Neurological Manifestations of Malaria

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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%

Trans Roy Soc Trop Med Hyg 2000, 94

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 parentral 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

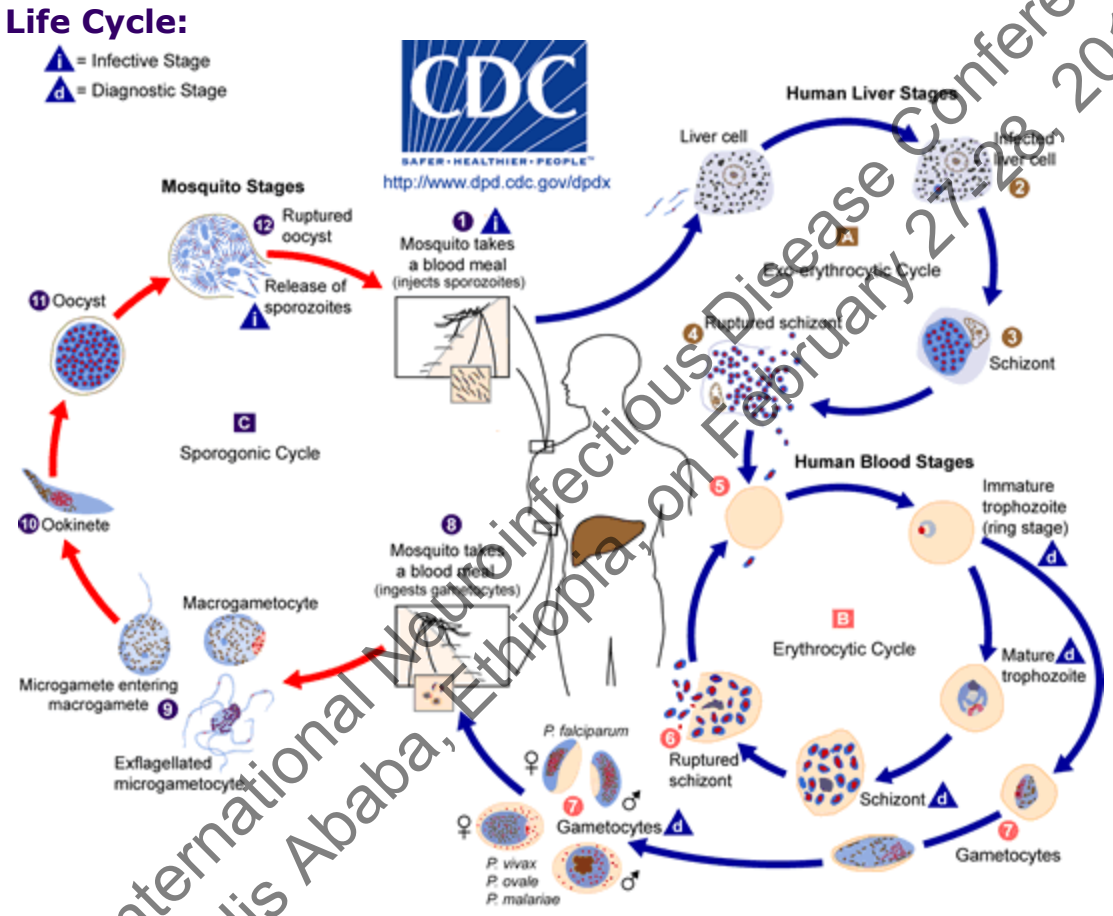
Group 2

- 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 parentral therapy) but lack any of features of groups 1 or 2

Life Cycle



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, *var,* genes of the parasite
    - Parasite ligand, P falciparum erythrocyte membrane protein-1, PfEMP-1
    - Endothelial receptors, CD36, E-selectin, Chondrotin sulphate

Rowe JA et al Expert Rev Mol Med, 2009,26;11

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

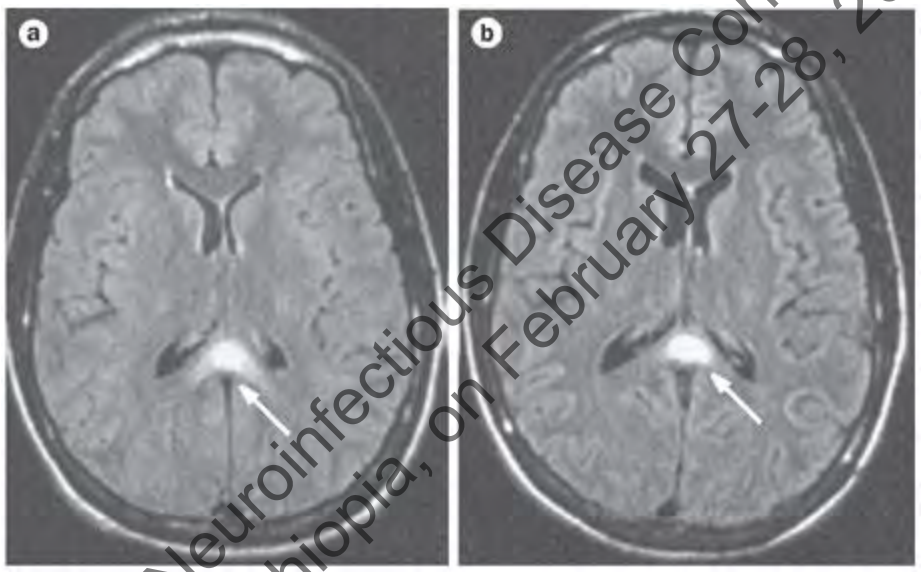
Cell 1995, 82
FASEB J.2009; 23(10)

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
2. Krishna et al. Trans Roy soc Trop Med Hyg 1994, 88; 67
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

nature REVIEWS NEUROLOGY

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***
  - Glascow 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

***Trans Roy Soc Trop Med, 94; 2000**

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

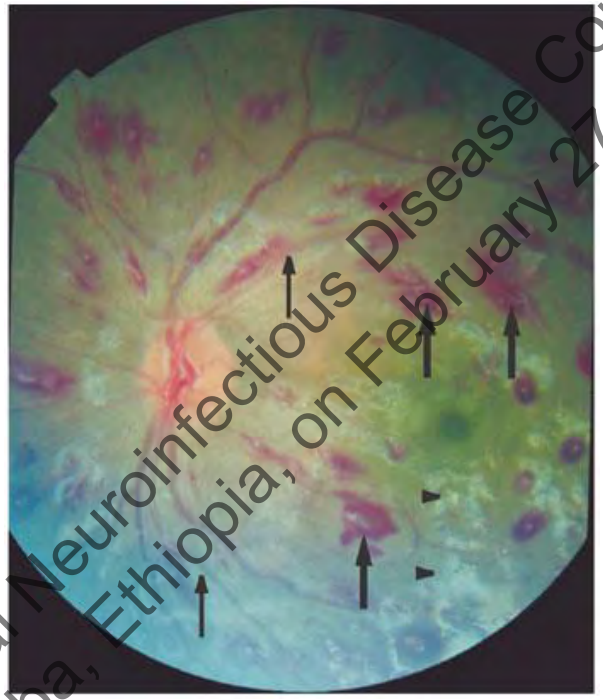
- Retinal hemorrhages
- Cotton wool spots
- Papilledema
- Retinal whitening/non perfusion
- Retinal vessel abnormality

White VA, PLoS One,2009; 4 (1)

Beare NA, Am J Trop Med Hyg. 2006, 75 (5)

Richard JM, Trans R Soc Trop Med Hyg 2009, 103;661

Figure 1 Malarial retinopathy



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nature REVIEWS NEUROLOGY

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 agent s may play future role in malaria prevention and treatment

Arch Intern Med 2007; 167;1827
1.Whitworth et al. Lancet 2000, 356:1051
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 parentral anti malarial drugs

Management of cerebral malaria

- Patients with suspected cerebral malaria should be treated in the ICU
- In addition to parentral 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 1 Artesunate vs quinine, Outcome 1 Death.

Review: Artesunate versus quinine for treating severe malaria

Comparison: 1 Artesunate vs quinine

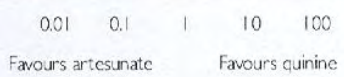
Outcome: 1 Death

Study or subgroup	Artesunate n/N	Quinine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anh 1989	2/19	7/22		3.0 %	0.33 [0.08, 1.41]
Anh 1995	8/99	18/91		8.7 %	0.41 [0.19, 0.89]
Cao 1997	4/37	5/35		2.4 %	0.76 [0.22, 2.59]
Dondorp 2005	107/730	164/731		76.3 %	0.65 [0.52, 0.81]
Hien 1992	5/31	8/30		3.8 %	0.60 [0.22, 1.64]
Newton 2003	7/59	12/54		5.8 %	0.53 [0.23, 1.26]
Total (95% CI)	**975**	**963**		**100.0 %**	**0.62 [0.51, 0.75]**

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

Heterogeneity: Chi^2 = 2.26, df = 5 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 4.82 (P < 0.00001)



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