>
</tr>
<tr>
<td></td>
<td>OR 2.44 CI 0.70-8.56</td>
<td>OR 4.82 CI 1.28-18.17</td>
<td>OR 2.37 CI 1.02-5.49</td>
<td>OR 3.52 CI 1.63-7.59</td>
</tr>
<tr>
<td>Max temp</td>
<td>39.4 v 38.5</td>
<td>39.2 v 38.6</td>
<td>38.6 v 38.6</td>
<td>38.9 v 38.5</td>
</tr>
<tr>
<td></td>
<td>p=0.01</td>
<td>p=0.04</td>
<td>p=0.97</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Seizures</td>
<td>91.7 v 63.3</td>
<td>64.3 v 66.1</td>
<td>71.4 v 61.3</td>
<td>73.2 v 62.6</td>
</tr>
<tr>
<td></td>
<td>OR 6.37 CI 1.02-141.20</td>
<td>OR 0.92 CI 0.29-2.94</td>
<td>OR 1.58 CI 0.63-3.96</td>
<td>OR 1.63 CI 0.72-3.66</td>
</tr>
</tbody>
</table>
Inflammation?  Hypoxia?  Edema?

Pathology, neuropathology

Pathological Categories

Clinical Manifestations

Eye Findings

Seizures

Respiratory arrests
Imaging “CM” patients during life: data on survivors, serial images
Malawi’s MRI:

0.35 Tesla Signa Ovation Excite MRI scanner
The University of Malawi College of Medicine recognizes that the extraordinary presence of an MRI machine in Malawi represents the culmination of:

- The willingness of the Government of Malawi to provide the land and to support biomedical research
- The unwavering and creative encouragement for over 20 years of Myron S. Magen, D.O., founding dean of the College of Osteopathic Medicine at Michigan State University (1926-2008)
- The audacious vision and persuasive powers of Dr. E. James Potchen Chair of Radiology at Michigan State University
- The generosity of Joe Hogan, President and CEO of General Electric Healthcare, for the donation of this MRI machine to Malawi
- The encouragement of William D. Strampel, D.O., Dean of the College of Osteopathic Medicine at Michigan State University, who underwrote the entire cost of constructing this building
- The research support provided by the US National Institutes of Health, in particular the National Institute of Allergy and Infectious Diseases.

John Valentine’s resourceful and imaginative project management saved the day on many occasions and we greatly appreciate his efforts on behalf of the MRI Centre.
An MRI, in Malawi

- General Electric donated the magnet
- QECH donated the land
- MSU-COM donated the building
- An NIH grant and private (paying) patients support the running costs
• Twenty-nine hours after admission: respiratory arrest → failed resuscitation → death
What next?

• Cause(s) of death
What next?

- Cause(s) of death
- Significance of brain swelling
What next?

- Cause(s) of death
- Significance of brain swelling
- Etiology of brain swelling
  
  Increased brain volume?
  Increased vascular volume (congestion)?
  
  Increased water content (cerebral edema)?
  intracellular?
  extracellular interstitial?
What next?

- Cause(s) of death
- Significance of brain swelling
- Etiology of brain swelling
- Neuroprotection
What next?

• Cause(s) of death
• Significance of brain swelling
• Etiology of brain swelling
• Neuroprotection
• Neuro/cognitive/psych rehabilitation
Mutu umodzi, susenza denga
Pali funso?