The interaction between *Plasmodium falciparum* and HIV-1 on the CNS of African children

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When two elephants collide, beware, for the ground will shake. So it is with HIV and malaria.

Jimmy Whitworth
Outline

- Malaria
  - Epidemiology
  - CNS manifestations
  - Neuro-cognitive sequelae

- HIV
  - Epidemiology in Africa
  - CNS involvement in children
  - CNS involvement in African children

- Interaction between malaria and HIV
  - Pathogen and clinical manifestations
  - Potential CNS effects
Falciparum malaria in Africa

- In 2002
  - 515 million clinical episodes of malaria in the world
  - 70% in Africa
- Mostly in young children
- Kills over 1M children per year
Natural history of infection

Uninfected ↔ Infected 20-40% ↔ Clinical Disease 10% ↔ Severe clinical Complications 1% → Death

- Headaches
- Seizures / Convulsions
- Agitation
- Psychosis
- Impaired consciousness
- Coma
Plasmodium falciparum
Pathology

- Sequestration of schizonts
  - deep vascular beds
  - brain more than other organs
- correlation between clinical severity and pathology can be poor
Cerebral malaria

- Clinical definition
  - Unarousable coma
  - Asexual parasites in peripheral blood
  - Exclusion of other causes
- Diffuse encephalopathy
- Mortality 17-20%
Neurological deficits

- Following cerebral malaria
  - 10.5% have deficits on discharge
- Many improve
  - Ataxia
  - Hemiparesis
  - Cortical blindness
- Some die
  - Quadriparesis
- Others develop
  - Epilepsy
Impairment following malaria

Post CM - 24% had any impairments
  – 42% had ≥ 2 impairments
  – Language and cognitive 13.8%
  – Epilepsy 9.2%
  – Neurological deficits 10.5%

Post M/S - 24% had any impairments
  – 28% had ≥ 2 impairments
  – Language and cognitive 6.7%
  – Epilepsy 11.5%
  – Neurological deficits 8.3%

Carter JA et al JNNP 2005; 76: 476-481
Kilifi Follow up study: Speech and Language

<table>
<thead>
<tr>
<th>Lower estimated scores</th>
<th>CM</th>
<th>M/S</th>
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<tbody>
<tr>
<td>Receptive vocabulary</td>
<td>Lexical semantics</td>
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<td>Higher level language</td>
<td>Pragmatics</td>
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<td>Word finding</td>
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<tr>
<th>Significant difference in mean scores</th>
<th>CM</th>
<th>M/S</th>
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Carter JA et al TMIH 2004; 10(1): 3-10
Kilifi Follow up study: Non-verbal, Memory & Behaviour

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<th>CM</th>
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<tr>
<td><strong>Non-verbal</strong></td>
<td>Construction task</td>
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<tr>
<td><strong>Memory</strong></td>
<td>Prospective items</td>
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<td></td>
<td>Orientation</td>
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<td><strong>Behaviour</strong></td>
<td>Habits</td>
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Carter JA et al. TMIH 2004; 10(1): 3-10
Neurological deficits

Based upon 6 studies across Africa persistent (> 6 months) motor deficits

<table>
<thead>
<tr>
<th>Deficit</th>
<th>On discharge (%)</th>
<th>Long-term residual (%)</th>
<th>Events 0-15 years p.a.</th>
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</thead>
<tbody>
<tr>
<td>Hemiparesis</td>
<td>2.5</td>
<td>0.6</td>
<td>360-400</td>
</tr>
<tr>
<td>Quadriparesis/Severe deficit</td>
<td>4.1</td>
<td>1.3</td>
<td>770-860</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>1.9</td>
<td>1.1</td>
<td>650-730</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>2.3</td>
<td>0.5</td>
<td>300-330</td>
</tr>
<tr>
<td>Behavioral difficulties</td>
<td>1.3</td>
<td>2.6*</td>
<td>1,540-1,720</td>
</tr>
<tr>
<td>Language deficits</td>
<td>1</td>
<td>11.8*</td>
<td>7,000-7,800</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.8</td>
<td>4.6*</td>
<td>2,700-3,000</td>
</tr>
</tbody>
</table>

Snow RW et al DCCP 2004
Sequelae following malaria

Uninfected ← Infected ← Seizures ← Impaired consciousness → Cerebral malaria

Epilepsy \[\text{Cognitive impairment}\] \[\text{Neurological deficits}\]
Epidemiology of HIV in African Children

- In 2001 ~2.2 M children infected
- Acquired infection
  - Mother (>95%)
  - Blood transfusions
  - Contaminated needles
  - Sexual
Maternal Transmission

Cumulative 40%

- Breast-feeding
  - 10-20%
  - Accounts for >40% of the transmission overall

- At birth
  - 10-20%

- In utero
  - 5-10%
Prognosis for Children

Of those infected

- 35% die by 1 year
- 52% die by 2 years
- Mortality higher in
  - East and West Africa
  - Early infections
  - Maternal deaths
  - Maternal CD4 counts < 200
  - Infant infection

Mortality likely to be greater in those not in the trials.

CNS involvement in children

Encephalopathy

- Developmental arrest
- Loss of developmental milestones
- Impaired brain growth
- Impaired motor function
- Impaired expressive language
- Movement disorders
Secondary effects

- CNS infections
  - Other viruses eg CMV, Human Herpes
  - Bacterial
  - Cryptococcal
  - Toxoplasmosis
  - TB
- Stroke
- Tumours
- Seizures
CNS involvement in children

- More commonly involved than adults
- More progressive than adults
- Early infection and greater viral load leads to more severe encephalopathy
- Early impairment of growth predicts developmental delay
Pathological differences

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<thead>
<tr>
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<th>African (n=70)</th>
<th>North American (n=156)</th>
</tr>
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<tbody>
<tr>
<td>Age of death median months</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>CNS pathology</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>HIV encephalitis</td>
<td>6%</td>
<td>38%</td>
</tr>
<tr>
<td>Lymphocytic meningitis</td>
<td>34%</td>
<td>Not described</td>
</tr>
<tr>
<td>Other CNS infections</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>41%</td>
<td>65%</td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>0</td>
<td>5%</td>
</tr>
</tbody>
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Bell et al. J Neuropath Exp Neurol 1997;
HIV-1 infections in Africa

- Brains of HIV-1 infected children
  - Smaller despite lack of HIV encephalitis
- Would suggest that other factors are responsible
  - Nutritional status
  - Other CNS infections
  - Maternal factors
- Malaria only in 3%
Neurological abnormalities in African children

- 15-40% have neurological abnormalities
- Motor most common
- Progressive encephalopathy relatively rare
Neuro-developmental abnormalities in African children

- 3 studies
- Developmental delay can be detected under 2 years
- Motor delay most common
- Impairment of mental processing in some studies
- None examined the effect of confounding factors
  - Nutrition
  - Other CNS infections
Interaction between HIV and falciparum malaria

HIV-1 infection
- Impairs function of T and B cells
- Pregnant women
  - Peripheral and placenta malaria
- Non-pregnant adults
  - Malaria and clinical disease
- Children
  - Malaria and severe disease

P. Falciparum
- Immunosuppression
- Pregnant women
  - Doubling of viral load
- Non-pregnant adults
  - Acute disease 7x viral load
- Children
  - ?
Summary

- HIV-1 infection in African children
  - Most acquired after or at birth
  - Co-morbidity in Africa
  - High and early mortality
- Differences in African children compared to Western children
- Associated with increase severity of malaria
Areas for further research

- Does HIV-1 infection aggravate neuro-cognitive sequelae following severe malaria?
- Would prevention of malaria during infancy improve neuro-development in HIV-1 infected children?
- Would better nutritional supplements improve the development of HIV-1 infected children?
- What are the indications for ARVs in this population?
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