Respiratory tuberculosis in children and adolescents: Assessment of radiological severity pattern and age-related changes within two decades

Tuberculoza respiratorie la copii și adolescenți: evaluarea severității aspectului radiologic și a modificărilor legate de vârstă în două decenii

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Abstract

Introduction: *Despite the global decline of tuberculosis (TB), the annual risk of TB infection in children from developing countries remains high. Giving the global and regional epidemiological context in the past 20 years and a recent classification, dividing childhood TB into severe and non-severe disease, our aim was to find possible differences regarding disease severity in the pediatric population, as assessed by chest radiography (CXR) over 2 decades.*
Materials and method: *A retrospective analysis of CXRs from newly confirmed respiratory TB patients was performed at the Pediatric Pulmonology Department of a tertiary-care university hospital that acts as a referral TB center in Transylvania. CXRs were reviewed for all patients suffering from respiratory TB in 1994-1999 (Group A) and all respective cases from 2008-2013 (Group B).*
Results: *In the 110 respiratory TB cases identified in group A and 73 respective cases found in group B, the male:female distribution was similar, 56%-44%. In group A a severe pattern was present in 34% of patients, while in group B there were 43% of respective cases. The median age for severe disease in group A was 10 years, and 15 years in group B ($p<0.05$). Furthermore, in group B there was less mediastinal lymphadenopathy (55% vs. 68% in group A), more cavities (11% vs. 6% in group A) and a significantly higher number of consolidation, 38% vs. 25% ($p=0.04$).*
Conclusion: *CXR findings in the pediatric population have evolved from a mainly nonsevere TB pattern to an increased prevalence of severe disease, found mostly in the adolescents.*
Keywords: *chest radiography; children; disease severity; tuberculosis*

Rezumat

Introducere: *În ciuda declinului global al tuberculozei (TBC), riscul anual de infecție TBC la copiii din țările în curs de dezvoltare rămâne ridicat. Conform unei clasificări recente, împărțind TBC pediatrică în boala severă și nonseveră, scopul nostru a fost de a găsi o posibilă tendință în ceea ce privește severitatea bolii la copii, evaluată prin radiografie toracică în decursul a două decenii.*
Materiale și metodă: *S-a efectuat o analiză retrospectivă a radiografiilor toracice la pacienții <18 ani cu TBC respiratorie nou confirmată în perioada 1994-1999 (Grupul A) și toate cazurile respective din perioada 2008-2013 (Grupul B).*
Rezultate: *În cele 110 cazuri de TBC respiratorie identificate în grupul A și 73 de cazuri găsite în grupul B, distribuția pe sexe (masculin:feminin) a fost similară, 56%-44%. În grupul A boala severă a fost prezentă la 34% dintre pacienți, în timp ce în lotul B aceasta au fost prezentă în 43% din cazuri. Vârsta medie de boală severă în grupul A a fost de 10 ani, iar în grupul B de 15 ani ($p<0.05$). Grupul B a prezentat o frecvență mai redusă a adenopatiei mediastinale (55% vs. 68% în lotul A), mai multe cavități (11% vs. 6% în grupul A) și un număr semnificativ mai mare de focare de condensare, 38% față de 25% ($p=0,04$).*
Concluzie: *Aspectele vizibile pe radiografia toracică la copii au evoluat de la un model nonsever de TBC la o prevalență crescută a bolii severe, întâlnit mai ales în rândul adolescenților.*
Cuvinte-cheie: *Copii, radiografie toracică, severitatea bolii, tuberculoză*

Introduction

According to the World Health Organization (WHO) estimations, in 1990 there were 13 million new cases and 450,000 deaths by tuberculosis (TB) among children under 15 years of age[1]. TB incidence among children younger than 15 years old in 2012 was estimated at 530,000, accounting for about 6% of the total number of 8.6 mil incident cases[2]. Although childhood tuberculosis contributes to only 3–6% of the total caseload in industrialized countries, it sums up to a large proportion (15– 20%) of all TB cases in developing countries, with an annual risk of TB infection in children of 2.5%[1,3]. Consistent with the global decline of the disease, in Romania the incidence of TB in children aged 0-14 years decreased constantly from $48.2\%_{000}$ in 2002 to $22.2\%_{000}$ in 2013[4,5].

TB in children remains a neglected area of research despite considerable morbidity, mortality and disease diversity, which varies substantially between different age groups. The common perception is that the children rarely develop severe forms of TB and have little contribution to the maintenance of the tuberculosis epidemic. However, children can transmit Mycobacterium tuberculosis and

those with latent infection become the reservoir of disease reactivation in adulthood, fueling future TB epidemics[1,6,7]. TB control programs around the world use the cut-off point of 15 years to categorize patients as children or adults, and data referring to adolescents can not be retrieved. The WHO definition of adolescence includes individuals aged 10 through 19 years[8].

Recently a new comprehensive classification was proposed, dividing childhood TB into severe and non-severe disease. Non-severe disease implies limited disease pattern, non-disseminated and uncomplicated. In the thorax these findings include an uncomplicated Ghon focus, with or without uncomplicated intrathoracic lymphadenopathy. In contrast, severe disease implies either uncontrolled disease, resulting in local or peripheral tissue damage and caseous necrosis, dissemination or complicated disease manifestation. Intrathoracic complications refer to parenchymal lesions such as expansive alveolar consolidation, bronchopneumonia, multilobar alveolar opacification and cavitation. Disseminated disease refers to disease resulting from hematogenous bacillary spread, such as miliary TB. Pleural effusion is classified as non-severe if there is no evidence of severe underlying lung disease[9].

Chest radiography (CXR) remains the mainstay of pulmonary TB diagnosis in children[10,11], and can differentiate various severity patterns[12].

Giving the global and regional epidemiological context in the past 20 years and the new proposed standard classification, our aim was to find possible differences in the radiographic appearances and age-related disease severity of respiratory TB in children, assessed by CXR.

Materials and method

A retrospective analysis of patient medical record was performed at the Pediatric Pulmonology Department of the "Leon Daniello" Pulmonology and Tuberculosis Care Clinics in Cluj-Napoca, a tertiary-care university hospital that acts as a referral TB center in Transylvania and manages all TB cases reported in the last 20 years in Cluj County.

This research is in compliance with the Helsinki Declaration and ethics approval for this study was obtained from the local Human Medical Research Ethics Committee Board (clearance certificate 108/5.03.2014); informed consent was waived due to the retrospective nature of the study.

This study included two groups of consecutive patients, aged 0-18 years, with newly confirmed respiratory TB, in Cluj County: group A consisted of all children with cases between January 1994 and December 1999, and Group B of all cases from January 2008 to December 2013.

A positive diagnosis of respiratory TB was established by the presence of a positive 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[13]), and at least two of the three criteria: contact with a confirmed TB infectious 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).

All children underwent standard, frontal analog CXR. The radiological assessment of all images was made by consensus between a radiologist and a pediatric pulmonologist, who were aware of the clinical symptoms, and included non-severe disease features: presence and distribution of lymphadenopathy, Ghon focus and pleural effusion. Parenchymal complications, with particular attention on presence and localization of consolidation (including expansive pneumonia, collapse, macronodular infiltrates or bronchopneumonic changes), cavitation and miliary nodules, were reported.

Statistical Analysis

Continuous variables were summarized using median [interquartile range] while categorical variables as frequency (percentage).

All data were analyzed using R statistical software version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). The chi-square test or Fisher's exact test were used to assess differences between the two groups regarding each radiological feature and for the association between lymphadenopathy and parenchymal complications. To compare the proportion of complications and group age for each radiological pattern, the Wilcoxon rank sum test was applied. All probability values were 2-sided, with a level of significance of <0.05.

Results

The number of respiratory TB cases decreased by 34%, per 6 year interval, from 110 cases in group A (1994-1999) to 73 cases in group B (2008-2013). In group A there were 62 males (56%) and 48 females (44%), with ages ranging from 4 months to 18 years, mean age 7.4 years. In group B the distribution was similar between genders, there were 41 males (56%) and 32 females (44%), with ages ranging from 6 months to 18 years, mean age 9.2 years. In both groups the largest age category was that of infants, 28/110 patients (25%) and 21/73 cases (29%) respectively. An immunodeficiency disorder was present in two children (one congenital immunodeficiency syndrome and one HIV positive) from each group, respectively.

In group A, non-severe disease was assessed in 73/110 (66%) of cases, while a severe disease pattern was found in 37/110 (34%) of children. In group B, 42/73 (57%) of cases were classified as non-severe disease, whereas 31/73 (43%) of cases were defined as severe disease. The difference between the two groups did not reach statistical significance, $p=0.2$.

Lymphadenopathy was reported more frequently with a right side involvement, 41/110 (37%) vs. 30/73 (41%) of positive CXR. Bilateral distribution was seen in 31/110 (28%) and respectively 14/73 (19%) cases from each group. A total of 88 instances of parenchymal complication were identified in 37/110 (34%) vs. 31/73 (43%) children. The

Table 1 Frequency of signs of severe and non-severe respiratory TB as detected by CXR

Radiological feature	Group A N (%)	Group B N (%)	P-value*
Severe disease[1]	37 (34)	31 (43)	0.20
Non-severe disease[2]	73 (66)	42 (58)	0.02
Consolidation	27 (25)	28 (38)	0.04
Cavitation	7 (6)	8 (11)	0.20
Miliary nodules	3 (3)	1 (1)	1.00**
Lymphadenopathy	75 (68)	40 (55)	0.06
Pleural effusion	21 (19)	20 (27)	0.02

Group A: 1994-1999; Group B: 2008-2013

1. Severe disease is considered if at least one of the following patterns was present: consolidation, cavitation, military nodules.
2. Non-severe disease is considered when no severe disease pattern was present.
*assessed by chi-square; **assessed by Fisher's exact test;

Table 2 Number of instances and laterality for each parenchymal complication subtype

Lung parenchymal complication	Group A			Group B		
	Right	Left	Total	Right	Left	Total
Expansive pneumonia	18	6	24	19	10	29
Collapse	1	0	1	0	0	0
Macronodular infiltrates	3	1	4	3	1	4
Bronchopneumonic changes	5	1	6	2	3	5
Cavity	5	2	7	5	3	8
Total	**32**	**10**	**42**	**29**	**17**	**46**

Group A: 1994-1999; Group B: 2008-2013

Table 3 Median age for the main CXR findings of respiratory TB in the two groups

Radiological pattern	Group A Median [IQR]	Group B Median [IQR]	P-value*
Non-severe disease	4 [2-11]	5.5 [1-15]	0.95
Severe disease	10 [4-14]	15 [9-16]	0.049
Lymphadenopathy	3 [2-8]	2 [1-10]	0.18
Consolidation	7.5 [3-13]	14.5 [7-16]	0.03
Cavity	14 [11-15]	15 [14-16]	0.37
Pleural effusion	11 [8-15]	15 [13-17]	0.11
Total	**6 [2-13]**	**12 [1-15]**	**0.15**

Group A: 1994-1999; Group B: 2008-2013

*assessed by Wilcoxon rank sum test

findings on severe and non-severe forms of respiratory TB are summarized in Table 1. 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 lower in group A, 1.1 (42/37), than in group B, 1.5 (46/31), p<0.01. One case of lymphobronchial fistula was found in each group. Table 2 shows the instances of specific parenchymal complication subtypes together with laterality of the lesions.

The number of patients with parenchymal complications associated with lymphadenopathy was 15/110 (14%) in group A and 11/73 (15%) in group B. A very strong statistical correlation was found between the presence of lymphadenopathy and parenchymal complication in group A (p<0.0001), but lower correlation in group B (p<0.01). There were three cases in each group showing pleural effusion associated to parenchymal complications.

The median age for severe disease in group A was 10 years, and was 15 years in group B (p=0.049). Detailed distribution by age of the main radiological findings is presented in Table 3.

Discussion

Many studies have been analyzing the different imaging patterns of pulmonary TB, but to the best of our knowledge none did address the possible differences in the radiographic appearances and age-related disease severity of respiratory TB in patients over the age of 20. Therefore, we compared CXR features of respiratory TB in children who presented the disease between 1994 and 1999 with those in the last 6 years in order to find possible changes in respiratory TB radiological severity pattern.

Constant with the national evidence, the incidence of TB in children aged 0-14 years in Cluj county, dropped significantly from 41‰ in 2002 to 5.4‰ in 2012[4,5]. In the context of a decreasing incidence of childhood pulmonary TB, CXR findings evolved from a mainly non-severe pattern, 2/3 of cases in group A, to a tendency of incidence equalization between severe, 43%, and non-severe forms, 57%, in group B. Yet, this trend did not reach statistical significance, p=0.2.

Lymphadenopathy is considered to be 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[7,14,15]. Our results 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 years in group A vs 9.2 years in group B) may indicate the efficiency of prevention programs and the evolution of the first presentation to an older age. Moreover, the results show an important decrease of lymphadenopathy prevalence, from 68% to 55%, but this did not reach statistical significance (p=0.06). The distribution is typically unilateral and right sided, with bilateral impairment in about 1/3 of cases. However, CXR interpretation of lymphadenopathy is subjective and suffers from low sensitivity and specificity especially for detecting subcarinal and paratracheal adenopathies[16].

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. A retro-obstructive infiltrate in primary TB most commonly appears as an area of homogenous consolidation. Its appearance is often indistinguishable from that of other 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 commonly reported at the level of bronchus intermedius[7,17]. 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 went from a very strong to a low statistical significance, we believe these findings are due to longer duration of symptoms and a delay in diagnosis and treatment, or due to extensive time of exposure to an infectious source, which allowed a longer evolution of the TB process. However, it is not possible to differentiate consolidation secondary to lymphobronchial TB from that of an advanced primary local TB process, as the radiologic appearances are indistinguishable[17]. The 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[18].

Griffith-Richards et al. described three groups into which children with cavitation due to pulmonary TB can be placed[19]. In the two groups included in our study, adult-type cavitary lesions were found in children >6 years old, mainly adolescents, with an increasing incidence from 6% to 11%. These findings coincide with the literature which describes an incidence of cavitation on CXR between 5% and 16%, rarely seen in prepubescent children[20,21].

Overall, the differences in radiological findings (less lymphadenopathy, more consolidations and cavitations in the latter group) seem to be closely related to age profile and may partially be explained by the groups median age (7.4 vs 9.2 years), severe disease subgroups age (median: 10 vs 15 years), and the age of children with consolidation (median: 7.5 vs 14.5 years), which reached statistical significance.

Pleural effusion was reported in our study in up to 1/4 of patients, but remained an uncommon finding in infants. Usually unilateral, 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[7,22]. In our study, however, the increased number of parenchymal complications did not correlate with an increased incidence of pleural effusion and its occurrence was interpreted as being mainly due to the hypersensitivity of the reaction.

The traditional classification of TB into primary and postprimary should be avoided as the pathologic differences between these and the corresponding classic imaging pat-

terns characterizing the disease in adults and children have become unclear. There are several reasons for the change in the age-related distinction. Primary infection can occur at any age[23]. In countries with a high TB burden, primary TB is more common in children than in adults, because of the high likelihood of contact with Mycobacterium tuberculosis during childhood, while in developed countries, the likelihood of developing TB primo-infection can be postponed to adolescence or adulthood. Other responsible factors include exogenous reinfection in endemic areas, cavitation occurring within 6 months of initial infection, reducing its status as indicator of reactivation, and HIV co-infection resulting in atypical patterns of disease[8,23]. Moreover, several factors can pose a variety of diagnostic challenges in developing countries: in high incidence communities the children do not necessarily have a household member or a known adult index case; the rate of infection with multi-drug resistant TB (MDR-TB) strains in regions with high MDR-TB incidence is as high as with drug-susceptible strains; children infected both with HIV and TB present the same symptoms as children infected with HIV alone and may have a negative tuberculin skin test, while the latter may be positive in healthy children from high incidence areas; and limited access to basic and advanced investigations[24].

Findings on CXR may serve as a valuable tool to categorize TB severity in children, allowing for a stratified patient management, new diagnostics and treatment strategies and a more appropriate approach in children perceived to be at higher risk of further disease progression or poor outcome[9]. Our study suggests that a special attention should be given to adolescents, who tend to develop more severe forms of disease.

The limitations of our study are mainly due to its retrospective nature. One great limitation is that there is no reference test in the study. However, confirmation by culture of *Mycobacterium tuberculosis*, the gold standard of diagnosis in adult TB, is particularly difficult to obtain in children. We therefore used the Diagnosis and Treatment Guide in Childhood Tuberculosis elaborated by the National Institute for Healthcare Research and Development[13] for positive diagnosis. A second limitation is that demographic and clinical data were not analyzed in this study. This was due to the fact that our aim was to evaluate the radiographic appearances and age-related disease severity of respiratory TB in children, considering that CXR was the most constant assessment on a 20 years interval. Furthermore, one study showed that patients' symptoms could not be confidently used to differentiate between children with culture proven TB to those presenting other lung diseases; the only clinical differences between the two groups were contact with a TB infected adult and a positive tuberculin skin test[25]. Third, we included only standard, frontal CXRs. Both frontal and lateral views should be obtained, since the latter permits a better evaluation of the mediastinal and hilar lymphadenopathy, but the diagnostic is improved only by 11%[26]. Yet, this aspect probably had a small influence in the final results regarding severe forms of the disease in our study.

Conclusion

TB is a progressively evolving, dynamic pathological process. Our study shows that CXR findings in children, in the context of a decreasing incidence of the disease, have evolved from a mainly non-severe pattern to an increased prevalence of severe disease. These findings were due to a decreasing incidence of uncomplicated lymphadenopathies and a higher frequency of parenchymal complications, such as pulmonary consolidation and cavitary lesions, which show an increasing prevalence in adolescents. ■

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