The chronic headache of TUBERCULOUS MENINGITIS

Suzaan Marais
March 2012

Tuberculous Meningitis
- Pathogenesis
- Clinical presentation
- TBM & HIV
- Diagnostic methods
- Treatment
- Neurological TB-IRIS

Introduction
- TBM pathology first described-1836
- Robert Koch stained & cultured MTB-1882

TBM Pathogenesis
- Primary infection/ reactivation:
  - Bacillaemia
  - Tuberculous foci in brain/ meninges
  - Subependymal foci rupture into subarachnoid space
  - Inflammatory host response

Mortality of TBM

Arachnoiditis

Vasculitis

Tuberculoma(ta)
Clinical Presentation (1)

3 Phases:
§ Prodromal - 2-3 weeks: insidious onset of malaise, headache, low-grade fever, personality change.
§ Meningitic - meningeal, protracted headache, vomiting, lethargy, confusion, cranial nerve and long-tract signs.
§ Paralytic - coma, seizures, hemiparesis.

Clinical Presentation (2)

TBM can mimic:
§ Bacterial meningitis
§ Dementia

Clinical Presentation (3)

Severity grading:
§ Grade I
  Alert and orientated, no focal neurological deficit
§ Grade II
  GCS 11–14 or GCS 15 with focal neurological deficit
§ Grade III
  GCS ≤ 10

Clinical Presentation (4)

Symptom %
§ Headache 50–80
§ Fever 60–95
§ Vomiting 30–60
§ Photophobia 5–10
§ Anorexia 60–80

Clinical Presentation (5)

Clinical signs %
§ Neck stiffness 40–80
§ Confusion 10–30
§ Coma 30–60
§ Any cranial nerve palsy (VI, III, VII) 30–50
§ Hemiparesis 10–20
§ Paraparesis 5–10
§ Seizures
  - adults 5
  - children 50

Clinical Presentation (6)

Clinical variables of value in diagnosis:
§ Symptoms > 5 days
§ Systemic symptoms of TB
§ History of contact with person with active PTB (children)
§ Cranial nerve palsies
§ Other focal signs
§ Altered consciousness

Thwaites et al. J Infect 2009
Marais et al. Lancet Infect Dis 2010
TBM + HIV

- 5x higher CNS involvement in HIV 32% vs 18%
- Same clinical presentation but:
  - ↑Extra-meningeal TB
  - ↑Mortality:
    - In hospital: 13-72% vs 18-64%
    - 9 Month follow-up: 65% vs 28%

Marais et al. Tuberculosis 2010 Thwaites et al. NEJM 2004

Diagnosis (1)

- Early diagnosis and treatment increase survival and decrease morbidity
  - BUT
- Diagnosis often difficult !!!

Diagnosis (2)

Typical CSF findings:
- clear/yellow
- Total cell count: 10-500 cells/μL
- ↑Lymphs >50%
- ↑prot >1g/L
- ↓glucose ratio CSF:Plasma<50%

<table>
<thead>
<tr>
<th>CSF</th>
<th>HIV (%)</th>
<th>HIV+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acellular</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Neutrophil predominance</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Normal protein</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>Normal glucose</td>
<td>15</td>
<td>25</td>
</tr>
</tbody>
</table>

Marais et al. Lancet Infect Dis 2010

Question 1

What percentage of HIV-infected patients with confirmed TBM may have completely normal CSF?
1) 1%
2) 3%
3) 6%
4) 16%
5) 30%

Diagnosis (3)

Bacteriology
- AFB + 5-20 %
- Culture + 40 %
Question 2

Which of the following will improve the diagnostic yield in patients with TBM?
1) increasing the volume of CSF sent
2) repeated LP
3) prolonged microscopy time
4) all of the above
5) none of the above

Question 3

At least what volume of CSF should ideally be sent for TB microscopy and culture?
1) 1 ml
2) 3 ml
3) 4 ml
4) 6 ml
5) 15 ml

Diagnosis (3)

Bacteriology
- AFB + 5-20 %
- Culture + 40 %
- Improve yield: Repeated LP
  ↑volume CSF
  Prolonged microscopy

Diagnosis (4)

Molecular diagnosis
- CNAAs
  (Commercial Nucleic acid Amplification Assay):
  - Sensitivity: 56%
  - Specificity: 98%
- Improved results (85-94%) with Multiplex PCR
- ? Utility of GeneXpert MTB/RIF

Question 4

What test should be performed in all patients with suspected TBM?
1) Urinary LAM
2) Sputum (spontaneous or induced) for TB investigations
3) Abdominal ultrasound
4) CT head
5) Chest X-ray

Diagnosis (5)

Neuroradiology:
- Grade 1-30% N- good prognosis
- Basilar meningeal enhancement
- Hydrocephalus
- Infarcts
- Tuberculomas

TB elsewhere:
- CXR + latent/active TB ~ 50%
- AFB in sputum, urine, L/nodes etc.
- Urinary LAM

Treatment (1)

- TBM is a medical emergency!!!
- Delay in treatment → ↑mortality
  - 24 Hours: 58% → 91%
  - 3 weeks delay/2 weeks interruption: 5x ↑
- Start treatment on strong clinical suspicion
- Choice of drugs, doses, duration- unknown


Treatment (2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>300 mg</td>
<td>Oral</td>
<td>9-12 months</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>600 mg</td>
<td>Oral</td>
<td>9-12 months</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>15 mg kg</td>
<td>Oral</td>
<td>9-12 months</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg kg</td>
<td>Oral</td>
<td>9-12 months</td>
</tr>
</tbody>
</table>


Question 5

Which TB drug has the worst CSF penetration?
1) Isoniazid
2) Rifampicin
3) Pyrazinamide
4) Ethionamide
5) Levofloxacin

Table 5: British and American guidelines for the treatment of TBM

Question 5
Which TB drug has the worst CSF penetration?
1) Isoniazid
2) Rifampicin
3) Pyrazinamide
4) Ethionamide
5) Levofloxacin

Treatment (3)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bactericidal/static</th>
<th>Penetration in inflamed meninges</th>
<th>Penetration normal meninges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Bactericidal-intra + extracellular organisms</td>
<td>+++ (90% plasma levels)</td>
<td>+ (20% plasma levels)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Bactericidal-intra + extracellular organisms</td>
<td>+++ (similar to plasma levels)</td>
<td>+++ (similar to plasma levels)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Bactericidal-intra + extracellular organisms</td>
<td>+ (10-20% plasma levels)</td>
<td>No</td>
</tr>
</tbody>
</table>

Fluoroquinolones
- Good in vitro activity and sterilizing activity in sputum
- Levofloxacin (500mg bd) has best CNS penetration (AUC₀₋₂₄/AUC₀ ≈75%)
- Tolerable
- Easy administration
- Low levels of resistance

Drug resistant TBM
- Associated with HIV
- MDR: 100% mortality
- INH resistance: increased mortality
- Ethionamide, cycloserine – good CSF penetration
- Aminoglycosides - poor CSF penetration

Steroids (1)
- Randomised trial of steroids vs placebo
- 545 patients (98 HIV+)
- ↓ risk of death (RR=0.69, 95% CI=0.52-0.92)
  - all grades of severity
  - HIV+ and HIV-
- ↓ severe A/E's

When to start ART?
- Trial of immediate (≤7 days) vs delayed (2 months) ART in TBM
  - no difference in outcome (76/127 vs 70/126)
  - significantly more Grade 4 adverse events (80% vs 69%, P=0.04)
  - mortality similar to historic group of patients not on ART (58% vs 65%)
- Retrospective review: ART associated with decreased mortality (HR: 0.3, 95% CI:0.08-0.82)
Neurological TB-IRIS
- Common in high TB/HIV prevalence settings
- 12% of paradoxical TB-IRIS cases
- 21% of cases with central nervous system deterioration during first year of ART
- 16/34 (47%) of TBM patients started on ART


TBM-IRIS presentation
- ART started 2 weeks after TB treatment
- IRIS occurred in spite of prednisone treatment 14 days after starting ART
- Presentation: severe features of inflammation
  - E.g. Radiculomyelitis
  - Isolated aphasia
  - Brainstem encephalitis
  - Myoclonus

TBM diagnosis
- TBM-IRIS

Baseline characteristics in IRIS and non-IRIS
- Similar between IRIS and non-IRIS, but:
- Worse disease:
  - more systemic symptoms
  - lower BMI
  - lower sodium (123 vs 131)
- Higher CSF neutrophil count (50 vs 2)

CSF M. tuberculosis culture positivity
- IRIS 15/16 (15-30 days)
- No IRIS 6/18 (14-32 days)
- Relative risk of IRIS if culture positive= 9.3 95% CI 1.4-62.2 P=0.0004

Management and Outcome
- Prednisone increased in IRIS to 1.5-2 mg/kg/day (n=16), ART stopped (n=1)
- 2/16 TBM-IRIS patients died due to TBM-IRIS vs no deaths in non-IRIS group
Conclusions

- Many unanswered questions remain
- Early diagnosis NB- start TB treatment on strong clinical suspicion
- Increase diagnostic yield by increasing volume of CSF sent for culture/repeated LP
- Fluoroquinolones may improve prognosis if started early??
- Neuro TB-IRIS is serious complication in TB/HIV co-infection which is associated with increased culture positivity and high CSF neutrophil count

Acknowledgements

Monica Magwayi
Dominique J Pepper
Zahiera Ismail
Charlotte Schutz
Ronnett Sheldon
Nzwaki Bangani
Armin Deffur
Kathy Wood
Graeme Meintjes
Katalin Wilkinson
Robert J Wilkinson

Carnegie corporation