

CHARACTERISTICS OF PEDIATRIC TUBERCULOSIS IN A HIGH ENDEMIC AREA

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Abstract

Introduction: Tuberculosis (TB) is an important cause of morbidity and mortality in children, especially in high endemic regions as Romania. Pediatric TB reflects both the epidemic level of the region and the control measures efficiency of national programs in the territory. Supporting the diagnosis of TB in children is more difficult than in adults, because the bacteriological test for Mycobacterium tuberculosis is usually negative.

Objective: observe the clinical, bacteriological and radiological profile of tuberculosis in children and adolescents, including difficulties in diagnosis, monitoring and treatment.

Methods: the data were collected from patients' files from 1st January 2014 until 1st November 2015, for all the children and adolescents under the age of 18, diagnosed with pulmonary TB in the Pediatric Department of Clinic Pneumophysiology Hospital Constanta, Romania. We reviewed the patient files and noted a number of variables which included: age, sex, family history, patient's history, signs and symptoms, bacteriological examination (smear and culture), tuberculin skin test, TB exposure, smoking habits, lesions on chest x-ray, treatment and evolution.

Results: During the 22 months, 101(13,5%) patients out of the 748 patients treated in the pediatric pulmonology department were diagnosed with TB. The gender distribution was uniform: 53 (52,5%) female and 48 (47,5%) male. The frequency of TB cases increased with age: 3 (3%) cases under 5 years old, 26 (25,7%) between 5 and 9 years old, 31(30,6%) between 10-14 years old and 41(40,5%) cases between 15 and 18 years old. Most patients were symptomatic (87%), the most frequent symptoms reported were: fever (65%), cough (74%), decreased appetite (70%) and decreased weight (65%). A close contact with a contagious secondary TB disease was found in 50 patients (49,5%). The tuberculin skin test (TST) was positive in 82 patients (81%). We found 47 patients with benign form of primary TB, 4 primo-secondary TB (post-primary TB), 26 secondary TB and 24 pleural TB effusions. 23 patients had smear-positive and positive culture. The chest X-ray

included adenopathy (+- elements of the Gohn Complex), nodules, infiltrate or parenchymal cavity.

Conclusions: In our study, the largest share of TB cases was met in the age group: 15-18 years. Most patients reported the presence of suggestive classic symptoms of tuberculosis. There were differences between the two groups of children and adolescents, in relation to diagnostic criteria role in supporting the diagnosis of certainty or diagnosis of probability. The benign primary TB was the most frequent form, being present in all age groups, in a significantly higher proportion of cases compared to primo-secondary, secondary and pleural forms. Pleural effusion was present in one third of the TB cases occurred between 15-18 years old, in 31,7% of cases. Culture-confirmed cases were more common in the group of adolescents. The diagnosis of TB disease in children remain a challenge for the pulmonologist based on the fact that bacteriological confirmation is rarely achieved.

Key words: pediatric tuberculosis, TB contact, primary TB, adenopathy, tuberculin skin test, cavitory TB

Introduction

Tuberculosis (TB) is an important cause of morbidity and mortality in children, especially in high endemic regions as Romania. Pediatric Tuberculosis reflects both the epidemic level of the region and the control measures efficiency of national programs in the territory¹⁻⁴. Worldwide, there were reported 1 million new TB cases in children in 2014, and 140000 deaths⁵. Pulmonary TB is a contagious infectious disease caused by Mycobacterium tuberculosis (*M. tuberculosis*)¹. The source is the infectious index TB patient who spreads bacilli during coughing, sneezing, talking, singing^{6,7}. Children who are exposed to a contagious case can get infected, but only 5-10 % of them get active TB disease during their life^{6,8}.

In Romania, the global incidence of TB being high (70/000 inhabitants), TB infection occurs during childhood, compared to low endemic countries where age moves towards young adult.

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TB infection is asymptomatic in many children (85% cases), they remaining healthy carriers of the TB bacillus. During childhood and adolescence the risk of developing active TB disease is different, the most exposed being those under 5 years old and the HIV infected⁷. Generally, for children under 2 years old, infection progress to disease the in first year after infection⁸.

Prolonged household contact, malnutrition, immune debilitating diseases, particularly HIV infection, genetic factors and virulence of the bacillus are high risk TB factors, that favour progression infection to active disease^{1,8,9}. The diagnosis of TB disease in children is often difficult and it is based on epidemiological criteria, positive tuberculin skin test, suggestive sign of TB on chest radiograph, bacteriological exam for M tuberculosis or histopathologic examination⁸.

The clinical examination is nonspecific and the bacteriological confirmation is rarely achieved^{1,3,8}. In the absence of the gold standard diagnostic criteria (bacteriology or histopathology), the decision to establish the diagnosis and specific antituberculosis treatment depends on clinician's experience, in most cases being a diagnosis of exclusion.

Objective

The present study aims to determine child tuberculosis particularities depending on age period and the most important changes of the disease in adolescents. Since this is the only hospital in Constanta county where pediatric TB is diagnosed and treated, we consider that the study cohort is representative to characterize the features of this disease.

Material and Methods

The data were collected from patient's files from 1st January 2014 to 1st November 2015 from children and adolescents under the age of 18, diagnosed with tuberculosis in the Pediatric Department of Clinical Pneumophysiology Hospital Constanta, Romania. We reviewed the patient files and noted a number of variables which included: age, sex, family and patient's history, signs and symptoms (fever, cough, decreased weight and appetite), bacteriological examination (smear and culture), TST, TB exposure, smoking habits, chest X-Ray, treatment and evolution. We defined as Group 1 patients aged 0-4 years (infants and newborns included), Group 2 - preschool and school children aged 5-9 years, group 3 - school children between 10 and 14 years old (puberty included) and group 4 - adolescents aged between 15 and 18 years, considering that there are differences in terms of hormonal and immune status, as well as particularities in terms of exposure to infectious agents and different risk of developing TB.

Subsequently tuberculosis characteristics were compared between the group of children and the adolescents', invoking the threshold of 15, according to the notification data used by WHO and guidance TB report^{5,10}. The children performed TST through Mantoux method using 5 tuberculin units (TU) of M. tuberculosis PPD RT 23 (Statens Serum Institut, Copenhagen, Denmark). After 72

hours the transverse diameter of induration was measured. We considered a positive TST with an induration higher or equal to 10 mm in diameter (all being immuno-competent and BCG vaccinated children). A close contact was considered when the child had been exposed to a recent contagious TB case (sputum smear-positive).

A standard antero-posterior (AP) followed by a lateral chest X-Ray was done for all cases. Those with suggestive radiological signs of TB were subjected to bacteriological examination of sputum or gastric aspirate. In the presence of pleural effusion we perform thoracentesis with biochemical and cytological examination of pleural fluid. In order to sustain TB etiology we considered a value of adenosine deaminase (ADA) more than 40 UI associated to lymphocytic exudative effusion being strong criteria for high probability of TB diagnosis and start anti-TB treatment.

Statistical analysis of the data was carried out using the Graph Pad Prism software. The statistical significance of tests performed was interpreted according to *p* value. The frequencies of symptoms, radiological signs, results in TST and bacteriological confirmation were compared between the age groups.

Results

From January 2014 until October 2015, 101 children and adolescences aged between 0 and 18 years (13,5% out of the 748 patients) were diagnosed with TB and treated in the pediatric pulmonology department. The gender distribution was uniform: 53 (52,5%) female and 48 (47,5%) male. Frequency of TB cases increasing with age: 3 (3%) cases under 5 years old, 26 (25,7%) between 5 and 9 years old, 31 (30,6%) between 10-14 years old and 41(40,5%) between 15 and 18 years old. 47 (46,5%) patients were diagnosed with primary TB, 4 (4%) patients ere diagnosed with primo-secondary TB, 24 (23,7%) patients with pleural effusion and 26 (25,7 %) patients with secondary TB (fig. 1). The benign primary TB was the most frequent form, being present in all age groups, in a significantly higher proportion of cases compared to primo-secondary, secondary and pleural forms ($p < 0.05$). Primo-secondary forms in patients over 10 years old were present in 4% of the cases, being more rare than other forms of TB ($p < 0.001$).

The incidence of primary TB forms was significantly higher in the age groups 5-9 years (44,70%) and 10-14 years (36,19%), compared to groups under 5 and those between 15-18 years old ($p < 0.05$), and secondary TB forms were more frequent (76%) in the age group 15-18 years ($p < 0.05$), and being absent in children under 10 years old. Pleural effusion was present in one third of the TB cases occurred between 15-18 years old, in 31,7% of cases, and in 15,3% of TB cases in children of 5-9 years old ($p < 0.001$) (figure 1).

Most patients were symptomatic, the most frequent symptoms being fever (65%), cough (74%), decreased appetite (70%) and weight loss (65%). A close contact with an active secondary TB disease was found in 50 patients (49,5%). The tuberculin skin test was positive in 82 patients (81%) (table 1).

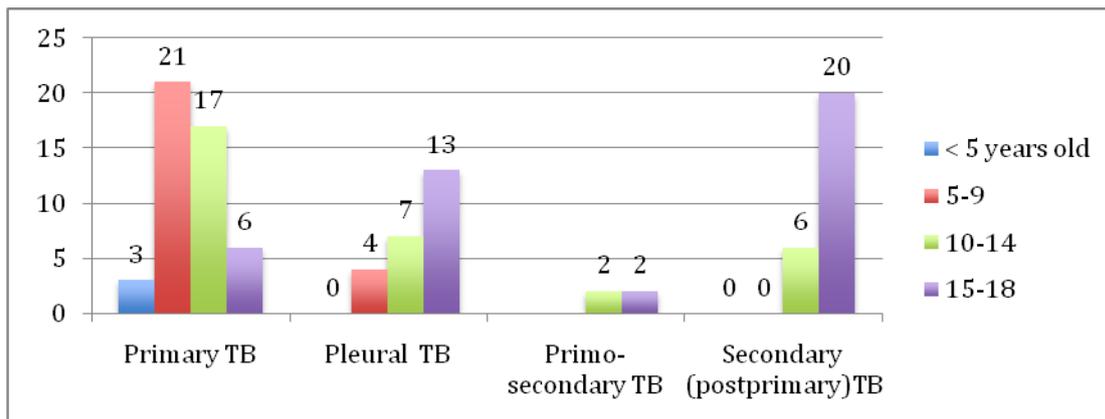


Figure 1. Distribution of TB forms by age group.

Table 1. Characteristics of TB forms: primary, primo-secondary, secondary and pleural TB.

N= (%)	Primary TB n=47; (46,5)	Pleural effusion n=24 (23,7)	Primo-Secondary TB n =4 (3,9)	Secondary TB n=26 (25,7)
Female	20 (46)	10 (41)	2 (50)	16 (61)
Male	27 (57)	14 (58)	2 (50)	10 (38)
BCG	47 (100)	23 (95)	4 (100)	26 (100)
Age:				
Under 5,	3 (6)	0		0
5-9,	21 (44)	4 (16)		0
10-14,	17 (36)	7 (29)	2	6 (23)
15-18.	6 (12)	13 (54)	2	20 (84)
Close TB contact	30 (63.8)	5 (20.8)	3 (75)	11 (42.3)
Smoker/ nonsmoker/UN	2/41/5 (4.2/87.2/10)	8/15/1 (33.3/62.5/4,1)	1/3 (25/75)	7/11/8 (27/42.3/30)
Fever	25 (53)	19 (79)	3	19 (73)
Cough	27 (57)	22 (91)	3	23 (88)
Loss weight	25 (53)	20 (83)	4	17 (65)
Loss appetite	23 (48)	21 (87)	4	23 (88)
TST positive	44 (93.6)	20 (83.3)	3 (75)	15 (57.7)
TST negative	3 (6.3)	3 (12.5)		2 (7.7)
TST UN		1		10 (37)
Chest X-Ray				
Adenopathia (+_ other elements of the Gohn Complex)	47 (100)	1	4	0
Nodule	4 (8.5)	0	2 (50)	15 (57)
Parenchymal cavity	0	0	3 (75)	14 (53)
Infiltrate	1 (2.1)	0	2 (50)	13 (50)
M tuberculosis				
baar +	1 (2,1)	0		17(65.3)
Culture positive	1 (2,1)	4		13 (50)

BCG: bacilli Camette Guerin, UN- unknown

Distribution TB forms by sex was uniform, with no significant statistical differences ($p>0.05$) (table 1). Primary and primo-secondary forms reported TB contact in a higher proportion of cases compared to secondary TB forms, but without statistical significance, statistically significant differences being observed in those cases with pleural involvement ($p<0.05$).

Symptoms and TST positive were present in equal proportions in all forms of TB, noting that in secondary forms, TST test was not performed in a third of cases (in smear-positive cases). Hilar adenopathy was the radiological feature regularly present in primary and primo-secondary forms, whereas nodules, cavity and infiltrate were found in approximately equal proportions in secondary forms of TB. These radiological aspects were correlated with bacteriological examination, most confirmations being encountered in secondary forms, over 65% positive cases after the direct microscopic examination. Tuberculosis in children was more common among girls (53.3%), and in adolescents, among boys (51.2%).

Regarding the smoking habit, it was more commonly encountered in primo-secondary, secondary and pleural forms, compared to the group of patients presenting primary forms ($p<0.05$). No smoker was reported in children with TB, whereas this habit was present in 44% cases in adolescents.

Symptoms and TST were observed with approximately equal frequency in children and adolescents. Adenopathies were significantly more common in children ($p=0.01$), whereas nodular forms, cavities and infiltrations were more frequent in adolescents ($p=0.01$) (figure 2).

Culture-confirmed cases were statistically significantly more in the group of adolescents (34.7% vs. 8.3%, $p=0.01$), and the smear-positive were more common in this age group, but without statistical significance (table 2). Pleural effusions were observed in approximately equal proportions in the two age groups, with an ADA value of over 64 U/l in both groups of patients.

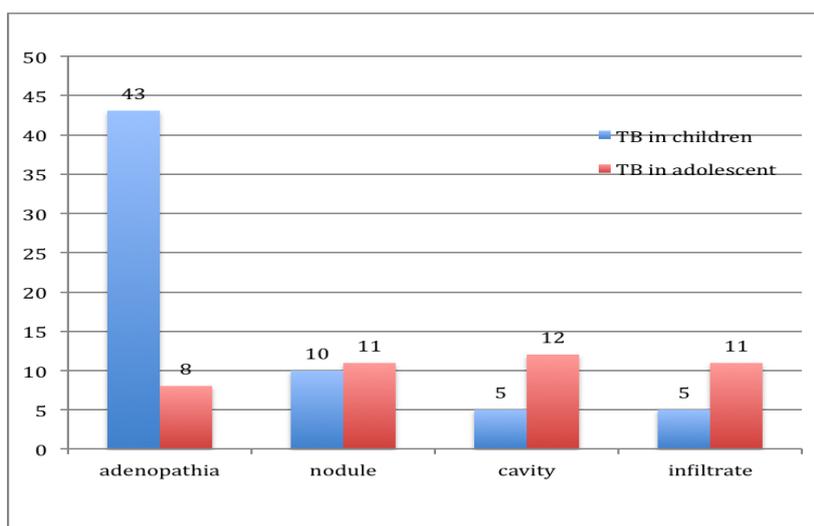


Figure 2. Distribution of radiological forms in children cohort and adolescent cohort.

Table 2. Characteristics of TB in child compared to TB in adolescent.

TB patients n=, (%)	Male	TB contact	Smokers	Sympt.	TST +	smear +	M. tuberculosis Culture +	Pleural effusion	ADA (U/l)
Children n=60 (59,4)	28 (46,7)	32 (53,3)	0	36 (87)	54 (90)	10 (16,6)	5 (8,3)	11 (18,3)	64,58
Adolescents n=41(40,6)	21 (51)	18 (43,9)	18 (44)	52 (86)	28 (68)	14 (34)	13 (31,7)	13 (31,7)	64,09
p value	ns	ns	$p<0.05$	ns	ns	Ns	$p=0.01$	ns	ns

Discussion

The study pursued the clinical, imaging, bacteriological and immunological (TST) characteristics of tuberculosis forms present in children, compared to those observed in adolescents. All cases diagnosed in the Department of Pediatric Pneumology during the period 1st of January 2014 until 1st of November 2015 were evaluated. The Department is unique in Constanta and Tulcea counties, reason for which we consider the cohort characteristic for Dobrogea region. The TB surveillance in Constanta County highlights increased values of global incidence 80%000 in 2014 and global incidence in children (0-14 years old) 34%000, Constanta being in the first 5 counties with the highest incidence in Romania. In 2014, 38 new cases were registered in the National Unique TB Registry and by 1st of November 2015, another 37 new TB cases in the population aged 0-15 years. In the present study, assessment of tuberculosis cases showed that TB frequency has increased with age, a small number of cases were found in patients aged under 5, and this period of time is known in literature as the period with the highest risk for tuberculosis^{1,7}.

Distribution of patients by sex was uniform, both in children and in adolescents (46%: 54% respectively 51%:49%), different from the data at national level, which show a male : female ratio of 2:1¹¹. The percentage of TB cases for which the source had been identified, was higher than in other studies (53,3% vs. 43,9% in the children cohort vs. adolescent cohort, totally different from 27,8% in Marais' study)². In children, a close contact with family members is more frequently identified. Smoking as a TB risk factor in children is debatable, but the present study showed the fact that 44% of adolescents were smokers when they were TB diagnosed. This result may be considered an alarm regarding the early age they started smoking, that bronchial mucosal is exposed to substances that alter the ability of local defense, the so-called cell-mediated immune response, against *M. tuberculosis* infections. Symptoms were present in most patients (87%).

The most common symptoms include fever (over 60%), chronic cough for more than 3 weeks (over 70%), weight loss (over 63%), loss of appetite (over 65%). No significant differences in symptom prevalence existed between age groups (0-15 years old, 15-18 years old). The results are similar to those in other studies. For example, Marais' study that followed the prevalence of symptoms associated with pulmonary tuberculosis in children from a high burden community showed the constant presence of a combination of symptoms traditionally associated with tuberculosis, but have limited diagnostic value.

Weight loss and coughing have a positive predictive value of 5%². WHO reports a frequency of 0.6%–3.6% of smear-positive in children under 14 years old and 95% negative smear in children under 12 years old⁷. In our study we found 16.6% cases of smear-positive, in more severe TB cases. Other studies report less than 15% acid fast bacilli smear-positive and 30-40% confirmation in culture^{7,12,13}.

It is difficult to obtain a sample of good quality sputum in children and for this reason induced sputum method is

recommended^{14,15}. Positive TST supports the diagnosis of infection and it should be interpreted with caution as a diagnostic criterion in BCG vaccinated population or in the endemic areas. In younger age groups, it is required differentiation of post-vaccination immunity given by BCG by performing Quantiferon test. Intrathoracic adenopathies and lung lesions were present on chest-X-Ray up to 80% of the child's TB¹⁶. As literature showed, hilar enlarged lymph node was the most frequent modification observed in our patients (78% under 15 years of age). 11 children presented pleural effusion (26%).

The TB diagnosis was confirmed by positive culture but this appears in extensive forms like cavity specific in adolescent TB. In the negative smear and culture forms of TB, guidancelines recommend other criteria for diagnosis: household contact, complex of symptoms, chest X-Ray, TST and excluding other causes of illness. In high endemic countries contact may be extended extra-domiciliary¹⁷. Computed tomography of chest was not routinely used to confirm the presence of adenopathies given the risk of radiation at that age. Fiberbrochoscopy was performed in 7 cases of extrinsic compression suspicion and it was confirm in 6 cases. Ganglio-bronchial fistula was present in one case. Pleural effusion was the main TB form of presentation in the adolescents' cohort (31.7 % vs18%). 4 cases (20%) of pleural effusion were confirmed by positive *M. tuberculosis* culture in pleural fluid, and the mean value ADA was 64 UI in both cohorts, similar with literature data¹⁸. Pleural biopsy was not possible in the department.

The study had several limitations. It is estimated that diagnosis for child tuberculosis is one of exclusion. Correct diagnosis by positive culture was established only in 21 cases (20.7%), 15 being from adolescents' group. In this case, as in the others, presented above, the data are consistent with those in specialized literature. Clinical, epidemiological, TST and radiological criteria remain key elements for high probability diagnosis sustained by the specialist.

Conclusions

In our study, the largest share of TB cases was met in the age group: 15-18 years. Most patients reported the presence of suggestive classic symptoms of tuberculosis. There were differences between the two groups of children and adolescents in relation to diagnostic criteria role in supporting the diagnosis of certainty or diagnosis of probability. The benign primary TB was the most frequent form, being present in all age groups, in a significantly higher proportion of cases compared to primo-secondary, secondary and pleural forms. Pleural effusion was present in one third of the TB cases occurred between 15-18 years old, in 31,7% of cases. Culture-confirmed cases were more common in the group of adolescents. The diagnosis of TB disease in children remains a challenge for the pulmonologist based on the fact that bacteriological confirmation is rarely achieved.

References

1. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. *Int J Tuberc Lung Dis* 2004;8:636–647.
2. Marais BJ, Obihara CC, Gie PR, et al. The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high burden community. *Arch Dis Child* 2005; 90:1166–1170. doi: 10.1136/adc.2004.060640
3. Donald PR. Childhood tuberculosis: out of control? *Curr Opin Pulm Med* 2002;8:178–82.
4. Walls T, Shingadia D. Global epidemiology of paediatric tuberculosis. *J Infect* 2004;48:13–22.
5. http://www.who.int/tb/publications/global_report/2015/en/index.html. 2015
6. Batra V. Pediatric tuberculosis. UpToDate
7. Swaminathan S, Rekha B. Pediatric Tuberculosis: Global Overview and Challenges. *Clinical Infectious Diseases* 2010;50(S3):S184–S194
8. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre- chemotherapy era. *Int J Tuberc Lung Dis* 2004; 8:392–402.
9. <http://www.who.int/tb/publications/en/index.html>. Accessed 24 March 2010.
10. Enarson D A, Rieder H L, Arnadottir T, Trebucq A. Management of tuberculosis. A guide for low income countries. Fifth edition. Paris, France: International Union Against Tuberculosis and Lung Disease, 2000
11. [http://www.ms.ro/documente/GHID%20Metodologic%20PNPSCT%20FINAL%20-17.06.2015%20\(aprobat%20Comisie%20Pneumo\)%20ultima%20varianta_1124_2279.pdf](http://www.ms.ro/documente/GHID%20Metodologic%20PNPSCT%20FINAL%20-17.06.2015%20(aprobat%20Comisie%20Pneumo)%20ultima%20varianta_1124_2279.pdf)
12. Cruz AT, Starke JR. Clinical manifestations of TB in children. *Pediatr Respir Rev* 2007;8:107–117.
13. Eamranond P, Jaramaillo E. Tuberculosis in children: reassessing the need for improved diagnosis in global control strategies. *Int J Tuberc Lung Dis* 2001;5:594–603.
14. Marais BJ, Pai M. New approaches and emerging technologies in the diagnosis of childhood tuberculosis. *Pediatr Respir Rev* 2007;8: 124–133.
15. Swaminathan S, Datta M, Radhamani MP, et al. A profile of bacteriologically confirmed: pulmonary tuberculosis in children. *Indian Pe- diatr* 2008;45:743–747.
16. Starke JR. Tuberculosis. In: Jensen HB, Baltimore RS, eds. *Pediatric infectious diseases: principles and practices*. Philadelphia: WB Saun- ders, 2002:396–419.
17. Marais BJ, Pai M. Recent advances in the diagnosis of childhood tu-berculosis. *Arch Dis Child* 2007;92:446–452
18. Reechaipichitkul W, Kawamatawong T, Teerajetgul Y, Patjanasontorn B. Diagnostic role of pleural fluid adenosine deaminase in tuberculous pleural effusion. *Southeast Asian J Trop Med Public Health*. 2001 Jun;32(2):383-9.

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