Neurological Manifestations of HIV infection
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
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
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
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
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 CIRCUMFERENCE 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
Basal Ganglia calcifications
Global atrophy
White matter changes
Clinical Presentation and Course of Illness

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Course</th>
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<tbody>
<tr>
<td>Static</td>
<td>Developmental Arrest: No loss or gain of milestones</td>
</tr>
<tr>
<td>Progressive</td>
<td>Sub-Acute</td>
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<tr>
<td></td>
<td>Plateau</td>
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## Impact on Function

<table>
<thead>
<tr>
<th>Area of Function</th>
<th>Age</th>
<th>Features</th>
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</table>
| **Motor**        | Can start at young age | **Early**
|                   |     | - Spastic diparesis
|                   |     | - Increased tone
|                   |     | - and pathological
|                   |     | - reflexes mainly
|                   |     | - in the legs
|                   | Late | - Spastic quadriparesis,
|                   |     | - Pseudo-bulbar palsy
|                   | Rare | - 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
Opportunistic Infections

- Meningitis (TB / Bacterial)
- Cryptococcus neoformans
- Toxoplasmosis
- Cytomegalo virus
- Herpes simplex virus
- Varicella zoster virus
- PML
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
Contra-indications to doing a LP

- Comatose state
- Cardiovascular instability
- Raised intra cranial pressure
- Focal neurological signs
- Recent focal or prolonged seizures
- Coagulation disorder
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
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 blood culture, start empiric AB treatment before CT imaging (where available)
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)
Treatment

- Isoniazid, Rifampicin and Ethionamide 20mg/kg and Pyrazinamide 40mg/kg, all given once daily in hospital for 6-9 months.
- Prednisone 4mg/kg/day (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
CSF pressure monitoring
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
Cryptococcal Meningitis

Cryptococcal meningitis - A coronal section of the brain

Mucoid material in subarachnoid space

Mucoid material in ventricular wall
Cryptococcal Meningitis: Management

- Mild- Moderate (normal mental status)
  - PO fluconazole 8-10 weeks
  - Secondary prophylaxis indefinitely after therapy

- Moderate- Severe
  - Requires hospitalization
  - IV Amphotericin B for 14 days
    - Measure electrolytes 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)
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
CMV: Clinical Presentation

- Neonates
  - Small for gestational age
  - Purpura/petechiae, jaundice
  - Hepatosplenomegaly, retinitis, hearing loss
  - Microcephaly, intracranial calcifications
- Children
  - Non-specific symptoms: fever, poor growth, poor neurodevelopment
  - Laboratory: Anemia, thrombocytopenia, elevated lactate levels
  - CNS: encephalopathy, myelitis, polyradiculopathy
  - Retinitis (loss of peripheral vision, blurred vision, retinal infiltrates or haemorrhages
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 x 14-21 days
• Lifelong maintenance therapy required after initial treatment
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
## PML

<table>
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<tr>
<th>Diagnosis</th>
<th>Management</th>
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| • Clinical presentation  
  • CT Scan / MRI | • HAART |
Progressive Multifocal Leuкоencephalopathy
**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
Toxoplasma Gondii
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
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.
South to South