Typical and atypical aspects of pulmonary tuberculosis in children: has anything changed in the past 20 years?

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Aims and objectives

In 1993 the World Health Organization (WHO) declared tuberculosis (TB) a "global emergency": 1.7 billion people were infected with *M. tuberculosis*, 3 million died from it, and approximately 8 million new cases occurred [1]. According to the WHO estimations, in 1990, there were 13 million new cases and 450,000 deaths among children less than 15 years old. In 1994, it was estimated that the global incidence of TB in children aged 0-14 years would be more than 1 million cases by 2000 [2]. Furthermore, regional data from the WHO in 2007 showed that, in children younger than 14 years, smear-positive TB accounted for 0.6-3.6% of reported cases, underestimating the true burden of the disease, because #95% of cases in children under 12 years of age are smear negative [3]. Although childhood tuberculosis contributes to only 3-6% of the total caseload in industrialized countries, it makes up a large proportion (15- 20%) of all TB cases in developing countries, with an 2.5% annual risk of TB infection in children [1,4].

Consistent with the global endemic decline of the disease, in Romania the incidence of TB in children aged 0-14 years decreased constantly from 47.2‰ in 2002 to 23.6‰ in 2011 [5].

Classically, tuberculosis is divided into primary, common in childhood, and postprimary, usually presenting in adults [6]. Primary tuberculosis is respiratory of origin and is seen in patients not previously exposed to *M tuberculosis*, having the highest prevalence in children under 5 years of age. It results from the inhalation of airborne droplets containing the causative organism [1,7,8]. Inoculation takes place most often in the best ventilated areas of the lungs, most frequently in the anterior segments of the upper lobes, middle lobe, and lingula, and the basal segments of the lower lobes. The bacillus enters the airways, is carried by cilia to the terminal bronchioles and reaches the alveoli where a usually small lung infiltrate is produced due to the invasion and replication within alveolar macrophages [1,6,8,9].

From the local infective focus, called the Ghon focus, bacilli spread to regional lymph nodes via lymphatic vessels. The tree entities are known as the primary complex, the Ranke or Ghon complex [1,6,8-10]. This regional lymphadenopathy is considered the hallmark of the radiologic diagnosis of primary TB in children [8,12,13]. The further extent of the primary infection, occurring after inhalation of TB bacilli, is dependent on different factors such as number and virulence of the agent, natural and acquired resistance of the host, and hypersensitivity [1].

The macroscopic hallmark of hypersensitivity is the development of caseous necrosis in the pulmonary focus and/or in the involved lymph nodes [1]. In 2/3 of cases,
the parenchymal focus resolves without sequelae at conventional radiography. In the remaining number of cases, the initial parenchymal focus of pulmonary TB undergoes healing by transformation of the granulomatous tissue into mature fibrous tissue or may enlarge and result in airspace consolidation or progressive disease with multilobar involvement and cavitary development [6,7,10,14].

Therefore, primary tuberculosis manifests as four main entities: parenchymal disease, lymphadenopathy, miliary disease, and pleural effusion [7].

Chest radiography remains the mainstay of pulmonary TB diagnosis in children; however, normal radiographic findings may be seen in up to 15% of patients with proved tuberculosis [7,11].

Giving the global and regional epidemiological context in the past 20 years, our aim was to compare the radiological features of pulmonary TB in children who presented the disease 15 to 20 years ago with those in the last 5 years and search for a possible evolution in pulmonary TB radiological pattern.
Methods and materials

A retrospective analysis of patient record was performed at the Paediatric Pulmonology Department of the "Leon Daniello" Pulmonology and Tuberculosis Care Clinics in Cluj-Napoca, a tertiary-care university hospital that acts as a referral tuberculosis center in Transilvania. This study included two groups of consecutive patients with confirmed pulmonary TB, in Cluj county. Group A consisted of all children (n=110) in evidence between January 1993 and December 1997, and Group B (n=83) of all cases from January 2007 to December 2011.

Diagnosis

The diagnosis of pulmonary TB was established by the presence of at least two of the four criteria: positivity of the tuberculin skin test read after 48-72 hours (>10mm induration independent on the prior immunization with Bacillus Calmette-Guérin; >5mm in children with immunodeficiency disorders, including HIV; according to the Diagnosis and Treatment Guide in Childhood Tuberculosis elaborated by the National Institute for Healthcare Research and Development), contact with a confirmed TB infected source in the entourage, suggestive clinical presentation (persistent, unremitting coughing, wheezing, fever and weight loss) and/or subsequent clinical or radiological improvement from anti-TB treatment (isoniazid, rifampicin, pyrazinamide).

Radiological findings

All children underwent a standard chest radiography (CXR) and all images were reviewed by the same senior radiologist, who was aware of the clinical presentation. The radiological assessment included classical features: presence and distribution of lymphadenopathy, focal bodies, pleural effusion, and atypical pattern with particular attention on presence and localization of parenchymal complications: consolidation (including expansile pneumonia, collapse, macronodular infiltrates or bronchopneumonic changes), cavitation and miliary nodules.

These radiological findings were entered into the database as categorical and binary variables.

Ethics approval was not required as anonymous and routinely collected data were used.

Statistical analysis
All data were analyzed using R statistical software version 1.9-2 (R Foundation for Statistical Computing, Vienna, Austria). The chi-square test was used to assess differences between the two groups regarding each radiological feature. A $P$ value of $<0.05$ was considered to indicate a significant statistical difference. Results were expressed as frequencies and percentages for categorical variables.
Results

The incidence of TB decreased with 24.55%, from 110 cases in 1993-1997 to 83 cases in 2007-2011. In group A there were 62 males (56.36%) and 48 females (43.64%), with ages ranging from 1 to 18 years, mean age 7.4 years. In group B there were 44 males (53.01%) and 39 females (46.99%), with ages ranging from 6 months to 18 years, mean age 9.6 years. In both groups the largest age category was that of infants, 19 patients (17.27%) and 21 cases (25.3%) respectively. An immunodeficiency disorder was present in two children (one congenital immunodeficiency syndrome and one HIV positive) from each group.

Lymphadenopathy was reported in 56 (50.91%) and respectively 40 (48.19%) patients in the two groups, more frequently with a right side involvement (41 vs. 30 of positive CXR). Bilateral distribution was seen in 31 and respectively 14 cases from each group (Fig 1.).

Fig. 1: 3 year old child with primary TB manifesting as bilateral pseudotumoral hilar and paratracheal lymphadenopathies

References: Paediatric Pulmonology Department, "Leon Daniello" Pulmonology and Tuberculosis Care Clinics, Cluj-Napoca/ Romania2013
A total of 91 instances of parenchymal complication were identified in 35/110 (31.82%) vs. 35/83 (42.17%) children. The most common parenchymal complication was consolidation (14.55% vs. 37.35%) (Fig. 2 and Fig. 3), followed by cavitation (7.27% vs. 10.84%). A significant statistical difference was found between the two groups regarding the presence of consolidation (p<0.001), as well as the presence of pleural effusion (p<0.05). These findings are summarized in Table 1.

Fig. 2: 7 year old child with primary TB manifesting as right hilar lymphadenopathy and right upper lobe expansile pneumonia

References: Paediatric Pulmonology Department, "Leon Daniello" Pulmonology and Tuberculosis Care Clinics, Cluj-Napoca/ Romania 2013
Fig. 3: 2 year old child with primary TB manifesting as right hilar lymphadenopathy and right upper lobe collapse.

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Table 1. Instances of pulmonary TB detected by CXR in children from the two groups

<table>
<thead>
<tr>
<th>Radiological feature</th>
<th>Group A Number of children (%)</th>
<th>Group B Number of children (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical appearance</td>
<td>75 (68.18)</td>
<td>48 (57.83)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>56 (50.91)</td>
<td>40 (48.19)</td>
<td>0.7</td>
</tr>
<tr>
<td>Parenchymal complication</td>
<td>35 (31.82)</td>
<td>35 (42.17)</td>
<td>0.1</td>
</tr>
<tr>
<td>Consolidation</td>
<td>16 (14.55)</td>
<td>31 (37.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cavitation</td>
<td>7 (7.27)</td>
<td>9 (10.84)</td>
<td>0.3</td>
</tr>
<tr>
<td>Miliary</td>
<td>3 (2.72)</td>
<td>2 (2.41)</td>
<td>ns</td>
</tr>
</tbody>
</table>
Table 2 shows the instances of specific parenchymal complication subtypes together with laterality of the lesions. Expansile pneumonia was the feature most frequently assessed (21 respectively 29 lesions). Overall, parenchymal complications were more frequent in the upper lobes (19 vs. 26 cases in the two groups). The mean number of complications per child was 1.2 in group A (35/42) and 1.4 in group B (35/49). One case of lymphobronchial fistula was found in each group (Fig. 4).

Table 2. Instances of specific parenchymal complication subtypes and laterality of the lesions in the two groups

<table>
<thead>
<tr>
<th>Parenchymal complication</th>
<th>Group A</th>
<th></th>
<th></th>
<th>Group B</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right lung</td>
<td>Left lung</td>
<td>Total</td>
<td>Right lung</td>
<td>Left lung</td>
<td>Total</td>
</tr>
<tr>
<td>Expansile pneumonia</td>
<td>18</td>
<td>6</td>
<td>24</td>
<td>21</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Collapse</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macronodular infiltrates</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Cavitation</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>10</strong></td>
<td><strong>42</strong></td>
<td><strong>32</strong></td>
<td><strong>17</strong></td>
<td><strong>49</strong></td>
</tr>
</tbody>
</table>
Fig. 4: 4 year old child with primary TB manifesting as cavitation of the left hilar lymphadenopathy after lymphobronchial fistula

References: Paediatric Pulmonology Department, "Leon Daniello" Pulmonology and Tuberculosis Care Clinics, Cluj-Napoca/ Romania 2013

The number of patients with parenchymal complications associated with lymphadenopathy was 15 in group A and 14 in group B. A significant statistical correlation was found between the presence of lymphadenopathy and parenchymal complication in group A (p<0.0001), but not in group B (p=0.6).

In group A, lymphadenopathy was most frequently reported in infants, with constant decreas by age, while group B presented 2 peaks, in infants and adolescents. Consolidation was seen mainly in children under 14 years of age in group A, and in patients >14 years in group B. In both groups, cavitary lesions and pleural effusion were reportend more frequently in adolescents. Table 3 shows detailed data regarding patients age and radiological aspects in the two groups.

Table 3. Number of cases by age for each radiological feature in the two groups

<table>
<thead>
<tr>
<th>Lymphadenopathy</th>
<th>Consolidation</th>
<th>Cavitation</th>
<th>Pleural effusion</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>28</td>
<td>20</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-4</td>
<td>18</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4-6</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6-8</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8-10</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>10-12</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>12-14</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14-16</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>16-18</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>
Fig. 1: 3 year old child with primary TB manifesting as bilateral pseudotumoral hilar and paratracheal lymphadenopathies

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Conclusion

In this study, we searched for possible time-related trend in the radiographic appearances of pulmonary TB in children. Therefore, we compared CXR features of pulmonary TB in children who presented the disease 15 to 20 years ago with those in the last 5 years in order to find possible changes in pulmonary TB radiological pattern.

Lymphadenopathy is considered the hallmark of the radiological diagnosis of TB in children and was reported in previous studies in up to 96% of cases, with a prevalence that decreases with age [7,13,14]. Our result show similarities regarding the first group, but not for group B, where a second peak was present in adolescents. This findings related to the mean age of the children in the two groups (7.4 vs 9.6) indicate the efficiency of prevention programs and the evolution of the first presentation to an older age. The distribution is typically unilateral and right sided, with bilateral impairment in about 1/3 of cases [7,17]. However, CXR is very subjective and presents low sensitivity and specificity for detecting subcarinal and paratracheal adenopathies [15]. In contrast to the age-related occurrence observed with lymphadenopathy, Leung et al. [13] showed that the prevalence of parenchymal involvement was significantly lower in children up to 3 years of age. In our groups there was an increased prevalence of parenchymal complications in infants.

Gangliopulmonary TB may be complicated by perforation of an adenopathy in a bronchus, retroobstructive pneumonia, and/or compression of a bronchus by an adjacent enlarged node resulting in atelectasis (epituberculosis). The most frequently radiographic finding of pulmonary parenchymal lesion is consolidation. A retro-obstructive infiltrate in primary TB most commonly appears as an area of homogenous consolidation. Its appearance is often indistinguishable from that of bacterial pneumonia; however, they can be differentiated on the basis of radiographic evidence of lymphadenopathy and the lack of response to conventional antibiotics. Compression, with subsequent lobar or segmental atelectasis, is more frequent and more severe in infants. The compression is most commonly reported at the level of bronchus intermedius [7,16]. The most frequent complication documented in our study was consolidation, with an increasing prevalence in recent years, which reached statistical significance. As this increased prevalence was accompanied by a decrease in the presence of lymphadenopathy and their correlation did not reach statistical significance, we believe these findings are due to longer duration of symptoms and diagnosis delay, which allowed a longer evolution of the TB process. However, it is not possible to differentiate consolidation secondary to lymphobronchial TB from that of advanced primary local TB process, as the radiologic appearances are indistinguishable [16].
The incidence of cavitation on CXR is between 5% and 16% and is rarely seen in prepubescent children [17,18]. There are three groups into which children with cavitation due to pulmonary TB can be placed. The adult-type of pulmonary TB in children occurs in adolescents; cavitation becomes progressively more common, frequently involving the apical and posterior segments of the upper lobe and apical segments of the lower lobe. Immunocompromised children <2 years of age develop cavities as a result of enlargement and caseous liquefaction at the centre of the Ghon focus which ruptures into an airway, leading to bronchopneumonic changes. Children up to 3 years of age have a higher prevalence of adenopathy. If an airway is completely obstructed, destructive caseating pneumonia may result with bulging fissures and cavitation. Lymph nodes can cause complications as they erode into adjacent structures, leading to a lymph node cavitary image [19]. In the two groups included in our study, cavitary lesions were found in children >6 years old, mainly adolescents, with an incidence of 7.27% and 10.84% respectively. Cavitations were single or multiple, almost always unilateral and often associated with consolidation.

Miliary disease refers to widespread dissemination of TB by hematogenous spread and occurs in 1-7% of patients. The classic radiographic findings are evenly distributed diffuse small 2-3-mm nodules, with a slight lower lobe predominance [7,15]. Our study shows a constant low incidence of miliary pulmonary TB, between 2-3% of the total cases.

Pleural effusion is often seen, in up to 1/4 of patients with TB. The sole manifestation of tuberculosis and usually unilateral, pleural effusion is a very uncommon finding in infants. The causes could be the rupture of a pulmonary caseous focus in the subpleural region, by contiguity of the pulmonary lesion, by rupture of a mediastinal lymph node or via hematogenous dissemination [7,20]. In our study, the increased incidence of pleural effusion, which reached statistical significance, was constant with the increased number of parenchymal complications, and therefore we believe contiguity was the main cause of this finding.

The traditional classification of TB into primary and postprimary should be avoided as the pathologic differences between these and the corresponding classic imaging patterns characterizing disease in adults and children have blurred. The age-related distinction has changed because primary infection can occur at any age (especially in countries with low TB incidence), exogenous reinfection in endemic areas and cavitation occurring within 6 months after initial infection [21].

**Limitations**

The limitations of our study are mainly due to its retrospective nature. All CXRs were interpreted by a single senior radiologist, an approach that provides overall consistency, but does not allow any assessment regarding inter-observer variability. We included only
standard, frontal CXRs. Both frontal and lateral views should be obtained, since a lateral view permits a better evaluation of the mediastinal and hilar lymphadenopathy. However, this aspect had a small influence in the final results, considering the large number of cases.

Conclusion

TB is a progressively evolving, dynamic pathological process. Imaging findings in children, in the context of a decreasing incidence of the disease, include typical aspects, frequently associated with lymphadenopathies, still the most common feature, and parenchymal complications, such as pulmonary consolidation and cavitary lesions, which show an increasing prevalence. However, the miliary form presented no time-related trend.
References


