South to South

Neurological Manifestations of HIV infection

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Learning Objectives

- To recognize the impact of HIV on the central nervous system
- To diagnose and manage opportunistic infections of the CNS in the HIV infected child

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Background: HIV and Neurology

- 40-70% of children affected
- The HIV virus is a neurotropic virus
  - Infects macrophages and microglial cells
  - Involves both the central and peripheral nervous system
  - In children this leads to neuro-developmental delay and cognitive dysfunction (HIV encephalopathy)
- Opportunistic organisms can cause CNS infection as complication of severe immune compromise

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HIV-related neurologic disease:

Primary complications

- HIV encephalopathy
- HIV (aseptic) meningitis
- HIV myelopathy
- HIV neuropathy
- HIV myopathy
- Ocular manifestations

Secondary complications

- Opportunist infections
- Stroke
- Neoplasm's-Primary CNS Lymphoma, Lymphoma metastatic

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Why is it important to diagnose neurological manifestations in the HIV infected child?

- Related to HIV
  - First presentation of HIV infection
  - Sign of HIV disease progression
- OI
  - High mortality and morbidity if undetected
- Treatment
  - Neurotoxic effects of ARVs

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HIV Encephalopathy

- 21% of HIV infected African Children affected
- Can occur in the absence of other signs and symptoms
- Presentation:
  - Can cause symptoms in all stages of HIV disease
  - Impaired brain growth / acquired microcephaly
    - SERIAL HEAD CIRCUMFERANCE MONITORING IMPORTANT FOR EARLY DIAGNOSIS
  - Failure to attain / loss of neuro-developmental milestones or intellectual ability
  - Progressive symmetrical motor dysfunction
  - Variable neuro-developmental course
    - Periods of spontaneous improvement and stabilization
- LP: nonspecific
- CT: atrophy calcification basal ganglia

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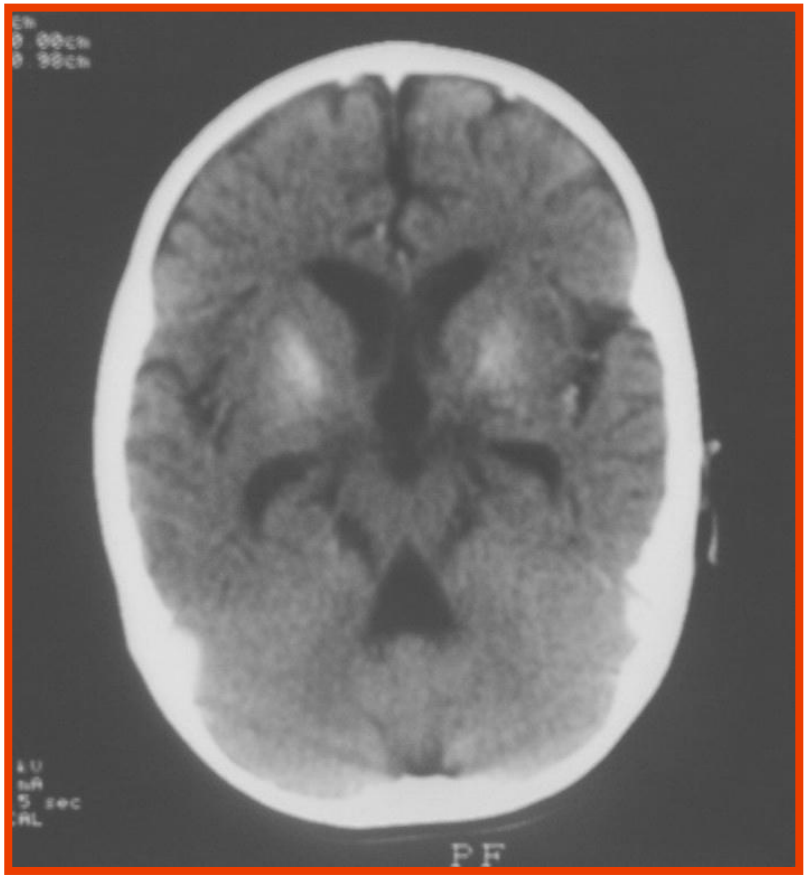
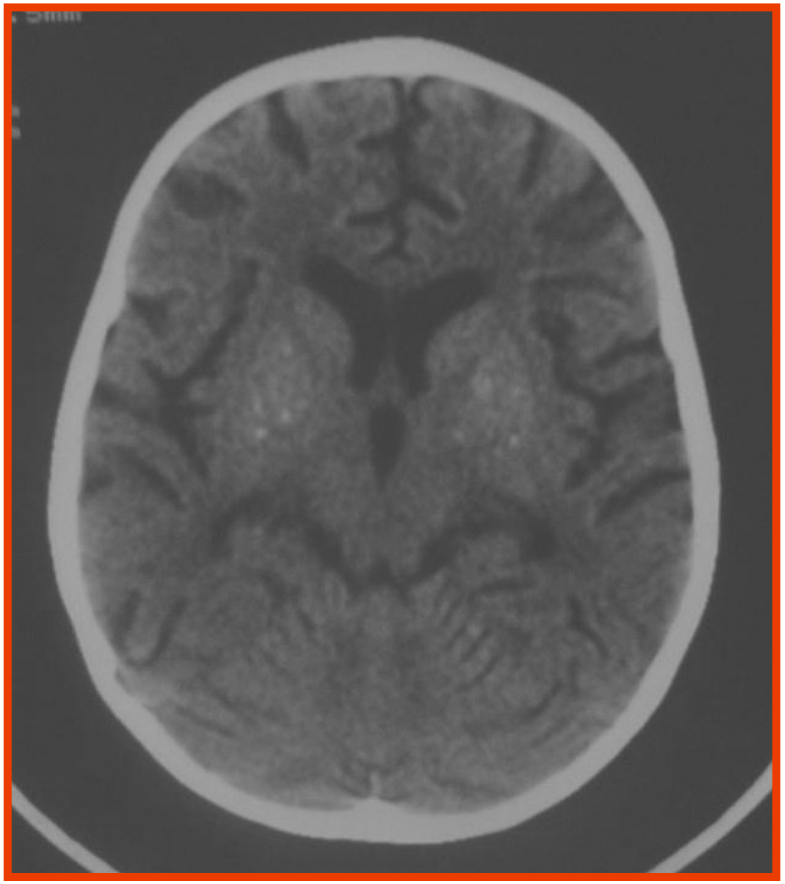
Basal Ganglia calcifications





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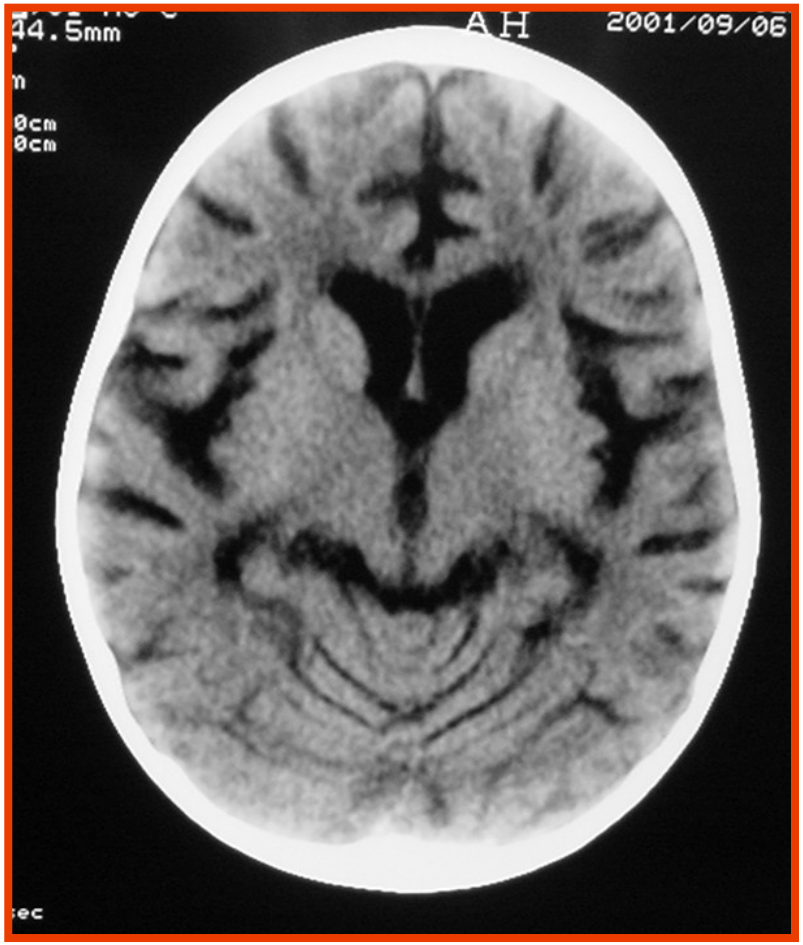
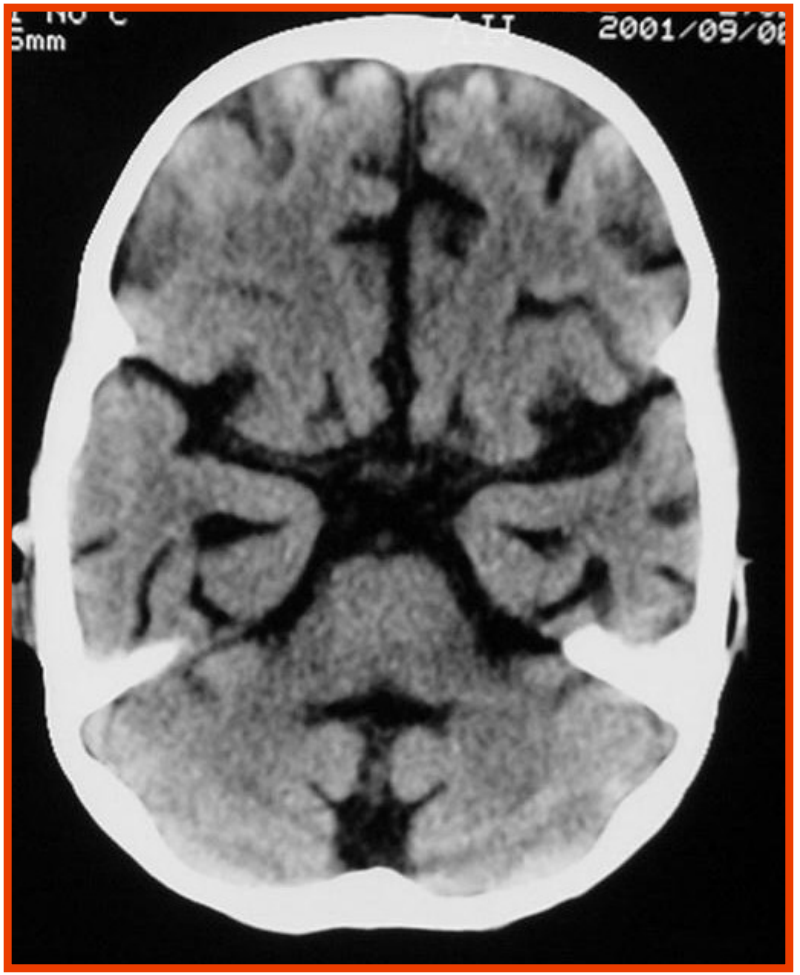
Global atrophy





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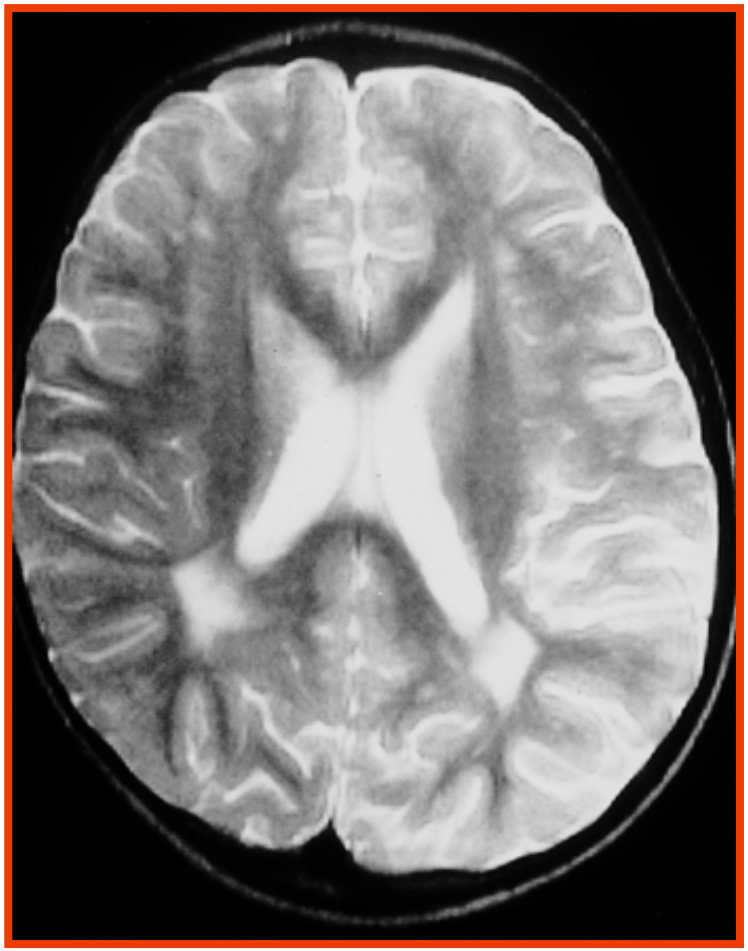
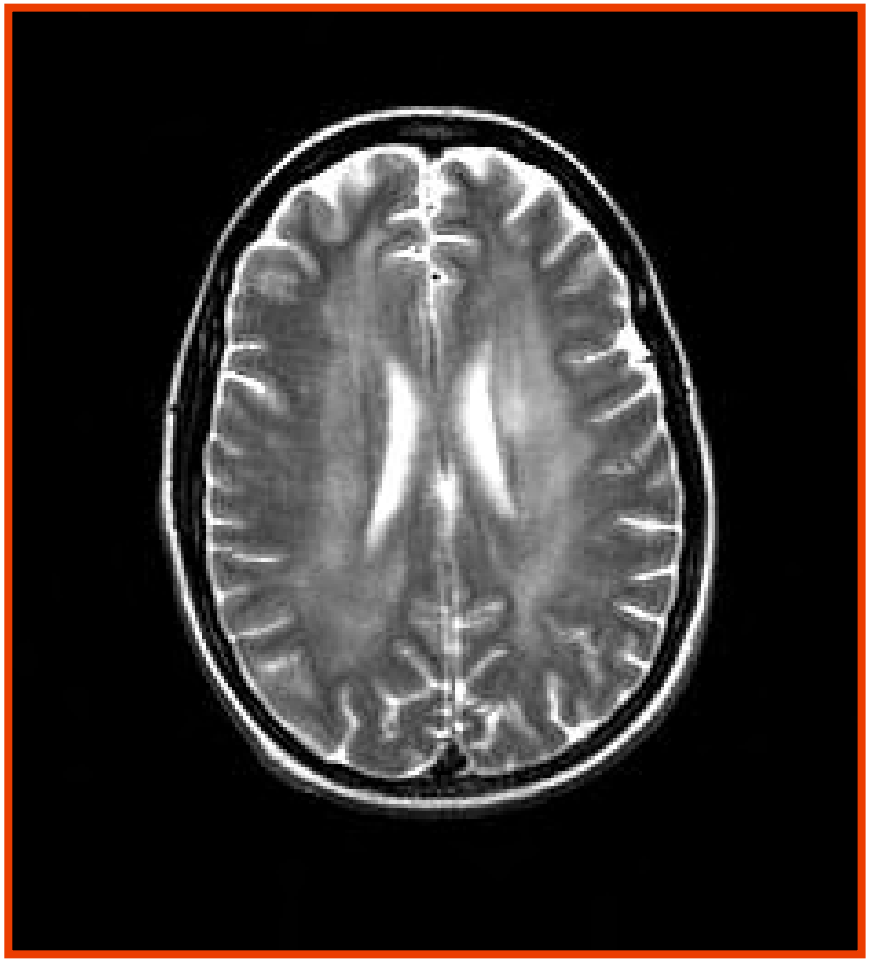
White matter changes





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Clinical Presentation and Course of Illness

Presentation		Course
Static		Developmental Arrest: No loss or gain of milestones
Progressive	Sub-Acute	Rapid and relentless
	Plateau	Indolent

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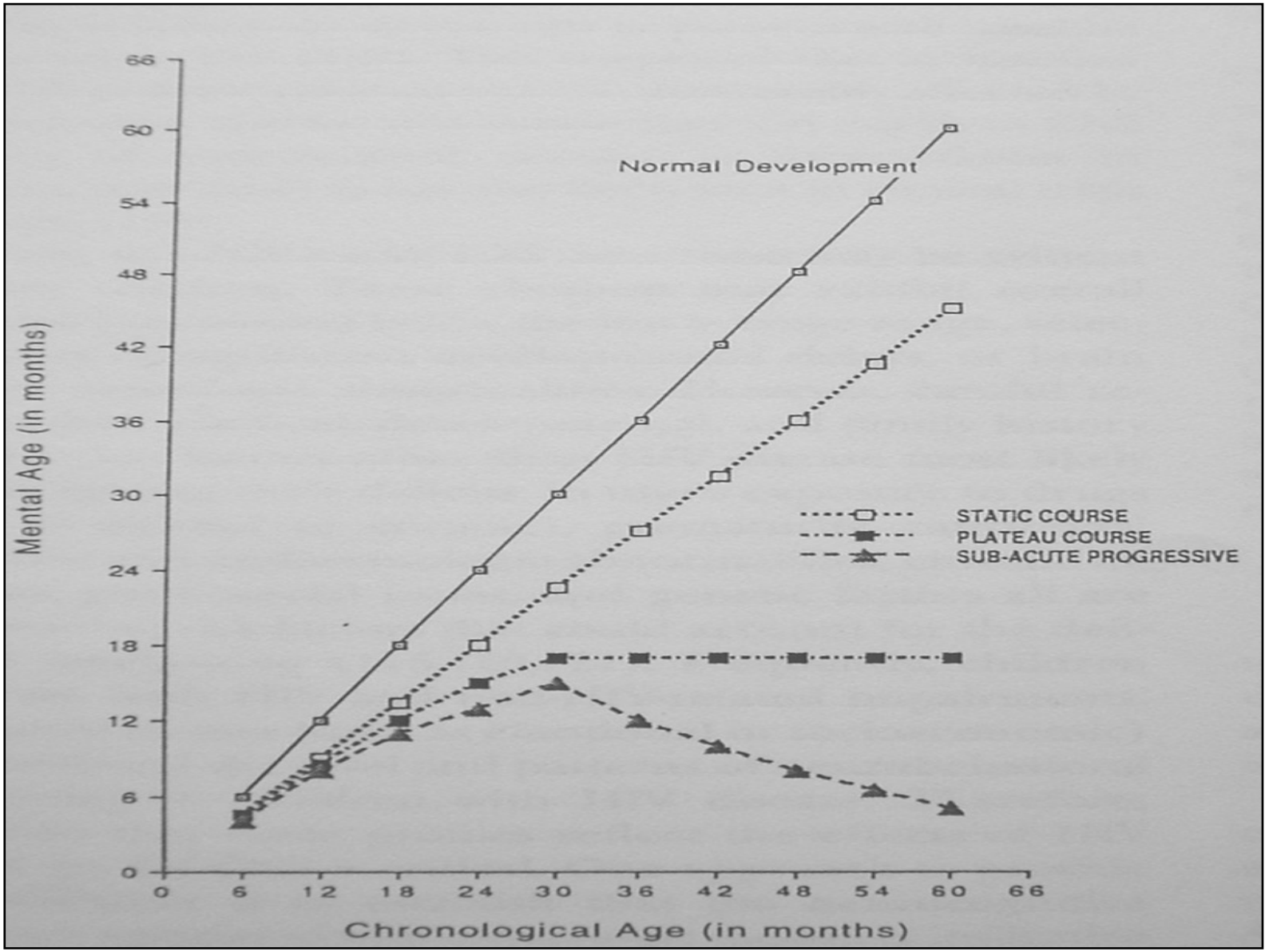

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Impact on Function

Area of Function	Age	Features		
		Early	Late	Rare
Motor	Can start at young age	•Spastic diparesis Increased tone and pathological reflexes mainly in the legs	•Spastic quadriparesis, Pseudo-bulbar palsy	•Dystonia, tremors, ataxia, focal signs
Behavioural	Often detected in older children	•Attention deficit hyperactivity disorder •Anxiety •Oppositional defiance •Conduct disorder		
Cognitive	All ages	•Expressive language deficit •Learning disabilities •Cognitive scores below childhood norm		

Management

- Stage 4 HIV Disease
- Important to note sucking and swallowing of child as nasopharyngeal in co-ordination common
  - Could add to CLD and FTT
- Rx HAART
  - May improve symptoms
  - Supportive care
    - Physiotherapy
    - Occupational therapy
    - Psycho-social support

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Opportunistic Infections

- Meningitis (TB / Bacterial)
- Cryptococcus neoformans
- Toxoplasmosis
- Cytomegalo virus
- Herpes simplex virus
- Varicella zoster virus
- PML

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What can be analyzed in cerebrospinal fluid?

- Direct investigation: amoebae, trypanosomes, filaria
- Cell counts and differential (type)
- Biochemistry: protein content , glucose (50-80% of the serum glucose)
- Serology: Syphilis
- Antigen-detection: Cryptococcus
- PCR: Mycobacteria, JC virus, herpes, toxoplasmosis
- Stains: Gram, Indian ink (cryptococcus), Ziehl (AFB)
- Culture: virus, bacteria, mycobacteria, fungi
- Cytology: only in case of suspected carcinomatous meningitis

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Contra-indications to doing a LP

- Comatose state
- Cardiovascular instability
- Raised intra cranial pressure
- Focal neurological signs
- Recent focal or prolonged seizures
- Coagulation disorder

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Meningitis/ encephalitis

- Pathogens: bacteria, viruses, fungi, TB
- Meningism as a clinical sign relatively uncommon in HIV infected children
- May present with lethargy, fever, poor feeding, vomiting, headache, seizures, focal neurological signs, coma
- High index of suspicion

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South to South

Meningitis/ encephalitis cont.

- Diagnosis:
  - LP for cerebrospinal fluid analysis:
    - microscopy, biochemistry (glucose, protein), culture
    - latex agglutination
    - indian ink smear
  - Blood for glucose, full blood count, CRP, serology
  - CT brain if available
  - MRI if available

- If bacterial meningitis suspected and unable to do LP, do bloodculture, start empiric AB treatment before CT imaging (where available)

South to South

TB meningitis

- The CSF findings in HIV infected children with TB meningitis is also similar to uninfected children.

- The likelihood of radiographic evidence of pulmonary tuberculosis is higher in HIV-infected children, whilst classical signs of TB meningitis on computed tomography such as obstructive hydrocephalus and basal meningeal enhancement tend to be less prominent (compared to uninfected children)

- The presence of hydrocephalus warrants air encephalography to determine whether the hydrocephalus is of an obstructive (shunting required) or communicating nature (medical therapy)

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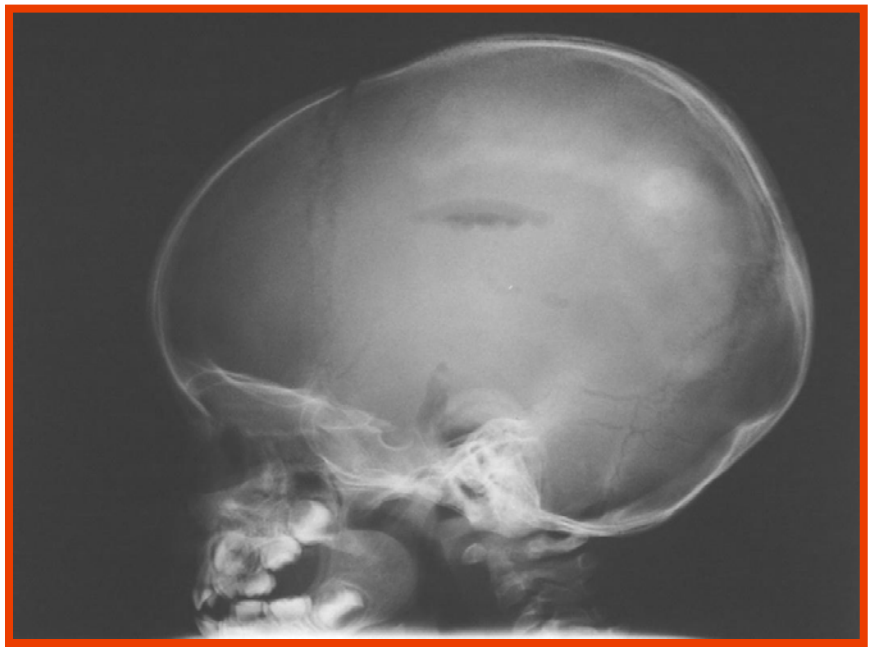

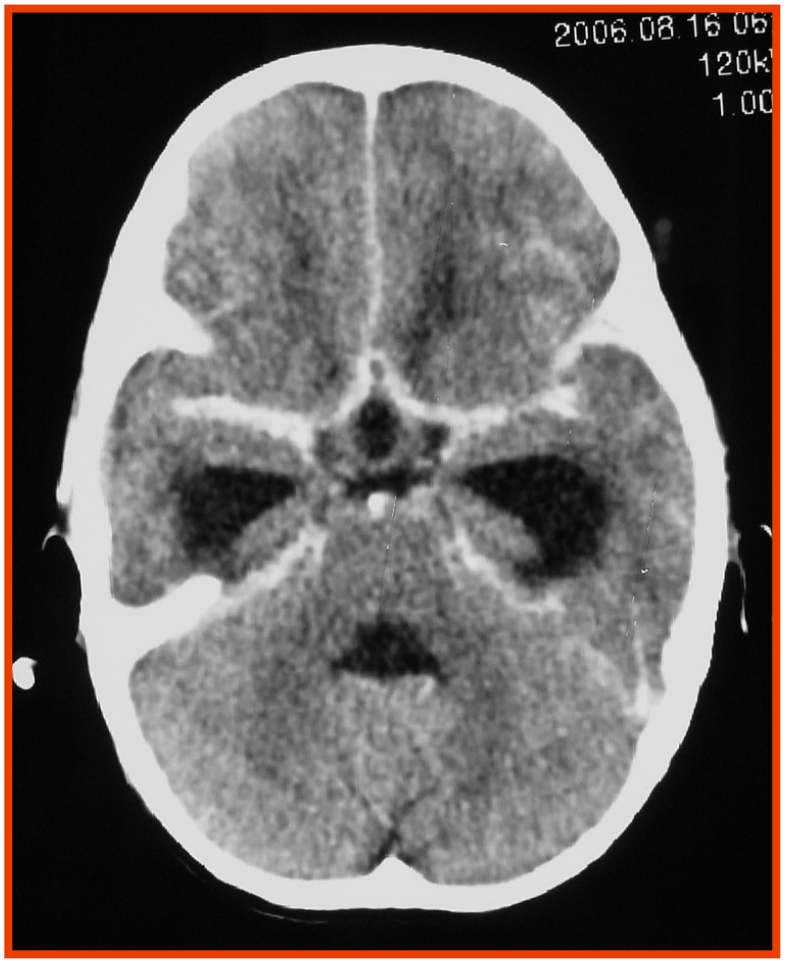

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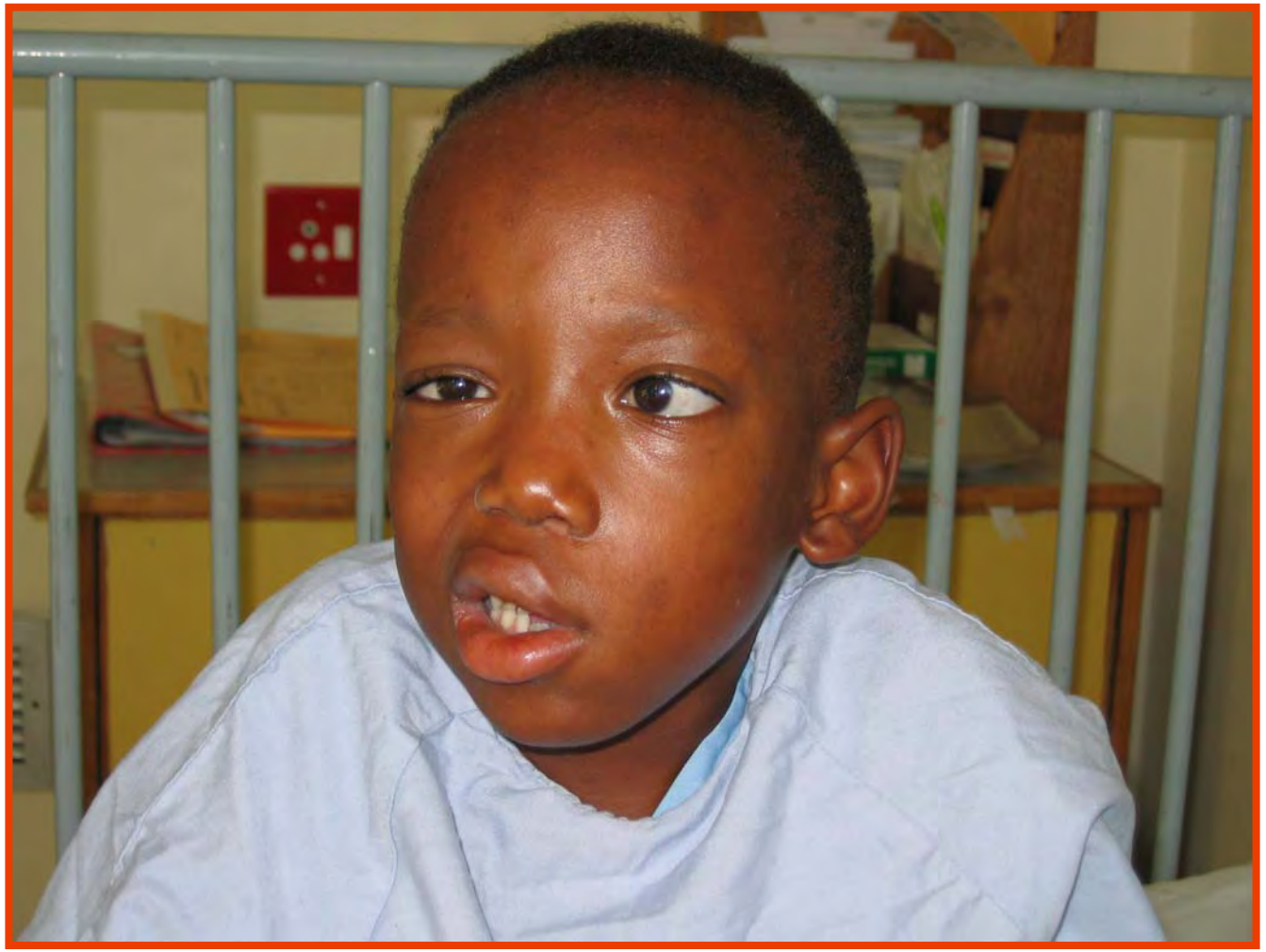
Treatment

- Isoniazid, Rifampicin and Ethionamide 20mg/kg and Pyrazinamide 40mg/kg, all given once daily in hospital for 6-9 months.
- Prednisone 4mgkgday (maximum dose 60mg) is added during the first month of treatment.
- Medical treatment of hydrocephalus consists of Acetazolamide 50-100mg/kg/day in 3 divided doses and Furosemide 1mg/kg/day in 3-4 divided doses for 4 weeks duration.
- To minimize the risk of IRIS, the initiation of HAART should be delayed 2-4 weeks after anti-tuberculosis treatment has been started where possible.

Cryptococcal Meningitis

- Onset over days to weeks
- Signs and symptoms can be very subtle early in the disease
- Clinical Presentation: Headache, nausea, fever, vomiting, seizures, focal neurological signs
- Usually older child with severe immuno-compromise
- Considered a WHO stage 4 illness
- May occur as a result of IRIS

South to South



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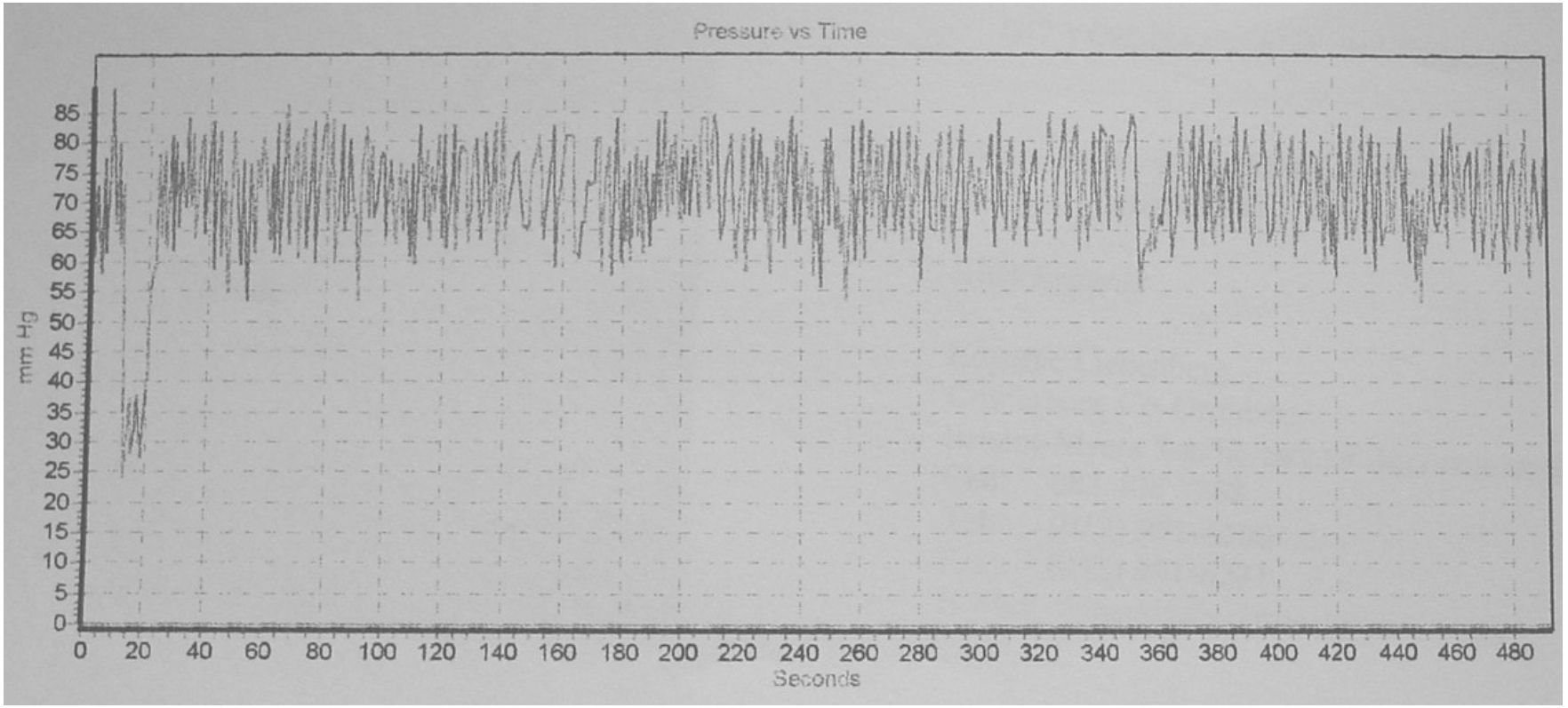
CSF pressure monitoring



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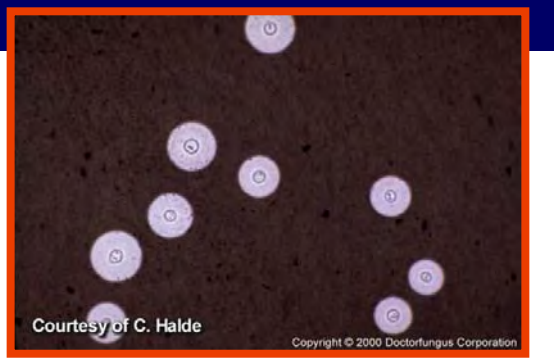
Investigations and Diagnosis



- **Lumbar puncture** with CSF pressure measurement
  - High opening pressure
  - Cell count mildly raised or normal
  - CSF glucose low, protein raised
  - India ink stain: helpful, cannot exclude diagnosis if negative (low sensitivity)
- **Culture:** definite diagnosis, take weeks
- **Cryptococcal antigen** test in serum > 95% sensitivity in AIDS patients
  - Good marker for HIV associated cryptococcal meningitis
- Ophtalmologic assessment (concomitant arachnoiditis)
- If relapse suspected
    - Cryptococcal culture investigation of choice as antigen remains elevated for long periods

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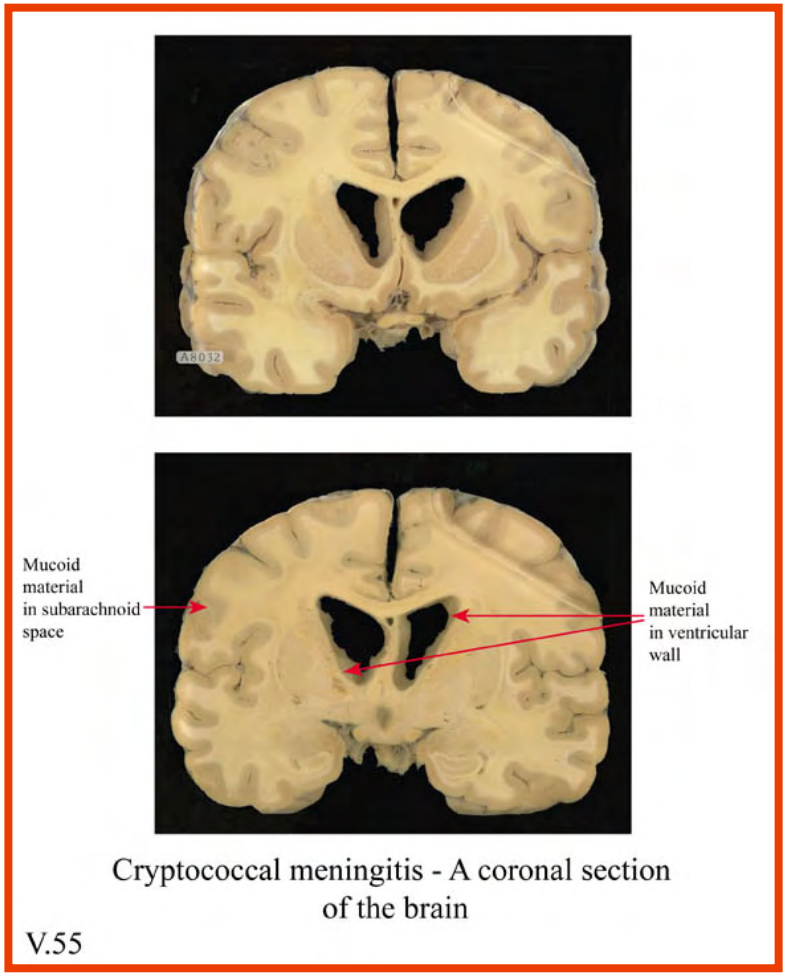
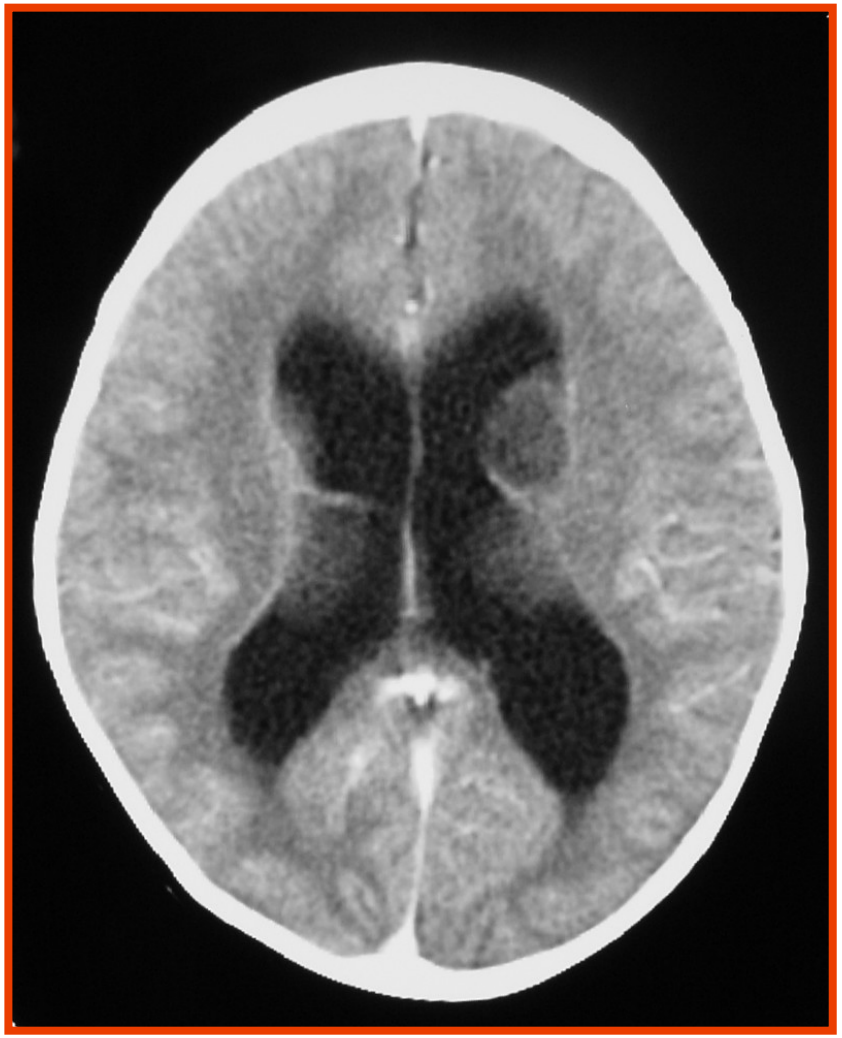
Cryptococcal Meningitis



Cryptococcal meningitis - A coronal section of the brain

V.55



Cryptococcal Meningitis: Management

- Mild- Moderate (normal mental status)
  - PO fluconazole 8-10 weeks
  - Secondary prophylaxis indefinitely after therapy
- Moderate- Severe
  - Requires hospitalization
  - IV Amphoteracin B for 14 days
    - Measure elecrolytes regularly as hypokalaemia and hypomagnesaemia common side effects
  - Followed by fluconazole (6-12 mg/kg/day) for 8-10 weeks
  - Secondary prophylaxis indefinitely after therapy
- Some patients may need serial spinal taps to reduce intracranial pressure and alleviate symptoms (associated with poor outcome)

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Cytomegalovirus (CMV)

Pathophysiology

- Vertical and horizontal transmission
- Most common perinatally transmitted infection.
- Transmission rates higher in HIV infected mother.
- AIDS defining illness
- High morbidity and mortality

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CMV: Clinical Presentation

- Neonates
  - Small for gestational age
  - Purpura/petechiae, jaundice
  - Hepatosplenomegaly, retinitis, hearing loss
  - Microcephaly, intracrainial calcifications
- Children
  - Non-specific symptoms: fever, poor growth, poor neuro-development
  - Laboratory: Anemia, thrombocytopenia, elevated lactate levels
  - CNS: encephalopathy, myelitis, polyradiculopathy
  - Retinitis (loss of peripheral vision, blurred vision, retinal infiltrates or haemorrhages

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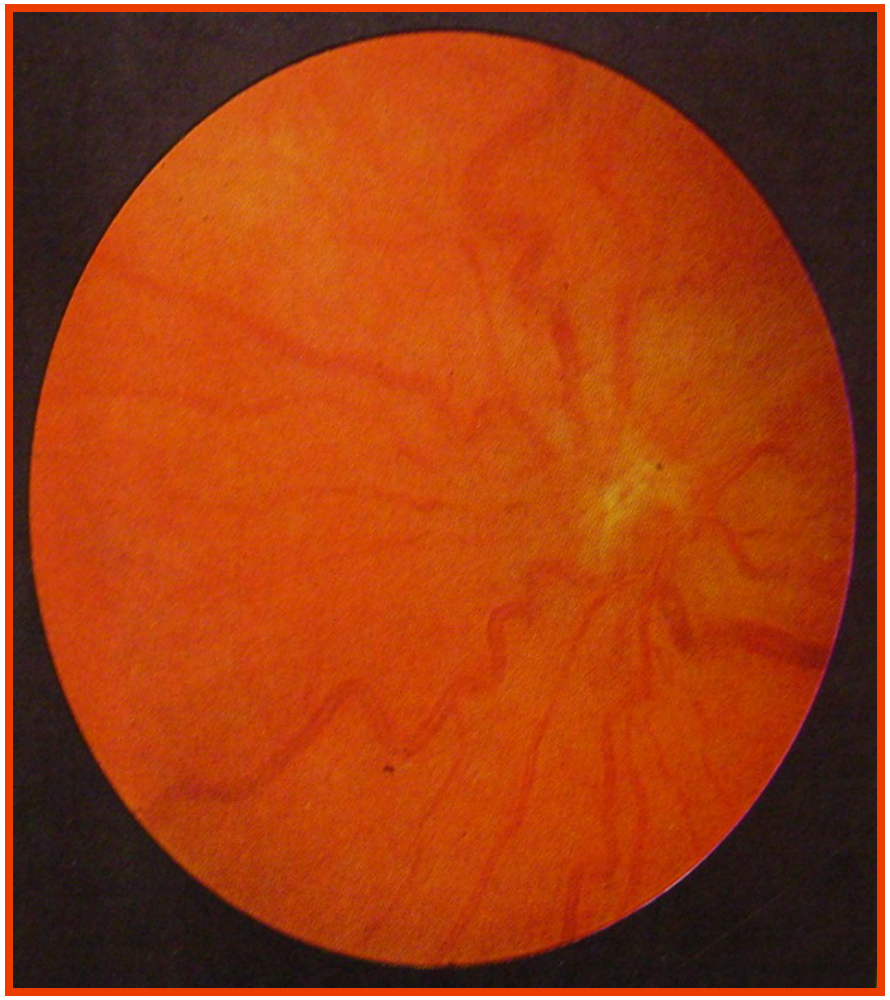
Severe CMV retinitis



Diagnosis and Treatment

Diagnosis:

- Suspicious clinical features
- Serology – Not good as often positive in normal individuals
- Culture- Indicates shedding if in urine and disease if cultured from tissue specimens
- Histology – indicates disease
- PP65 – Indicates viremia
- PCR- expensive, quantitative or qualitative , quantitative assessment can be used in series

Treatment:

- For symptomatic neonates
  - IV Ganciclovir 12 mg/kg OD x 6 weeks
- For disseminated disease in children
  - IV Ganciclovir 5 mg/kg BD x 14-21 days
- Consider IV Foscarnet 60 mg/kg Per 8 hours x14-21 days

- Lifelong maintenance therapy required after initial treatment

South to South

Progressive Multifocal Leukoencephalopathy (PML)

Pathophysiology

- Caused by JC virus
- Rapidly progressing
- High rates of morbidity and mortality
- WHO Stage 4
- Can be IRIS

Clinical Presentation

- Personality change
- Memory loss
- Cognitive impairment
- Visual impairment

South to South

PML

Diagnosis

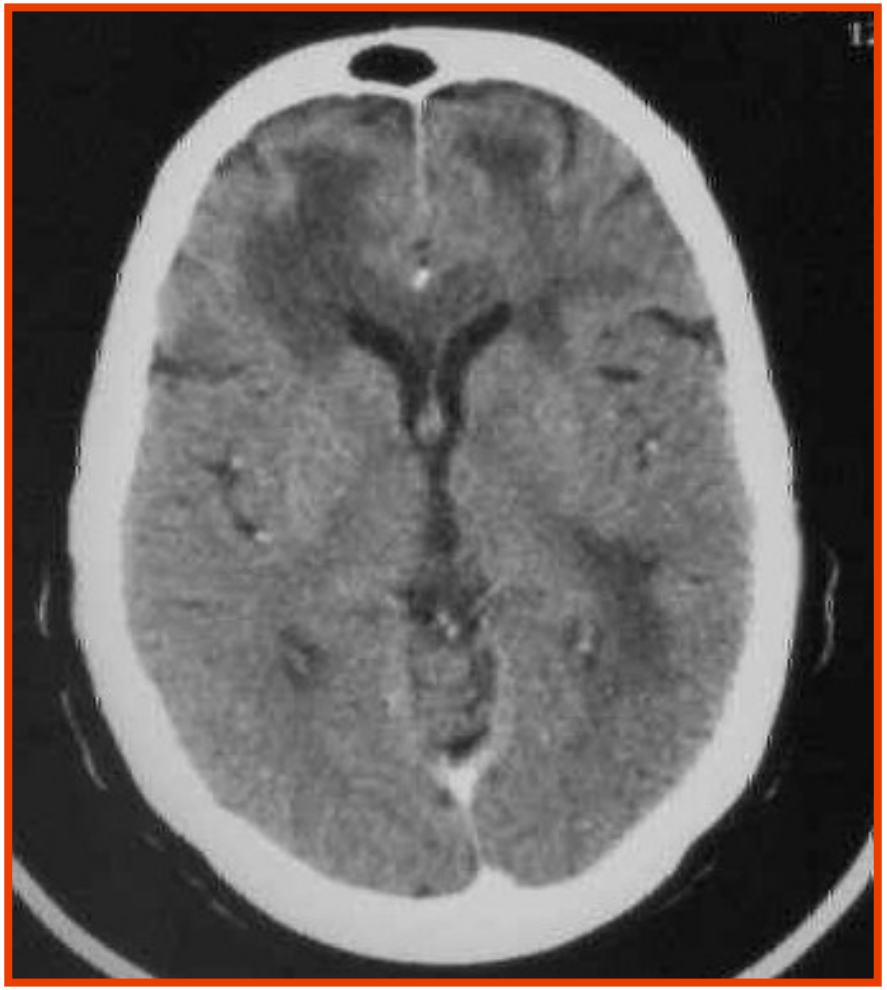
- Clinical presentation
- CT Scan / MRI

Management

- HAART

South to South

Progressive Multifocal Leuco - encephalopathy



South to South

Toxoplasma Gondii

Pathophysiology

- Congenital transmission
- Can also be transmitted via raw or undercooked meat or cat faeces
- More common in adults than children
- WHO Stage 4

Clinical Presentation

- Primarily infects the brain: Altered mental state (confusion, delusional behavior), severe headaches, fever, seizures and coma. Focal neurological deficits (brain abscesses), microcephaly, hydrocephalus
- Can also affect the eye causing eye pain and blindness
- Systemic presentation: fever, organomegaly, lymphadenopathy, malaise, maculopapular rash, sore throat

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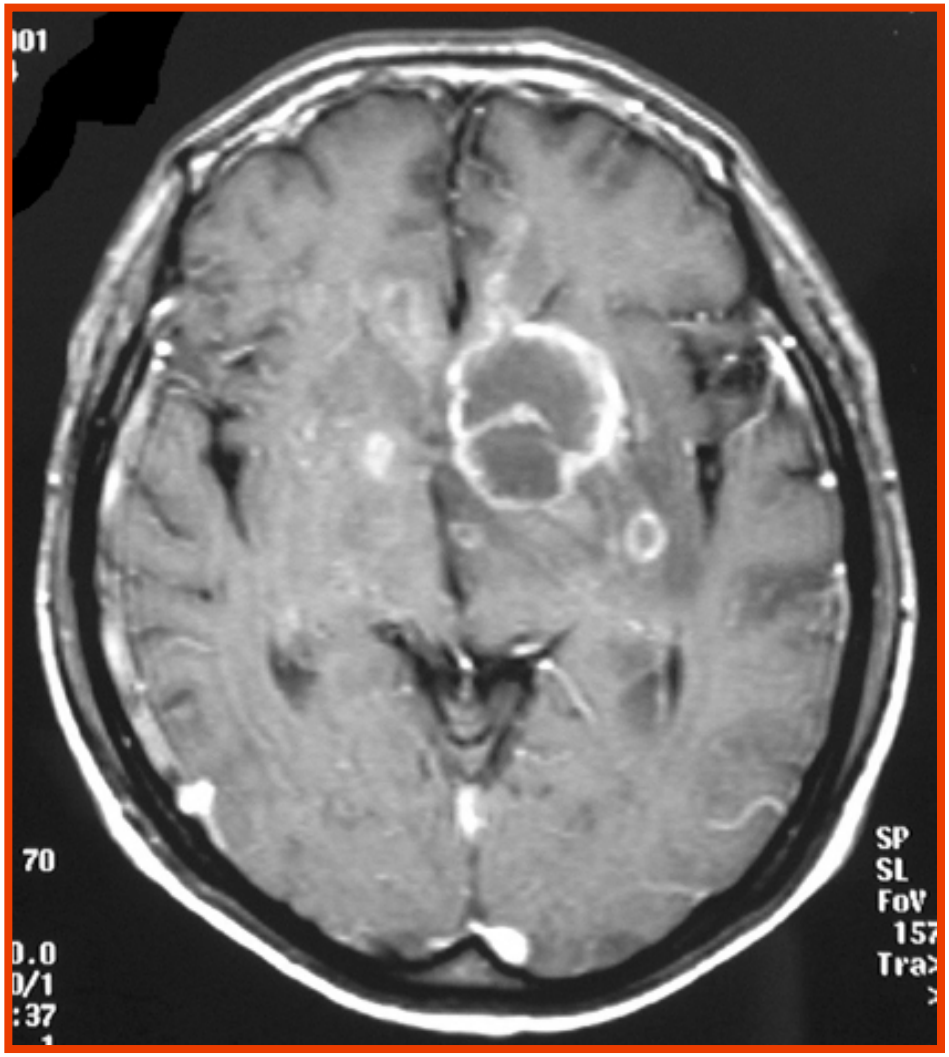
Toxoplasma Gondii



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Toxoplasma Gondii

Diagnosis

- CT scan for multiple ring enhancing brain lesions,
- Antibody titer in blood or cerebral spinal fluid (CSF) ,
- CSF culture
- If needed, brain biopsy to rule out lymphoma

Management

- Pyrimethamine, Sulfadiazine and folinic acid
- Prevention
  - Primary prophylaxis: Co-tramoxazole
  - Secondary prophylaxis: Pyrimethamine, Sulfadiazine and folinic acid
  - Cook meat thoroughly
  - Hand washing

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Summary

- The most frequent neurological impairment observed in HIV infected children are due to HIV infection itself, rather than OIs or CNS tumors
- But CNS OIs must always be considered in HIV infected children with CNS manifestations, as death may occur if these infections goes untreated
- Frequent neurological and cognitive assessment are important to recognize and monitor HIV encephalopathy

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