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Evaluation of the relationship between smear positivity and high-resolution CT findings in children with pulmonary tuberculosis

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Summary

Background:

The aim of this study is to find a relationship between the radiological manifestations of childhood tuberculosis on a high-resolution computed tomography (HRCT) and the results of sputum smear. This study aims to propose an alternative indicator of infectivity in terms of prevention of disease transmission through selective isolation policy in children whose clinical condition is highly suggestive of tuberculosis.

Material/Methods:

This retrospective comparative study was performed on 95 children under 15 years of age diagnosed with tuberculosis based on both WHO criteria and positive sputum culture for mycobacterium Tuberculosis. The children were admitted for TB screening in the pediatric department of national research institute of tuberculosis and lung disease (NRITLD) between 2008–2012. Direct smear collected from sputum or gastric lavage, as well as HRCT were performed in all children prior to administration of medical therapy. Children were divided into 2 groups based on positive and negative smear results. HRCT abnormalities, as well as their anatomical distribution were compared between these 2 groups using multivariate analytic model.

Results:

The most prevalent abnormalities in the positive smear group were consolidation, tree-in-bud pattern, upper lobe nodular infiltration and cavitation. The negative smear group featured lymphadenopathy, consolidation, collapse and nodular infiltration in the upper lobe. Cavity, tree-in-bud pattern and upper lobe nodular infiltration were highly associated with smear positivity in children. Conversely, lymphadenopathy and collapse had significant association with a negative smear.

Conclusions:

This study revealed that cavity, tree-in-bud and upper lobe nodular infiltration has significant association with smear positivity in childhood tuberculosis. On the other hand, lymphadenopathy and collapse were closely associated with smear negativity in this age group. It was also demonstrated that children with a positive smear most likely presented with radiological features of post primary tuberculosis, while the negative smear group most often manifested with primary tuberculosis.

Keywords:

Pulmonary Tuberculosis • Children • Smear Positivity • HRCT

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Background

Disease transmission plays a minor role in pediatric tuberculosis and the condition remains a hidden epidemic in most countries, because the vast majority of cases are associated with negative sputum smear results [1,2]. Therefore, children hospitalized with TB are seldom considered infectious and hence are rarely isolated. This approach has led to the neglect of isolation in the minority of patients with positive smear results and increased the risk of disease transmission, especially in the pediatric wards and the emergency departments. On the other hand, isolation of all children admitted for TB evaluation is not achievable, especially in countries burdened with lack of facilities. Therefore, in terms of selective isolation, a system based on criteria with high predictive value for infectivity seems to be imperative. Positive sputum smear result is a well-known indicator of disease transmission. However, obtaining a sufficient sample from children who are generally unable to produce adequate amounts of sputum or performing a technically difficult gastric lavage are usually associated with low yield. Radiological investigation, especially a CT scan, is the mainstay of early management of TB [3]. A CT scan can help distinguish between an active and an inactive form of tuberculosis. Radiological characteristics associated with a diagnosis of TB are highly dependent on a previous exposure to mycobacterium Tuberculosis where the features of primary and postprimary tuberculosis are well described. There are reports which indicate that CT findings can predict smear positivity in adults [4,5]. Regarding the fact that the behavior of Mycobacterium tuberculosis shows significant difference between children and adults, the results of studies in adults may not be validated in children. The aim of this study was to find a relationship between the radiological manifestations of childhood tuberculosis observed on a high-resolution CT and the results of sputum smear and propose an alternative indicator of disease transmission and infectivity for the purposes of disease prevention through selective isolation of children whose clinical condition is highly suggestive of tuberculosis.

Material and Methods

Patients

This cross-sectional retrospective study was performed on 135 children under 15 years of age with a past history of close contact with a family member with active pulmonary tuberculosis. As a result, the children were admitted for tuberculosis screening at the pediatric department of National Research Institute of Tuberculosis and Lung Diseases referral center for tuberculosis and respiratory diseases in Iran, between 2008–2012. All medical records were reviewed. Patients with a clinical condition highly suggestive of mycobacterium tuberculosis based on WHO criteria, as well as those with a definite diagnosis of tuberculosis based on a positive sputum culture for mycobacterium tuberculosis, were included in the study. Exclusion criteria included: a history of any pulmonary or extrapulmonary disease associated with HRCT abnormalities, any surgical procedure or radiotherapy over the lung fields, administration of any medications with known major

pulmonary complications (n=3), lack of a definite diagnosis of mycobacterium tuberculosis based on a positive sputum culture (n=12), undergoing tuberculosis treatment (n=4), positive HIV status (n=2), lack of HRCT investigation prior to treatment (n=9), less than 3 consecutive day sputum smears (n=5) and the lack of concurrency between sputum sampling and HRCT investigation (n=5). Ultimately, 95 children were found to be eligible for inclusion in the study.

Diagnostic criteria

Diagnosis was made based on both meeting the WHO criteria and a positive sputum culture for mycobacterium Tuberculosis. All children met the WHO criteria for the diagnosis of TB and had a positive culture result for Mycobacterium Tuberculosis. The WHO criteria include a history of a close contact with a smear-positive family member (2+), relevant symptoms (1+), recent conversion of TST (>15 mm) (1+) and imaging abnormalities compatible with TB diagnosis (1+). Patients with a score of at least 3+ were considered clinically as highly suspicious for tuberculosis and were started on antituberculosis treatment. Isolation of the microorganism from the sputum samples using Lowenstein Jensen medium and Bactec 460 TB system had been considered as a definite diagnostic criterion. The TST was performed with an intradermal injection of 0.1 cc solution containing 5 units of Tuberculin in the anterior part of the forearm. Induration of >15 mm after 48–72 hours was considered positive in case of previously healthy children. Collection of samples was performed on 3 consecutive days from either sputum or gastric wash in those children who were unable to produce adequate sputum samples. The protocol used for gastric lavage was as follows: a small smooth rubber tube was inserted into the stomach by either swallowing or by gently inserting into the nostril, a syringe was attached to the free end of the tube, as soon as the tube reached the stomach the contents were withdrawn and placed in a bottle. Next, a cup of warm saline was infused into the stomach in an attempt to wash it and the contents were once again aspirated. The process of washing was repeated several times until a sufficient sample had been obtained. Finally, the tube was withdrawn and the patient's part in the gastric lavage was completed. These procedures had been repeated for at least 3 continuous days. All the collected samples were sent for a direct smear, a staining by Ziehl-Neelsen and a specific culture.

HRCT acquisition and findings

HRCT, with or without an IV contrast, was performed using Siemens Somatom Emotion Plus device in all children while holding breath and before administration of any medications. HRCT performance was as follows: (40 mAs, 110 KV), 20 cm field of view, 1 mm slice thickness, 10 mm slice interval, 1.0 second scanning time, window width and window level of 1200 Hounsfield units [HU] and of -600 [HU], respectively, as needed for the best visualization of the lung parenchyma and the mediastinum.

HRCT abnormalities were recorded and included into statistical analysis. HRCT findings were described as follows: (1) hilar/mediastinal adenopathy, (2) consolidation

Table 1. Prevalence of CT scans findings in Smear positive and Negative patients.

Findings	Smear positive	Smear Negative	Significant difference (p value)
LAP	5/22 (22.72%)	33/57 (57.89%)	Yes(0.006)
Tree – in- bud Nodule	12/22 (54.5%)	3/57 (5.6%)	Yes (0.02)
Upper lobe Nodular infiltration	10/22 (45.45%)	14/57 (24.56%)	Yes (0.05)
Consolidation	13/22 (59.09%)	18/57 (31.57%)	No
Cicatrical volume loss	4/22 (18.18%)	7/57 (12.28%)	No
Bronchiectasis/Bronchial wall thickening	5/22 (22.72%)	10/57 (17.54%)	No
Collapse	0/22	15/57 (26.31%)	Yes (0.04)
Cavity	10/22 (45.45%)	2/57 (3.5%)	Yes (0.000)
Pleural effusion	0/22	7/57 (12.3%)	No

(opacities concluded air bronchogram >10 mm); (3) ground glass opacity (GGO) (opacities not concluding air bronchogram >10 mm) (4) tree-in-bud nodule (2 to 4 mm sharply margined linear branching opacities) (5) nodular infiltration (<4 mm), (6) pleural effusion, (7) collapse, (8) cavity, (9) bronchial wall thickening, bronchiectasis, (10) cicatricial volume loss (scar associated volume loss) and (11) hyperaeration. Anatomic distribution of the lesions was considered as the upper zone (above the level of the carina), the middle zone (between the level of the carina and the level of the inferior pulmonary veins) and the lower zone (below the level of the inferior pulmonary veins.), on the right or the left side.

Statistical analysis

Children were divided into 2 groups based on a positive and negative smear results. HRCT abnormalities, as well as their anatomical distribution, were compared between these 2 groups using multivariate analytic model. The significance of the difference was calculated using Fisher exact test. P values less than 0.05 were considered statistically significant.

Result

Out of a total of 135 records reviewed, 95 patients were included in the study. The median age was 8.1 years (ranging from 4 months to 15 years of age), 46 (48.8%) were males and 49 (51.6%) were females. Thirty-nine (41%) children were Iranian, 1 patient came from Azerbaijan (0.9%) and the remaining (55 patients) were Afghan (57.9%). History of a close contact with a smear-positive family member with active pulmonary tuberculosis and BCG vaccination was observed in 91 (95.78%) and 63 (66.31%) cases, respectively. Sixty-two (65.26%) children had relevant clinical symptoms appearing in the following order of prevalence: 42 (44.2%) lack of appetite and weight loss /failure to thrive, 37 (44.2%) fatigue and 22 (23.16%) prolonged cough (38%).

Among the 95 culture-positive children, 31 (32.6%) patients had a positive smear, (mean age 10.3 years) and 64 (67.4%)

had a negative smear (mean age 7.08 years). In the positive smear group, the degree of smear positivity was as follows: 8 patients (25.8%) had (1+), 10 patients (32.3%) had (2+), 10 patients (32.3%) had (3+) and 3 patients (9.7%) had (4+). Normal and abnormal CT results were observed in 19 (20.2%) and 75 (79.8%) children, respectively. Overall sensitivity of a CT scan and a direct sputum smear were found to be 79.8% and 32.6%, respectively. Table 1 summarizes the prevalence and significance of the difference for the statistically significant CT findings in the smear-positive and the smear-negative groups and according to a multi variate statistical analysis. Volume sample was insufficient for a statistical analysis of hyperaeration and ground glass opacity, the prevalence of which was 5 and 3, respectively. With the exception of upper lobe nodular infiltration, the evaluation of lobar distribution of the lesions did not show significant difference between the 2 groups. The anatomical distribution of lymph node enlargement was as follows: 3 hilar (7.7%), 12 mediastinal (30.8%), 24 hilar and mediastinal (61.5%), 14 paratracheal (56.0%), 3 pretracheal (13.0%), 2 prevascular (7.8%), 10 subcarinal (43.5%), 3 azygosophageal (13%) and 1 pericardial (4.7%). Twenty-two (57.9%) enlarged lymph nodes were observed on the right side, 6 (15.8%) on the left side and 10 (26.3%) on both sides. Calcification, necrosis and airway compression were found in 11 (28.9%), 2 (5.3%) and 2 (5.3%) lymph nodes, respectively.

Discussion

Pediatric tuberculosis is a challenging diagnosis in the clinical practice. Children infected with tuberculosis are considered major reservoirs of adulthood tuberculosis, as well as sources of disease transmission. Isolation of all the children with suspected TB is not achievable in all tuberculosis-referral centers due to lack of facilities and isolation rooms, especially in most endemic countries. Therefore, consideration of a focused triage system aimed at selected isolation is crucial for the management of children with suspected tuberculosis infection, especially those with a history of a close contact. Positive smear is a well-known indicator of infectivity. However, the diagnostic yield of a smear is less than

15%, reflecting the pauci-bacillary nature of the disease, as well as technical challenges in collecting samples in children [6]. On the other hand, collection of samples by endoscopic procedure or saline wash may potentially facilitate disease transmission. Therefore, the development of highly reliable practical criteria for the degree of infectivity, other than direct smear, seems to be imperative in the early management of childhood tuberculosis. Many reports have shown a correlation between various HRCT abnormalities and smear positivity in adulthood tuberculosis. Strong predictors of infectivity in adulthood tuberculosis include cavitation, nodular infiltration, consolidation, ground glass opacity, clusters of nodules and tree-in-bud pattern [4,5,7]. In addition to the type of the lesions, the extent of pulmonary involvement has been proposed to be another major predictor of smear infectivity, in adulthood tuberculosis. However, there is limited research available concerning childhood tuberculosis. This study aimed at determining any associations between HRCT abnormalities and smear positivity in children.

Radiological features of pulmonary tuberculosis at any age, are strongly dependent on a previous exposure to mycobacterium tuberculosis. Therefore, historically, it has been divided into primary and postprimary tuberculosis. However, there is a significant overlap between primary and postprimary tuberculosis in terms of clinical and radiological features. Primary tuberculosis, which is more prevalent in children under 5 years of age, is characterized by lymphadenopathy (96%), consolidation, miliary tuberculosis (1–7%), pleural effusion (25%) and atelectasis. The number of adults presenting with primary tuberculosis is currently increasing. This implies the effectiveness of disease control programs worldwide [8,9]. On the other hand, postprimary tuberculosis can manifest as multi-segmental consolidation, mainly in upper zones, cavitation as the hallmark of the disease (50%) and airway disease, especially tree-in-bud pattern as an indicator of active pulmonary tuberculosis [10]. This study demonstrated that the most prevalent abnormalities observed on HRCT in smear-positive children were consolidation, three-in-bud pattern, upper lobe nodular infiltration and cavitation, which is associated more with postprimary tuberculosis. Additionally, the most common radiological manifestations of pulmonary tuberculosis in the smear-negative group were lymphadenopathy and consolidation, which suggest primary tuberculosis. Although the prevalence of pleural effusion was 0/22 in cases with a positive-smear versus 7/57 (12.3%) in the negative-smear patients, the difference was not statically significant ($p=0.08$). In other words, about 81% of patients with a positive smear presented with radiological features of postprimary tuberculosis, while 58% of patients with a negative smear manifested with primary tuberculosis. It can be postulated that smear positivity in children is mostly related to a primary exposure to mycobacterium tuberculosis or a secondary reactivation of a dormant focus, rather than the behavior of the bacillus in children. However, further research is needed, especially in adults who present with primary tuberculosis.

Cavitation is a well-known, independent and strong indicator of active pulmonary tuberculosis and infectivity in both children and adults. One limited study [11] demonstrated that there may be 3 mechanisms responsible for the development of cavitation in pediatric tuberculosis:

- Enlargement and liquefaction of primary focus leading to endobronchial spread of the disease and the so-called progressive primary disease. In this group, there are multiple cavities bilaterally with either thin or thick walls.
- Reactivation of a dormant focus in postprimary tuberculosis. This group most commonly presents with single, unilateral cavities with thin walls.
- Compression effect of lymph node enlargement resulting in obstruction and leading to caseous liquefaction and cavity formation distal to the obstruction.

This report also demonstrated that the prognosis in children with cavitory pulmonary tuberculosis strongly depends on the mechanism of cavity formation. In this study, only 2 patients with a negative smear presented with a cavity on a CT scan. One of them was due to a compression effect of enlarged lymph nodes and resulting obstruction and the formation of distal segmental caseous necrosis/cavity. The second one was a 14-year-old girl with diffuse bilateral consolidations, nodules and cavities on a CT scan, who was not expected to have negative sputum smear results, unless due to a technical error confounding the results. Analysis of the same studies performed on adults, indicates that the overall frequency of cavity formation in the adult population is 3 times higher than in children (44–48% [12] vs. 15.4%). While the frequency of cavity formation in children with a negative smear was nearly negligible, it was significant in the adult smear-negative group. It seems that factors such as those suggested to play a key role in cavity-associated smear positivity, size, number, distance to major airways and wall thickness, play a less important role in the presence of positive sputum smear results.

Many studies in adults have shown that air space consolidation is a strong independent predictor of infectivity. They had stated that caseous necrosis and liquefaction, which occur in the centrally located granuloma in consolidation, ultimately drain into the airways and deliver their high bacillus content to the sputum. On the contrary, such results were not demonstrated in this study. Consolidation was not demonstrated as an independent predictor of smear positivity. In other words, although univariate analysis demonstrated a significant correlation between smear positivity and consolidation, multivariate analysis did not. According to this study's statistical analysis, a significant correlation exists between consolidation and cavitation. In terms of consolidation, total prevalence and the prevalence in the smear-positive group is much higher in adults than in children (69% vs. 39% and 85% vs. 59%, respectively). However, prevalence in the smear-negative groups was nearly the same (35% vs. 31%). It can be stated that due to the paucibacillary nature of tuberculosis in children, necrotic material which drains into the airways as the result of caseous necrosis and liquefaction of centrally located granulomas, do not contain a high bacillus content. Another hypothesis explaining this discrepancy suggests that if consolidation occurs during the initial exposure to mycobacterium tuberculosis, i.e. primary tuberculosis, smear positivity is not anticipated. However, reactivation of bacillus can have a high correlation with smear positivity via consolidation and cavity formation. In other words, paucibacillary behavior of tuberculosis in children is mostly

related to primary tuberculosis when an uninfected child inhales the infected droplet, which is not true in case of a secondary reactivation of mycobacterium tuberculosis in the setting of a postprimary tuberculosis.

Upper lobe micronodular infiltration was demonstrated to have a high correlation with smear positivity in children. Micronodular infiltration was the only lesion that displayed a significant difference in the anatomical distribution. As a result only an upper micronodular infiltration demonstrated a significant difference between the 2 groups. In this study, micronodular infiltration was defined as nodules under 4 mm in size. Although the reports of micronodular infiltration in adults are highly controversial [4,5,13–15] and seem to depend on the definition of the nodule size, where the larger nodules correlate more with smear positivity [4], this finding was not observed in the children evaluated in the current study.

Tree-in-bud pattern is a radiological manifestation of an early endobronchial spread of the disease defined as centrilobular nodules, 2 to 4 mm in size with sharply marginated linear branching opacities representing severe bronchiolar impaction, and with clubbing of the distal bronchioles [3]. Although the radiopathologic studies demonstrated that centrilobular nodules, and especially tree-in-bud pattern, represent the bronchogenic spread of the disease, there exists a debate concerning their correlation with smear positivity [4,5,7]. One study which did not find a correlation between smear positivity and the presence of centrilobular nodules, suggested that a smaller size of the areas affected and hence the fewer amount of the infected material, as well as the greater the distance from the centrilobular nodules, are responsible for the negative results [7]. This subject cannot be explained by the results of this study, because mycobacteria show paucibacillary behavior in children. These findings are also in favor of the hypothesis which suggests that the paucibacillary nature of tuberculosis can only be true in case of a primary tuberculosis.

In this study, lymphadenopathy as radiological hallmark of childhood tuberculosis, demonstrated a significant correlation with smear negativity. At first glance, it appears that these results confirmed the current belief that childhood tuberculosis is not associated with a high rate of disease transmission. However, the prevalence of lymphadenopathy as a radiological hallmark of childhood tuberculosis was significantly lower than that cited in most references (48.7% vs. >90%) and is nearly compatible with the frequency found in adulthood tuberculosis in population with an effective disease control program (43%) (radiological review of tuberculosis). As mentioned earlier, it can be inferred that children in this study presented mostly with the radiological features of post primary tuberculosis. However, the prevalence of smear positivity in children and adults shows significant differences (32% vs. >60%, p value <0.05). On the other hand, the smear-negative group most commonly manifested with primary tuberculosis; i.e. lymphadenopathy, consolidation and pleural effusion. This discrepancy can be explained by either a paucibacillary nature of the disease or technical problems in obtaining samples from the children. An exact estimate of the prevalence of smear-positive pulmonary tuberculosis in the adult

population with the prevalence of 40% primary tuberculosis is needed for a more appropriate differentiation.

Atelectasis/collapse was found to have a significant correlation with negative smears. This was expected as atelectasis is usually considered as a sign of an inactive disease in most literature sources.

A global comparison between the results of the current study and the reports in adults revealed that the prevalence of smear positivity is significantly different between these 2 groups (32% vs. more than 60%). The most common findings in the order of prevalence were lymphadenopathy, consolidation, nodules and nodular infiltration. Conversely, one study in adults showed that the most prevalent HRCT abnormalities in patients with a positive smear were ground glass opacity, consolidation and bronchial wall thickening, while paratracheal adenopathy, interlobular septal thickening, cavitation, calcification and fibrosis were the most prevalent findings in the smear negative group [7]. Another study stated that the prevalence of air space consolidation, cavitation and ground glass opacity were significantly higher in the smear-positive group than the smear-negative group, while a centrilobular nodule was not associated with any significant differences [5].

The present report revealed that cavitation, tree-in-bud pattern and upper lobe nodular infiltration were highly associated with smear positivity in children. Conversely, lymphadenopathy and lung collapse were highly associated with negative smears.

These results are fairly compatible with the same study in adults which demonstrated that in adults, upper lung consolidation, cavitation and clusters of nodules had a high and independent association with smear positivity, in contrast to centrilobular nodules, which show a negative correlation [7]. Another study found that nodules, cavitation, bronchial lesions, consolidation and GGO were highly associated with smear positivity and suggested that nodules, cavitation and bronchial lesions may provide a predictive value for smear positivity [4].

Conclusions

This study revealed that cavitation, tree-in-bud pattern and upper lobe nodular infiltration have a significant association with smear positivity in pediatric tuberculosis. On the other hand, lymphadenopathy and lung collapse were significantly associated with smear negativity in this age group. It was also demonstrated that children with a positive smear most likely presented with radiological features of a postprimary tuberculosis, while the smear-negative group most often manifested with primary tuberculosis. It can be inferred that the paucibacillary nature of tuberculosis in children is mostly true in the setting of primary invasion by Mycobacterium tuberculosis, rather than a secondary reactivation of dormant foci, most of which behave similarly to adult tuberculosis and hence are associated with positive smear results. Therefore, in countries with poorly controlled tuberculosis, childhood TB is associated with a higher prevalence of positive smears and a significant role in the transmission of the disease.

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