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Review Article :

Clinical Markers of Tuberculosis in Children

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Abstract:

Clinical markers of tuberculosis are varied and involve all systems with classical and non-classical features; presence of its hallmarks makes the suspicion strong. It is erroneous to give antibiotic therapy for confirming TB. It is very simple with good history taking and the clinical markers with the supportive evidences to arrive at a diagnosis of childhood TB. This situation is especially applicable to India, the rural setup and the urban slums to have high index of suspicion and thereby reduce the spread, morbidities and mortality.

Key words: Childhood tuberculosis, Clinical diagnosis of TB, Mycobacterium tuberculosis

Introduction

Tuberculosis in children presents in a varied manner, from classical features to totally asymptomatic children. It is highly prudent to be aware of clinical markers of tuberculosis that help us make a clinical diagnosis with certainty. When compared to the disease in adults, clinical manifestations of pulmonary TB in children are minimum if any barring when the child has disease, which is severe.

Mycobacterium tuberculosis infection in childrenhas a natural history and clinical manifestations substantially different when compared with adults. Majority of children with tuberculosis develop neither signs nor symptoms [1]. Even though children do often not present with classical features of tuberculosis as in adults like cough, wasting, hemoptysis; children with tuberculosis constitute significant proportion of patients diagnosed with tuberculosis, constituting 10% of hospital admissions [2].

The natural history depends also upon the age and immune status of the host. Children infected prior to 4yrs age have a very high rate of developing immediate clinical or radiographic manifestations or both, but development of reactivation disease in adulthood is questionable. Those children who are acquire infection in preadolescence or adolescence are more vulnerable to develop severe adult-type pulmonary tuberculosis immediately after infection or in adulthood[3].

Most children who develop tuberculosis experience pulmonary manifestations, but about one fourth of children have an extrapulmonary presentation in the form of lymphatic disease (most cases) and. meningeal disease occurring in 13% of extrapulmonary disease in children [2].

One of the diagnostic key is to link a child to a confirmed adult pulmonary TB case[4].

In high prevalence area, TB tends to be over diagnosed and in low prevalence areas, it seems to be underdiagnosed or diagnosed late[5]. It is said that clinical suspicion acts as a missing link, and once tuberculosis is suspected, the diagnosis is half way, and you can expect "Every" unexpected!

Symptom complexes in tuberculosis:

In routine office practice, tuberculosis should be suspected in the following situations:

1. Cough of more than 2 weeks duration without sneezing, running nose or wheeze.

2. Low grade fever of more than 2 weeks duration without any response to first line antibiotics.
3. Lymphadenopathy: This may be generalized, but most commonly involving cervical lymph nodes.
4. Hepatosplenomegaly, where other infections and noninfectious possibilities have been ruled out.
5. A child having positive history of contact with tuberculosis along with amalgamation of any of the aforesaid clinical features.
6. Failure to gain weight or slight loss of energy over 2-3 months, usually with intermittent fever
7. Sudden "fever of onset" lasting upto 3 weeks, with erythema nodosum and phlyctenular conjunctivitis.
8. Failure to gain weight with respiratory wheeze and hard cough
9. Sudden febrile illness with pleural pain or effusion
10. A hard painless abdominal mass
11. Onset of limp or painful swelling in weight bearing joint
12. Refusal to bend stoop a painful back and spinal deformity
13. Painless firm swelling of superficial node with satellite nodes
14. Lymph node abscess of slower onset
15. Skin ulcers without any obvious cause
16. Unexplained vomiting headache and sensory change
17. In adolescent with weight loss and productive cough
18. Clinical progression after any viral infection like measles
19. convulsion stroke or unconsciousness of unknown origin
20. Child with sterile pyuria
21. Pericardial effusion without any obvious cause
22. Any child with malnutrition, particularly Grade III and IV* (I.A.P. classification) or Severe acute malnutrition with any of the constellations mentioned above[1-8].

In all above cases, tuberculosis should be strongly suspected and common etiologies need to be ruled out. A clinical score was derived from various clinical features. (see table1). A score of 7 or more was considered suggestive of tuberculosis in endemic countries.

Hallmarks of tuberculosis:

Apart from clinical features, following clinical associations are hallmarks towards diagnosis.

1. Contact of TB case
2. Decreased host immunity
3. Hyponutrition and malnutrition
4. Chronicity
5. Poor socioeconomic status

1. Contact:

A child gets infected only from an infecting "contact adult" that is spreading the infection. A contact can be a family member, friend or a regular visitor who is in active phase of infection and/ or on irregular and inadequate treatment. Therefore every attempt should be made to trace an infected adult contact. Even though a single family member is harboring the bacilli or has been treated inadequately in past, he still may be able to transmit infection in the family. Contact may be at home, nursery or school. It requires great precision to elicit the contact history due to various social inhibitions on part of doctor or the parent.

2. Decreased Host immunity:

Immunity decides the gap between TB

infection and TB disease. During a post infective immunosuppression, unusual prolongation of viral infection or its sequealae/ complicating into tuberculosis is not uncommon, e.g. following measles. If there is good immunity the disease may not manifest (to its severity); as host immunity is adequate to generate a reaction or heal a primary focus. Similarly a case of nephrotic syndrome on steroid therapy may get an endogenous exacerbation or a fresh infection of TB. Children immunized with BCG usually get less severe and milder forms of tuberculosis infection and its complications compared with others.

3. Hyponutrition and malnutrition:

Hyponutrition / malnutrition can occur hand in hand with poverty among lower socioeconomic groups, reduce the host immunity, thus attributing for the progression or flaring up of the disease. Kwashiorkor could get precipitated in a child suffering from primary infection. Even asymptomatic PEM gr III/IV or severe acute malnutrition should always be investigated for tuberculosis.

4. Chronicity:

Although this is a significant factor in adults, it need not be so in children. Grossly any symptom (including fever) usually respiratory or otherwise (like skin ulcer), of infective origin; persisting for more than 2 weeks raises doubts about tuberculosis. Other chronic granulomatous diseases should also be kept in mind.

5. Poor socioeconomic status:

Although TB can affect any status, droplet spread is maximum in areas of overcrowding, thus resulting in faster dissemination of infection.

Host factors:

1. Age: Infants and adolescents are more susceptible. Young infants and adolescents do have significant signs /symptoms, whereas school-age children often manifest with a silent disease. Pulmonary tuberculosis in more than one half of infants and young children with moderate to severe radiological findings have neither symptoms nor physical findings. See Table 2

2. Sex: There is no specific sex predilection for infection or disease.

3. Geographic location: Erythema nodosum, phlyctenular conjunctivitis and pleural effusion are more common in temperate areas. Similarly, lymph node disease, TBM and caseation are more common in tropical countries.

Cardinal Symptoms of tuberculosis in children:

Apart from the various clinical features mentioned in table 3, malnutrition can be the only presenting feature of childhood TB. A contact in family or neighborhood, and lack of appetite with or without weight loss may strongly point towards tuberculous etiology, particularly in an unimmunized child. The characteristic manifestations of anorexia and weight loss are not any more considered as a marker of TB, and may be associated as a sign in children with HIV infection. Similarly, headache in a case of suspected tuberculosis should alert clinician to perform a lumbar puncture[9]. A case of chronic backache should be examined for tender spine, a kyphus or gibbus and a fluctuant swelling along ribs, in flanks or thigh.As the mycobacteria consume proteins and also the anorexia sets in, the progressive weight loss follows manifesting over few months as failure to thrive.

The Course of disease:

TB is known to disseminate via the hematogenous route to various organ depending on the age and host immunity. Wallgren had proposed a time scale of events of progression of various pathologies in TB [5]. (Table 5)

Stigmata of tuberculosis on general examination:

A thorough general physical examination should be done in all patients with tuberculosis9, 10. Vital parameters may be stable in most children, except in cases of raised intracranial tension in meningitis or hydrocephalus wherein hypertension and bradycardia may be present.Miliary disease commonly has tachypnoea and marked respiratory

distress or indrawing is not observed in tuberculous effusions. Tachycardia with gallop or weak heart sounds may be seen in pericardial effusion with wide pulse pressure.Fever may not be present except in cases of TB meningitis or effusion.It is mandatory to look for a BCG scar; presence of a BCG scar has been associated with reduced incidence of disseminated TB/ TB meningitis.Miliary TB and bronchiectasis in addition may have clubbing and hypoxia.Other stigmata of TB that can be picked up on general examination are:

Head: Hydrocephalus, macro or microcephaly, with or without neck stiffness.

Eye: Primary conjunctival TB: Hypertrophic granulation tissue with yellow nodular area over palpebral conjunctiva with swollen conjunctiva and enlarged preauricular nodes. Phlyctenular conjunctivitis is an early hypersensitive marker of tuberculosis; however choroid tubercles and / or optic atrophy, may be equally sensitive markers of tuberculous origin and an early referral to the pediatric ophthalmologist may be rewarding. It may also appear along with erythema nodosum, as a hypersensitivity phenomenon. Symptoms: Irritation, lacrimation and soreness, leaving behind small grey spots or phlycten at the limbus, initially rounded, then irregular and nodular disappearing in a week. Cornea may get ulcerated and lacrimal glands may get secondarily infected.

Choroid tuberculosis:

a rare finding, seen in miliary or primary TB with dissemination. Usually more than one tubercle is seen around the disc as a faint yellow bulge, sometimes multiple or solitary giants too, central yellow area gradually fades and leaves behind a pale scar with small spots of black pigments at the periphery by around 3 months. The white patch later gets filled with black pigment.

Ear: Chronic otorrhoea with mastoid tenderness suggests mastoid tuberculosis.

Nose: Tuberculous sinusitis may present with anosmia and rhinosinusitis

Throat: Tonsillar TB usually manifest as solitary tonsillar node resistant to antibiotics, the same side tonsil may be asymmetrically enlarged with a yellowish tubercle over tonsil. Peritonsillar abscess or a cervical abscess may track down as prevertebral abscess as also seen in TB of cervical spine.

Lymphadenopathy:

It may be generalised, local (cervical, axillary) or may also follow BCG immunization. Usually the nodes are more than two, and discrete, but very often they could be matted with satellite nodes which may turn into caseating abscess, sinus or fistula. A non-healing ulcer overlying a lymph node following its rupture is also called as scrofula. Tonsillar tuberculosis commonly manifests as cervical lymphadenopathy. The anterior cervical, supraclavicular and submandibular nodes are common sites of involvement. Skeletal system TB may be associated with inguinal, epitrochlear or axillary lymph nodes[6].

Extra pulmonary TB will have its own clinical presentations depending on the area affected.

Tuberculous pericarditis is the commonest cause of pericarditis in children and a case of tuberculous pericarditis may have JVP raised.

Abdominal TB:

Manifests as distention of abdomen, ascites, doughy feel over abdomen and with or without fever. It can be peritoneal TB with only ascites and adhesions. It can also present as an ileocecal mass or subacute intestinal obstruction; and secondary malnutrition[6,9].

Disseminated TB:

commonly these children present with hepatosplenomegaly with or without mesenteric or generalised lymphadenopathy; and hepatosplenomegaly> many a times other chronic disseminated diseases like kala azar or a malignancy may mimic similar findings on examination.

Skeletal TB is usually a disease of adolescent

children and manifests as a kyphus or gibbus of the spine following vertebral compression. Subsequent cord compression leads to limb weakness and paraplegia. A patchy limb weakness may be a form of spinal tuberculosis with tuberculous arachnoiditis. A cold abscess (Pott's spine) tracks anteriorly along the rib, or along the psoas muscle and TB hip may present with acute synovitis, joint destruction and/or abduction-lateral rotation deformity of the respective limb. Tuberculosis of the digit (spina ventosa) manifests as tuberculous dactylitis. Mild pallor and stigmata of malnutrition are usually present. There can be thickened spermatic cord in chronic TB of genitourinary origin, or in adolescent females there may be delayed menarche.

Skin tuberculosis:

Skin may show various skin lesions including lupus vulgaris.

It is suspected wherein a child has a skin lesion with:

1. A small transparent jelly like nodule in dermis without surrounding inflammation
2. A raised papular lesion or plaque with silvery scales covering a nodule
3. An indolent painless ulcer or scab which remains after abscess rupture

Erythema nodosum: red nodular eruption over shins after weeks of infection as a hypersensitivity to TB antigen. Lesions grow and become palpable, over a week, skin wrinkles, lesions deepen, change to purple and fade out over few weeks with a brown staining. It may be associated with phlyctenular conjunctivitis[7,10]

All these lesions are painless and slow to heal.

Pulmonary tuberculosis:

Pediatric tuberculosis is usually pulmonary even without respiratory signs and symptoms. It is a dictum that diagnosis of tuberculosis is incomplete without a chest ski gram (And the Mantoux skin test). Onset of TB is usually insidious, with early systemic signs, anorexia, weight loss and low grade fever. Onset can be explosive in TB bronchopneumonia and military TB [1,11.]

Pediatric Neurotuberculosis:

It is the gravest presentations of extrapulmonary tuberculosis in children and is one of the commonest presentation of TB in developing country toddlers, so much so that the dictum that ruled years was that "any focal CNS neurodeficit is likely to be TB in children".It usually presents as vasculitic stroke, convulsions, tuberculoma or TB meningoencephalitis. It can closely mimics a pyogenic meningitis at times, but presence of optic atrophy, hydrocephalous, Chronicity of symptoms and CSF study will point towards tuberculosis. Tuberculous arachnoiditis presents with patchy peripheral neurological signs with or without radicular pain, spinal tenderness and cold abscess[12-14.]

1. Tuberculous meningitis [TBM]:

- TBM is most commonly seen in the age group from 6 months to 4 years1.
- In early childhood more frequent is tubercular meningitis whereas older children generally have tuberculoma.
- The troika of tubercular meningitis include fever, headache and signs of meningismus, even though all patients may not present with all three. They three stages of TBM presentation [Table 6].
- In Tubercular meningitis the most common presentation is altered mental status and most common cranial nerves involved are III, VI, VII.
- Mortality in TBM is high, despite anti tubercular treatment, varying from 20 upto 69%. Almost half the cases have permanent neurological sequelae15.
- The patients with immunocompromised state also present with altered mental status than the triad of fever, headache and signs of meningismus [16]

2. Tuberculoma:

- Tuberculoma is collection of caseous tubercles manifests commonly as space occupying

agent1.

- Tuberculoma characteristically occurs in most commonly seen in infratentorial region cerebellum, accounting to a third of brain tumours.

- Tuberculoma mimics an intracranial space occupying lesion in its clinical presentation. Neurotuberculosis can also present as acute or subacute meningoencephalitis with varied neurological findings.

- Headache is most common presentation of tuberculoma [Table 7].

Congenital TB:

Though congenital TB is rare the there can be Symptoms which can be characteristically occur in the second or third week of child's life which include feeding poorly, inadequate weight gain, lethargy and irritability, associated with or without breathlessness. Further symptoms can be fever, discharge from ear and skin lesions. To diagnose congenital TB the infant must have documented TB lesions (pulmonary or hepatic) and minimum of one of the following: (modified Betzke's criteria)

1. Skin lesions like papules or petechiae seen in first week of life.
2. TB infection being documented from the placenta or the maternal genital tract
3. Demonstration of primary complex in liver
4. Exclusion of the likelihood of postnatal transmission

Clinical markers of tuberculosis are diverse and involve all systems with classical and nonclassical features; presence of its hallmarks makes the suspicion strong. It is erroneous to give antibiotic therapy for confirming TB.

A case of TB can be easily diagnosed from history and no evaluation of a case of tuberculosis is complete without an X-ray chest, Mantoux test, family screening and an attempt towards documenting bacilli by smear or culture. Pattern of clinical features still plays a vital role as presence of positive investigational markers boosts the diagnosis of TB but its absence can't rule out the same. Detailed approach in diagnosing tuberculosis with the help of X-ray markers and Mantoux test is however beyond the scope of this article.

Points to remember:

1. Majority of children with tuberculosis develop neither signs nor symptoms except malnutrition.
2. Association of the child to an adult with diagnosed pulmonary TB is the diagnostic key
3. Even asymptomatic PEM grade III/IV or severe acute malnutrition should always be investigated for tuberculosis.
4. The typical presentation of anorexia and weight loss is no longer a marker of TB, and may be associated as a sign in children with HIV infection or severe disseminated disease.

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Table 1: Clinical Score for diagnosis of TB in children [7].

Features	0	1	3	Score
Length of illness	Less than 2 weeks	2-4 weeks	More than 4 weeks	
Weight of child	Above 80% of expected for age	60 to 80% of expected for age	Less than 60% of expected for age	
Family history past/ present	None	Reported by family	Sputum positive	
Positive skin test	3			
Large painless nodes, sinuses	3			
Unexplained fever, night sweats, no response to malaria	2			
Malnutrition not improving by 4 weeks	3			
Angle deformity of spine	4			
Joint swelling / bone swelling/ sinus	3			
Unexplained abdominal mass / ascites	3			
Altered sensorium, convulsions	3			
Total (total score of 7 or more is suggestive of TB)				

Table 2: Age distribution of various tuberculosis complexes [5.]

Age	Probable form of TB (example)
Newborn	Congenital TB
Infant	Primary complex, bronchopneumonia, BCG lymphadenitis
Toddler	Progressive primary complex, TB Meningitis (TBM), Miliary TB
Preschool age	Lymph node disease, TBM, disseminated or abdominal TB
School age	Lymph node disease. TBM, disseminated or abdominal TB
Adolescent	Pleural effusion, disseminated or abdominal TB

Infants are more likely to experience signs and symptoms, because of their small airway diameter, relative to the parenchymal and lymph node changes. TB tends to localize with development of immunity.

Table 3: Cardinal Symptoms of tuberculosis in children [1,7]

Symptom	Duration	Details
Fever	>2 weeks	Daily evening rise or high intermittent or mild continuous
Cough	>2 months	Dry persistent, due to lymph node compressing bronchus or tonsillar TB
Lymph nodes (LN)	> 2 weeks, Antibiotic resistant	Usually cervical. Toddlers and upto 7-8 years of age. LN can be in groups with satellites, matted, caseating or solitary, thoracic, abdominal and visceral LN, there may be sinuses or scrofuloderma or an abscess.
Breathlessness or wheeze	a 1-2 weeks	As a part of pleural effusion of insidious onset with fever, although in infants and immuno-compromised children it could be bronchopneumonia or miliary TB. Rarely as an idiopathic pericardial effusion or pneumonia.
Convulsion with or without unconsciousness or cranial nerve deficit	Acute	Acute vascular strokes of short duration may manifest with seizures and focal deficit; similarly it can also be produced due to tuberculous serous meningitis with meningeal signs due to rupture of cortical tuberculous granuloma.
Abdominal distension with pain / constipation/ vomiting/ loose motions	>2 months	This could be a manifestation of abdominal / peritoneal TB, ascites and hepato-splenomegaly; if a lump palpable as an ileocecal mass, and /or a part of disseminated TB. May cause intestinal obstruction/ adhesions.
Skin lesions	> 3 weeks	Chronic non healing ulcers, abscesses, and sinuses; or lichenification may be tuberculous.
Deformities	>3 weeks	Of back (gibbus), of finger (dactylitis), of hip (flexion deformity), due to bony destruction or a cold abscess, an unusual form of TB in children.

Any one or more of above may be the presenting feature of tuberculosis. TB in children is often asymptomatic.

Table 4: Wallgren's TB Timescale: Modified1, [10]

Time Scale	Comments	Events
0-4 weeks	TB Infection	None
4-8 weeks	Hypersensitivity / Latent TB, most children get MT positive	Febrile illness, E. nodosum, Phlyctenular conjunctivitis
2-4 months	Primary focus, nonspecific resistance, greater risk of local and disseminated	Ghon's complex with progressive healing in most cases, Pleural effusion
3-12 months	Primary Focus complications	Pleural effusion (75% cases), Cavity, Coin shadow
3-9 months	Complications of nodes	Rupture, empyema, bronchopneumonia, consolidation, hyperinflation
9 - 24 months	Diminished risk of dissemination	Meningitis, miliary, subcortical tuberculoma rupture, in < 5 yr age, in < than 4% cases
1-3 years	Disseminated TB	Bone, joints, kidneys (>3 yrs)
Resistance reduced by early infection, PEM, measles, whooping cough, steroids etc.		

Table 5: clinical manifestations and differential diagnosis of childhood pulmonary TB[1,7,13]

Type of TB	Clinical signs	Differential Diagnosis
Endobronchial TB	LN rupture - acute bronchopneumonia. Persistent cough - bronchial obstruction, dysphagia- esophageal compression. hoarseness - Vocal cord compression Wheeze- tracheal compression.	Foreign body inhalation, mucusplug as in asthma and viral bronchopneumonia
Primary Parenchymal focus, Ghon's focus	No or minimal signs on examination, if its progressive primary disease, asymmetric signs may be seen due to pneumonia, atelectasis, and air trapping	Bacterial or aspiration pneumonia
Miliary disease	Baseline tachypnea with or without cyanosis, or an apparent normal examination with symmetric signs	Bronchopneumonia, occupational diseases
Pleural effusion or empyema	Chest pain that escalates in intensity with deep inspiration and shortness of breath.	Empyema, synpneumonic effusion
Collapse, consolidation synpneumonic effusion, abscess, cavity pneumothorax hydropneumothorax	Respective asymmetric signs over varied parts of lung, in the form of bronchophony, absent air entry or decreased air entry, with or without mediastinal shift, shifting signs, whispering pectoroloque , classic signs of pneumonia- tachypnea, nasal flaring, grunting, dullness to percussion, decreased breath sounds, crackles.	Pneumococcal pneumonia, staphylococcal pneumatoceles

Table 6: Stages of clinical presentations of tubercular meningitis [1, 17].

Feature	Stage 1	Stage 2	Stage 3
Duration	Usually 1-2 weeks	-	-
Symptoms	Fever, headache, drowsiness, irritability and malaise. Loss or static developmental milestones.	Lethargy, nuchal rigidity, seizures, vomiting	Hemiplegia, paraplegia
Signs	Conscious, No focal neurological deficits	Confusion, Positive Kernig's and Brudzinski signs, hypertonia, cranial nerve palsies and other focal neurological signs.	Stupor or coma, decerebrate posturing
Complications	-	Hydrocephalus, raised intracranial tension, encephalitis, movement didorders, speech impairment.	Hypertension, deterioration of vital signs finally death.

Table 7: Clinical symptoms and signs of Neurotuberculosis [1, 17.]

Tubercular Meningitis	Symptoms	Headache (69%), fever (69%), nausea/vomiting (61%), anorexia (54%), weight loss (37%), cough (33%)
	Signs	Altered mental state (58%) and drowsiness (28%).
	clinical variables predictive of TBM include	Continuance of symptoms for more than 6 days, optic disc atrophy, focal neurologic deficit, abnormal movements and leukocyte differential of less than 50% neutrophils in CSF.
Tuberculoma	Symptoms	Headache, fever, nausea, vomiting, convulsions
	Signs	Conscious, focal neurological signs, and

Figure I: clinical lesions in childhood TB