CNS tuberculosis diagnosis and management

Moderators – Dr MMS
Dr SS
Introduction

- As old as history of mankind.
- Odier, Ford described meningeal TB 1790.
- Caused by Mycobacterium tuberculosis (Acid fast bacillus, obligate aerobe)
CNS TB complicate 10% of all tuberculosis.

Always secondary to primary focus elsewhere in body (pulmonary, GIT etc).

Route of dissemination - haematogenous or contagious spread.

Incidence has increased with emergence of HIV infection.
CNS tuberculosis

- Intracranial
  - Parenchymal
  - Meningeal
  - Osseous

- Spinal
  - Parenchymal
  - Meninges
  - Arachnoiditis
  - Osseous
Parenchymal lesion

- Abscess
- Tuberculoma (Micro)
  - Tuberculoma en plaque
  - Tuberculous abscess
  - Cystic tuberculoma
  - Multiple grape like tuberculoma
  - Microtuberculoma
  - Calcified tuberculoma
  - Tubercular encephalopathy
- Meningeal - meningitis + HCP
- Calvarial – osteomyelitis
- Spinal - parenchymal – tuberculoma
  - meningeal - arachnoditis
  - vertebral – pott’s spine
Diagnosis

- Hb/ ESR
- CXR
- Mantoux test
- ELISA
- CSF
- PCR
- Imaging
- Biopsy
Tubercular Meningitis

- Most common manifestation of CNS TB.
- Considered disease of childhood, however in India all age groups susceptible.
- Acute, chronic phase & its sequelae.
- Of neurosurgery interest are sequelae – HCP, tuberculoma or chiasmal arachnoiditis.
- Other sequelae - vasculitis, infarcts.
  
  TBM with HCP
- Invariably occurs after 4-6 weeks.
- Communicating (mostly) or obstructive.
Diagnosis of TBM

- Diagnosis of TBM still pose considerable difficulties.

- Supportive - H/O tuberculosis
  - Hgm / ESR
  - CXR
  - Mantoux test

- CSF analysis – Sugar - low
  - Protein – high
  - Cells - lymphocytosis
Bacteriological test (CSF)

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-N stain</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>18-83%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Limitations – CSF should be examined before or just after start of ATT
- Time for growth – 2-4 weeks.
Molecular and Biochemical assay

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>56%</td>
<td>98%</td>
</tr>
<tr>
<td>ELISA (Antigen)</td>
<td>52-93%</td>
<td>58-98%</td>
</tr>
<tr>
<td>ELISA (Antibody)</td>
<td>38-94%</td>
<td>95-100%</td>
</tr>
</tbody>
</table>

- Rapid and positive after starting treatment.
- Drawback – can’t differentiate acute or chronic infection, cross-reactivity
  - often poor sensitive and specific
**CSF ADA level - >5-15 iu/L**

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>44-100%</td>
<td>10-100%</td>
</tr>
</tbody>
</table>

- High CSF ADA levels- malaria, lymphoma, pyogenic & cryptococcal meningitis, brucellosis.
- Not recommended as routine diagnostic test

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Imaging

- **NCCT:**
  - Scans may be normal
  - Obliteration of basal cisterns by hypo/iso dense exudate
  - En plaque dural thickening
  - Popcorn calcification
  - Hydrocephalus
  - Sequelae of chronic meningitis
    - Infarcts

- **CECT:**
  - Abnormal meningeal enhancement
  - Leptomeningeal enhancement sylvian fissures, tentorium
  - Granulomas in the basal meninges
  - Ependymitis
Imaging

Basal exudates

HCP

Infarct
Exudates along sylvian fissure

Basal exudates enhancement
Periventricular lucency indicates transependymal flow of CSF – a sign of raised ICP; however, in TBM, it could be spread of inflammatory process making it an unreliable sign of raised intraventricular pressure.

R Patir, R Bhatia, Tandon PN. Surgical management of tuberculous infections of the nervous system. Schmidek and Sweet operative neurosurgical techniques 5th edition; 1617-1631
Tuberculous meningitis. Axial contrast-enhanced T1-weighted magnetic resonance (MR) image shows florid meningeal enhancement that is most pronounced within the basal cisterns.
Ahuja and colleague set criteria for clinical diagnosis of TBM based on:
- Clinical feature
- CSF
- CT scan
- Presence of extra neural tuberculosis.

- Definite, Highly probable, Probable and Possible TBM.
- 91% of highly probable & 66% of probable group improved with ATT.

Treatment for TBM

- ATT
- Anti convulsant
- Steroids

- Role of surgery - V-P shunt or ETV
- Optico –chiasmatic decompression for arachnoiditis
### ATT

<table>
<thead>
<tr>
<th>Intensive phase treatment</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months of HRZE(^a)</td>
<td>4 months of HR</td>
</tr>
</tbody>
</table>

\(^a\) WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative PTB or EPTB who are known to be HIV-negative. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin

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Duration of Anti–Tubercular treatment

- Pulmonary and extra pulmonary disease should be treated with the same regimens. Note that some experts recommend 9–12 months of treatment for TB meningitis given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints because of the difficulties of assessing treatment response. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

British infection society recommendation 2009 –
12 months

Indian academy of pediatrics 2010 recommendation –
In patient with TBM on category I Tt, 4 drugs can be used either HRZE or HRZS, continuation phase of TBM Tt should extend for 6-7 months, extending total duration of treatment for 8-9 months.
American thoracic society and centre for disease control (2003) recommendation

TBM and tuberculoma is for 12 months if bacterial strain sensitive.

For MDR TB – 24 months.

For patients who do not receive pyrvinamide in first 2 months extend Tt for 18 months.
Steroids – Dexamethasone should be given to all irrespective of age and stage.


Role of steroids –

- Improve survival and intellectual outcome
- Enhance rate of resolution of basal exudate.

- Kumar Velu and assoc: Randomised control trial of dexamethasone in TBM, Tuber Lung Dis, 5 page 203-207.
- No change in incidence of basal ganglia infarction, ICP.
- Age >14 - Dexamethasone for 4-6 weeks.
- Age <14 – Prednisolone for 8 weeks.

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## British MRC grading for TBM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully conscious, no paresis</td>
</tr>
<tr>
<td>2</td>
<td>Decreased level of consciousness, localizing pain</td>
</tr>
<tr>
<td>3</td>
<td>Deeply comatose ± gross paresis</td>
</tr>
</tbody>
</table>
Role of surgery

TBM with HCP

- V-P shunt OR ETV
Role of ETV

- Success rate of ETV is 77% in 35 patient with 60% had early and 17% delayed recovery.


- 68% benefited from ETV

  Hussain et al., neurosurgery review 2005, role of neuroendoscopy in management of patient with TBM

- Success rate for ETV 73.1%

  *J. Neurosurg.: Pediatrics / Volume 3 / May 2009*
Success rate of ETV depend upon –
Stage of disease (I & II)
Presence of cisternal exudates
Duration of pre-op ATT (4 weeks)

Surgical outcome of tuberculous meningitis hydrocephalus treated by endoscopic third ventriculostomy: prognostic factors and postoperative neuroimaging for functional assessment of ventriculostomy
Prognosis of TBM

- Based on Palur et al (mean follow up 45.6 months)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>20%</td>
</tr>
<tr>
<td>II</td>
<td>34.7%</td>
</tr>
<tr>
<td>III</td>
<td>51.9%</td>
</tr>
<tr>
<td>IV</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Grade of TBM at time of admission is most significant factor determine outcome.
CNS Tuberculoma

- Mostly cortical and subcortical
- In children mostly posterior fossa is involved, while in adult supratentorial compartment is common
- Can occur at brainstem, thalamus, pituitary gland
### Tuberculoma

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUPRATENTORIAL</strong></td>
<td>78</td>
</tr>
<tr>
<td>PARIETAL</td>
<td>28</td>
</tr>
<tr>
<td>FRONTAL</td>
<td>26</td>
</tr>
<tr>
<td>TEMPORAL</td>
<td>15</td>
</tr>
<tr>
<td>BG / THALAMUS</td>
<td>4</td>
</tr>
<tr>
<td>SELAR/SUPRASELLAR</td>
<td>4</td>
</tr>
<tr>
<td>ORBITAL FISSURE</td>
<td>1</td>
</tr>
<tr>
<td><strong>INFRATENTORIAL</strong></td>
<td>50</td>
</tr>
<tr>
<td>CEREBELLUM</td>
<td>44</td>
</tr>
<tr>
<td>CP ANGLE</td>
<td>3</td>
</tr>
<tr>
<td>TENTORIUM</td>
<td>1</td>
</tr>
<tr>
<td>BRAINSTEM</td>
<td>2</td>
</tr>
</tbody>
</table>

R Patir, R Bhatia, Tandon PN. Surgical management of tuberculous infections of the nervous system. Schmidek and Sweet operative neurosurgical techniques 5th edition; 1617-1631
CT appearance of tuberculoma

- Cerebritis stage – hypodense lesion with out of proportion edema.
Posterior fossa lesion

Mature tuberculoma
Immature Tuberculoma -
with out contrast – iso to hyper dense area, with edema
With contrast – either ring or nodular or irregular enhancement

Mature tuberculoma – well enhancing ring or disc shape lesion with perilesional edema, target sign, calcification seen often.
Sensitivity of CT – 100%, specificity – 85.7% and positive predictive value - 33%.
Caseating tuberculosis granuloma involving the left temporal lobe. CECT shows a rim-enhancing lesion in the left temporal lobe consistent with a caseating tuberculosis granuloma.
Imaging (MRI tuberculoma)

- T1: isointense
- T2: central hyper with hypo ring
- Marked thin rim enhancement
- Hypo on T2: fibrosis, gliosis, macrophage infiltration
MRI appearances

T1 MRI – isointense lesion in Left parietal area
hypointense lesions in the bilateral gangliathalamic regions

centrally hyperintense granuloma with a peripheral hypointense rim.
Par enchymal tuberculosis. contrast-enhanced T1-weighted MR image demonstrates multiple enhancing caseating and non-caseating tuberculomas, predominantly within the left frontal and parietal lobes.
Milliary CNS tuberculosis. Axial contrast-enhanced T1-weighted MR image shows multiple small high-signal-intensity foci within both cerebral hemispheres.
Tubercular abscess

- 4-8% of all patients with CNS TB, and 20% of all patients with HIV infection.

- MRS for TB abscess – lipid and phosphoserine
- Pyogenic abscess - lactate
Figure 15. Tuberculosis abscess and granulomas in a 21-year-old woman. (a) Axial T2-weighted magnetic resonance imaging reveals a large hypointense left cerebellar lesion with associated oedema. Another small low-signal lesion containing a central dot-like high signal is noted in the right cerebellar hemisphere (arrow), also with surrounding hyperintense oedema. (b) Axial T1-weighted magnetic resonance imaging after intravenous gadolinium injection reveals a uniformly thin smooth wall of enhancement surrounding the large left cerebellar lesion consistent with a tuberculosis abscess, and solid nodular enhancement of several contiguous tuberculosis granulomas. The tiny right cerebellar lesion shows rim enhancement and is consistent with a caseating soft tuberculous granuloma.
Treatment of tuberculoma

- Medical therapy –
  - ATT
  - Anti epileptics
  - Steroids

- Role of Surgery -
  - Vision or life threatened by mass effect
  - Failure of response to medical therapy
  - Paradoxical increase in lesion size with therapy
  - Diagnosis in doubt
Anti Tubercular Treatment

- Intensive phase - HRZE (3-4 months)
- continuation phase - HR (12-16 months)
- Pyridoxine
Duration of treatment

6 months


12 months


18 months or Longer

Rate of radiological resolution of intracranial tuberculoma

<table>
<thead>
<tr>
<th>Series</th>
<th>duration of ATT</th>
<th>residual lesions %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang 1996 (16)</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Rajeshwari 1995 (6)</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Awada 1998 (2)</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

- In all above studies diagnosis is based on imaging.
Rate of resolution of histopathologically proven tuberculoma with ATT

- Duration of ATT – 9 months - 18.2% complete resolution
  - 18 months - 69.2% residual lesion
  - 24 months - 54% complete resolution
Duration of ATT must be tailored to radiological response of lesion to therapy, pt’s clinical status should not govern the discontinuation of drugs.

The radiological findings should dictate the continuation or termination of ATT or the administration of alternative drugs.

Size of lesion (4 cms) and extent of surgical resection can affect duration of treatment.

## Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Contraindication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Drug induced liver disease</td>
<td>Hepatotoxicity, peripheral neuritis, optic neuritis, convulsion, lupus syndrome</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Jaundice, pregnancy</td>
<td>Liver toxicity, GI disturbances</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuritis</td>
<td>Optic neuritis, color blindness, peripheral neuritis</td>
</tr>
<tr>
<td>Pyrizinamide</td>
<td></td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Pregnancy</td>
<td>Ototoxicity, renal damage</td>
</tr>
</tbody>
</table>
## Second-line drugs

<table>
<thead>
<tr>
<th>Group</th>
<th>Drugs (abbreviations)</th>
</tr>
</thead>
</table>
| **Group 1:** First-line oral agents | • pyrazinamide (Z)  
• ethambutol (E)  
• rifabutin (Rfb)                                                                                       |
| **Group 2:** Injectable agents      | • kanamycin (Km)  
• amikacin (Am)  
• capreomycin (Cm)  
• streptomycin (S)                                                                                   |
| **Group 3:** Fluoroquinolones      | • levofloxacin (Lfx)  
• moxifloxacin (Mfx)  
• ofloxacin (Ofx)                                                                                   |
| **Group 4:** Oral bacteriostatic second-line agents | • para-aminosalicylic acid (PAS)  
• cycloserine (Cs)  
• terizidone (Trd)  
• ethionamide (Eto)  
• protionamide (Pto)                                                                                   |
| **Group 5:** Agents with unclear role in treatment of drug resistant-TB | • clofazimine (Cfz)  
• linezolid (Lzd)  
• amoxicillin/clavulanate (Amx/Clv)  
• thioacetazone (Thz)  
• imipenem/clastatin (Ipm/Cln)  
• high-dose isoniazid (high-dose H)  
• clarithromycin (Clr)                                                                                   |

Use at least 4 drugs

*Use any of the first-line oral agents (Group 1) that are likely to be effective.*  
*Use an effective aminoglycoside or polypeptide by injection (Group 2).*  
*Use a fluoroquinolone (Group 3).*  
*Use the remaining Group 4 drugs to complete a regimen of at least four effective drugs.*  
*For regimens with fewer than four effective drugs, consider adding two Group 5 drugs. The total number of drugs will depend on the degree of uncertainty, and regimens often contain five to seven.*
Role of surgery

- Life threatening edema
- Risk of vision loss
- Diagnosis is in doubt
- No response to drugs clinically and radiologically
- Obstructive HCP
Principles of surgery

- Non eloquent areas total excision (small lesion)
- Subtotal/partial excision (eloquent cortex)
- Conservative excision around vital structures
- Evacuation of central liquifactive portion in deep seated lesions.
Thank you