Epidemiological aspects of tuberculosis in children and adolescents in Rio de Janeiro

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Abstract

Objective: To describe the epidemiological aspects of childhood tuberculosis (TB) in a Brazilian reference hospital.

Methods: This was a retrospective study (1999-2008) of 473 subjects (0-14 year olds) with confirmed TB, or with clinical improvement by the fourth month of treatment under the unit's care, including the review of medical records, monitoring reports and notifications by the TB unit.

Results: Among 473 TB cases included in the study, positive tuberculin skin test was observed in 52%, history of contact with a patient with pulmonary tuberculosis in 66%, mostly intra-household, and with the father/stepfather most commonly involved; and disseminated TB in 22%. The result of HIV testing was obtained in 265 (56%) cases, being positive in 45 (17%). The diagnosis of TB was confirmed in 31% of cases, most frequently in children older than 5 years, with negative tuberculin skin test, and in disseminated forms. Of the 65 cultures positive for TB performed in the study, drug sensitivity testing to anti-TB drugs was done in 30 (46%) clinical samples, among which 10 (33%) were resistant to one or more anti-TB drugs, and 2 (0.8%) were multi-drug-resistant. Among patients with confirmed pulmonary TB, 31% did not meet the criteria for starting anti-TB treatment according to the scores of the Ministry of Health (≤ 25 points).

Conclusion: The high proportion of drug-resistant TB and co-infection with HIV identified in this study highlight the necessity to carry out additional studies in order to evaluate the impact of TB control activities on childhood TB.

J Pediatr (Rio J). 2012;88(4):335-40: Tuberculosis-diagnosis, epidemiology, tuberculosis-child.

Introduction

Tuberculosis (TB) is an important cause of child morbimortality in the world. According to the World Health Organization, the estimated percentage of TB in children under 15 years ranges from 3 to 25% in different nations.[1] Corbett et al.[2] estimated that, in 2000, there were 23,520 cases of TB in children from 0 to 14 years in Brazil, representing 20% of total cases, while Sant'Anna et al.[3] estimated 15% for the same period. In local studies performed in Brazil, it was observed that TB affected 5% of children in this age group at a unit in Ribeirão Preto,[4] 6.7% in the municipality of Rio de Janeiro,[5] 9% at a unit in Salvador[6] and 13.3% in Vale do Paraíba.[7]

The diagnosis of childhood TB usually based on clinical criteria remains as a challenge. Until the present moment, the new diagnostic approaches (molecular testing or liquid culture) that have been used in TB assessments in adults have not been incorporated into the clinical practice, due to the large variability of accuracy and low positivity in

children.[8] In 2002, the Brazilian Ministry of Health (MH) included in the Manual of Recommendations for Tuberculosis Control, a scoring system, which was updated in 2010,[8] aiming to assist the diagnosis of pulmonary TB in children with negative bacilloscopy in services of low complexity, especially on an outpatient basis.[3] Variables considered relevant received individual points which, added, classified the suspect patients as follows: very likely diagnosis of TB (≥ 40 points), allowing thus, the start of the anti-TB treatment; likely diagnosis (30 to 35 points), cases in which the treatment could be initiated according to clinical criteria; unlikely diagnosis (< 25 points), cases in which the suspect child should continue under clinical investigation.[8] This clinical score was assessed in some studies with sensibility ranging from 89 to 99%, and specificity ranging from 70 to 87%.[6,9,10]

In this age group, infection with human immunodeficiency virus (HIV) is a complicating factor for the diagnosis of TB. Children carrying the virus are more susceptible to exposure to *Mycobacterium tuberculosis* at the household level, to the development of severer clinical forms, to the non-reactivity of the tuberculin test, to low weight, besides the possibility of association with other pulmonary comorbidities, such as bronchiectasis or pneumonias.[11,12] Regarding the TB co-infection with HIV in childhood, Oliveira et al.[5] found association in 4.1% of cases.

Epidemiological studies on TB in children and adolescents are limited, which hampers the identification and the monitoring of more adequate interventions for epidemic control. The aim of this study was to describe the epidemiological characteristics of children with TB treated at a reference pediatric Hospital in Rio de Janeiro, which is the state with higher incidence of TB at the national level.

Methods

This study, which was approved by the Research Ethics Committee of the Health and Civil Defense Department of the City Hall of Rio de Janeiro, consists of an epidemiological, descriptive study, with data collection from January 1999 to December 2008. Data sources include medical records, clinical monitoring reports of TB from the Pediatric Pulmonary Service and TB notification records from the hospital. In this period, 530 cases of TB were monitored, and 473 were included in the study. The excluded patients were the following: (a) patients without confirmed diagnosis or without clinic improvement until the fourth month of anti-TB treatment (n = 33); (b) patients with change of diagnosis (n = 15); (c) patients from whom it was not possible to retrieve the information from the records (n = 8); (d) patients who restarted the treatment after abandonment, whose initial diagnosis of TB was outside the period of the study (n = 1).

In a specific form, the following variables were collected: age, sex, city of residence, weight, situation of the vaccine against tuberculosis (BCG), history of contact with a patient with bacilliferous pulmonary TB, results of tuberculin skin test, tests performed, anti-HIV serology, clinical presentation, onset of symptoms, seek for treatment at health services, start of treatment, hospitalization, complications and outcome. Analyses were performed in the Statistical Package for the Social Sciences version 13.0 for Windows. We used the percentile and the chi-square test with significance level of ≤ 0.05 for comparison between variables.

The clinical diagnosis of TB was made by the medical staff based on clinical evaluation of the suspected patient, along with epidemiological data, interpretation of the tuberculin test and radiological findings. This study considered the cases in which there was no confirmation of etiology, but the patient showed clinical improvement (weight gain and remission of symptoms) and/or radiological improvement (complete resolution of the initial injury) until the fourth month of specific anti-TB treatment.

TB was considered confirmed when clinical samples presented resistant acid-fast bacilli, growth of *M. tuberculosis* in culture, and/or histopathological report with typical granulomatous process. Cases of miliary TB, tuberculous meningitis and TB affecting two or more sites simultaneously (excluding association of pulmonary and pleural TB) were considered disseminated TB. The tuberculin test was considered positive if ≥ 10 mm in BCG vaccinated children until 2 years old and if ≥ 5 mm in all other subjects.

The MH score was applied retrospectively in accordance with the 2010 Manual of Recommendations for Tuberculosis Control,[8] in all patients with identification of pulmonary focus, isolated or not.

The study was conducted at the Hospital Municipal Jesus, at an exclusively pediatric unit, which is a reference in the municipality of Rio de Janeiro. The hospital has nursing-led inpatient units, intensive and semi-intensive care units, surgical center, pathology service, laboratory, and ambulatory care. It has an average capacity of 120 beds for inpatient care and performs over 90,000 consultations per year. The hospital receives the demand of patients from the host and neighboring municipalities, patients transferred from other health services or referred for hospitalization by expert opinion. It has several pediatric subspecialties, among which: pediatrics pneumology, infectious diseases (with an excellence service for HIV infection), pediatric orthopedics and pediatric surgery.

Results

The total of 473 subjects included corresponds to 16% of TB cases in patients from 0 to 14 years old reported in the municipality of Rio de Janeiro in the study period. Out

of all patients included, 68% lived in the host municipality. Figure 1 shows the distribution of cases during the study period. There was a progressive decrease in the occurrence of TB cases in the period between 2001 and 2004.

According to age criteria, TB occurred: with < 1 year in 13% (63 cases); from 1 to 4 years in 40% (191 cases); from 5 to 9 years in 31% (145 cases); and from 10 to 14 years in 16% (74 cases). Males included 55% of cases and weight below the 10th percentile occurred in 45% of cases.

Vaccination with BCG was found in 99% of cases, and the positive tuberculin test in 52% of cases. The history of contact with a patient with bacilliferous pulmonary TB was present in 66%, most of them intra-household, being the father/stepfather the most implicated family member.

The diagnosis of disseminated TB (miliary TB, tuberculous meningitis or TB affecting two or more sites simultaneously) was identified in 22% (104 cases) in similar proportions in the different age groups. Pulmonary involvement was present in 66% of cases, followed by the clinical ganglionic and bone forms, respectively, in order of frequency.

Out of the 65 positive cultures for TB obtained in the study, the antibiogram was performed in 46%, among which one third presented resistance to one or more anti-TB drugs. The simultaneous resistance to rifampicin and isoniazid (multidrug resistant tuberculosis) occurred in 0.8% of cases. In the tests performed, the following positivity was observed: 24% bronchoalveolar lavage cultures, 28% bacilloscopy tests, 35% gastric lavage cultures, 63% endobronchial lesions among the flexible bronchoscopies performed and 83% histopathologic abnormalities consistent with TB.

The co-infection with HIV was identified in 17% of cases. The result of the anti-HIV test was obtained in 56% of cases.

In Table 1, epidemiological aspects, laboratory aspects and the result of the anti-TB treatment are compared between patients with confirmed diagnosis and those with clinical diagnosis. Confirmed TB was more frequent in children aged over 5 years and significantly higher (p ≤ 0.05) in carriers of negative tuberculin skin test (p = 0.02) and of disseminated forms (p = 0.009). The diagnosis of TB was confirmed in 31% of cases, and out of the patients with confirmed TB and pulmonary involvement, 31% did not meet the inclusion criteria to start of treatment according to the MH scores (≤ 25 points).

Table 2 compares the epidemiological aspects, laboratory aspects and the treatment outcomes between patients infected with HIV and those not infected. Patients known to be infected with HIV presented lower rates of completion of the anti-TB treatment, as well as significantly lower weight (< 10th percentile, p = 0.013), besides lower tuberculin test positivity (p = 0.000).

Hospitalization occurred in 70% of the cases, 63% of them lasting over 15 days. Complications during anti-TB treatment were identified in 12% of cases, and one third occurred in patients who were HIV seropositive.

Regarding the result of the anti-TB treatment, it was observed completion in 83%, death in 2.5% (mostly HIV positive) and abandonment in 12% (more frequent around the 2nd month of treatment).

Discussion

The number of TB cases followed by this unit suffered a progressive decrease in the period between 2001 and 2004, remaining stable thereafter. One of the factors associated with this scenario was the publication by the MH, in 2001, of the punctuation score for childhood TB with negative bacilloscopy, officially included in the guidelines for the national management of TB in 2002, and which enabled the diagnosis of probability in units of low to medium complexity.
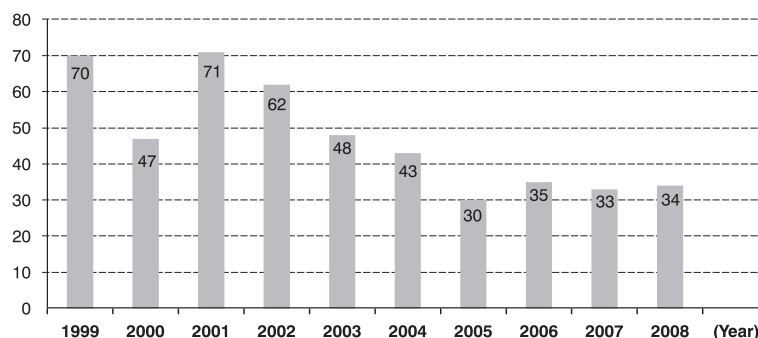

Figure 1 – Distribution of the patients in the study period

Table 1 -   Distribution according to the diagnostic criterion used

Variable	Confirmed diagnosis (n = 146)	Clinical diagnosis (n = 327)	p
Age			
< 5 years	69 (47.3%)	185 (56.6%)	0.06
≥ 5 years	77 (52.7%)	142 (43.4%)	
Percentile			
≥ 10	74 (51.0%)	184 (56.4%)	0.28
< 10	71 (49.0%)	142 (43.6%)	
Unknown	1	1	
BCG Vaccination			
Yes	146 (100%)	321 (98.5%)	0.13
No	0 (0%)	5 (1.5%)	
Unknown	30	1	
Tuberculin test			
Positive	66 (52.0%)	180 (64.1%)	0.02*
Negative	61 (48.0%)	101 (35.9%)	
Unknown	19	46	
Type of contact			
Intra-household	71 (87.7%)	209 (90.9%)	0.41
Extra-household	10 (12.3%)	21 (9.1%)	
Unknown	65	97	
Form of TB			
Pulmonary or extra-pulmonary	103 (70.5%)	266 (81.3%)	0.009*
Disseminated	43 (29.5%)	61 (18.7%)	
Anti-HIV serology			
Positive	29 (29.9%)	52 (31.0%)	0.86
Negative	68 (70.1%)	116 (69.0%)	
Unknown	49	159	
MH Score for pulmonary TB			
Positive (≥ 30 points)	56 (69.1%)	138 (72.6%)	0.55
Negative (≤ 25 points)	25 (30.9%)	52 (27.4%)	
Not applicable	65	137	
Completion of anti-TB treatment			
Completed	123 (84.2%)	269 (82.5%)	0.64
Uncompleted	23 (15.8%)	57 (17.5%)	
Unknown		1	

BCG = vaccine against tuberculosis; HIV = human immunodeficiency virus; MH = Brazilian Ministry of Health; TB = tuberculosis.
* p ≤ 0.05.

There was a slight male predominance, similar to that described in literature.[6,13,14] Epidemiological history of contact with a bacilliferous patient was observed in 66% of cases, confirming the relevance of contacts control in preventing the spread of this disease.

Vaccination coverage was high; however, higher morbidity was still identified in patients younger than 5 years. Patients under 5 presented higher frequency of disseminated forms and non-completion of treatment, mainly due to treatment abandonment. Oliveira et al.[15] reported an apparent vulnerability to the abandonment of anti-TB treatment in children younger than 1 year old, associated with a previous history of noncompliance with treatment and absent and/or drug user father.

Co-infection with HIV, in this study, was high (17%), probably due to the existence of a reference pediatric service for monitoring HIV infection in the unit. Most seropositive patients presented weight below the 10th percentile, lower positivity in the tuberculin test and tendency towards non-completion of the specific treatment for TB, a scenario that was consistent with the literature.[11,12]

Etiological confirmation occurred mostly in children older than 5 years old, with negative tuberculin test and in the form of disseminated TB. In children over 5 years the spontaneous obtaining of lung material is easier, favoring the diagnosis.[8] The disseminated TB is characterized, in general, by several potential material foci for laboratory analysis, facilitating the identification of the bacillus.

Table 2 - Assessment of patients with known HIV serological status (265 cases)

Variable	Positive (n = 81)	Negative (n = 184)	p
Idade			
< 5 years	40 (49.4%)	111 (60.3%)	0.10
≥ 5 years	41 (50.6%)	73 (39.7%)	
Percentile			
≥ 10	28 (34.6%)	94 (51.1%)	0.013*
< 10	53 (65.4%)	90 (48.9%)	
BCG Vaccination			
Yes	81 (100%)	179 (97.3%)	0.13
No	0 (0%)	5 (2.7%)	
Tuberculin test			
Positive	18 (25.4%)	97 (62.6%)	0.000*
Negative	53 (74.6%)	58 (37.4%)	
Unknown	10	29	
Type of contact			
Intra-household	48 (94.1%)	115 (90.6%)	0.44
Extra-household	3 (5.9%)	12 (9.4%)	
Unknown	30	57	
Form of TB			
Pulmonary or extra-pulmonary	58 (71.6%)	137 (74.5%)	0.63
Disseminated	23 (28.4%)	47 (25.5%)	
Diagnosis			
Confirmed	29 (35.8%)	68 (37%)	0.86
Clinical	52 (64.2%)	116 (63%)	
MH Score for pulmonary TB			
Positive (≥ 30 points)	51 (71.8%)	65 (64.4%)	0.30
Negative (≤ 25 points)	20 (28.2%)	36 (35.6%)	
Not applicable	10	83	
Completion of anti-TB treatment			
Completed	66 (81.5%)	163 (89.1%)	0.09
Uncompleted	15 (18.5%)	20 (10.9%)	
Unknown		1	

BCG = vaccine against tuberculosis; HIV = human immunodeficiency virus; MH = Brazilian Health Ministry; TB = tuberculosis.
* p ≤ 0.05.

The resistance to one or more drugs observed in 33% of patients who had an antibiogram performed is worrying. According to Kritski,[16] multi-resistant TB is associated with high level of mortality, especially in children and individuals infected with HIV. It is necessary to perform investigations on anti-TB drugs resistance in children and adolescents to confirm these results observed in this reference hospital unit.

It was observed that 31% of confirmed cases of pulmonary TB did not meet the inclusion criteria for treatment according to the MH score, with the use of the same cutoff point of other studies (≤ 25 points).[6,9,10] This scenario points out to the importance of assessing the need to continue this clinical research in units of greater complexity in patients with suspected pulmonary TB who obtain ≤ 25 points, once the idea of the score is to assist, on an outpatient basis, the diagnosis of children with negative bacilloscopy

tests.[3,8] According to Coelho Filho et al.,[6] if all patients with score > 25 points start anti-TB treatment, at least 30% of them will be carriers of other diseases than TB. New studies are needed in order to confirm the findings.

Although the study was performed in a tertiary unit, which, therefore, receives more complex cases that require further clinical investigation, the hospitalization rate observed (70%) is worrying. In the cases of diagnosis established in hospitals, a hospitalization longer than 15 days was observed in more than half the cases. This scenario contributes to the rising costs of TB for the Brazilian public Unified Health System. It is essential that the early diagnosis of TB and the correct outpatient follow-up be performed to change this situation.

Data were obtained at a reference pediatric unit, which does not allow, at first, inference to the universe of all patients with TB treated in the municipality of Rio de Janeiro. Data

from retrospective studies are questionable; however, it was possible to demonstrate the quality of the information on the medical records over the years.

TB in children and adolescents has been neglected historically. However, this situation has been reversed in recent years with the increasing publications and research development on the subject. Diagnosis is still a sensitive issue in the management of this age group. Thus, prospective studies should be conducted in this population, in order to enhance the development and improvement of new clinical scores, coupled with an assessment of the impact of such scores or further diagnostic methods. The co-infection with HIV is a confounding factor, and also a subject in need of further studies to assess the real impact of TB in this group in different epidemiological settings.

Acknowledgements

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