Latent Tuberculosis in Children: Diagnosis and Management

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Received: 26 August 2010 / Accepted: 1 November 2010 / Published online: 3 December 2010
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Abstract Control of tuberculosis in children often escapes attention because of the paucibacillary nature of the illness. However, they contribute much of the morbidity, mortality and future reservoir of the disease which reiterates the importance of risk-factor based screening for latent infection and appropriate treatment. We review the modalities and importance of diagnosis and treatment of latent tuberculosis infection in children. At this time, the role for interferon-gamma release assays in low-income, high-burden settings is rather limited but further research in the coming years might clear their role in children. An important emerging area of research is the development of an improved skin test for TB that uses specific mycobacterial antigens rather than tuberculin, thus is more feasible and useful in resource limited settings.

Keywords Latent tuberculosis · Children · Diagnosis · Treatment · Interferon-gamma

Introduction

Latency has been defined by Anderson [1] as “the presence of any tuberculous lesion which fails to produce symptoms of its presence.” Latent tuberculosis infection (LTBI) is defined as a positive tuberculin skin test (TST) in a child who has no signs and symptoms of pulmonary or extra pulmonary TB disease and has a chest radiograph that is either not suggestive or has evidence of healed TB disease (e.g. granuloma, calcification) [2]. Such persons are not infectious in contrast to active tuberculosis cases who are infectious as well as symptomatic [3].

Among children in developing countries, tuberculosis contributes to 2–5% of annual risk of infection and 8–20% of deaths, the infection being acquired primarily from the adults in their surroundings. The estimated life time risk of developing active disease for a child infected with Mycobacterium tuberculosis as indicated by positive TST is about 10–20%, out of which 5% are likely to develop disease in the first year after infection and another 5% in the rest of their lifetime [4]. Approximately 40% of infected infants, if left untreated, develop radiologically significant lesions compared with 24% between 1 and 10 years and 16% in 11–15 years of age [5]. Marais et al. [6] have shown the effect of age of the child at acquisition of infection on the occurrence of TB disease (Table 1).

LTB Diagnosis

As patients with LTBI are by definition healthy and do not present with radiological abnormalities, screening must rely on immunological markers of infection. An overview of the available diagnostic modalities is presented with shifting focus from the century old TST to the more accurate T-cell interferon gamma release assays (IGRAs) [7–9]. The major differences amongst the IGRAs and TST are presented below in Table 2.

Tuberculin Skin Test

First described by Robert Koch in 1890, the Mantoux test (Tuberculin sensitivity test, Pirquet test, or PPD test for Purified Protein Derivative) is named after Charles Mantoux,
a French physician who created his test in 1907. Tuberculin is a glycerol extract of the bacillus while PPD introduced in 1934 is its standardized version. In 1939, PPD-S was produced by Seibert and Glenn which remains the international standard. A standard dose of 5 tuberculin units (0.1 ml) is injected intradermally (except in UK where 2TU of SSI {Staten Serum Institute} tuberculin RT23 in 0.1 ml solution is used). A person exposed to the bacteria should mount an immune response in the skin containing the bacterial proteins which is read 48–72 h later by measuring the diameter of induration across the forearm in millimeters and gauged against standard cutoffs [10]. Due to its low specificity, false-positives are caused by non-tuberculous mycobacteria or previous administration of BCG vaccine [11]. Conversely, immunologically compromised children, such as with HIV and low CD4 counts or severely malnourished fail to mount an immune response, thus falsely negative. Paradoxically, the TST has more false negative results in populations with higher risk of TB reactivation; 10% of children with confirmed TB do not react to the TST at the time of diagnosis. A new generation of LTBI diagnostics, the IGRAs seem to be significantly more accurate than the skin test [12] and three of them have been approved for clinical use by Food and Drug Administration (FDA).

| Table 1 Risk of progression from tuberculosis (TB) infection to disease |
| Age at primary infection (yr) | No disease (%) | Pulmonary disease (%) | Miliary or central nervous system TB (%) |
|<1 | 50 | 30–40 | 10–20 |
|1 to 2 | 75–80 | 10–20 | 2.5 |
|2 to 5 | 95 | 5 | 0.5 |
|5 to 10 | 98 | 2 | <0.5 |
|>10 | 80–90 | 10–20 | <0.5 |

Quantiferon-TB Gold (QFT-G)

Approved by FDA in 2005, QFT-G is an enzyme-linked immunosorbent assay (ELISA) based whole blood test in which blood samples are incubated with the mycobacterial antigens (ESAT-6 and CFP-10) for 16 to 24 h. If the patient is infected with M. tuberculosis, their white blood cells will release interferon-gamma in response to contact with the TB antigens which is quantified.

Quantiferon-TB Gold In-Tube Test (QFT-IT)

Approved by FDA in Oct 2007, this ELISA-based assay for quantification of interferon-gamma uses heparinized whole blood sample drawn directly into specialized three blood collection tubes with antigens (ESAT-6, CFP-10, and TB7.7 proteins) dried onto their walls and transferred to an incubator within 16 h of collection. It is marketed to have specificity of >99% in low risk individuals and sensitivity of 92% in individuals with active disease [10]. Regarding its utility in children, a study by Lighter et al. [13] reveals that QFT-IT is a specific test for M. tuberculosis exposure in children, with performance characteristics similar to those for adults residing in regions with low levels of endemic disease though sensitivity for children <2 years of age needs further evaluation.

**T-SPOT.TB**

It is a type of enzyme-linked immunospot (ELISPOT) assay in the whole blood to count the number of effecter T cells i.e. white blood cells that produce interferon-gamma. This gives an overall measurement of the antigen load on the immune system, which can reveal the presence of subclinical disease faster (within 24 h) and accurately. Studies describe a sensitivity of 85% for ELISPOT vs 70% for TST in children with confirmed or

| Table 2 Main differences between tuberculin skin test (TST) and T-cell interferon-gamma release assays (QFT-G and T-SPOT.TB) [16] |
| Influence by prior BCG vaccination | TST | QFT-G | T-SPOT.TB |
| Influence by non-TB mycobacteria | Yes | No | No |
| Booster effect if repeated | Possible | No | No |
| False positives | Possible | No evidence | No evidence |
| False negatives | Possible | Possible | Possible |
| Correlation with exposure intensity | Partial | Yes | Yes |
| Antigens used | PPD RT23 | ESAT-6, CFP-10 | ESAT-6, CFP-10 |
| Technique | In-vivo skin test | ELISA | ELISPOT |
| Results reported in | mm of induration | IFN-gamma units | Spot-forming units |
| Adverse reactions | Rare | None | None |
| Patient visits to complete testing | Two | One | One |
| Laboratory infrastructure required | No | Yes | Yes |
highly probable TB [14] and sensitivity up to 93% for established culture proven cases [15].

Individual observations hint that the IGRA's convert to positive before the TST [17] and are significantly more specific than the latter [12]. Recent longitudinal studies indicate higher positive predictive values for development of future TB with IGRA's compared to TST [18, 19]. While Connell et al. [7] described a high rate of indeterminate test results among children exposed to TB but not among children with documented TB, Nakaoaka et al. [20] reported better correlation of the blood tests with intensity of exposure than the TST. The reason for these discrepancies is unclear but perhaps is related to the tuberculin used, the cutoff considered for positivity or the background prevalence rate of non-TB mycobacteria infection. Detjen et al. [15] have shown that the blood tests allow a distinction between infection with Mycobacterium tuberculosis and with non-tuberculosis mycobacteria in children in a low prevalence country.

Though ELISPOT assay has been reported to correlate more closely with M. tuberculosis exposure and to be unaffected by BCG vaccination [21], it proved slightly less sensitive than the TST in its diagnosis of infection from recent exposure in Gambian children with no confounding effect of prior BCG vaccination on either tests. It was also suggested to combine the two tests for maximal sensitivity in recently exposed cases [22, 23]. Nicol et al. [24] observed that the sensitivity of T-SPOT.TB was no better than that of the TST for culture confirmed tuberculosis (50% and 80% respectively), poorer for the combined group of culture-confirmed and clinically probable tuberculosis (40% and 52% respectively) and the specificity of both the tests was 84% for children clinically categorized as not having TB. The most important findings of this study were that negative T-SPOT.TB results could not be used to exclude active TB in young children at risk because children <12 months of age were more likely to have positive T-SPOT.TB results while TST remained unaffected by age.

Thus, though IGRA's have high specificity, correlate better than TST with the intensity of contact with the infectious case in children [20] and can be repeated without any booster effect, yet they do not differentiate between LTBI and active disease just like TST and hence their use for the diagnosis of tuberculosis remains controversial [8, 25, 26]. The possible influence of a TST performed before blood sampling for IGRA's has been shown by some [27] while refuted by others [17]. Among the IGRA's, QuantiFERON-TB tests were more likely than T-SPOT. TB to give indeterminate results in children <4 years of age as per one study [28].

As a new specific skin test, Arend et al. [29] compared rdESAT-6 skin test to TST in adults in a double blind randomized phase 1 study and found it safe as well as feasible though it's utility in children, sensitization after repeated doses and role of additional CFP-10 on sensitivity needs evaluation.

Why Children Need Treatment

Treatment is recommended for the following reasons [30] in all children and adolescents diagnosed with LTBI-

1. Infants and children less than 5 years of age are more likely to be infected recently, so the risk for progression to TB disease is high,
2. Risk for severe disease, including meningitis and military forms, is inversely related to the age of the child at acquisition of the disease,
3. Children with LTBI have more years at risk for the development of disease later in life,
4. Children with LTBI become adults who act as reservoirs,
5. The drugs used for treatment are relatively safe in the pediatric population

Thus, screening children in contact with TB cases is in the best interest of the child for personal health and public health at large for disease control.

Terminology

CDC [31] recommends the use of terminology “Treatment of Latent Tuberculosis Infection” rather than “Preventive Therapy” and “Chemoprophylaxis” used previously as the latter rarely result in true primary prevention (i.e. prevention of infection in persons exposed to an infectious case) rather means prevention of development of active TB disease in persons currently well but infected with M. tuberculosis.

Treatment Regimens Currently in Use

It is imperative to rule out active TB before treatment for LTBI is begun. To treat latent TB in a child with active disease is a serious error with grave risk of inadequate treatment and emergence of drug-resistant strains. Based on the results from the clinical trials [32–34], the currently recommended treatment regimen in developed countries is 9 months of Isoniazid (INH) monotherapy with a protection efficacy of 70–90%. Daily Rifampicin is used for the same when INH is not tolerated or the child was exposed to an INH-resistant, Rifampicin-susceptible source case [10]. Children generally tolerate INH better than adults with
minimal risk for drug-related hepatitis [35, 36]. The duration of 9 months is recommended because the maximal beneficial effect of INH is likely achieved by this time and minimal additional benefit is gained by extending the therapy to 12 months [33]. Also, routine administration of pyridoxine is not advised unless there are (a) breastfeeding infants (b) children with diets likely to be deficient in pyridoxine (c) children experiencing paresthesias while taking INH.

Because of high prevalence of INH resistance, Finnell et al. [37] suggest the use of Rifampicin for 6 months for children originating from countries with >11% INH resistance. As per their study, the risk of TB reactivation was maximum with 9 months of INH and minimum with 6 months of Rifampicin, whereas combination of INH and Rifampicin is the most effective. Safety and acceptability of Rifampicin therapy (10 mg/kg/day for 6 months) in adolescents has been found satisfactory by Villarino et al. previously [38]. In fact, Ormerod et al. [39] in their observational study over 15 years period suggested that 3–4 month regimens of Rifampicin plus INH (10 mg/kg/ day each) were effective in the treatment of LTBI in children and adolescents ≤15 years of age. The mild increase in serum liver enzymes seen in many children with these drugs is generally clinically silent [36, 40]. Combined treatment approach with INH and Rifampicin is used assuming an increased likelihood of the pathogen being susceptible to at least one of the two drugs. A 3 months regimen of the aforesaid combination has been used in UK [41] with programmatic data showing both longer and shorter regimens to be equally efficacious [39, 42]. However, Finnell [37] found this regimen least costly but 0.7% less efficacious than rifampin for 6 months (in areas with INH resistance <80% and regimen’s effectiveness was 50% for susceptible bacteria).

Recent studies in adults using shorter regimens of Rifampicin plus Pyrazinamide for 2 months were fraught with unexpected high rates of hepatotoxicity including fatalities from liver failure. Though reports of this regimen being well-tolerated in a small number of children are there [43], yet in view of lack of efficacy and large safety data in children, CDC has not recommended its use in the pediatric age group [44].

Indian Academy of Pediatrics (IAP) in 1997 [45] issued guidelines for chemoprophylaxis with 6 months of INH and Rifampicin (HR) for: asymptomatic Mantoux positive <3 years of age, asymptomatic Mantoux positive <5 years of age with grades III or IV malnutrition, Mantoux positive recent converter/no signs, children <3 years of age with history of positive contact, children <5 years of age with grades III or IV malnutrition with history of positive contact. According to the recent guidelines by IAP [5], 6 months of INH preventive therapy is recommended for all contacts of an infectious case under 6 years of age, irrespective of their BCG or nutritional status. PPD positive children over 6 years of age who do not have any evidence of active disease but are planned for immunosuppressive therapy (e.g., children with nephrotic syndrome, acute leukemia etc.) should also receive prophylaxis. Though the HR combination can make the duration shorter evidently but the group does not recommend it due to the risk of misuse of Rifampicin. Also, all household contacts should be screened for symptoms of the disease and INH is provided to those less than 5 years of age and to all HIV-infected children.

References


