Neuro-TB and HIV

Umesh G Laloo
Durban ICTU - AACTG
Nelson R Mandela School of Medicine
Faculty of Health Sciences
University of KwaZulu-Natal
Durban, South Africa
Outline of presentation

• Epidemiology of TB and HIV
• Mechanism of CNS involvement
• Clinical features and diagnosis
• Treatment of TB and HIV
• Special considerations
• Prevention
Risk of developing TB with HIV

- 1/3 world’s pop TB infected
- 8m new cases and 2m deaths
- 10 million co-infected
  - 90% in developing countries
- TB kills 1 out of every 3 AIDS patients
- Extrapulmonary disease is common
Risk of developing TB with HIV

- HIV- : lifetime risk of 10%
- HIV+ : risk of 10% per annum
- In KwaZulu Natal, South Africa:
  - almost 2/3 TB cases are HIV+
  - About 50% cure rate
- DNA fingerprinting confirmed a significant proportion of reinfection
Tuberculosis Caseload and Antenatal HIV Prevalence

Source: Hlabisa Hospital Records
### Distribution of complications associated with HIV/AIDS in medical wards at KEH in 2000

<table>
<thead>
<tr>
<th>complication</th>
<th>Number</th>
<th>Percentage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>1582</td>
<td>46.9%</td>
<td>(21%)</td>
</tr>
<tr>
<td>• pulmonary</td>
<td>1362</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• meningitis</td>
<td>163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• pericardial</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteritis</td>
<td>423</td>
<td>12.5%</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>409</td>
<td>12.1%</td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>364</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>171</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>156</td>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td>Pancytopaenia</td>
<td>49</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>HIVAN (Nephropathy)</td>
<td>51</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>49</td>
<td>1.4%</td>
<td></td>
</tr>
</tbody>
</table>
Frequency of neuro-TB?

• 70-90% have neuro signs or symptoms during course of HIV
  - AIDS dementia complex
  - Acute meningitis
  - Toxoplasmosis
  - CMV
  - Crypto
  - PMFL
  - Lymphoma
  - TB
  - Histoplasmosis
  - Stroke
Neuro-TB

• Frequency of extrapulmonary TB increases as immune suppression progresses
• No evidence (yet) that neuro manifestations are different to non-HIV
• Chest X ray abnormal in about 80%
Neuro-TB

Developing vs developed countries

• AIDS patients
  - 120 from Mexico City
  - 500 from Houston

• AIDS dementia complex common in both groups

• Tuberculomas (10%) only in Mexicans

• Primary brain lymphoma > in US pop.
  - Reflects high TB prevalence in Mexico and > mortality

Trujillo et al; JAIDS 1995
Morbidity and mortality

- Hydrocephalus common in patients who survive the first 4-8 weeks
- Infarction occurs in >50%
- Ventriculitis
Pathogenesis of neuro-TB

Extra-pulmonary TB

CNS spread:
- Tuberculoma (rare)
- TB meningitis
  - Headache
  - Stiff neck
  - Coma

Adrenal TB
→ Addison's disease
  (commonest cause worldwide)

GU disease
- Renal TB
- Fallopian tube
  (infertility)

Bone and joint
(Pott's disease = TB spine)

Skin TB
(lupus vulgaris)
Clinical syndromes

- Meningitis
- Tuberculoma
- Brain abscess
- Encephalitis
- Myeloradiculopathy
- Spinal cord abscess
- Vertebral TB

Remember: multiple infections are common!
TB Meningitis - symptoms

HIV n=37

- Fever - 89%
- Headaches - 59%
- Altered mentation - 43%
- Focal deficits - 14%
- Malaise - 27%
- Sputum - 19%
- Cough - 22%

Non-HIV n=19

- Fever - 89%
- Headaches - 63%
- Altered mentation - 32%
- Focal deficits - 11%
- Malaise - 32%
- Sputum - 16%
- Cough - 16%

Berenguer et al; NEJM 1992
### TB Meningitis - signs

<table>
<thead>
<tr>
<th>HIV n=37</th>
<th>Non-HIV n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Temp - 81%</td>
<td>• 79%</td>
</tr>
<tr>
<td>• Meningeal signs - 65%</td>
<td>• 84%</td>
</tr>
<tr>
<td>• Altered mentation - 43%</td>
<td>• 32%</td>
</tr>
<tr>
<td>• Focal deficits - 19%</td>
<td>• 11%</td>
</tr>
<tr>
<td>• Hepatomegaly - 46%</td>
<td>• 21%</td>
</tr>
<tr>
<td>• Adenopathy - 41%</td>
<td>• 11%</td>
</tr>
<tr>
<td>• Splenomegaly - 19%</td>
<td>• 11%</td>
</tr>
</tbody>
</table>

Berenguer et al; NEJM 1992
Intracranial mass lesions

- In South Africa
  - Toxoplasmosis
  - Encephalitis of obscure origin
  - Brain abscess
  - Tuberculoma
  - Cryptococccoma

Bhigjee et al; SAMJ 1999
Tuberculous myeloradiculopathy

• Underreported
• A complication of TBM
• Symptoms and signs
  - Subacute paraparesis
  - Radicular pain
  - Bladder disturbances
  - Subsequent paralysis
• Features
  - High CSF protein
Tuberculoma

- Granulomas from CSF extension or blood spread
- Central zone of caseation
- Paucibacillary
- Widely distributed
- Usually multiple and less than 1cm diameter
- May be indistinguishable from toxo, but:
  - Cisternal enhancement
  - Basal ganglia infarction
  - Communicating hydrocephalus

May help to distinguish TB
Tuberculous brain abscess

- Probably more common in HIV infected
  - 20% of HIV neuroTB in one series
    - Whiteman et al; AJNR 1995
- Tend to be larger than tuberculomas
- Usually solitary
- Ring enhancement invariable
Diagnosis

A high index of suspicion and neuroanatomic localisation

CT / MRI

Microbiology / histology of local or distant sites or empiric diagnosis
Petechial haemorrhages in subcortical white matter in a patient with TBM

Source: Prof P Corr, Dept of Radiology, Univ of KwaZulu-Natal
Extensive R basal ganglia and internal capsule infarcts

Source: Prof P Corr, Dept of Radiology, Univ of KwaZulu-Natal
Contrast enhanced CT in patient with TBM showing marked enhancement in the basal cisterns

Source: Prof P Corr, Dept of Radiology, Univ of KwaZulu-Natal
T1 weighted gadolinium-enhanced MRI with multiple enhancing tuberculomas in both cerebral and cerebellar hemispheres

Source: Prof P Corr, Dept of Radiology, Univ of KwaZulu-Natal
T1 weighted gadolinium-enhanced MRI in a child with a TB brain abscess in the left parietal lobe

Source: Prof P Corr, Dept of Radiology, Univ of KwaZulu-Natal
T1 weighted gadolinium-enhanced MRI of the cord showing dural enhancement

Source: Prof P Corr, Dept of Radiology, Univ of KwaZulu-Natal
LP

- Any patient who has unexplained mental confusion, depressed level of consciousness or meningism
- Typical changes
  - Raised pressure
  - Raised protein
  - Lymphocytosis
  - Low glucose
- ADA is neither sensitive nor specific
- PCR of no clinical value
- Microscopy for AFB rarely helpful and culture takes up to 6 weeks
LP

• Of value in excluding
  - Cryptococcal meningitis
  - Other bacterial meningitides
Treatment

- Prolonged (12 months TB treatment)
- Adjunctive corticosteroids for
  - Myeloradiculopathy
  - SOL
  - Encephalitis
Treatment

- **MDR TB**
  - Real problem
  - Poor response to second line treatment
  - High mortality: >60%
  - Must be suspected in any patient with prior exposure to TB drugs and meningitis
Treatment

• Shunt surgery
  - Value of shunting not established in HIV and TB hydrocephalus
  - Local experience suggests high mortality
    • 66.7% vs 26.7% in HIV vs non HIV
  - Propose that ventricular or lumbar CSF drainage first and only those demonstrating significant neuro improvement should have shunt surgery
    - Nadvi et al; Neurosurgery 2000
HAART and TB treatment

• No data to support any standard strategy
• Individualize patient
• Experience from PTB suggests benefit of concomitant treatment
• Await AACTG trial on HAART in setting of opportunistic infections?
Paradoxical worsening of TB

• Development of new signs or symptoms of TB or exacerbation of existing manifestations on appropriate TB treatment.
  - Usually within 4-12 weeks of TB treatment and 4 weeks of commencing ARVs
• Other explanations must be excluded first
  - Treatment failure
  - Poor adherence
  - Drug resistance
  - Malabsorption
  - Adverse drug reactions
  - Lymphoma
Paradoxical worsening of TB

- Thought to represent the host's immune response to the TB antigen.
- ARVs may aggravate the condition.
  - Patients on co-treatment may be at higher risk; but conflicting data.
Paradoxical worsening of TB

- Manifestations may be more devastating with neuro-TB.
- Treatment:
  - Careful clinical vigilance and early recognition
  - Corticosteroids
  - Delaying HAART until TB under control (4-8 weeks)
Has HAART altered manifestations of neuro-TB?

- Not sure
- Antinori et al (abstract, 2001)
  - Suggests a decrease in neuromanifestations
  - Extrapolation from incidence of PTB should anticipate a reduction in neuro-TB but definitive prospective studies required