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REVIEW

Clinical practice

Diagnosis of childhood tuberculosis

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Abstract Childhood tuberculosis (TB) represents an important part of the disease burden, yet its diagnosis remains challenging. This review summarizes the clinical, radiological, and bacteriological approaches to diagnose TB infection and disease in children. Fever (possibly intermittent or low grade), weight loss or failure to thrive, and a persistent cough for >2 weeks are the most important clinical signs for pulmonary tuberculosis. Extra-pulmonary TB, which might occur in over 40% of the patients, can have in addition some specific clinical symptoms or signs. Chest radiographs provide important information in many patients and advanced imaging can be applied in case of (and should be restricted to) inconclusive diagnosis. The Mantoux test is positive in up to 70% of non-immunocompromised TB patients, whereas HIV co-infection or malnourishment results in a lower reactivity. Evidence of an adult TB index case is clue for diagnosis of childhood TB in low-endemic countries. Bacteriological confirmation remains difficult and is useful for doubtful cases or when drug resistance is suspected.

Keywords Children · Tuberculosis · Diagnosis · Disease · Infection

Introduction

As in adults, childhood tuberculosis (TB) is mostly due to *Mycobacterium tuberculosis*. Exposure, infection, and disease can be more clearly distinguished in children, although progression of a recent infection towards disease can be rapid with a short incubation period. The vast majority of children with TB infection develop no signs or symptoms nor radiographic abnormalities at any time. Development of disease is mainly determined by the cell-mediated immunocompetence of the patient, which is influenced by external factors such as malnutrition, steroid treatment, and HIV infection. Asymptomatic primary infection can progress to primary TB as a result of bacillary migration through hilar or mediastinal lymph nodes. Further lympho-hematogenous dissemination can bring bacilli to the bronchi, causing endobronchial TB, progressive pulmonary TB (PTB), miliary or pleural TB, or to other parts of the body leading to various types of extra-pulmonary TB (EPTB) such as meningoencephalitis, peripheral lymphadenopathy, abdominal or osteo-articular TB. TB affecting the eye, middle ear, sinuses, kidneys, or skin may occur, but is fairly rare in children.

The chance of developing disease is greatest shortly after infection and then steadily decreases as time goes by. Approximately 60% of the pediatric TB cases in the USA occur in children <5 years [32] and even in 53% of infants <3 years in high endemic regions [18]. However, immunocompromised children remain at high risk irrespective of their age [18]. Most children with TB have pulmonary TB, although in high endemic regions, only 48% presented with non-complicated hilar adenopathy [18]. The age at which a child is infected also determines the pattern of primary disease. Meningoencephalitis complication is most frequent among children <2 years, representing 5–10% of TB cases in this age group. Children under the age of 5 years are frequently affected by peripheral lymphadenopathy, of which 65–75% has a thoracic and mediastinal location. Pleural involvement is more common among adolescents [32].

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Diagnosis of TB infection

TB infection is diagnosed by estimating the TB immune response in children with no signs or symptoms of disease and with a normal chest radiograph. This can be achieved by in vivo assays known as tuberculin skin tests (TSTs) detecting a delayed hypersensitivity type reaction or by ex vivo assays grouped as interferon gamma releasing assays (IGRAs) measuring T cell responses in blood after incubation with TB-specific antigens. TSTs consists of subcutaneous injection of purified protein derivate (PPD) either with a single injection (Mantoux test) or by multiple punctions [multiple punction tests (MPTs); Mono-Vac, Applitest, Tine]. MPTs are not widely used because of the high rates of both false positive and false negative results that have been reported [1]. According to the standard protocol, reading of TST results should be done 72 h after injection. A recent study among Indian children <10 years demonstrated that reading after 48 h did not compromise the validity of the test [12], but more large-scale studies are needed to validate this finding. Various recommendations for the interpretation of TST results are available, taking into account bacillus Calmette–Guérin (BCG) vaccination and whether the patient belongs to a risk population [1, 14, 35] (Table 1).

Several factors may have an impact on the results. Although PPD is a cocktail of antigens shared by *M. tuberculosis* and *Mycobacterium bovis* (BCG), BCG vaccination did not have an impact on TST results in children from Uganda [23], Gambia [13], India [6], or Lebanon [31]. Also, IGRAs that use the *M. tuberculosis*-specific antigens ESAT-6 and CFP10 were not influenced by prior BCG vaccination. On the other hand, there is a general trend of increasing likelihood of positivity of TST and IGRAs with increasing age [26]. A lower TST reactivity is noticed among HIV-positive patients [34], and IGRAs were found more sensitive compared to TST in HIV-positive children [16, 17].

Evidence is currently insufficient to estimate sensitivity, specificity, and reproducibility of TST and IGRAs in children, but even combined TST and IGRA failed to give 100% sensitivity to detect latent TB [26]. Comparative studies evidenced that the interpretation of results remain challenging. Among children suspected for TB in India and Gambia, a high agreement between the IGRA test and TST was noticed [6, 13], whereas a three-way comparison of TST and the two currently used IGRAs among children with a TB contact history in Australia or among HIV-infected children in South Africa showed comparable results for the IGRAs while being commonly discordant with TST [4, 17].

Diagnosis of disease

Diagnsosis of TB in adults is mainly based on clinical signs and symptoms, imaging by X-ray, direct smear microscopy, and, if available, by culturing *M. tuberculosis* bacilli from clinical specimens or by nucleic acid amplification techniques (NAAT). In children, diagnosis of TB disease is complicated by its paucibacillary nature, resulting in atypical clinical signs and a lower probability of bacteriological confirmation. Therefore, a different approach is required for diagnosis of childhood TB. Most determining factors to investigate are: compatible clinical signs and symptoms, X-ray suggestive for TB, and likelihood of infection with *M. tuberculosis*.

Table 1 Interpretation of positive Mantoux tests in children

British Thoracic Society [14]	World Health Organisation [35]	American Academy of Pediatrics [1]
10 TU PPD per 0.1 ml	5 TU PPD-S per 0.1 ml (alternatively 2 TU PPD RT23)	5 TU PPD per 0.1 ml
5–14 mm if not BCG vaccinated	≥5 mm if one of the following:	>5 mm and if one or more of the following:
	HIV positive child	Child in close contact with known or suspected infectious TB case
	Severely malnourished child (clinical evidence)	Child suspected for TB disease (clinical and/or radiological data)
		Child with immunosuppressive conditions or therapy
>15 mm if BCG vaccinated	≥10 mm for all other children	> mm and if one or more of the following:
	Whether BCG vaccinated or not	Child at increased risk of disseminated disease (<4 years, medical condition)
		Child at increased risk of infection (high-risk population)
		>15 mm
		Child >4 years without any risk factor

TU tuberculin unit, *PPD* purified protein derivate, *BCG* Bacille Calmette–Guérin

Clinical disease evaluation

The clinical presentation of childhood TB is variable and nonspecific, often mimicking other common pediatric diseases [22]. Detailed descriptions of various forms of pediatric TB can be found in Munoz and Starke's paper [22].

The most frequent signs in children with TB are:

- a persistent non-remitting cough (>2–3 weeks) not improving after a course of antibiotics;
- fever (possibly intermittent, or low-grade, especially in infants) of unknown origin; and
- weight loss or failure to gain weight.

Enlarged non-tender lymph nodes—especially in the neck—, night sweating, pneumonia, pleural effusion, and mass lesion in the lung that does not improve with standard antibacterial therapy are clinical signs highly likely to have been caused by TB and warrant investigation. Abdominal TB can be characterized by non-specific constitutional signs or abdominal distension with ascites [3], whereas abnormal neurological signs and symptoms like neck stiffness, altered sensorium and convulsions are suggestive of meningitis Differential diagnosis for tuberculous meningitis (TBM) requires a lumbar punction (see below).

Imaging

Chest X-ray analysis (frontal, posterior, and lateral) constitutes an important tool in the diagnosis of childhood TB. Hilar or mediastinal lymphadenopathy and lung parenchymal changes are very suggestive for PTB. Segmental hyperinflation, atelectasis, alveolar consolidation, pleural effusion, and empyma are the most common parenchymal changes. Cavities are rarely present and seen mostly in older children and adolescents [30]. Also, in EPTB cases, abnormalities of the lung image can provide clue information for diagnosis. In 40% of children with abdominal TB, thoracic X-ray showed evidence of a primary focus [3].

Advanced imaging like computed tomography (CT) scanning, ultrasonography (US), and magnetic resonance imaging can provide important information in PTB and EPTB like meningoencephalitis, abdominal, and skeletal TB [2, 3, 33]. Detailed descriptions are given in a review by Andronikou and Wieselthaler [2] who concluded the following: "imaging should be as basic as possible at first, including the continued use of chest radiographs. Equivocal results should prompt further imaging. Definitive findings should end the imaging series unless other complications are sought. When results are negative, do not discount TB, but rely on clinical suspicion to guide further imaging. For pulmonary TB, begin with a chest radiograph; for intracranial TB, begin with a CT and for abdominal TB begin with US."

The additional use of frontal high-kilovolt radiography did not increase the sensitivity for PTB among children in South Africa [5].

Evidence of a TB contact or infection

In non- or low-endemic regions, most pediatric TB patients can be traced to a TB household contact, especially in infants and young children. In a 10-year survey among TB patients aged between 1 and 15 years, 64% had a history of TB contact [10]. A known adult index case is therefore clue in scoring systems for childhood TB. The probability of being infected by an external contact increases as children get older [32] and in high endemic regions [18]. True congenital TB is very rare [22].

Although a positive tuberculin reaction by itself does not indicate the presence or extent of TB disease, in children, it constitutes an important tool for diagnosis of disease. It may take up to 3 or 4 months from the time of infection to develop a positive TST. In the UK, up to 90% of children with bacteriologically proven TB had a positive TST [30]. In Brazil, there was a nine times higher risk of finding a TST >10 mm in individuals with a probable TB in comparison with the patients with a possible or unlikely TB; however, 60% of malnourished children had a TST <5 mm upon diagnosis [27]. Also, only 22% of HIV-positive children with a proven pulmonary TB in South Africa had a positive TST [34].

Bacteriological diagnosis/confirmation

Bacteriological confirmation is complicated in childhood TB because of the paucibacillarity and the difficulty to obtain a good specimen. Fortunately, bacteriological confirmation is not really a cornerstone for diagnosis if the child can be linked to an (infectious) adult TB case, has a positive TST, a compatible clinical condition, and/or radiographic findings suggestive of TB. The Brazilian score system for pediatric PTB reached a sensitivity of 89% to 98% and a specificity of 86% to 98% without inclusion of bacteriological confirmation [27, 28]. Nevertheless, specimens should be collected for culture when the source case is unknown or has a drug-resistant TB, in case of EPTB, or when the diagnosis is doubtful, especially in immune compromised children [32].

Specimen collection for pulmonary TB

Children under 12 years old are rarely able to produce a sputum and voluntarily expectorate. Therefore, in case of suspected pulmonary TB, gastric aspiration (GA) is often used in the youngest (<6 years) presuming that they have coughed up and swallowed their bronchial secretions. GAs should be

carried out in the morning immediately after waking up and before arising, optimally from three consecutive days, and should be neutralized by adding 10% $NaCO_3$ if decontamination for culture cannot be performed within 4 h [21]. GA from hospitalized children proved as effective as bronchoalveolar aspiration [18]. Alternatively, nasopharyngeal aspirates (NPA) can be obtained from outpatients by stimulating a cough with a feeding catheter at the esopharynx level and trapping the coughed sputum [9]. Gastric and nasopharyngeal aspirates proved equally effective for polymerase chain reaction (PCR) analyses, whereas GA was better for culture analysis and NPA slightly better for direct smear microscopy [9]. The yield of one sample from induced sputum after nebulization was similar to that from three GAs [38, 39] and comparable with results from NPA [24], but this technique still raises concerns of safety for transmission of TB.

Specimen collection for extra-pulmonary TB

Depending on the location of suspected disease, the following specimens can be sampled for bacteriological confirmation: surgical removed lymph node tissues, fine needle aspiration, pleural fluid, cerebrospinal fluid, bone marrow, urine, blood, or intraabdominal biopsies. Early morning urine must be collected and immediately sent for analysis, as the *M. tuberculosis* bacilli are only relatively resistant to the acid pH of the urine [21]. Blood should be anti-coagulated with heparin and processed with a lysis system or inoculated into special media designed for mycobacterial blood cultures. Tissues and other body fluids can be sent without additives to the laboratory.

Acid-fast stain and culture

In general, detection of acid-fast bacilli (AFB) in direct smear microscopy is one of the cornerstones of early diagnosis and management of TB, and the presence of AFB is considered highly specific. However, in children, less than 20% of sputum or GA specimens are found microscopy positive compared to up to 70% in adults [30]. Detection of even a single organism in a smear is therefore highly suggestive of TB in children.

Whereas smear microscopy requires about 5,000 bacilli per milliliter specimen in order to yield a positive result, cultures can become positive with a bacterial load of about 100 bacilli and is therefore considered the definitive method to confirm TB diagnosis. It also allows species confirmation and drug susceptibility testing. However, culture takes 2 to 8 weeks to become positive.

The success of smear and culture depends on the location and extent of the disease and is therefore also age-related. But even under optimal conditions, three consecutive morning GAs yield a positive result in only 30–50% of cases [30]. The culture isolation rate from body fluids in children with EPTB is usually lower than 50% [30], and it is estimated that only 10–20% of all pediatric forms can be diagnosed by culture [21]. Therefore, a negative culture result never excludes the diagnosis of TB in a child.

Other laboratory techniques

A summary of recent diagnostic advances, their potential application, and perceived problems and/or benefits is presented in detail by Marais and Pai [18].

NAAT such as PCR can be a sensitive tool for smear-positive and, to a lesser extent, for smear-negative adult TB [29], but only few studies evaluated the use of these techniques in children. In-house and commercial PCRs showed sensitivities ranging from 25% to 83% PTB in children [7, 11, 32]. In general, PCR can be a supportive tool for childhood TB, but in some severe forms of TB, it can have a real added value as a rapid diagnostic test. An in-house PCR system followed by Southern hybridization yielded a sensitivity of 90% among clinically diagnosed TBM [15], and a nested PCR reached a 96% sensitivity for cervical TB lymphadenitis compared to 26% for culture and 15% for smear [25]. But again, other studies reported low sensitivities of 33% and 60% for TBM [15]. Specimen processing and the way amplified DNA is detected seems most determinant for the variation in sensitivities.

Alternatively, lumbar fluid shows a typical profile in case of TBM: high protein (>100 mg/l) and very low sugar (<40 mg/l) concentrations with a modest lymphocytic pleiocystosis. Further differential diagnosis with bacterial or cryptococcal meningitis can be done by Gram and Indian ink stains, respectively. In addition, determination of the cerebrospinal fluid lysozyme level was found to be the best single test for rapid and early diagnosis of TBM with a sensitivity and specificity of 93.7% and 84.1%, respectively, for a cutoff value of 26 U/l [20]. Lysozyme is a bacteriolytic enzyme that is released in the fluid of tuberculous lesions. Similarly, the mean fluid lysozyme level was significantly raised in tuberculous pleural, ascites, and pericardial effusions with a cutoff value of 50 U/l when cases of empymea thoracis were excluded [19].

Cytomorphology on fine needle aspirates proved more sensitive to detect lymphadenopathy compared to smear microscopy and culture [37]. A recent report of the WHO declines the use of currently available serological tests for the diagnosis of TB in general [36].

Management of TB in children

Both HIV-positive and HIV-negative children with TB disease can be treated with the 6–8 month standard treatment. Children

under 5 years of age exposed to an infectious patient or infected with TB (TST-positive) who are asymptomatic must receive preventive chemotherapy (isoniazid for 6 months). Babies born to mothers with active TB must be managed carefully, as they could have congenital TB, and if they do not have TB, they will need preventive chemotherapy [8].

Conclusion

Diagnosis of childhood TB remains challenging and is mainly based on clinical evaluation (fever, weight loss or failure to thrive, and cough for >2 weeks), radiographs suggestive for TB, evidence of TB infection and, especially in low-endemic countries, evidence of an adult TB index case. Advanced imaging can be applied in case of (and should be restricted to) inconclusive diagnosis. Bacteriological confirmation remains difficult and is useful for doubtful cases or when drug resistance is suspected.

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