TUBERCULER MENINGITIS
INTRODUCTION

Tuberculosis

- Tuberculosis
  - major global health problem

- 2nd leading cause of death from an infectious disease worldwide - after HIV

- In 2013
  - 9.0 million new TB cases
  - 1.5 million TB deaths
• Central nervous system (CNS) disease caused by Mycobacterium tuberculosis is an uncommon yet highly devastating manifestation of tuberculosis.

• Infection of the CNS is one of the most devastating clinical manifestations of tuberculosis.
EPIDEMIOLOGY

• Approximately 95% of tuberculosis cases occur in the developing world.

• Worldwide (2013) -- 8.7 million incident cases,
  -- 12 million prevalent cases,
  -- 1.4 million deaths from tuberculosis

• The WHO estimates that in 2013 - 550,000 childhood cases and 80,000 tuberculosis-associate deaths among non–HIV-infected children.

• India accounts for 1/5 of the global TB burden.

• The global burden is influenced by - the HIV pandemic;
  - the development of MDR tuberculosis.
  - the disproportionate access of populations in low-resource settings
## BURDEN OF TB - INDIA 2014

<table>
<thead>
<tr>
<th>TB burden</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>2.2 million</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.27 million</td>
</tr>
</tbody>
</table>
MYCOBACTERIA

• Discovered by Robert Koch at Berlin on 24\textsuperscript{th} March 1882.

• 24\textsuperscript{th} March is World Tuberculosis day.

• \textit{M. tuberculosis} is pathogenic for humans.

• Slender, non-spore-forming, non motile, pleomorphic, weakly Gram-positive curved rods 1-5 μm long.

• Habitats - water or soil or intracellular pathogens of animals and humans.

• Aerobes grows in tissues with a high oxygen content - lungs.
• They are obligate aerobes that grow in synthetic media containing glycerol and ammoniums alts (LJ Media).

• Grow slowly, with a generation time of 12-24 hr.

• Mycobacteria grow best at 37-41°C (98.6-105.8°F).

• A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement.

• **Acid fastness—the capacity to form stable mycolate** complexes with arylmethane dyes (crystal violet, carbol fuchsin, auramine, and rhodamine) and resist discoloration with ethanol and hydrochloric or other acids.
TERMINOLOGY

• **Exposure**: a child has had significant contact ("shared the air") with an adult or adolescent with infectious tuberculosis but lacks proof of infection. Tuberculin skin test (TST) or interferon-γ release assay (IGRA) result is negative.

• **Infection**: the individual inhales droplet nuclei containing M. tuberculosis, which survive intracellullarly within the lung and associated lymphoid tissue. The hallmark of tuberculosis infection is a positive TST or IGRA result.

• **Disease**: signs or symptoms or radiographic manifestations caused by M. tuberculosis become apparent
TRANSMISSION OF M. TUBERCULOSIS

• Spread by droplet nuclei

• Transmission is by inhalation of airborne mucus droplet nuclei, particles 1-5 μm in diameter that contain bacilli.

• Close contacts at highest risk of becoming infected

• Transmission occurs from person with infectious TB disease (not latent TB infection)

• Young children with tuberculosis rarely infect other children or adults.
PATHOGENESIS

• By inhalation of infected droplets containing Mycobacterium

• Deposited in distal bronchiole or alveoli

• Alveolar macrophages phagocytose but not able to kill the bacilli

2-4 weeks later
PATHOGENESIS

• Cell mediated response develops

• CD4 helper T Cells appear and activate the macrophages

• Low level bacteremia leads to seeding of distant foci by the hematogenous spread to the areas of rich vascular supply like brain

• Activated macrophages phagocytose and kill the Tubercle bacilli
PATHOGENESIS

1. Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

2. Tubercle bacilli multiply in the alveoli.

3. A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the lungs, kidneys, brain, or bone).

4. Macrophages form a hard shell & keeps bacilli under control.

5. Hard shell breaks down and tubercle bacilli escape and multiply (in this example, TB disease develops in the lungs).
LYMPHO HEMATOGENOUS SPREAD

- CNS involvement in 2-6 months
- Endobronchial TB in 3-9 months
- Bone and joint lesion after several years
- Renal
EVOLUTION OF TBM

• Usually as hematogenous spread.

• May also result from direct rupture or extension of a subependymal or subpial focus (Rich focus) and may be located in the meninges, brain or direct extension from cerebrospinal fluid (CSF) infection

• Location of these foci and the capacity to control them ultimately decide the form of CNS Tuberculosis.
PATHOGENESIS

• TB Bacillemia (primary or late reactivation)
  → subependymal tubercles
  → rupture into the subarachnoid space
  → meningitis.

• Dense gelatinous exudate develops at the base of the brain
  → surround arteries and CN at the base of the brain
  → hydrocephalus, vasculitis
  → infarction, hemiplegia, quadriplegia
Tuberculous Meningitis. Donald and Shoerman, NEJM. 351:17. 10/21/2004
TB – HOW TO APPROACH

- Step 1: Detailed history
- Step 2: Thorough clinical examination
- Step 3: Investigation
- Step 4: Treatment
Always secondary to primary tuberculosis.

• Tuberculous meningitis complicates approximately 0.3% of untreated tuberculosis infections in children.

• Neuro TB occurs in all ages

• Most common between 6 mo-4 years of age
1ST STAGE - PRODROME STAGE / STAGE OF INVASION

• lasts 1-2 wk and is characterized by nonspecific symptoms
  - such as fever, headache, irritability, drowsiness, and malaise.
  - Anorexia & vomiting may be present.
  - Child may present with head banging and resents exposure to sunlight.

Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones.
2ND STAGE – STAGE OF MENINGITIS

- Begins more abruptly.
- The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs.
- The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis.
- Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment.
Kernig’s sign
Brudzinski’s neck sign
3RD STAGE – STAGE OF COMA

- Loss of consciousness, rise of temp and altered respiratory pattern
- Pupils are dilated, often unequal with nystagmus and squint.
- Ptosis and ophthalmoplegia.
- Progression of disease -- coma deepens, episodic decerebration, Chyne Stokes breathing, bradycardia and eventually death
DIAGNOSIS

• Mainly by indirect evidences due to
  – Paucibacillary nature of the infection in children
  – Requirement of sophisticated instruments
  – More false positive results
  – Cost factor
INVESTIGATIONS

Direct evidence

• Detection - M. Tb
• Demonstrate AFB in sputum / body fluids / nodes
• Grow AFB in culture – solid / liquid
• Detect AFB using nucleic acid amplification

Indirect evidence

• Biochemical markers
• Immunological techniques
• Supportive investigations – Tuberculin test
• Blood examination
• Radiology
• Family screening
## CSF EXAMINATION: LUMBAR PUNCTURE

<table>
<thead>
<tr>
<th></th>
<th>Tuberculous meningitis</th>
<th>Acute bacterial meningitis</th>
<th>Partially treated bacterial meningitis</th>
<th>Viral meningitis or meningoencephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRESSURE (mm H2O)</strong></td>
<td>Normal 50-80</td>
<td>Usually elevated 10-500</td>
<td>Normal or elevated</td>
<td>Normal or slightly elevated (80-150)</td>
</tr>
<tr>
<td></td>
<td>10-500</td>
<td>Usually elevated (100-300)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEUKOCYTES (mm3)</strong></td>
<td>≥ 75% Lymphocytes</td>
<td>100-10,000 or more; usually 300-2,000; PMNs predominate</td>
<td>5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time</td>
<td>Rarely &gt; 1,000 cells.</td>
</tr>
<tr>
<td>&lt; 5, ≥ 75% Lymphocytes</td>
<td>; PMNs early, but lymphocytes predominate</td>
<td>100-10,000 or more; usually 300-2,000; PMNs predominate</td>
<td>5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time</td>
<td>Rarely &gt; 1,000 cells.</td>
</tr>
<tr>
<td><strong>PROTEIN (mg/dL)</strong></td>
<td>100-3,000 may be higher in presence of Block.</td>
<td>Usually 100-500</td>
<td>Usually 100-500</td>
<td>Usually 50-200</td>
</tr>
<tr>
<td>20-45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLUCOSE (mg/dL)</strong></td>
<td>&lt; 50 in most cases; decreases with time if treatment is not provided.</td>
<td>Decreased, usually &lt; 40 (or &lt; 50% serum glucose)</td>
<td>Normal or decreased</td>
<td>Generally normal; may be decreased to &lt; 40 in some viral diseases,</td>
</tr>
</tbody>
</table>
CONTRAINDICATION FOR LP

- Increase intracranial pressure.
- Unstable patient.
- Skin infection at site of LP.
- Thrombocytopenia.
- Papilledema.
• ZN tech - AFB + if > 10,000 bacilli /ml.
• Rapid detection (< 1 hr.)
• Low cost
• High operator dependence
• Labor intensive
• Do not differentiate live/ dead AFB/ NTM
– CBNAAT (Genexpert TB) - endorsed by WHO
  • Heminested, cartridge based real time PCR

– Detects M Tb & Rifampin resistance -105 minutes

<table>
<thead>
<tr>
<th>Method</th>
<th>Direct smear</th>
<th>Culture</th>
<th>CBNAAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum no. of bacilli needed / ml</td>
<td>10,000/ml</td>
<td>100/ml</td>
<td>131/ml</td>
</tr>
<tr>
<td>Time to get result</td>
<td>1 hour</td>
<td>42 days (MGIT)</td>
<td>2 hours</td>
</tr>
</tbody>
</table>
IMAGING AND RADIOLOGY

- Brain imaging –
  - basilar enhancement
  - communicating hydrocephalus with signs of
  - cerebral edema or early focal ischemia
  - Tuberculoma.

- CT SCAN

  Helpful with diagnosis of CNS tuberculosis and bone

- MRI

  Contrast- enhanced MRI Considered to be superior to CT in detecting and assessing CNS Tuberculosis.

  Limitation is the limited availability and affordability.
Axial contrast-enhanced T1-weighted magnetic resonance (MR) image showing florid meningeal enhancement

Tuberculous meningitis.
Parenchymal tuberculosis.

Axial contrast-enhanced T1-weighted magnetic resonance (MR) image shows florid meningeal enhancement

Burrill J et al. Radiographics 2007;27:1255-1273
CT OF TUBERCULOMA
• Axial contrast-enhanced T1-weighted MR image shows multiple small high-signal-intensity foci within both cerebral hemispheres.

Miliary CNS tuberculosis.
CHEST RADIOGRAPH....ADJUNCTIVE IN DX

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
  - sometimes Miliary pattern

- May have unusual appearance in HIV-positive persons

- Cannot confirm diagnosis of TB

Arrow points to cavity in patient's right upper lobe.
Miliary TB

Hilar and Mediastinal Adenopathy
MANTOUX TEST (TST)

• Type IV hypersensitivity reaction
• 2 tuberculin unit [TU] PPD RT23 with Tween 80 read 48-72 hrs after intradermal injections

**Positivity:**
Induration 10 mm / more – immunocompetent
Induration 5 mm / more – immunosuppressed
Erythema – don’t take it as positive test

• If child does not turn for results - positive results can be read within 7 days
MANTOUX TEST (TST)

- False negative - infants, HIV positive / immuno-compromised children, malnutrition extensive or miliary TB.

- False positive – retesting same site, non-tuberculous (environmental) mycobacteria, higher strengths used
DIAGNOSIS - CONTACT TRACING

• Any person on anti tuberculosis treatment is considered as a contact for a period of two years
  b) Tuberculin test
  c) Bacteriological evidence
BIOCHEMICAL MARKERS

• Adenosine deaminase (ADA) –
  – level co–relates with proliferation and differentiation of lymphocytes.
  – Normal levels – 13 – 60 units / ml

• Bromide partition test –

• High performance liquid chromatography

• Tuberculostearic acid detection by gas chromatography
IMMUNODIAGNOSIS

• Antibody detection
  – Antibodies to crude antigen/ specific antigen (35 KDa, P 64, P 32, 38 KDa etc)

• Antigen detection
  – Protein antigens : using polyclonal antibodies / monoclonal antibodies
  – ELISA / RIA test used
CULTURE

• Solid Media –
  – Lowenstein – Jensen Medium,
  – Dorsets Medium,
  – Petroff’s Medium

• Liquid Media – Middle – brooks Medium

• Disadvantages
  – Difficult to collect  CSF & others,
  – Takes 2 – 8 weeks for result,
  – Only 5% results come true positive
RECENT CULTURE TECHNIQUES.

- Bactec:
  - Radiometric culture system
  - Duration time 8 – 14 days
  - Radiolabelled substrate is used
  - Growth of AFB is detected radiometrically by measuring the metabolite radiolabelled CO2 that is released
- Septicheck: modified middlebrok broth used
- Rapid slide culture method
- Mycobacterium growth inhibitor tubes
- **Remember**
  WHO has cautioned regarding the molecular and genetic testing.
DIFFERENTIAL DIAGNOSIS

- Incompletely treated Bacterial meningitis
- Fungal Meningitis
  - Crypto, Histo, Blasto, Cocci
- Viral meningoencephalitis – HSV, Mumps
- Parameningeal Infection
  - Sphenoid sinusitis, brain abscess, spinal epidural abscess
- Neurosyphilis
- Neoplastic Meningitis – Lymphoma
- Neurosarcoid
TREATMENT: ANTIMICROBIAL THERAPY

• Same Guidelines as those for pulmonary TB

• Tuberculous meningitis, initial hospitalization is recommended.

• Ethambutol is replaced by streptomycin in the intensive phase and continuation phase of the treatment is for 7 months.

• Steroids as adjunctive therapy may be useful in pericardial and meningeal tuberculosis.
Intensive Phase:

4 drug regimen of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol or Streptomycin for 2 months. (2HRZE)

Continuation Phase:

– Isoniazid and Rifampicin for another 7 – 10 months (10HR).

- Management of Complication
## DRUG & DOSAGES

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Thrice a week</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>15 mg/kg</td>
<td>10 mg/kg (max 300 mg)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>15 mg/kg</td>
<td>10 mg/kg (max 600 mg)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>35 mg/kg</td>
<td>30-35 mg/kg (max 2000 mg)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>30 mg/kg</td>
<td>20-25 mg/kg (max 1500 mg)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15 mg/kg</td>
<td>15 mg/kg (max 1 g)</td>
</tr>
</tbody>
</table>
DIRECTLY OBSERVED TREATMENT SHORT COURSE (DOTS)

Six weight bands and three patient wise boxes

- 6 - 8 kg
- 9 - 12 kg
- 13 - 16 kg
- 17 - 20 kg
- 21 - 24 kg
- 25 - 30 kg
<table>
<thead>
<tr>
<th>Weight</th>
<th>INH</th>
<th>RMP</th>
<th>EMB</th>
<th>PYZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 - 8</td>
<td>100</td>
<td>100</td>
<td>200</td>
<td>250 (x 1)</td>
</tr>
<tr>
<td>9 -12</td>
<td>150</td>
<td>150</td>
<td>300</td>
<td>400 (x 1½)</td>
</tr>
<tr>
<td>13 -16</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>500 (x 2)</td>
</tr>
<tr>
<td>17-20</td>
<td>250</td>
<td>250</td>
<td>500</td>
<td>650 (x 2½)</td>
</tr>
<tr>
<td>21-24</td>
<td>300</td>
<td>300</td>
<td>600</td>
<td>750 (x 3)</td>
</tr>
<tr>
<td>25-30</td>
<td>400</td>
<td>400</td>
<td>800</td>
<td>1000 (x 4)</td>
</tr>
</tbody>
</table>
INH

- Introduced in the year 1952
- Inhibits the synthesis of mycotic acid in mycobacterial cell wall- bactercidal drug
- Dose: 15mg/ kg  Max: 300mg/day
- Hepatotoxicity, peripheral neuritis - but rare in pediatric age
RIFAMPICIN

- Introduced in the year 1962
- It inhibits RNA synthesis in mycobacteria
- Bactericidal drug
- Well absorbed in empty stomach
- Dose - 10mg/kg  Max: 450mg/day
- INH and Rifampicin always combined for beneficial effect
- Hepato toxic drug
PYRIZINAMIDE

• Introduced in the year 1947
• Sterilizing drug
• Bactericidal drug more effective in caseous acidic medium
• Resistance develops quickly
• Dose: 35mg/kg
• Side effects: elevation of uric acid
ETHAMBUTOL

- Introduced in the year 1952
- Bacteriostatic drug
- Dose: 30mg/kg  Max: 800mg/day
- Side effects: Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity.
- The side effects of all these 4 drugs are reversible
STREPTOMYCIN

• It is an aminoglycoside.

• Bactericidal drug.

• Dose : 15mg/kg ; max : 1g

• Side Effects : Auditory and vestibular toxic effects, nephrotoxic effects, rash
TREATMENT

Adjunctive steroid therapy

All patients regardless of stage/severity of the disease
To decrease neurologic sequelae and mortality
Lowering the intracranial pressure limits tissue damage and favors circulation of anti-tuberculosis drugs through the brain and meninges.
2mg/kg/24 hours of prednisolone for 6-8 weeks at the start of treatment starting 3 days after initiation of anti tuberculosis therapy.
II  LINE OF DRUGS

For MDRTB,

• Six drugs—
  kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine during 6–9 months of the intensive phase and

• Four drugs—levofloxacin, ethionamide, ethambutol and cycloserine during the 18 months of the continuation phase.
COMPLICATIONS

• The most common complication is communicating hydrocephalus, which can be seen at both MR imaging and CT and is caused by blockage of the basal cisterns by inflammatory exudates.

• Rarely non-communicating hydrocephalus occurs due to the mass effect of a tuberculoma causing the obstruction of CSF flow.

• Ischemic infarcts are also a common complication, being seen in 20%–40% of patients at CT, mostly within the basal ganglia or internal capsule regions and resulting from vascular compression and occlusion of small perforating vessels.
TREATMENT OF COMPLICATIONS:

Convulsions:
• Benzodiazepines and phenytoin

Cerebral edema:
• Initial therapy is with 20% Mannitol: 5ml/Kg IV over 15 minutes, f/b 3ml/kg 6th hrly till 48 hrs.
• I.V. Dexamethasone can then be used 0.15mg/kg/dose 6 hourly.
• Fluids – restricted to 2/3rd maintenance.
• Great care to be taken to maintain BP.
• Other drugs – Acetazolamide 20-50mg/kg/day in 3-4 doses
  oral glycerol 1ml/kg/dose
PROGNOSIS AND OUTCOME

If left untreated, its course is characterized by confusion and progressively deepening stupor and coma, coupled with cranial nerve palsies, pupillary abnormalities, foci neurologic deficits, raised ICP and decerebrate postures.

Fatal outcome then follows within 4 to 8 weeks at the onset.
PROGNOSIS

• Overall Poor
• Pts presenting in Stage I have 19% mortality
• Pts presenting in Stage III have 69% mortality
• Only 1/3 - 1/2 of patients demonstrate complete neurologic recovery
• Up to 1/3 of patients have residual severe neurologic deficits such as hemi paresis, blindness, seizure DO
• Most patients in the 3rd stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation.
• Prognosis for young infants is generally worse than for older children
PREVENTION

• BCG Vaccination provides protection against the CNS Tuberculosis with an efficacy of 75—85%.

REMEMBER

• History of BCG vaccination does not eliminate the need to investigate for CNS Tuberculosis in the right clinical situations.
REFERENCES

• Nelson textbook
• Basic of pediatrics
• WHO recommendations
• E-medicine
THANK YOU