Neurological Manifestations of Malaria

Neuro-infectious disease symposium
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Daniel Fekade, MD, MSc,
Faculty of Medicine
Addis Ababa University
Severe malaria

- Of all the four malarial parasites that infect humans, *Plasmodium falciparum* is the cause of severe malaria
  - *P vivax* rarely associated with severe /cerebral malaria

- Severe falciparum malaria causes 1 million deaths each year

- 70% of these occur in children in Sub-Saharan Africa

- “Cerebral malaria” is the most severe complication; associated with mortality of 15-20%

Definition of severe falciparum malaria
World Health Organization, WHO 2000

• Impaired consciousness
  – cerebral malaria and other neurological abnormalities
• Severe anemia, Hgb <5gm/dl, Hct<20%)
• Respiratory distress (acidotic breathing),
• Pulmonary edema, ARDS
• Circulatory collapse
• Haemostatic abnormalities, thrombocytopenia
• Hyperbiluribinaemia
• Haemoglobinuria, blackwater fever
Outline classification of severe malaria in children (WHO 200)

Group 1
- Children at immediate risk of dying, who require parenteral antimalarial drugs and supportive therapy
  - Prostrated; unable to sit upright, or to drink
  - Prostrated but fully conscious
  - Prostrate with impaired consciousness
  - Coma
  - Respiratory distress; Mild/severe

Group 2
- Children able to be treated with oral antimalarial drugs under supervision
  - Hgb<5gm/dl
  - Two or more convulsions

Group 3
- Children with persistent vomiting (require parenteral therapy) but lack any of features of groups 1 or 2
Life Cycle

Life Cycle:

\[ \Delta = \text{Infective Stage} \]

\[ \Delta = \text{Diagnostic Stage} \]

Mosquito Stages:

1. Ruptured oocyst
2. Release of sporozoites

Sporogonic Cycle:

1. Oocyst
2. Mosquito takes a blood meal (injects sporozoites)
3. Ookinetes
4. Exflagellated microgametocytes
5. Microgamete entering macrogamete
6. Macrogamocyte

Erythrocytic Cycle:

1. Mosquito takes a blood meal (ingests gamocytes)
2. Immature trophozoite (ring stage)
3. Mature trophozoite
4. Ruptured schizont
5. Schizont
6. Gametocytes

Human Liver Stages:

1. Liver cell
2. B cell

http://www.dpd.cdc.gov/dpxd

International Neuroinfectious Disease Conference
Addis Ababa, Ethiopia, on February 27-28, 2010
Pathogenesis of cerebral malaria

The pathogenesis of neurological manifestations is multifactorial

- **Sequestration of erythrocytes in cerebral capillaries/venules**
  - Parasite growth is promoted in the relatively hypoxic environment
  - Parasite evades destruction by the reticular endothelial system

- This results in critical reduction in supply of metabolic substrates to the brain
  - Aggravated by anemia, hypoglycemia, seizures, increased metabolism

Trends in Parasitology, 2009; 25: 7
Pathogenesis of cerebral malaria contd.

Mechanisms of sequestration of erythrocytes

- Cytoadherence
  - Adhesion of infected erythrocytes to endothelium of capillaries/venules
  - Mediated by proteins encoded by the highly variable, \textit{var}, genes of the parasite
    - Parasite ligand, \textit{P} falciparum erythrocyte membrane protein-1, PfEMP-1
    - Endothelial receptors, CD36, E-selectin, Chondrotin sulphate

Pathogenesis of cerebral malaria contd.

Mechanisms of sequestration of erythrocytes…

• **Rosetting**
  – Binding of infected erythrocytes to non infected erythrocytes
    • Blood group O protects against severe malaria through reduced rosetting

• **Platelet mediated clumping**
  – Platelet micro particles attaching to infected erythrocytes

Cell 1995, 82
FASEB J.2009; 23(10)
Pathogenesis of cerebral malaria contd.

• Impaired blood-brain barrier [1]
  – Brain swelling on neuroimaging
  – Increased intracranial pressure

• Increased levels pro inflammatory cytokines
  – Increased levels of TNF correlate with severity/mortality [2]
  – Several polymorphisms in the TNF gene promoter are associated with increased risk of cerebral malaria
  – Decreased levels of IL-10 [3]

• Increased production Nitric oxide
  – up regulation of NO synthase in brain
  – NO may reduce level of consciousness rapidly and reversibly

1 Int. J Parasitology, 2006, 36; 5
3. Ho et al 1998, JID, 178, 520
Figure 2 FLAIR, fluid attenuated inversion recovery, images of the brain of a patient with cerebral malaria

Mishra SK and Newton CRJC (2009) Diagnosis and management of the neurological complications of falciparum malaria
Nat Rev Neurol doi:10.1038/nrneurol.2009.23
Neurological manifestations of falciparum malaria

Clinical manifestations are different in children/pregnant women compared to non immune adults

“Cerebral malaria”
- Unrousable coma, and the presence of asexual p.falciparum in blood film; WHO 2000*
  - Glasgow coma scale<9
  - Blantyre coma scale<2
- exclude other encephalopathies
  - Post-ictal, hypoglycemia, meningitis, encephalitis
- However, patients with any degree of impaired consciousness should be treated as cerebral malaria

Neurological manifestations contd.

Seizures,
- Usually generalized, but may be focal
- Single or recurrent
- >50% in children, 20% in adults

Other neurological manifestations
- psychosis, hallucinations, delusions
- may occur as presenting symptoms or during recovery

Nature Reviews, Neurology 5, 2009
Neurological manifestations contd.

Malarial retinopathy
A set of retinal abnormalities that is unique to malaria.
Common in children with cerebral malaria.
Correlates with severity and outcome of cerebral malaria.
- Retinal hemorrhages
- Cotton wool spots
- Papilledema
- Retinal whitening/non perfusion
- Retinal vessel abnormality

White VA, PLoS One, 2009; 4 (1)
Figure 1 Malarial retinopathy

Mishra SK and Newton CRJC (2009) Diagnosis and management of the neurological complications of falciparum malaria

*Nat Rev Neurol* doi:10.1038/nrneurol.2009.23
Neurological manifestations contd.

Neurological sequelae

– 3% of adults and 10-23% of children have obvious neurological deficit on discharge; hemiparesis, cortical blindness, cranial nerve palsies
– Subtle neurocognitive sequelae are more severe and frequent in children than in adults,
– At 2-year follow-up of Ugandan children with cerebral malaria cognitive impairment was present in 25% of survivors vs. 7.5% of community children; 3.6 fold increase *

Post malarial neurological syndromes

• Acute confusional state/psychosis, generalized convulsions
• Cerebellar ataxia

John CC, Pediatrics, 2008, 122; 92
Neurological manifestations of falciparum malaria contd.

• Neurological examination
  – Symmetric upper motor dysfunction
  – Increased tendon jerks
  – Bilateral extensor plantar reflexes
  – Decorticate/decerebrate posturing
  – Gaze abnormalities
  – Hypotonia

Trans Roy Soc Trop Med hyg, 2000; 94
Malaria and Human Immunodeficiency Virus Interactions

- High prevalence of HIV and *P. falciparum* malaria in sub-Saharan Africa
- Malaria increases HIV viral load significantly; by up to 1 log
  - may persist as long as 8 weeks
- Acute malaria reduces CD4 count
- Malaria incidence rises with declining CD4 counts
  - Odds ratio for clinical malaria 6.1 in persons with CD4<200 Vs CD4>500[1]
  - Odds ratio for fatal malaria and HIV infection was 7.5 compared to on infected[2]
- Patients with HIV may be at risk of malaria treatment failure
- Anti retroviral agents may play future role in malaria prevention and treatment

Arch Intern Med 2007;167;1827
2. Girmawade et al. AIDS 2004;18:547
Diagnosis of malaria

Parasitological diagnosis
Thick film/Thin films
Parasite density correlates with disease severity
However, there might be a discrepancy between peripheral parasitemia and severity
Parasite density and prognosis varies with background level of immunity

Rapid tests
PfHRP2, *plasmodium falciparum* histidine-rich protein-2
PfLDH, *plasmodium falciparum* Lactate dehydrogenase

Patients with high clinical suspicion of severe malaria and repeated films are negative should be treated with parenteral anti malarial drugs
Management of cerebral malaria

• Patients with suspected cerebral malaria should be treated in the ICU
• In addition to parental antimalarial drugs early recognition and management common complications:
  – Hypoglycemia
  – Convulsions
  – anemia
  – Acidosis
  – Fluid and electrolytes imbalance
  – Renal failure
  – Respiratory failure
Management of cerebral malaria contd.

Initial management of patients with cerebral malaria
- Clear and maintain airways
- Position semi-prone
- Weigh the patient, calculate dosage
- Take blood for diagnostic smear, parasite count, HCT, RBS, BUN…
- Measure urine output
- Exclude/treat hypoglycemia
- Rule out meningitis, other infections
- Start immediate anti malarial chemotherapy
Analysis 1.1. Comparison of Artesunate vs Quinine, Outcome: Death.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

Outcome: 1 Death

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Artesunate n/N</th>
<th>Quinine n/N</th>
<th>Risk Ratio M-H (Fixed) 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anh 1989</td>
<td>2/19</td>
<td>7/22</td>
<td></td>
<td></td>
<td>0.33 [0.08, 1.41]</td>
</tr>
<tr>
<td>Anh 1995</td>
<td>8/99</td>
<td>18/91</td>
<td></td>
<td>8.7%</td>
<td>0.41 [0.19, 0.89]</td>
</tr>
<tr>
<td>Cao 1997</td>
<td>4/37</td>
<td>5/35</td>
<td></td>
<td>2.4%</td>
<td>0.76 [0.22, 2.59]</td>
</tr>
<tr>
<td>Dondorp 2005</td>
<td>107/730</td>
<td>164/731</td>
<td></td>
<td>76.3%</td>
<td>0.65 [0.52, 0.81]</td>
</tr>
<tr>
<td>Hien 1992</td>
<td>5/31</td>
<td>8/29</td>
<td></td>
<td>3.8%</td>
<td>0.60 [0.22, 1.64]</td>
</tr>
<tr>
<td>Newton 2003</td>
<td>7/59</td>
<td>2/54</td>
<td></td>
<td>5.8%</td>
<td>0.53 [0.23, 1.26]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>975</td>
<td>963</td>
<td></td>
<td>100.0%</td>
<td>0.62 [0.51, 0.75]</td>
</tr>
</tbody>
</table>

Total events: 133 (Artesunate), 214 (Quinine)

Heterogeneity: Chi² = 2.26, df = 5 (P = 0.80); I² = 0.0%

Test for overall effect: Z = 4.82 (P < 0.0001)
Antimalarial drugs in cerebral malaria

- Artesunate 2.4mg/kg IV; followed by 2.4mg/kg at 12, 24 hours; then daily if necessary
  - Arthmether 3.2 mg/kg IM, followed by 1.6 mg/kg daily
  - Artmesinin suppository  20mg/kg at 0 and 4 hours then daily
- OR
- Quinine 20mg salt /kg infused over 4 hours, maintenance 10mg salt /kg infused over 2-8 hours, at 8 hours interval
  - Quinidine 10mg base/kg infused over 1-2 hours, followed by 1.2 mg base/kg per hour
  - Quinidine  is used in preference to quinine in the US

Oral treatment should start as soon as patient can swallow
- A full course of artmesinin combination treatment should be given
  e.g. Arthmeter-lumefantrine 1.5/9mg/kg twice daily for three day

WHO 2006
Lancet 2005; 366: 717-725
Jones KI, 2009; the Cochrane Collaboration
Supportive and ancillary treatments

In addition to specific anti malarial therapy patients may require:

• Antipyretics
• Transfusion of whole blood/packed cells
  – Exchange transfusion
• Renal replacement therapy
• Positive pressure ventilation in patients with ARDS
• Fluids, isotonic
• Management of convulsions
Adjunct therapy

A number of agents have been tested in patients with severe falciparum malaria:

- Corticosteroids
- Iron chelating therapy
- Pentoxyfilline
- Antibody against TNF
- Osmotic diuretics
- Fluids
- Prophylactic anticonvulsants
- Erythropoietin
Adjunct therapy, contd.

Many adjuvant therapies have been suggested based on the prevailing pathophysiology

- However, none has shown evidence of improvement in clinical outcomes
- Therefore, none of these agents are recommended as part of standard management strategy