# Neurological manifestations of *Plasmodium falciparum*

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# Disclosures

- None

# Learning Objectives

- Epidemiology
- Clinical syndromes
- Pathogenesis
- Neuro-cognitive sequelae
- Post malarial syndromes

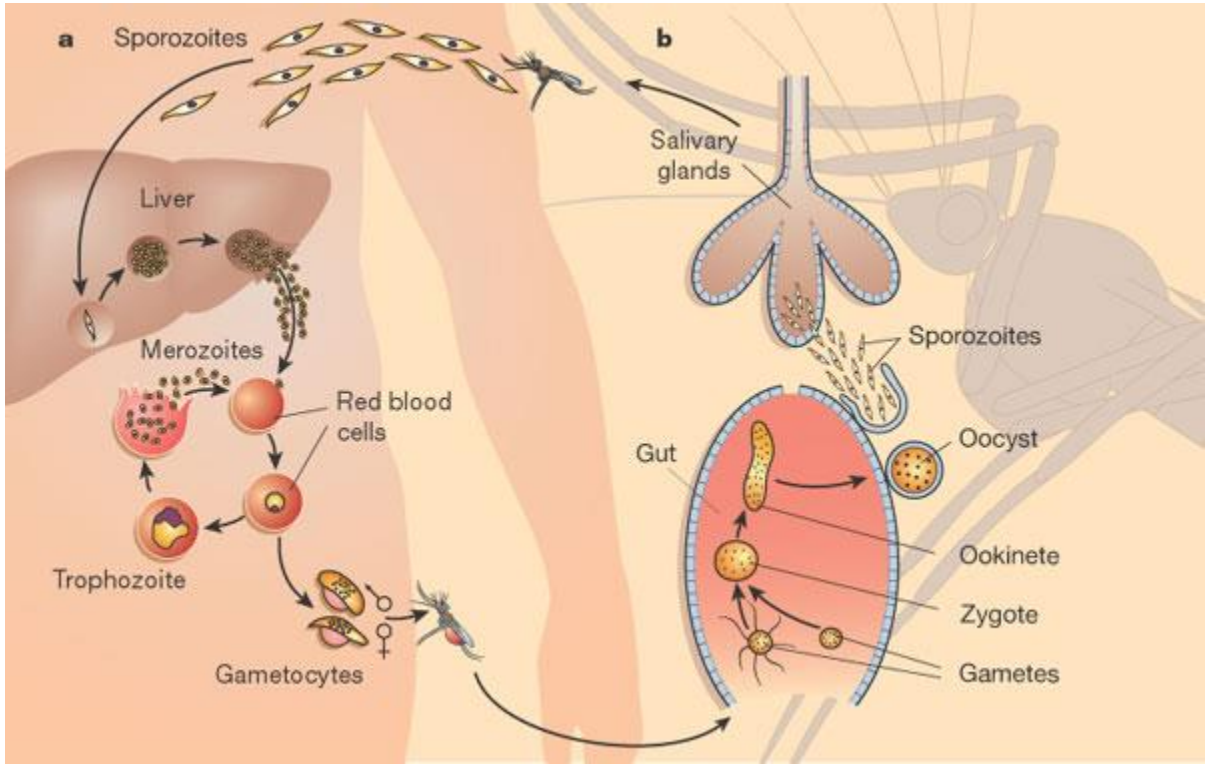
# Malaria infection of humans

5 species that infect humans

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*

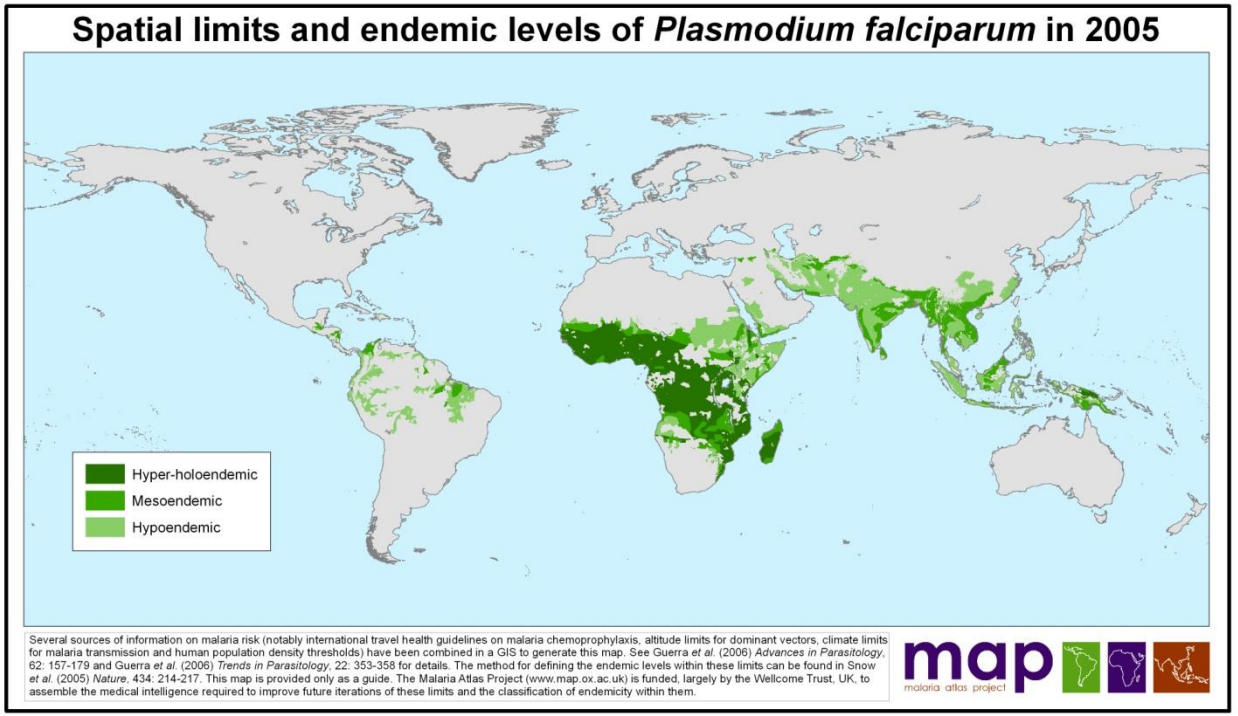
Exposure

- Malarious areas
- Blood
- Airports



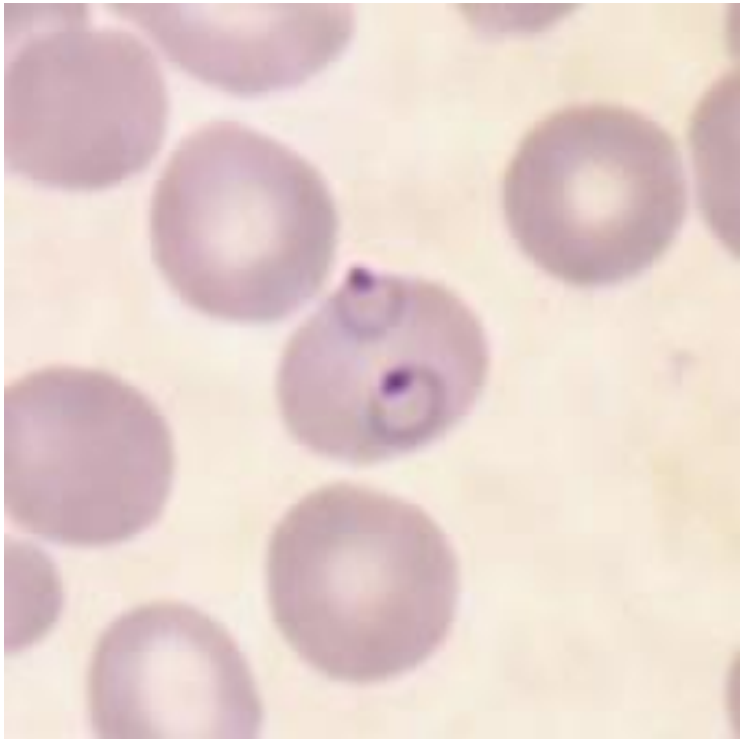
# Malaria in the world

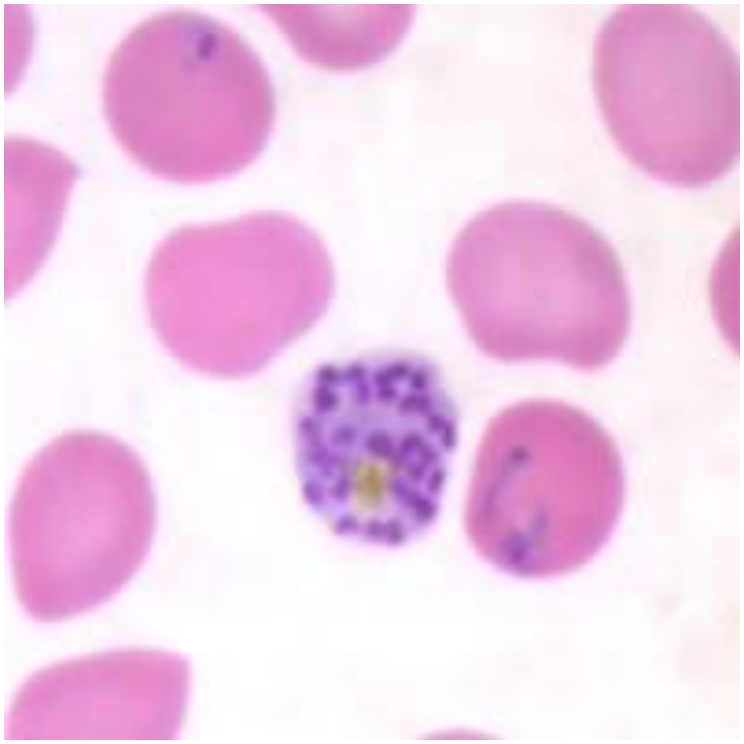
- 2 Billion exposed
- 515 million clinical episodes of malaria the world
  - 70% in Africa




- Mostly in young children
- Kills over 1M children per year

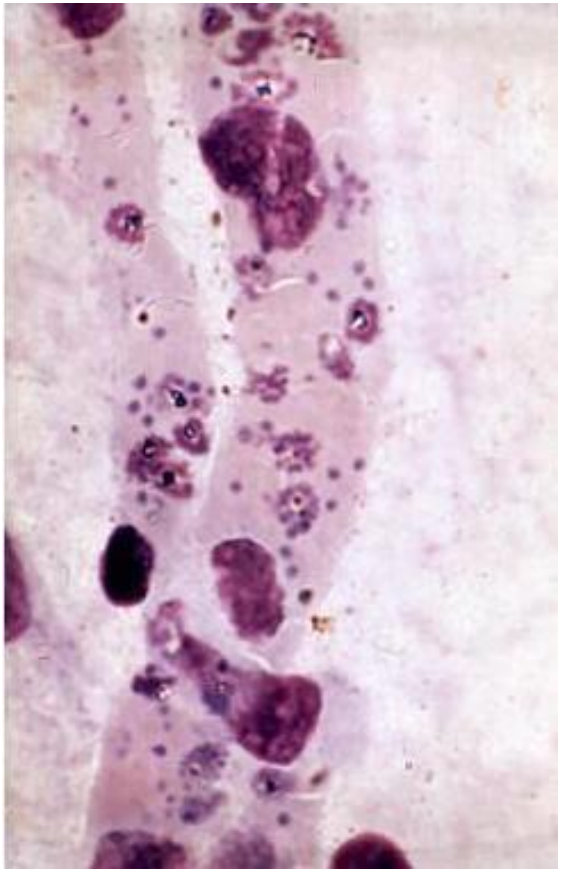
# Plasmodium falciparum





# 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
- Mortality 17-20%

# Malaria retinopathy

Diagnosis lacks specificity

31 Malawian children who died fulfilling WHO definition of cerebral malaria

7 (23%) had other causes of death

Malaria retinopathy was the only distinguishing feature

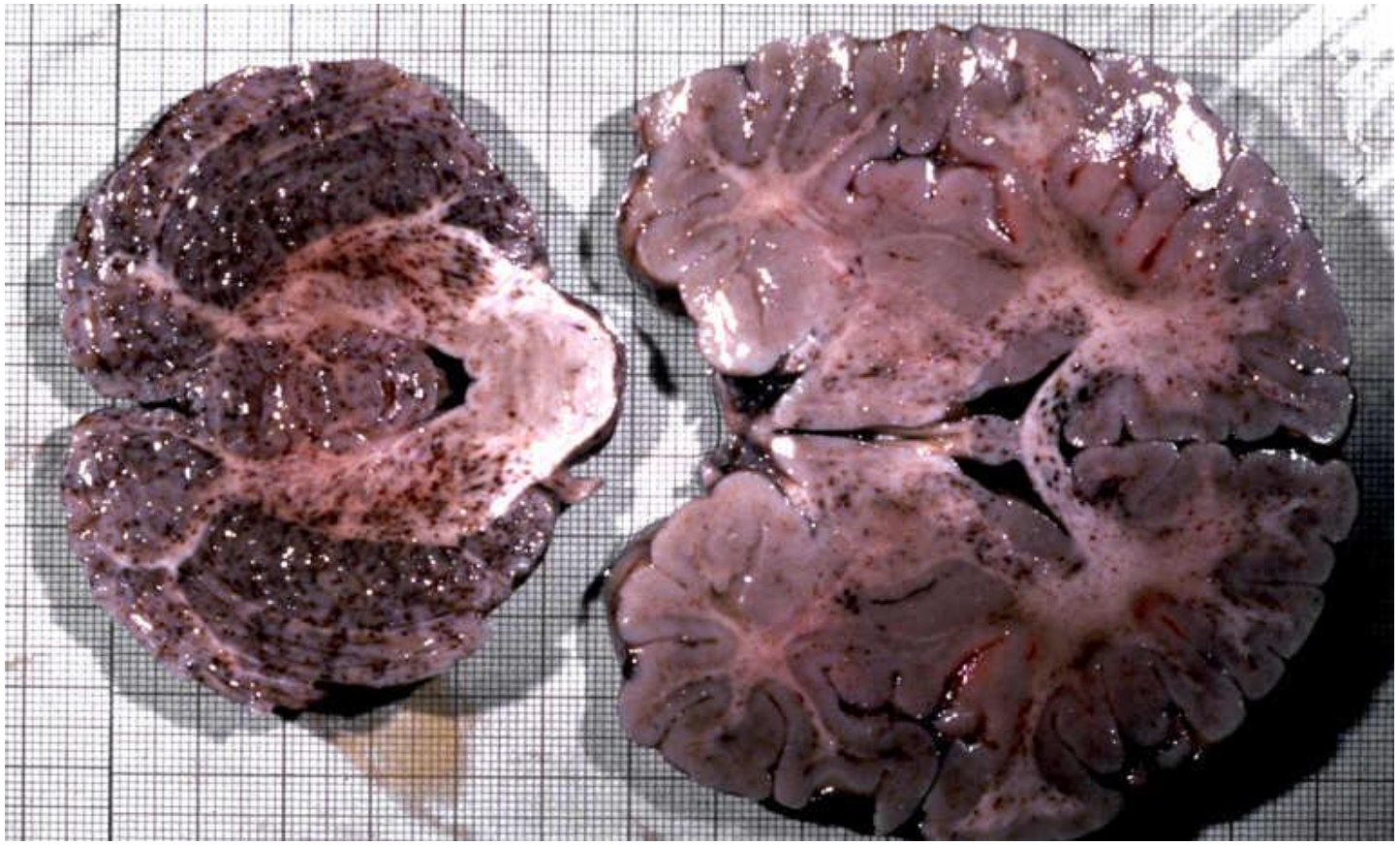
*Taylor et al Nature 2004, 10 (2): 143-145*

# Clinical Features of Cerebral Malaria

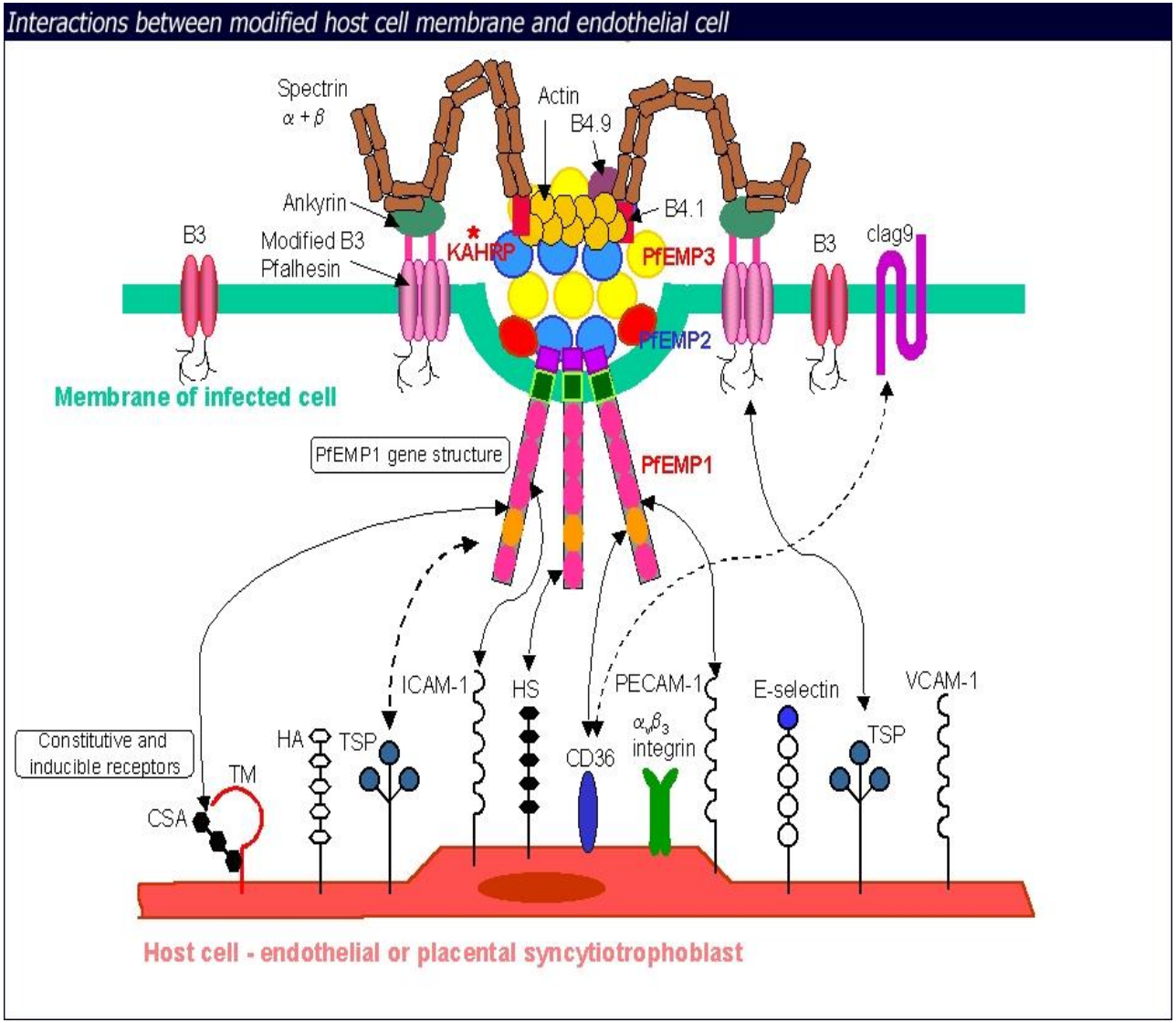
| | African children | SE Asian Adults |
|---|---|---|
| History of fever: median (days) | 2 | 10 |
| Seizures: prior to admission | 82% | 11-20% |
| after admission | > 60% | 11% |
| Deeply unconsciousness (GCS < 6) | 15% | 20% |
| Brainstem signs | 34% | 12% |
| Retinal hemorrhages | 6% | 15% |
| Parasitaemia: log median (per ml) | 5.2 | 4.2 |
| Hypoglycaemia (glucose <2.2 mmol/l) | 23% | 11% |
| Severe anaemia (Hb < 5.0 g/dl) | 46% | 34% |
| Metabolic acidosis | 42% | 28% |
| Duration of coma: median (hours) | 18 | 48 |
| Sequelae: | 11.5% | <5% |
| Death: | 18.6% | 17-20% |

*Newton et al Ann Neurol 1998, 43: 695-699*

# Cerebral Malaria



# Cytoadherence



# Pathogenesis of CNS manifestations

- **Microvascular obstruction**
  - Cytoadherence
  - Rosette formation
  - Agglutination
  - Decreased red cell deformability
- **Systemic factors**
  - Seizures
    - overt
    - subtle
    - post-ictal
  - Hypovolaemia
  - Acidosis
  - liver dysfunction
- **Impaired delivery of substrate**
  - Hypoglycaemia
  - Anaemia
  - Hypoxia
- **Toxins**
  - Cytokines
  - Nitric oxide
  - Reactive oxygen species
  - Excitotoxins
  - ?malaria toxin
- **Immunological**
  - Vasculomyelinopathy
  - Antibodies against VGCC

# Seizures in malaria

- 54% afebrile at time of seizure
- 84% are complex

| | 25-33% Febrile seizure |
|---|---|
| 74% ≥2 in 24 hrs | 15-20% |
| 48% focal | 4% |
| ? Prolonged | 8% |

*Waruiru C, et al. Trans R Soc Trop Med Hyg 1996 90: 152-155.*

- Incidence of convulsions in non cerebral falciparum malaria was 8.4%, compared to vivax malaria 4.7%
- Peak temperatures similar

*Wattanagoon et al Trans R Soc Trop Med Hyg 1994; 88: 426-8*

# Mechanisms of epileptogenesis

- Genetic

Family history: OR 1.41 (95%CI 1.06-1.88) of having a relative with seizures

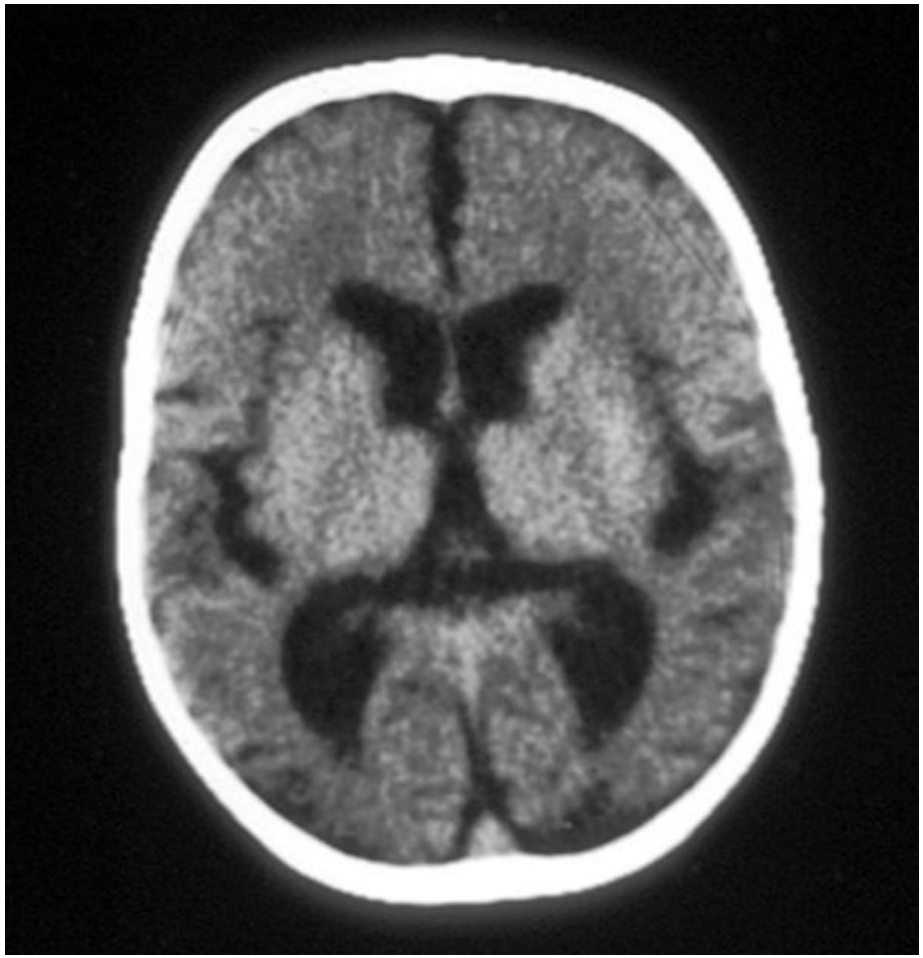
*Versteeg et al TMIH 2002 7 (12): 1-5*

- Fever
- Hypoglycaemia
- Electrolyte disorders
- Antimalarials

- Parasitaemia
  - More frequent with higher parasitaemia
  - Strain of parasite?
- Cytokines
  - TNF, IL-1
- Auto-antibodies
- Sequestration
- Focal damage

# Neurological deficits

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



# Neurological Syndromes after Malaria

Definition

- Occur after clearance of parasitaemia

Description

- Post-Malaria Neurological Syndromes (PMNS)
- Post-Malaria Cerebellar Syndrome (PMCS)
- Case reports of
  - –Post-Malaria Encephalopathy
  - –Opsoclonus
  - –Benign Intracranial Hypertension

# Post Malaria Neurological Syndrome (PMNS)

Definition

– recent symptomatic malaria

– development of neurological or psychiatric symptoms within 2 months of illness

- onset 96 (66-350) hrs of parasite clearance
- occurs in 1.2/1000 in Vietnam
- associated with
  - – severe disease RR 229 (40 -2223)
  - – mefloquine RR 9.2 (1.2-71.3) *Nguyen et al 1996*

# Features of PMNS

Clinical
- acute confusional state/psychosis (68%)
- generalised convulsions (27%)
- fine tremor

Febrile

CSF
- pleocytosis (36%)
- ↑ protein (100%)

# Outcome of PMNS

- All made a full neurological recovery
- Unknown sequelae
  - cognitive impairment
  - epilepsy
- role of mefloquine in neurotoxicity
- immune mechanism
  - no data

# Post Malaria Cerebellar Syndrome (PMCS)

- onset 3-4 weeks after febrile illness
- Clinical
  - unsteadiness of walking
  - cerebellar symptoms eg dysarthria
  - cerebellar signs eg nystagmus
  - afebrile
- CSF normal
- Complete recovery: 3 wks - 4 months

# Key Messages

Falciparum malaria

- propensity for the CNS
- causes a wide range of neurological manifestations
- Post malarial syndromes need to be considered if there is a history of an acute malaria infection

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