Tuberculosis in Children

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27-28 July 2013
Case scenario

- Name: EL
- Male
- DOB 29.9.2008 Age 4 years 4 months+
- Date of Admission: 20.2.2013
- Date of Discharge: 15.3.2013
- Referred case from Sarikei Hospital
Case scenario

Presenting History:

• Fever & headache since 14-2-2013, 6 days prior to admission
• No improvement with antibiotics, reduced oral intake and lethargy
• His condition worsened 1 day prior to admission, developed nausea & vomiting, inability to walk, altered consciousness and abnormal behaviour.

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Case scenario

On examination,

- GCS 13/15 (E3V4M6), Temp 37.8 HR 93 BP 115/75
- Confused, incoherent talk, unable to recognize parents
- Neck stiffness noted, no focal neurological signs.
- Rest of examination: unremarkable

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Case scenario

Initial investigations:

FBC:  Hb 11.7  TWC 26.0  Platelet: 815
     ESR 20
BUSE:  Na 128  K 2.9  Cl 89  BU 2.1  Cr 42
LFT:  TSB 7.3  AST 25  ALT 12  Alb 44  ALP 154
CXR:  normal
Mycoplasma serology: 1:40
Mantoux test (TST): no induration

Provisional diagnosis: Encephalitis ? SOL

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CXR on admission
Case scenario

- **Urgent CT scan of brain (20.2.2013):** Communicating hydrocephalus

- **Lumbar puncture after CT brain:** CSF clear & colourless
  - Direct smear: no gram organism seen
  - Total cells 25, all lymphocytes,
  - Protein 1.36 g/l (0.10-0.54),
  - Glucose 1.9 mmol/l RBS 6.6 Cl 101
  - Latex agglutination: negative
  - Indian ink: negative
  - Culture: no growth
  - CSF AFB & MTB PCR: negative

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CT scan of brain on admission
Case scenario

- **Urgent CT scan of brain (20.2.2013):** Communicating hydrocephalus

- **Lumbar puncture after CT brain:** CSF clear & colourless
  - Direct smear: no gram organism seen
  - Total cells 25, all lymphocytes,
  - Protein 1.36 g/l (0.10-0.54),
  - Glucose 1.9 mmol/l RBS 6.6 CI 101 (120-130)
  - Latex agglutination: negative
  - Indian ink: negative
  - Culture: no growth
  - CSF AFB & MTB PCR: negative

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Case scenario

- Empirical treatment for TB meningitis
- EHRZ plus pyridoxine
- Day 3 anti-TB, persistent vomiting
- Repeated CT scan of brain (23.2.2013): Communicating hydrocephalus as on 20.2.2013
- Oral prednisolone added, later changed to IV Dexamethasone for a few days.

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Case scenario

- Day 6 anti-TB, noted worsening neurology with unequal pupils & R 6\textsuperscript{th} /7\textsuperscript{th} cranial nerves palsy and slurred speech.
- **Urgent MRI brain on 27.2.2013:**
  1. Meningeal enhancement of basal cisterns and the cranial sheath, in keeping with TB meningitis with resulting hydrocephalus
  2. R sided pontine acute lacunar infarct which could be due to arteritis as a result of meningitis

Subsequently, his condition improved and discharged on 15.3.2013, ambulating but residual CN palsy.

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MRI brain: Basal meningeal enhancement
MRI brain: R sided pontine acute lacunar infarct
MRI brain: R sided pontine acute lacunar infarct
Case scenario

Child diagnosed as TB meningitis based on:

1. **CSF findings:** Total cells **25**, all lymphocytes,
   - Protein **1.36 g/l** (0.10-0.54),
   - Glucose **1.9 mmol/l** RBS 6.6  Cl 101 (120-130)
   - Latex agglutination: negative
   - Indian ink: negative
   - Culture: no growth

2. **CT scan & MRI scan findings**
   *However, diagnosis is still not confirmed:*
   - CSF AFB & MTB PCR: **negative**
   - CXR: **normal**
   - Mantoux test (TST): no induration (anergy)
   - ESR **20**

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Case scenario

• Despite of no ill contacts in the history,
• Screen the mother:
  • CXR: multiple cavitary lesions in both lung fields
  • Sputum AFB: 3+
  • Sputum C&S: M. tuberculosis complex susceptible to Streptomycin, Isoniazide, Rifampicin, Ethambutol

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Learning points about TB in children:

1. After exposure to MTB, higher risk of progression to tuberculosis disease (up to 40% in children <1 year old) when compared to adults (5-10% only).

2. Young children < 5 are at risk of severe forms of tuberculosis when compared to adults.
   ** BCG vaccine has estimated protective effect in young infants 60-80%
   More significantly is its effect in preventing tuberculous meningitis and disseminated disease

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Learning points about TB in children:

3. Young children with tuberculosis secretes few AFB (pauci-bacillary) when compared to adult with lung cavities / secretes ++++AFB
   ** Young children contribute little to disease transmission within the community.

4. The laboratory confirmation of tuberculosis in children is relatively difficult when compared to adults.
   ** Sputum microscopy is positive in <10-15% of children with probable PTB (adult 60%)

   ** Information from source case (esp culture and susceptibility results) help to guide therapy

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Risk Factors For TB Disease

- Poverty & malnutrition
- Overcrowding
- Poor access to Health Care
- HIV infection
- Young age < 3 years
Pathophysiology of Tuberculosis

• **Exposure stage** – the child ‘shares the air’ with an adult with infectious PTB and may have breathed in M. tuberculosis into the lungs but there are no clinical manifestation & tuberculin skin test (TST) remains negative.

• Young children are treated at the exposure stage (*Exposure (window) prophylaxis*) because progression to disease may occur rapidly.
**Perinatal Exposure**

- **Prophylaxis for Infants with Maternal TB after congenital or perinatal tuberculosis disease is ruled out**

<table>
<thead>
<tr>
<th>Active PTB diagnosed before delivery</th>
<th>Active PTB diagnosed after delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear negative just before delivery</td>
<td>Smear positive just before delivery</td>
</tr>
<tr>
<td>No prophylaxis for infant</td>
<td>Give prophylaxis: Isoniazid for six months OR isoniazid for three months followed by TST</td>
</tr>
<tr>
<td>BCG at birth</td>
<td>Defer BCG at birth, give after stopping isoniazid</td>
</tr>
</tbody>
</table>

BCG should not be given to babies on prophylactic tuberculosis (TB) treatment.

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Breastfeeding and Mother with PTB

• Breastfeeding mothers with TB should receive a full course of antiTB drugs
• First-line antiTB drugs are safe in breast feeding
• Mother and baby should stay together for continuation of breastfeeding if mother is on treatment and is non-infective.
• Women on isoniazid and breastfeeding should receive pyridoxine.

• If mother has active PTB and is still infectious: the newborn should be separated from mum for at least 2 weeks (till non-infective); avoid breastfeeding but EBM can be given.

*congenital TB is rare but should be suspected if the infant born to a tuberculous mother fails to thrive or symptomatic
Pathophysiology of Tuberculosis

• **Latent tuberculosis infection (LTBI)** is defined as infection with the tubercle bacilli without signs and symptoms or radiographic evidence of tuberculosis (TB) disease.

• Replication of M. tuberculosis has occurred in the body (lungs), but no clinical symptoms & signs and CXR normal.
Latent TB Infection (LTBI)

Fig 1 Ghon focus (top); asymptomatic healing (bottom)

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Latent TB Infection (LTBI)

• Diagnostic Tests For Latent TB Infection
  • Tuberculin skin test (TST) should be used as a standard test to diagnose latent tuberculosis infection (LTBI) in children.
  
  • Interferon Gamma Release Assay (Blood test) should not be used as a replacement for TST in diagnosing LTBI in children.

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Rationale for treating LTBI in children (chemoprophylaxis)

1. Young children are at greater risk of progression from latent infection to TB disease once infected:
   • Infants are at an especially high risk; up to **40%** develop disease without treatment.
   • In addition, children less than 5 years of age are at high risk for **developing severe forms of disease** once infected.

2. Infection is likely to be recent.

3. Medications used to treat LTBI are well tolerated by children and there is a low risk of toxicity.

4. Children have more years to potentially develop TB disease
## AntiTB Regimens for LTBI in Children

### Treatment of LTBI in non-HIV infected children

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
</tr>
<tr>
<td>Isoniazid + rifampicin</td>
<td>3 months</td>
<td>Daily</td>
</tr>
</tbody>
</table>

***Active TB must be ruled out before starting LTBI regimen.***

### Treatment of LTBI in HIV-infected children

WHO recommends 6-months isoniazid therapy

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Pathophysiology of Tuberculosis

- **Tuberculous disease** – clinical manifestations by clinical symptoms & signs, by CXR or by other diagnostic techniques

- Symptomatic primary infection or
- Endogenous reactivation after primary infection
- Exogenous reinfection
Pathophysiology of Tuberculosis

Reactivation TB:

Fig 2 Tuberculosis after primary infection
Tuberculous disease

Symptomatic primary infection:

• Develops about 4-5 weeks after primary infection (any of pneumonia, pleural effusion, or lobar collapse)
• Adolescents present like adults, with cough, haemoptysis, fever, night sweats, and weight loss.
• Symptoms in young children are fairly non-specific - fever, anorexia, and weight loss, with or without cough
• Children can develop substantial hilar lymphadenopathy, which may compress the bronchi, leading to obstruction and lobar collapse, especially of the middle lobe (Brock’s syndrome).
• Infants and children with HIV infection can spread through the bloodstream, or less commonly lymphatics, can result in disseminated disease and / or TB meningitis.
Tuberculous disease

**Tuberculosis after primary infection:**

- After asymptomatic healing, tuberculosis can recur at any time, often manifesting as apical cavitation.
- This can either be by endogenous reactivation or exogenous reinfection.
- Endogenous reactivation occurs when dormant bacteria establish infection if the child becomes severely malnourished or immunosuppressed (AIDS or vitamin D deficiency).
- Exogenous reinfection is more common in areas of high tuberculosis.
Clinical features

• Pulmonary TB is commonest:
  - symptoms include fever, cough, weight loss, night sweats, respiratory distress

• Extrapulmonary disease:
  - depends on site of infection

  CNS: prolonged fever, apathy, weight loss, enlarged lymph nodes, headaches, vomiting, increasing drowsiness, infant may stop vocalizing.

  Bone, joint or Spine: Swellings and loss of functions

• Hypersensitivity reactions of TB disease:
  - pleural effusion, phlyctenular conjunctivitis, erythema nodosum
Diagnosis of childhood TB

- Children suspected of pulmonary tuberculosis should have sputum examination, chest x-ray and tuberculin skin test performed.

- Gastric lavage/aspiration should be performed in infants and children who are unable to expectorate sputum. (Grade C)
Chest radiograph showing hilar lymphadenopathy

Chest radiograph showing apical consolidation and cavitation

Chest radiograph showing “snow storm” appearance of miliary tuberculosis

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Laboratory tests

• Sputum microscopy is positive in <10-15% of children with probable PTB (adult 60%)
• Culture yields are also low (<30-40%)
• Studies showed that the bacteriologic yield of gastric lavage microscopy 4 – 21% and culture were 17 - 50%

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Laboratory tests

- Presence of AFB on smears of clinical specimens and positive histopathology or cytopathology on tissues specimens are highly suggestive of TB.
- Isolation of M. tuberculosis by culture from appropriate specimens is confirmatory. Positive AFB culture can also be tested for drugs susceptibility.
Diagnosis of childhood TB

Usually difficult and features suggestive of TB are:

- Symptoms and signs suggestive of TB
- Positive Mantoux test (>10 mm induration at 72 hours: tuberculin strength of 10 IU PPD)
- Suggestive X-ray abnormalities
- Laboratory tests
  - Recent contact with active TB (adult index case)
  - Information from source case (esp culture and susceptibility results) help to guide therapy
Diagnostic workup

• **Pulmonary TB**
  - CXR
  - Early morning gastric aspirates
  - Sputum (if able to expectorate sputum)
  - Pleural fluid or biopsy

• **CNS TB**
  - CSF for FEME, AFB smear and TB culture
  - CT head with contrast

• **TB adenitis**
  - Excisional biopsy or fine needle aspirate (FNA)
Diagnostic workup

- Abdominal TB
  - CT abdomen with contrast
  - Biopsy of mass / mesenteric lymph node

- TB osteomyelitis
  - CT / MRI of affected site
  - Biopsy of affected site

- Miliary / Disseminated TB
  - As for pulmonary TB
  - Early morning urine
  - CSF
# Recommended Doses of AntiTB Drugs in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (range) in mg/kg</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>10 (10 - 15)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>15 (10 - 20)</td>
<td>600 mg</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>35 (30 - 40)</td>
<td>2 g</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>20 (15 - 25)</td>
<td>1 g</td>
</tr>
</tbody>
</table>

Pyridoxine 5 - 10 mg daily needs to be added if isoniazid is prescribed.

*Direct observation of drug ingestion is recommended especially during the initial phase of treatment and whenever possible during the continuation phase.*
## Treatment Regime in Children

<table>
<thead>
<tr>
<th>TB Cases</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>New smear positive PTB</td>
<td>2HRZ</td>
<td>4HR</td>
<td>Ethambutol can be added in the intensive phase of suspected isoniazid-</td>
</tr>
<tr>
<td>New smear negative PTB</td>
<td></td>
<td></td>
<td>resistance or extensive pulmonary disease cases.</td>
</tr>
<tr>
<td>Less severe EPTB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe concomitant HIV disease</td>
<td>2HRZE</td>
<td>4HR</td>
<td></td>
</tr>
<tr>
<td>Severe form of EPTB</td>
<td>2HRZE</td>
<td>10HR</td>
<td></td>
</tr>
<tr>
<td>TB meningitis/spine/bone</td>
<td></td>
<td></td>
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# Treatment Regime in Children

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<tr>
<td>Previously treated smear positive PTB including relapse and treatment after interruption</td>
<td>3HRZE</td>
<td>5HRE</td>
<td>All attempt should be made to obtain culture and sensitivity result. In those highly suspicious of MDR-TB, refer to paediatrician with experience in TB management.</td>
</tr>
<tr>
<td>Treatment failure TB</td>
<td></td>
<td></td>
<td>Refer to paediatrician with experience in TB management</td>
</tr>
<tr>
<td>MDR-TB</td>
<td></td>
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Treatment of TB disease

• **Corticosteroids**
  - Indicated for children with TB meningitis
  - May be used in pleural & pericardial effusion (hastens resorption of fluid), severe miliary disease (if hypoxic) and endobronchial disease
  - Give steroids only with anti-TB therapy

• Prednisolone 1-2 mg/kg/day for 3-4 weeks, then taper over 3-4 weeks.
Treatment of TB disease

Monitoring of drug toxicity:
1. Monitor LFT if:
   • Severe TB disease
   • Underlying hepatic disease
   • Clinical symptoms of hepatotoxicity
   • HIV infection
   • Use of other hepatotoxic drugs (esp anticonvulsants)

2. Monitor for visual acuity and colour discrimination if ethambutol is used
TB and HIV

- HIV infection is a potent risk factor for TB disease
- Extrapulmonary TB is more common
- Pulmonary TB has a more aggressive picture, often substantial infiltrates and cavitations
- Diagnosis can be difficult: negative skin test & microbiological confirmation hard to achieve
- Think of TB disease in HIV-infected child!
- Think of HIV infection in a child with TB disease!
Prevention

- BCG vaccine
- Estimated protective effect in young infants 60-80%
- More significantly is its effect in preventing tuberculous meningitis and disseminated disease
Prevention

• Tracing & Screening of contacts of index case
• Exposure (window) prophylaxis for infants ?? < 5 years old
• Treatment (chemoprophylaxis) of LTBI
# Children with PTB Exposure & LTBI

The evaluation should include a TST (Mantoux), a chest radiograph (regardless of TST reaction), a history, and physical examination.

<table>
<thead>
<tr>
<th>If the initial TST is positive ($\geq 10$ mm) and there is no evidence of disease, treatment for LTBI should be initiated</th>
</tr>
</thead>
</table>
| **Give prophylaxis:**  
Isoniazid for six months OR isoniazid + rifampicin for three months |

| If the initial TST is negative (< 10mm),  
Exposure to smear and/or culture positive PTB |
| --- |
| **Give window prophylaxis:**  
Isoniazid for six months OR isoniazid + rifampicin for three months  
A repeat TST at 3 months  
Stop chemoprophylaxis if TST negative |

A repeat TST test at 3 months after contact with the source (index) case has been broken or after the source (index) case has been deemed to be non-infectious.  
Give chemoprophylaxis if TST positive

Follow up

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Advances in Symptom-based Diagnosis

• Recent prospective, community- study by Marais BJ et al reported that the presence of 3 symptoms at presentation provided good diagnostic accuracy in immuno-competent children $\geq 3$ years of age:

1. Persistent non-remitting cough of $>2$ weeks’ duration,

2. Documented failure to thrive during the preceding 2 months

3. Fatigue

(sensitivity 82.3%, specificity 90.2%, positive predictive value 82.3%)
Summary

- Children account for major proportion of global tuberculosis disease burden.
- Accurate diagnosis of childhood tuberculosis remains a major challenge although many promising advances have been made in the development of new diagnostic tools.
- The provision of preventive treatment to high risk children with exposure and/or LTBI and active case detection with the use of symptom-based approaches, improved access to chest radiograph and anti-tuberculosis treatment will reduce severe TB related morbidity and mortality in TB-endemic countries.
- Breaking the cycle of poverty would be the ultimate goal to contain the TB epidemic.
References

1. CPG on Management of Tuberculosis (3rd Edition) 2012
2. Management of Latent Tuberculosis in Children and Adolescents: A Guide For Primary Care Provider, New Jersey Medical School Global Tuberculosis Institute
3. Recent advances in the diagnosis of childhood tuberculosis  BJ Marais, Madhukar PaiArch Dis Child 2007;92:446-452 doi:10.1136/adc.2006.104976