

# PULMONARY TUBERCULOSIS IN CHILDHOOD: CLINICAL FEATURES, TREATMENT SIDE EFFECTS AND FACTORS ASSOCIATED WITH RADIOLOGIC IMPROVEMENT

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A – study design, B – data collection, C – statistical analysis, D – interpretation of data, E – manuscript preparation, F – literature review, G – sourcing of funding

## ABSTRACT

**Background:** Tuberculosis (TB) is a common public health problem and early diagnosis and treatment is important.

**Aim of the study:** The aim was to evaluate complaints and radiological features, drug side effects, changes in radiological findings after treatment, and to evaluate the factors affecting this change in patients with pulmonary TB.

**Material and methods:** One hundred patients with pulmonary TB were evaluated, and the following data recorded: age, gender, contact with TB patient, complaints, physical examination, tuberculin skin test, acid resistant bacillus, polymerase chain reaction and culture results, posteroanterior/lateral chest radiographs and thorax computed tomography findings at presentation and after treatment, treatment duration, and side effects. Treatment adherence and follow-up data were evaluated, and radiological findings before and after treatment were compared. In predicting radiological improvement, the effects of age, sex, duration of complaints, living in rural/urban areas, treatment duration, treatment adherence, follow-up, and presence of cavitation were examined.

**Results:** Mean age was  $6.0 \pm 4.2$  years. 66 of the patients had contact history with TB patients. The most common complaint was cough, whilst infiltration and/or mediastinal lymphadenopathy were the most common findings in radiological examination at presentation. 84 patients were scheduled a treatment program for 6 months. Improvement in radiological findings were significantly better in patients who adhered to medication and follow-up protocols. Age, sex, complaint duration, living in rural/urban areas, treatment duration and presence of cavitation were not significantly associated with radiological improvement.

**Conclusions:** Pulmonary TB should be considered in patients presenting with cough, even if their physical examination and chest radiographs are normal. Adherence to anti-tuberculosis treatment and follow-up were the most important factors in radiological improvement.

**KEYWORDS:** child, prognosis, pulmonary, radiological, tuberculosis

## BACKGROUND

Tuberculosis (TB) is an important health problem in developed and developing countries [1]. With a burden of disease that accounts for more than 10 million new cases per year, the annual decline in the global TB incidence rate is currently 1.5% [1]; between 2000 and 2017, the global number of TB deaths fell by 42% [2]. TB can affect anyone, but specific population groups, e.g. people living with HIV infection, health workers, and others in settings with a high risk of transmission of *Mycobacterium tuberculosis*, have a higher risk of acquiring TB infection and progressing to disease once

infected. More than a million incident cases were estimated among children (aged <15 years) [3].

Over the past decade there has been a decrease of 5% in the incidence of TB in Turkey; in 2005, the total number of registered TB cases was 20,535 and the incidence rate was 29.4 per 100,000 population, which decreased to 14.6 per 100,000 population in 2017 [4].

The presence of TB in children is closely related to the prevalence of TB in adults. Therefore, it is of great importance to determine the index cases with childhood pulmonary TB source [2].

The diagnosis of childhood TB generally depends on clinically appropriate symptoms, contact history, positive tuberculin skin test (TST)/interferon- $\gamma$  release assay (IGRA) result and the presence of radiological findings. Specifically, for children over 5 years old, IGRA is preferred over TST. Since the count of TB bacilli is low in primary lung TB in children, the contribution of microbiological methods for the diagnosis is limited. Microbiological methods used for diagnosis include direct smear, molecular techniques, and TB bacterial cultures [5].

Posteroanterior and lateral chest radiographs, which are the first imaging modalities in the diagnosis of pulmonary TB, have been reported to be normal in 25-40% of cases. Thorax computed tomography (CT) can be useful in patients with normal posteroanterior and lateral chest X-rays [3].

The goals of children's follow-up during TB medication are, in order of importance, to ensure compliance with treatment, monitoring of drug side effects, and evaluation of clinical, radiological and microbiological response [4].

## AIM OF THE STUDY

Our aim was to evaluate the complaints and radiological features, drug side effects, changes in radiological findings after treatment, and to evaluate the factors affecting this change in patients with pulmonary TB.

## MATERIAL AND METHODS

### Study design

We retrospectively evaluated 100 patients who were diagnosed with childhood pulmonary TB at the Pediatric Infectious Diseases Clinic of the Health Sciences University Ankara Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital. We evaluated data recorded both during treatment, and 2 months post treatment, in order to determine the level of remission and potential drug side effects. No exclusion criteria were utilized.

### Data sources

The diagnosis of pulmonary TB was confirmed by the history, clinical, radiological and/or microbiological findings. Recorded measures included: patients' age, gender, place of residence, whether there was contact with adult patients with TB, symptoms at admission, duration of complaints between the time of the first complaints and the time of admission to our department, respiratory system examination findings, tuberculin skin test (TCT) results, acid-resistant bacillus (ARB) in fasting gastric juice and/or sputum, polymerase chain reaction (PCR) (TB AMPLICOR 1994; Roche Diagnostic Systems, Inc., Branchburg, N.J.), and Löwenstein-Jensen (LJ) (Salubris, İstanbul) culture results, posteroanterior and right side chest X-ray and thorax CT findings at presentation and following treatment,

index case detected by the family scan, treatment regimen, side effects, and the time of the occurrence of side effects during treatment. Patients presenting from the city center were recorded as urban areas, all others were recorded as rural.

The hemogram, serum transaminase, and uric acid levels were recorded both during and 2 months after treatment in order to determine drug side effects, with specific reference made to the timing of any incidents. Posteroanterior and lateral chest X-ray and/or thoracic CT results were recorded 2 months after the treatment was stopped. Initial radiological examinations were compared with those taken 2 months after treatment ceased, with patients being divided into 2 groups according to their remission as either complete or persistent/partial remitters.

### Bioethics committee approval

The study was approved by the Ankara Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital local ethics committee (24.05.2009/240).

### Statistical methods

Statistical analysis was performed using SPSS for Windows 22.0 (Statistical Package of Social Sciences Inc., Chicago IL). For normally distributing data, mean and standard deviation, for non-normally distributed data median values were reported. For categorical variables, chi-square test was used for group comparisons. To identify the parameters predicting the normalization of radiological findings after treatment, logistic regression analysis was used and  $p < 0.05$  was considered as significant.

## RESULTS

### Participants

Files of all patients with childhood pulmonary TB during the study period ( $n=100$ ) were retrospectively evaluated.

The mean age of the patients was  $6.0 \pm 4.2$  years (2 months-16 years); 20 (20%) were 0-2 years old, 27 (27%) were 2-5 years old, 35 (34%) were 5-10 years old, and 19 (19%) were 10-16 years old. Sixty-eight of the patients were male (68%). Of the patients, 24 (24%) were from rural areas, and 76 (76%) from urban areas.

### Main results

Symptoms were observed in 78 (78%) patients, 22 (22%) were asymptomatic. The most common complaint was cough (66%); this complaint was present for more than 2 weeks in 58 (87.8%) of these patients. The distribution of the patients according to their complaints is shown in Figure 1. Asymptomatic patients were as follows: 12 (54.5%) had contact history with a TB patient, 8 (36.4%) had TST positivity, and 2 (9.1%) had pathological chest radiological findings.

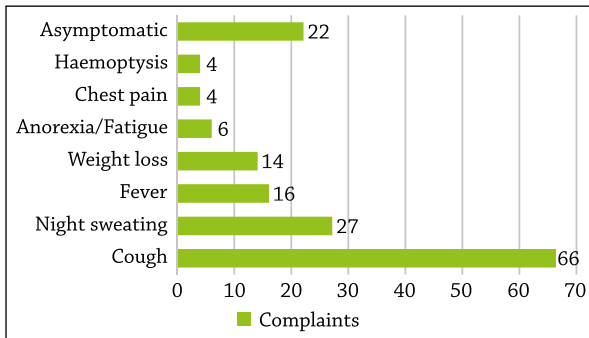


Figure 1. Patient complaints at presentation.

There was a history of contact with an adult with TB in 66 (66%) patients. Of these, 39 (59%) had contact with an adult living in the same house, and 27 (40.9%) had contact with an adult outside their home. Contact with mother and/or father occurred in 23 patients (23%), 15 patients (15%) with uncle/aunt, 23 patients (23%) with grandparents, 2 patients (2%) with schoolmates, 1 patient (1%) with brother, 1 patient with cousin (1%), and 1 patient with neighbor (1%).

Normal respiratory system examination findings were observed in 92 (92%) patients; 3 patients (3%) had rales, three (3%) had rhonchus, 1 (1%) had elongation of expirium, and 1 (1%) had decreased breath sounds.

TCT was found to be negative in 39 (39%) patients, and positive in 61 (61%) patients.

ARB in fasting gastric juice or sputum was negative in 91 (91%) patients and positive in 9 (9%) patients. Two of the 52 patients (3.8%) were found to have positive tuberculosis PCR results in fasting gastric juice or sputum. Four of the 44 patients (9.1%), whose fasting gastric juice or sputum culture results were available, had culture positivity. According to these microbiological data, 10 (10%) of the patients in our study were "definite TB cases".

The distribution of the posteroanterior, lateral chest radiographs and thorax CT findings of the patients were shown in Tab. 1.

The respiratory system examination and posteroanterior and lateral chest radiograph results were normal in 21 patients, and 5 of these patients were asymptomatic.

Eighty-four (84%) patients were planned to be treated for 6 months, 15 (15%) patients for 9 months, and 1 (1%) patient for 12 months. Seventy-eight of these patients (78%) completed the planned treatment regimen. The treatment of three patients (3%) was still ongoing at the time of writing. As 19 (19%) patients were lost to follow-up, the treatment completion data of these patients was not available.

Planned initial treatment regimens were as follows: 94 patients (94%) had INH (isoniazid) + RIF (Rifampicin) + PZA (pyrazinamide) / MZA (morphozinamide), 3 patients (3%) INH + RIF + PZA / MZA + ETB (ethambutol), 1 patient (1%) INH + RIF + MZA + prednisolone, 1 patient INH + RIF + MZA + SM (streptomycin) + prednisolone, and 1 patient and INH + RIF + PZA + SM. The daily dosage was 10 mg/kg for INH, 15 mg/kg for RIF, 20 mg/kg for PZA/MZA, 25 mg/kg for ETB, 20 mg/kg for SM, and 1 mg/kg for prednisolone.

Drug side effects were reported in 23 (26.1%) of the 88 patients who came to control at least once during the treatment. Time of the occurrence of these side effects was as follows: in 14 patients at the 1st-2nd week of treatment, in 5 patients at the 4th week of the treatment, in 1 patient at the 12th week of the treatment, in 1 patient at the 32nd week of treatment, in 1 patients at the 1st and the 4th week of the treatment, and in 1 patient at the 1st week and 10th week of the treatment. Nine of the patients (39.1%) had elevated levels of transaminases, 12 (52.2%) had elevated uric acid levels, 1 (4.3%) had neutropenia, and 1 (4.3%) had gastrointestinal side effects. The treatment of 13 patients was discontinued due to adverse effects and resumed a week later after the control of biochemistry values, or the discontinuation of the treatment was extended.

Table 1. The distribution of radiological findings at presentation.

Radiologic findings	Posteroanterior chest x-ray		Lateral chest x-ray		Thorax CT	
	n	%	n	%	n	%
Infiltration	48	57.1	38	51.3	32	37.2
Mediastinal lymphadenopathy	7	8.3	7	9.4	28	32.6
Cavitation	2	2.4	-	-	2	2.3
Infiltration + Mediastinal lymphadenopathy	1	1.2	-	-	17	19.8
Pleural effusion	-	-	-	-	2	2.3
Cavitation + Mediastinal lymphadenopathy	-	-	-	-	1	1.2
Cavitation + Pleural effusion	1	1.2	-	-	-	-
Infiltration + Mediastinal lymphadenopathy + Cavitation	-	-	-	-	1	1.2
Normal	25	29.8	29	39.18	3	3.48
TOTAL	84	100	74	100	86	100

When 81 patients were evaluated at the end of the treatment period, in terms of regular follow-ups and medication adherence, 69 (85.1%) patients came to regular controls and were adherent to their medications, and 12 (14.8%) patients did not attend regular follow-ups or were not adherent to their medications.

Posteroanterior/lateral chest X-ray and/or thorax CT results of 80 patients were available after 2 months of treatment. The radiological findings of the patients whose chest X-rays and/or thorax CT results were available at the end of the treatment are shown in Tab. 2.

Table 2. The radiologic findings of the patients after treatment.

Radiologic findings	Complete remitters		Persisters/partial remitters	
	n	%	n	%
Positive findings in posteroanterior chest x-ray or thorax CT	55	67.9	26	32.1

Complete radiological improvement was found to be significantly higher in patients who were adherent with their treatment and who attended regular follow-ups compared to those who did not attend regular follow-up controls and who were non-adherent to treatment ( $p < 0.001$ ) (Tab. 3).

Table 3. The distribution of the radiological findings according to treatment adherence and attendance to regular follow-ups.

	Complete remitters	Persisters/partial remitters	P
Treatment adherent and attending regular follow ups	53 (76.8%)	16 (23.2%)	<0.001
Non adherent and/or not attending regular follow-ups.	2 (16.7%)	10 (83.3%)	

Age, gender, rural/urban presentation, duration of complaints, duration of treatment, non-compliance to treatment/absence of regular controls, and the effect of cavitation on radiology were evaluated by multivariate logistic regression analysis. Age ( $p = 0.167$ ), gender ( $p = 0.641$ ), duration of complaints ( $p = 0.642$ ), rural/urban presentation ( $p = 0.378$ ), duration of treatment ( $p = 0.123$ ) and presence of cavitation in radiology at presentation ( $p = 0.499$ ) were not found to be significant in predicting radiological prognosis. Non-adherence to treatment or regular follow-up was associated with a poor prognosis ( $B = 4.221$ ,  $p = 0.001$ ).

## DISCUSSION

Prevention, early diagnosis and appropriate treatment of TB are important for public health [5]. Cough is one of the most common symptoms, and a child with cough lasting more than 3 weeks should be investigated for pulmonary TB [3,6]. In our study, most of the patients were symptomatic. The most common presenting symptoms were cough lasting more than 2 weeks,

followed by night sweats, fever, weight loss. Although it was rare in children, hemoptysis was detected in 4 patients. Physical examination findings of pulmonary TB in childhood vary with age. As the airway diameter is small in infants, wheezy breathing, tachypnea and respiratory sounds may be associated with the growth of paratracheal or hilar lymphadenopathy [6]. In our study, abnormal respiratory system findings were detected in only 8 patients, which were rales, rhonchus, elongation of expirium, and decreased respiratory sounds.

Although physical examination and direct X-rays may be normal in patients presenting with the typical complaints, thorax tomography examination and microbiological examinations should be performed and pulmonary TB diagnosis should be excluded [7,8]. In our study, the physical examination and direct radiographs of 16 patients who presented with various complaints were found to be normal.

Since many childhood TB cases are diagnosed clinically rather than by the isolation of the bacteria, the detection of index cases is important in terms of obtaining microbiological data. Further, drug resistance of the index case is important in the treatment of pediatric patients. If the index case is drug resistant, the pediatric case needs to be treated considering this resistance. In addition, the benefit of detection of the index case is important in the control of TB in preventing the occurrence of new cases by providing treatment and isolation [9–11].

Five TB positive patients in our study were asymptomatic, and had both normal respiratory system examinations and normal chest radiographs; they were included as a result of history of contact with the index case or due to their TCT positivity. It is of great importance to educate the community about the role of contact with the index case in the progression of the disease by identifying the asymptomatic cases and starting treatment. Although two-thirds of our cases had a history of contact with an adult TB patient, the index case was identified in only half of this group. The reason for this may be due to the screening of only the family members in the tuberculosis dispensary. In our study, almost half of the index cases were out-of-home contacts. This result showed us the importance of questioning the contacts outside the home, especially at school.

In our study, TST was found to be positive in only 61% of the cases. The negative value of TST in 39% of our patients who were diagnosed with TB may be considered as false negative results; this may be due to tuberculosis disease itself causing anergy. Cytokines formed during TB infection may cause cell apoptosis and anergy, thereby leading to a non-responsiveness to the skin test. It is also believed that cytokines of the innate immunity may be responsible for this non-responsiveness [12–14].

In adults, the diagnosis of TB is proven bacteriologically, whereas in children, the disease has paucy-bacillary character, which means low bacterial load, and in childhood it is difficult to diagnose TB bacteriologi-



cally due to the low number of *M. tuberculosis* colonies as a result of the absence of cavity formation [8,15–17]. In our study, the diagnosis of tuberculosis was confirmed microbiologically only in 10 (10%) patients. The low rate of microbiological diagnosis was consistent with the rates reported in the literature [11,18].

In children, in pulmonary TB, pulmonary or segmental infiltration, intrathoracic lymphadenopathy with infiltration, and intrathoracic lymphadenopathy are the most common radiological findings. In our study, the most common radiological findings were infiltration and mediastinal lymphadenopathy consistent with the literature [12]. Cavitation in children is rare in radiological findings; it is seen in 5-16% of patients [13]. Similar to the literature, only 4 of the patients in our study had cavitation.

Male sex, advanced age, previous history of TB, drug resistant TB, cavity and presence of fibrotic lesions have been identified as poor prognostic factors in terms of radiological improvement after TB treatment [14]. In our study, radiological improvement was detected at the end of the treatment or 2 months after, and the factors determining the prognosis in radiological recovery were examined by regression analysis. It was found that lack of drug compliance or irregular follow-ups predicted incomplete radiological improvement after treatment. Patients who did not have radiological improvement or were partially recovered were less likely to be treatment adherent or to attend regular follow-up. This has demonstrated once again the effect of treatment compliance and regular follow-up on prognosis, in line with the literature [19]. Since the number of patients who had cavity in their radiology at presentation was low, this may explain why the presence of cavity at presentation did not affect radiological prognosis.

In our study, approximately one quarter of patients had transient transaminasemia, transient hyperuricemia, neutropenia or gastrointestinal side effects such as nausea and vomiting. Similar to our study, the most common side effects in patients receiving pulmonary TB treatment were reported as transaminase elevation and hyperuricemia. Drugs responsible for these side effects are INH and RIF [8,20,21].

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Neutropenia was seen in the second week of treatment in a patient receiving INH, RIF and PZA treatment, and improved when RIF therapy was discontinued after 2 weeks. Neutropenia is a very rare side effect of antiTB drugs and has been reported rarely in the literature [17]. We also investigated the time of occurrence of side effects; although the side effects of antituberculosis drugs in the literature most frequently occurred after 2-3 weeks [22], it was shown that treatment side effects may even occur in the 12th and 32nd weeks of treatment, and the importance of regular follow-up of the patients after the first weeks has been demonstrated.

Some limitations of the study are as follows: since the study was designed retrospectively, more up to date diagnostic methods like interferon-gamma release assay were not available in the patients' files. Some of the data were based on patients' self-reports, therefore there may be issues with reliability. This study was conducted in only one tertiary medical facility, which may limit the generalization of the results.

## CONCLUSIONS

In our study the most common complaints were cough, night sweating and fever, and the most frequently encountered radiological finding was infiltration. The patients mostly had elevated transaminase and uric acid levels as side effects. Although chronic respiratory symptoms, fever, weight loss, fatigue, physical examination and plain radiographs are normal, detailed history and diagnostic tests should be considered for pulmonary TB. Patients undergoing drug therapy should be closely monitored for side effects and for treatment adherence. In this way, the morbidity caused by the side effects may be prevented, and complete radiological improvement will be ensured by regular drug use.

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