

Diagnostic challenges in childhood Tuberculosis

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- It is a neglected disease, “Orphan disease.”
- Accurate Dx is important to reduce morbidity & mortality.
- Goal 6 of the MDG includes the halting and reversal of the rising incidence of tuberculosis.
- Stop TB Partnership aims to halve the prevalence of tuberculosis and resulting deaths by 2015.

The manifestations of HIV/AIDS and the various infections that complicate it have made the diagnosis of TB in young children even more difficult.

Subjects for postmortem biopsies of lung and liver: 93 children with HIV. Rennert et al. (2002)

- TB was confirmed before death in only 4 children (4%)
- 17 children (18%) had been empirically placed on TB treatment on the basis of history and clinical and radiological features, and this diagnosis could not be confirmed post mortem.
- Chest radiographs from these children read by a panel proved incapable of distinguishing TB from *Pneumocystis carinii* pneumonia, cytomegalovirus pneumonitis or interstitial lymphocytic pneumonitis.

Causes of misdiagnosis of PPTB include

- non-specific signs/symptoms
- low bacillary load
- recovery methods (sputum or gastric aspirate) for obtaining a clinical sample with low bacillary yield.
- inherent low sensitivities of the diagnostic tests themselves.

Why???

Very low priority of Ped TB in global TB control programs based on cost-effective strategies.

Is the solution that far??



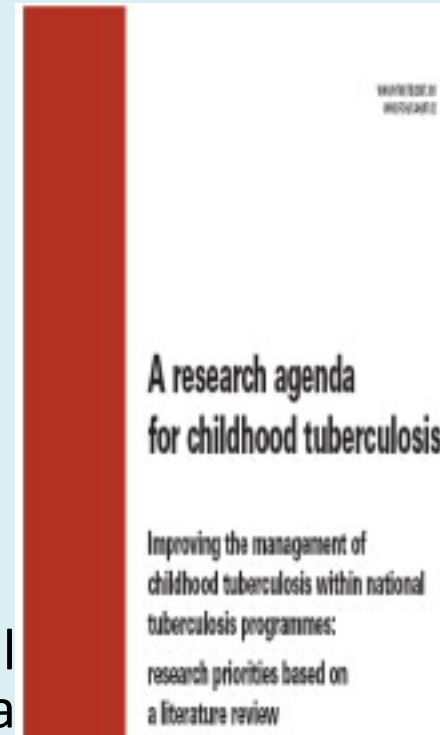
Symptom based Dx

- Scoring systems are severely limited by absence of standard symptoms definitions and inadequate validation.
 - Int J lung dis 2002, 6:1038

Using symptoms, of the 27 papers summarized

21 (78%) *contact* with a case of adult tuberculosis,
19 (70%) cough,
16 (59%) fever
14 (52%) failure to thrive or loss of weight.
9(33%) failure to respond to a course of antibiotics
6 (22%) presence of superficial nodes.
5 (19%), “symptom complex”.

Other symptoms infrequently used included abdominal difficulty in walking, sputum production, chest pain, ha anorexia, malaise/fatigue and bone deformities.



Contact with an adult case of tuberculosis might be: (WHO 2007)

- “... a tuberculous adult or a person with chronic cough” (Ghidey & Habte, 1983)
- “A person in the immediate household of the child had confirmed or probable tuberculosis” (Cundall, 1986)
- “History of close contact with a case of tuberculosis” (Luo et al., 1994)
- “... close household contact with a recently diagnosed adult case of pulmonary tuberculosis” (Schaaf et al., 1995)
- “Recent known exposure to an active case of tuberculosis” (Espinal et al., 1996)
- “Close household contact with an adult with active pulmonary tuberculosis diagnosed within the previous 12 months” (Houwert et al., 1998)
- “Family history of TB” (Van Beekhuizen, 1998)
- “An adult with active tuberculosis and/or who had received treatment within the previous 6 months” (Mahdi et al., 2000)
- “a household with an adult taking anti- TB therapy or who has taken such therapy in the past 2 years” (Indian Academy of Pediatrics, 2004).

TB meningitis (lancet 2010)

Adults and children

Nagesh Babu (2008)²¹

- Case definition includes definite and presumptive tuberculous meningitis cases
 - A) Clinical criteria: fever, headache, meningeal signs, and other clinical presentations of meningitis lasting for more than 2 weeks.
 - B) CSF criteria: typical features including pleocytosis (>20 cells/ μ L), lymphocytes $>60\%$, protein >1 g/L, and CSF: blood glucose ratio of less than 0.6
 - C) Supportive criteria:
 - i) Isolation of *M tuberculosis* from body secretion other than CSF in smear or culture
 - ii) CXR findings of pulmonary tuberculosis (reticulonodular pattern in upper lobes with or without cavitary lesions)
 - iii) Hydrocephalous from brain CT scan
 - D) Negative bacterial and fungal cultures and negative India ink
- Definite tuberculous meningitis diagnostic criteria not stated
- Diagnosis of presumptive tuberculous meningitis requires A, B, one or more of C, and D to be fulfilled

Rafi (2007)²²

- Patients: HIV seropositive and negative
- Case definition includes culture-confirmed and clinical tuberculous meningitis cases
- Diagnosis of clinical tuberculous meningitis requires A, B, and C:
 - A) Clinical findings: headache, fever, and vomiting for more than 3 weeks
 - B) CSF findings: pleocytosis and high protein concentration
 - C) Neuroimaging findings: the presence of a basal exudate with or without hydrocephalus

Consensus of TB meningitis definition (lancet 2010)

Clinical entry criteria

- Symptoms and signs of meningitis including one or more of the following: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy.

Tuberculous meningitis classification

Definite tuberculous meningitis

- Patients should fulfill criterion A or B:
 - A) Clinical entry criteria plus one or more of the following: acid-fast bacilli seen in the CSF; *Mycobacterium tuberculosis* cultured from the CSF; or a CSF positive commercial nucleic acid amplification test.
 - B) Acid-fast bacilli seen in the context of histological changes consistent with tuberculosis in the brain or spinal cord with suggestive symptoms or signs and CSF changes, or visible meningitis (on autopsy).

Probable tuberculous meningitis

- Clinical entry criteria plus a total diagnostic score of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should either come from CSF or cerebral imaging criteria.

Possible tuberculous meningitis

- Clinical entry criteria plus a total diagnostic score of 6–9 points (when cerebral imaging is not available) or 6–11 points (when cerebral imaging is available) plus exclusion of alternative diagnoses. Possible tuberculosis cannot be diagnosed or excluded without doing a lumbar puncture or cerebral imaging.

Not tuberculous meningitis

- Alternative diagnosis established, without a definitive diagnosis of tuberculous meningitis or other convincing signs of dual disease.

Drawback of the symptom based

- Lack of standard definition of symptoms
- The gold standard of bacteriological confirmation was not attained in most studies.
- The diagnostic approaches were not tested in an independent population or compared to control groups.
- The calculation of sensitivity and specificity insufficient and statistical evidence of the validity of most of these diagnostic approaches is lacking.
- Only one study was performed in a population with a high burden of HIV.

Radiologic Dx

- Useful if
 - At least in HIV-uninfected with suspicious symptoms, read by experienced radiologist
- In HIV-infected children its interpretation is further complicated by HIV-related chronic lung disease such as LIP.
- LIP can also manifest as opacification with mediastinal adenopathy, which further complicates the interpretation of chest radiographs.

Immunological Dx

- Highly variable sensitivity and specificity.
 - Thorax 2007.
- Cannot differentiate active TB vs latent TB
- MPB-64 skin patch test distinguished active from latent TB (sensitivity 88-98%, specificity 100%)
 - Scand J infect dis 2001, 33:405-407.

Immunological Dx (2)

- TST: poor sensitivity and low specificity.
- IFN- γ based (blood tests).
 - T-SPOT.TB : sensitivity 83-97%
 - QuantiFERON-TB Gold assay: sensitivity 70-89%

Bacteriology Dx

- Culture 30-40%
- Smear positive 10-15%
- PCR: highly variable
 - sensitivities ranging widely from 13 to 83% and specificities up to 100% (IJTLD 2001.)
 - Higher sensitivity and specificity than to culture (Montenegro et al., 2003).

Microscopic Observation drug susceptibility assay

- *M.tb grows faster in liquid medium.*
- rapid and direct drug-susceptibility testing concomitantly with the detection of bacterial growth.
- Sensitivity of detection was 97.8% for MODS culture, and 84.0% for Löwenstein–Jensen culture ($P < 0.001$);
- the median time to culture positivity was 7 days, and 26 days, respectively ($P < 0.001$)
(NEJM 2006)

Specimen collection

- Gastric aspirate
 - Diagnostic yield is only 25-50%.
 - Distressing to the child
 - Requires hospitalization
- Hypertonic saline-induced sputum
 - is more sensitive than gastric lavage *in both HIVinfected* and non-infected children (Zar H J et al 2000)
 - Nosocomial infection risk
 - Requires hospital setting
 - Lancet 2005, 365: 130-134
- String test
 - lancet 2005, 365:150-152
- Fine needle aspiration for LN
 - Ped infec dis j 2006, 25:142-146

*Dear baby do not lose hope.
One day you will find the solution when
you grow up. But do not forget you
were a child once upon a time.*



Thank you

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