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# Clinical, Radiological and Inmunological Features in Children with Pulmonary Tuberculosis: A Review

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**Abstract**

In the whole world, tuberculosis (TB) continues being an important health problem. It produces a great number of deaths in children, mainly in the wake of the HIV epidemic. In addition, the globalization with the increased of the international travels and the immigration makes that TB control be more difficult. This is a clinical, radiological and immunological review in children TB where we search to contribute the data in the literature.

## Context

Tuberculosis (TB) is one of the most important global health problems. The latest estimates included in the Global tuberculosis report are that there were 8.6 million new TB cases in 2012 and 1.3 million TB deaths worldwide. Of those, 530.000 cases and 74.000 deaths were children [1]. Clinical and radiological findings, such as hemoptisis, cough, caverns or upper-lobe condensations, might be reliable and well established in adults. By contrast, these findings might be more difficult to evaluate in children due to more nonspecific symptoms and heterogeneus radiological findings [2].

## Objective

The present work overviews the most important clinical and radiological findings in children diagnosed with tuberculosis infection and disease. We included articles that reported cases with children from 2 months to 13 years. Children were from different backgrounds, and from developed and underdeveloped countries.

## Data Sources

The selection of studies for analysis was as follows: all articles published from October 2008 to December 2013, which described clinical and radiological findings of children with TB were selected. These articles were obtained by searching throughout several international databases including Pubmed, Scopus, Highwire Press, Scientific Information Databases, Google Scholar and EBSCO-host.

To locate the articles to include in our review, the strategy consisted of an exhaustive search including the following medical subject headings (MeSH) terms: “tuberculosis” or “pulmonary tuberculosis" in combination with "children” or “infant” or “infancy”, in combination with "clinical symptoms”, “radiological findings”, “Mantoux”, “tuberculosis diagnosis”, “management of tuberculosis” and “tuberculosis treatment”.

## Study Selection

Inclusion criteria for systematic review were: 1) Retrospective or prospective cohort studies; 2) Reporting clinical, radiological or Mantoux results in TB patients 3) Studies including data at the national level; and 4) Studies on TB patients meeting either the WHO recommended definitions for “definite cases” or “other than definite cases” or TB patients meeting the possible, probable or confirmed case definition as published by the European Commission in 2008.

Opinion articles, editorials, comments, case studies and/or drug efficacy tested in vitro or through clinical trials were excluded from the systematic review. Furthermore, those articles not published in English or Spanish language were excluded from the review. Literature searching was performed until 1st December 2013. Using the search terms previously described above, fifty-three studies were considered to be relevant, among them, only 40 met all the inclusion criteria and none of the exclusion criteria. The first authors of these articles were mainly from China, India, Pakistan, the United Kingdom, Australia, and the United States. The analysis of the abstracts of the selected articles reported that 25 (64%) of the studies were retrospective, 5 (13%) were prospective, and 10 (23%) were other designs. Articles categorized as citations identified by the search strategy were reviewed for possible eligibility by two authors trough a blinded form (C. A. Amado and D. Ferrer) based on title and abstract, according to the inclusion criteria. Once the results were contrasted and the selection was completed, we proceeded to the systematic review of the selected articles.

## Data extraction

Clinical and radiological data from the included studies in the review was extracted and entered into a database. No attempts were made to obtain missing data from the researchers of the eligible studies.

## Results

### Clinical findings

Contact history was one of the keys to suspect TB in children. Different studies report contact history that varied from 42.5% [3] to 100% [4]. Several studies stated that concomitant diseases and risk factors such as malnutrition, vitamin D deficiency or HIV infection, should be considered as they have important diagnostic and pronostic implications [5-8]. Some studies suggested greater vulnerability of the female child [9].

Clinical symptoms in TB were reported almost always as nonspecific, mainly in children younger than 12 months (Table 1). Children with less than 1 year used only to present nonproductive cough, productive cough in general is rarely seen in pre-adolescent children [4,5]. TB should be suspected if cough lasted more than 2 weeks. Low grade or intermittent fever was also a common symptom mainly in older children, cold sweat or dyspnea can also be seen in children [10]. In 2005, Marais et al, proposed the use of well-defined symptoms to improve diagnostic accuracy of PTB [11]. In this initial study, the use of these well-defined symptoms seemed to be a very useful tool in the diagnosis of pulmonary TB (PTB). On the other hand this kind of approach to PTB was not widely used. Although therapeutic trials with anti-TB drugs are used sometimes in adult-TB, this kind of diagnostic approach is not recommended in children.

| Clinical Findings | Articles |
|---|---|
| Cough | 27/33 |
| Fever | 26/33 |
| Dysnea | 8/33 |
| Weight loss | 4/33 |
| Lumphadenopathy | 1/33 |
| Night sweet | 3/33 |
| Miliary | 10/33 |
| Cutaneus | 1/33 |
| Skeletal | 2/33 |

**Table 1:** Main clinical findings found in the selected articles

**Extra-thoracic TB:** TB may have important extra-thoracic symptoms. Lymphadenopathy was the most common extra-thoracic detected manifestation (67%), followed by central nervous system involvement (13%), pleural (6%), miliary and/or disseminated (5%), and skeletal (4%) TB forms. Tuberculous meningitis and disseminated disease were more commonly found in HIV infected children, or children younger than 3 years old [12]. Cutaneous TB was a significant medical problem in certain countries. In a recent review from India [13] it was reported that its prevalence varied from 18 to 54%. Spinal TB was a rare disease found in children, which needed a higher index of suspicion for diagnosis, but caused important systemic symptoms [14], and might lead to a difficult differencial diagnosis [15]. Haemophagocitic Syndrome, another important immunological complication of TB, was rarely seen but it could lead to death in children [16]. Childhood tuberculosis commonly extrapulmonary, disseminated, and severe, especially in children under 3 years of age, and it is associated with high morbidity and mortality [1]. Some authors [17] propose comprehensive disease classification systems in order to reflect the clinical TB disease spectrum in children although they are not widely used.

### Radiological findings

Chest x-ray findings are generally nonspecific. Gwee and colleagues described recently a study of 268 TB-infected children from Australia. Only 60 patients had chest x-ray findings suggestive of TB [18]. On the other hand, chest x-ray in younger children may be even more difficult to evaluate. In a study of 9 cases of children under 12 months, three patients (33%) showed a normal chest x-ray; consolidation was shown in three (33%); nodular lesions were found in three (33%), and among them, consolidation and ground glass were seen only in one (11%) [4]. Irregular hiliar and mediastinal images with central necrosis, at the beginning of the disease, and regular at the resolution of the disease are also commonly associated with TB. Other radiological findings such as a consolidation pattern can be seen in progressive primary pulmonary infection. This pattern is usually seen in posterior segments of inferior lobes, and it is produced due to low lymphatic drainage [19]. Athelectasia usually seen in middle lobe presented as radiopaque triangular lesions producing lung volume reduction and mediastinal distorsion are frequently seen after mediastinal lymph node enlargement, or pleural effusion, are also common findings especially among patients with an evolved progressive primary infection [20,21]. The absence of pathognomonic radiological findings, and the difficulty to get a positive Mycobacterial culture [22,23] makes it hard to get a definitive diagnosis in children with PTB. Miliary TB, a systemic form of the disease that typically affects children 6 to 11 years old, characterizes by a micronodular pattern consisting of well-defined nodules-in the shape of seeds of millet- uniformly distributed in all lobes, and it is seen usually 6 weeks after primary infection. In this kind of TB, radiological findings are more specific [24].

Computerised Tomography (CT) scan is a useful tool in patients with PTB. Traditionally, due to its high cost and elevated levels of radiation, CT is considered to be reserved for complicated or difficult to diagnose cases. However, if indicated, it may offer an opportunity for CT guided biopsy for tissue diagnosis (Table 2).

| Radiological Findings | Articles |
|---|---|
| Lymphadenopathy | 26/32 |
| Alveolar consolidation | 23/32 |
| Nodular infiltration | 17/32 |
| Cavitation | 9/32 |
| Interstitial | 10/32 |
| Bronchiectasis | 8/32 |
| Pleural effusion | 6/32 |

**Table 2:** Main radiological findings found in the selected articles

The most common radiological findings in the CT are mediastinal or hiliar lymphadenopathy with central necrosis and lung parenchymal lesions. The common radiological features of pulmonary tuberculosis in infants are also hiliar or mediastinal lymphadenopathy with central necrosis and air-space consolidations, especially mass-like

consolidations with low attenuation areas or cavities with the consolidation. Less common findings such as disseminated nodules, airway complications, bronchial wall thickening and bronchiectasias are also seen in this age group [21,25].

CT is a useful diagnostic technique in infants with tuberculosis because it can show parenchymal lesions and tuberculous lymphadenopathy better than chest radiography. CT scans can also be helpful when chest radiographs are inconclusive or complications of tuberculosis are suspected. CT is usually needed to confirm the suspected findings. High-resolution CT is the most currently sensitive tool available to detect hiliar lymphadenopathy and/or early cavitation although it should be used with caution in children [26].

### Immunological Tests

The objective of the embodiment of the Mantoux test in children is to detect cases of latent tuberculosis infection early to prevent and control disease evolution in exposed children. It takes 8-12 weeks after infection to have a positive Mantoux test. In children, Mantoux test is performed by intradermal injection of 0.1 ml of PPD containing 2 units PPD-R23. It should be read at 72 h, when the maximum induration is achieved, although it is possible to read it between 48 and 96 hours. Only maximum diameter induration transverse to the long axis of the arm should be measured. A test is considered positive when diameter induration is ≥ 5 mm in children in close contact with the index case, children with suspected clinical or radiological TB, children in situation of immunosuppression such as HIV infection, or children with previous negative Mantoux tests. A reaction of >10 mm of induration should be considered positive for those patients with an increased probability of recent infection or with other clinical conditions that increase the risk for TB (e.g., recent immigrants from high-prevalence countries and injection drug users). For any other case an induration ≥ 14 mm is considered as positive [27].

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 [28].

Interindividual variations (measurements carried out by different people) and intraindividual (measurements made by the same person) are rare when the induration is 0, but they are not uncommon when there is some degree of induration [29]. In addition to variations in measurements, other factors which influence the sensitivity and specificity of Mantoux are the severity of the infection itself which can appear until in 10% of the disseminated forms and in serious lung infections demonstrated by culture with negative Mantoux [30]. Some infections caused by virus such as measles and chickenpox may decrease tuberculin response transiently. After administration MMR (measless, mumps and rubella) vaccine, a decrease in the size of the induration may happens [31]. In this case, it is recommended to perform the vaccination and Mantoux test in the same day. Corticosteroid therapy also decreases the response to Mantoux test and even can becomes negative, mainly when high doses of prednisone or equivalent (>2 mg/kg/day) are used.. The hyporesponsiveness is transient and it recovers after removal of the drug. The BCG vaccination may result in false positive result [32], but in cases of high clinical or epidemiological suspicion the importance of prior BCG should be minimized or not considered, especially if vaccination was carried out at birth or in the first months of life. Less than 50% of infants who were managing a Mantoux after birth were positive at 6-12 months [33]. In fact, almost all children vaccinated at birth were negative at 5 years of age [34] and studies showed that there were differences in Mantoux positivity between the vaccinated and unvaccinated infants at birth [35]. Moreover, positivity equal to, or greater than 15 mm are unlikely to be in BCG vaccinated children and it should always be considered as tuberculosis infection.

Recently, Interferon Gamma Release Assays (IGRAs) have been developed and introduced for a rapid diagnosis of TB infection. They consist in measurement of interferon gamma (IFN-γ) levels secreted by specific T cells stimulated with Mycobacterium tuberculosis antigens in a whole blood assay. Two licensed IGRAs are commercially available: QuantiFERON TB Gold in tube (Cellestis, Carnegie, Victoria, Australia) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK). Several studies of both assays have been reviewed for their ability to identify latent infection and to diagnose active disease in various populations [36]. IGRAs and Mantoux are surrogate markers for *M. tuberculosis* infection, however, neither assay can distinguish between latent and active tuberculosis.. However, IGRAs might be useful in settings where Mantoux test result could give a false positive result result by cross-reactivity with environmental mycobacteria, BCG vaccination after infancy, or multiple BCG vaccinations (e.g. BCG therapy in bladder cancer) [37].

In children, several studies have been peformed regarding the use of IGRAs and the Mantoux test. Most of them concluded that IGRAs were more specific than Mantoux, but sensitivity varied from 40 to 100% suggesting the combined use of Mantoux and IGRA to increase sensitivity [38,39].

## Conclusions

After reviewing the selected studies, we could conclude:

1) Clinical and radiological findings in children with TB are difficult to evaluate because they are nonspecific. Contact history is one of the keys for diagnosis

2) TB should be suspected in children with other concomitant illness such as malnutrition or HIV infection. Contact with an adult with PTB is always the most important finding in this kind of patients.

3) Although cough might be the most common symptom in PTB, clinical symptoms are often subtle, and to our knowledge, no diagnostic scoring in matters of symptoms has been validated.

4) Chest x-ray is useful in order to evaluate the severity of the disease, but this test does not confirm disease etiology. On the other hand CT scan could be very useful in order to confirm PTB in children, even in early pulmonary disease. However, due to the high cost of CT and the high level of radiation to which the patient is exposed, it should be reserved for complicated cases.

5) Mantoux test or Interferon-gamma release assays (IGRAs) should be evaluated with caution in immunocopromised patient.

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