Extrapulmonary Tuberculosis in Colombian Children: Epidemiological and Clinical Data in a Reference Hospital

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Abstract

Background: The pediatric population is at increased risk of disseminated and extrapulmonary tuberculosis (TB). There is little information on children affected by this entity. The demographic, clinical, and outcome characteristics of the treatment of children with extrapulmonary TB, treated at a national reference institution between January 1, 2008, and December 31, 2016, are described and analyzed in this work.

Materials and Methods: This was a retrospective observational study. Cases of extrapulmonary TB were identified, and variables were collected based on each criterion used for diagnosis and treatment outcomes. A descriptive analysis of the variables collected was performed.

Results: Ninety-three cases were identified, of which 32 (34.4%) met the criteria for extrapulmonary TB. The mean age was 10.2 years (range 0.8–17 years), and the most frequent site of extrapulmonary TB was lymph node 40.6%, meningeal 21.9%, and ocular 18.8%. Bacteriological confirmation was obtained in 8 cases (25%) while the remaining 24 cases (75%) were classified as cases of clinically diagnosed TB. Two patients (6.2%) died during treatment although their death was not attributable to TB.

Conclusion: The clinical criterion was fundamental to establish the diagnosis. The microbiological isolation rate was low. Molecular biology tools increase bacteriological performance although their extended use is limited by cost. Regional multicenter studies are required to identify the target population and the tools necessary for timely management and treatment.

Keywords: Diagnosis, epidemiology, pediatrics, tuberculosis

Introduction

Colombia has an intermediate incidence of tuberculosis (TB) of 25 cases per 100000 inhabitants, and about 6.5% of the new cases detected occur in the pediatric population.[1] In children, a TB diagnosis represents a challenge, <15% of cases are sputum acid-fast bacilli smear positive, and mycobacterial culture yields are 30%–40%.[2] In addition, there is an increased risk of disseminated disease and extrapulmonary forms. Other methods such as QuantiFERON-TB Gold® and Xpert MTB/RIF® have shown a higher diagnostic performance[3] although their availability is limited.

Materials and Methods

A retrospective observational study was conducted considering the medical records of patients under 18 years of age, during the period between January 2008 and December 2016, with a diagnosis according to the International Classification of Diseases-10 for TB in any location. Cases were included according to bacteriological confirmation and/or clinical diagnosis.

The bacteriologically confirmed cases were defined as those with a positive biological sample by smear microscopy or culture and extrapulmonary forms. Other methods such as QuantiFERON-TB Gold® and Xpert MTB/RIF® have shown a higher diagnostic performance[3] although their availability is limited. There are no Colombian statistics about extrapulmonary TB in children; therefore, the objective of this study is to analyze cases of pediatric patients diagnosed with extrapulmonary TB in a Colombian pediatric reference institution.

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or positive epidemiological nexus (contact with a confirmed TB case). [4]

Extrapulmonary TB was defined as any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs or the tracheobronchial tree, for example, abdomen, genitourinary tract, joints and bones, lymph nodes, meninges, pleura, and skin. [1] Intrathoracic (mediastinal and/or hilar) lymph node TB or tuberculous pleural effusion without a radiographic pulmonary involvement was classified as a case of extrapulmonary TB. Cases with pulmonary and extrapulmonary involvement were classified as cases of pulmonary TB. Miliary TB was included in the pulmonary TB group, and in consequence, it was not included.

The diagnostic criteria included clinical, bacteriological, histological, tuberculin, and radiological criteria.

For the evaluation of the history of TB treatment, the following categories were used: new patient and previously treated patient (after relapse, after failure, recovered after loss of follow-up, and other previously treated patients). The results of the treatment were evaluated according to the following categories: cured and completed treatment, failure, death, loss in follow-up, and not evaluated. [5]

Clinical histories were reviewed to collect data, those that met the criteria were selected, and the following variables were recorded: demographic data (age, sex, TB exposure, and ethnicity), clinical data (weight, height, clinical manifestations, and comorbidities), and paraclinical tests (microbiology of biological samples, HIV status, images, and histopathology). The nutritional status was analyzed through Anthro and World Health Organization (WHO) Anthro for personal computers, version 3.2.2, 2011: Software for assessing growth and development of the world’s children. Geneva: WHO, 2010 by the WHO and interpreted according to WHO parameters. [6] The information collected was transferred to a Microsoft Excel 2007 database, and the descriptive analysis of the variables was performed using the tools provided by the statistical support of the IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. [7] Frequencies and averages are reported for the variables of interest. No treatment’s outcome association was determined because the data about follow-up were not complete.

This study follows the public research policies that provide the standards for research, which are based on principles of justice, respect, nonmaleficence, beneficence, autonomy, and capacity. It complies with international standards – particularly the Declaration of Helsinki – as well as with the ethical guidelines for biomedical research prepared by the Council for International Organizations of Medical Sciences and Resolution 8430 of 1993 by the Ministry of Health of Colombia. The project was assessed and approved by the Ethics and Research Committee of the institution where the project was carried out.

**Results**

During the study, 93 patients fulfilled the case requirements of TB, of which 32 (34.4%) corresponded to extrapulmonary TB.

**Demographic and general clinical data**

Of 32 patients diagnosed with extrapulmonary TB, 43.7% were women and 56.3% were men, with the highest prevalence among the 10–15 years of age group: 12 (37.5%). No coinfection with HIV was reported; the HIV status was not reported in 6 patients (18.8%). One case (3.1%) was classified as relapse. The most common extrapulmonary localization was lymph node with 13 cases (40.6%), followed by central nervous system (CNS) in 7 cases (21.9%) and ocular in 6 cases (18.8%). Comorbidities were found in 13 individuals (41.0%), the most frequent being hematological malignant diseases in 6 cases (18.7%), and neurological involvement in 4 cases (12.5%).

**Epidemiological nexus, history of vaccination, and tuberculin test**

Eight patients (25.0%) had a history of TB exposure, but finding additional clinical data related to the TB diagnosis was not possible. In 8 cases (25.0%), the history of Bacillus Calmette–Guérin vaccination was found in the clinical charts, and for only one of the 7 CNS TB cases, the history was found. The tuberculin test was done in 23 cases (71.9%), of which 16 (69.6%) were classified as positive. The summary of demographic data is detailed in Table 1.

**Clinical presentation**

All patients included met the clinical criteria. The most frequent systemic symptom was fever in 13 cases (40.6%), followed by cough (without quantifying the amount of days) in 6 cases (18.8%), weight loss in 5 cases (15.6%), and hypoxemia in 4 cases (12.5%). Regarding local symptoms, the most frequent were localized lymphadenopathy enlargement in 13 cases (40.6%), seizures in 3 cases (9.4%), hepatomegaly and splenomegaly in 1 case (3.1%), and other manifestations such as blurred vision, headache, and joint manifestations in 13 individuals (40.6%).

**Diagnostic tools**

**Microbiological evaluation**

Seventeen bacilloscopies (8 in gastric juice and 9 in sputum samples) were performed. No smear microscopy was positive, and one positive culture (3.1%) was recorded in a case of pleural TB. In cases of CNS TB, the analysis of cerebrospinal fluid (CSF), three Ziehl–Neelsen (ZN), and three cultures (42.8%) were positive. In addition, 15 biopsies (46.9%) were performed (12 samples of ganglia [80.0%], 1 of pleura [6.7%], 1 of synovial membrane [6.7%], and 1 of encephalic mass [6.7%]); granulomas and caseous necrosis were found in 11 cases (73.3%). Regarding molecular studies (performed in the institution since 2010), a polymerase chain reaction (PCR) was used in 13 specimens (40.6%): 4 in lymph nodes samples (30.8%), 4 in CSF (30.8%), 1 in bronchoalveolar...
lavage (7.7%), 1 in pleura (7.7%), 1 in gastric juice (7.7%), 1 in synovial membrane (7.7%), and 1 in aqueous humor (7.7%), yielding 5 positive results (38.5%). Another tool used was the adenosine deaminase test, performed in 6 cases (18.8%) using samples of pleural fluid, synovial fluid, and CSF, yielding 5 positive results (83.3%).

**Diagnostic imaging**

In cases of CNS TB, magnetic resonance imaging reported tuberculomas in 2 cases and evidence of basal meningeal enhancement in 5 cases.

**Diagnostic criteria**

The variables in each type of TB constitute the criteria used to define the diagnosis. For both cases of articular TB, evidence was based on clinical and tuberculin findings; in ocular cases, clinical evidence and tuberculin criteria were found in 6 patients, and one of them also documented an epidemiological nexus. The most frequent combination of criteria was clinical-tuberculin in 9 cases (28.1%), which included 5 ocular cases, 2 lymph nodes, and 2 articular cases. The second most frequent was clinical-histopathological criteria with 6 cases (18.8%): lymph node in 5 cases and pleural in 1 case. Finally, clinical and microbiological criteria were found in 3 cases (9.3%), 2 in CNS and 1 in renal, and clinical-tuberculin-histopathological criteria in two lymph node cases (6.3%).

In total, only 9 cases (28.1%) met the criteria of a bacteriologically confirmed TB case; the remaining 23 cases (71.9%) were classified as clinically diagnosed TB cases. Table 2 presents the summary of the criteria used for the diagnosis.

**Treatment**

One patient could not start the treatment because he died. In one case (3.1%), sensitivity tests were performed, with no documented resistance; in 10 cases (31.2%), no institutional follow-up was made, so the outcome is unknown; 15 individuals (46.8%) were classified by the infectious disease service as treated, and two deaths were reported (6.2%) during treatment although none could be related to TB. Of the patients followed during treatment, 5 (15.5%) presented adverse effects to this treatment. The summary of treatment results is shown in Table 3.

**Discussion**

In 2012, a total of 674 cases of children under 15 years of age in Colombia were reported, of which 150 (22%) presented with extrapulmonary TB; these data are similar to those reported by the Pan American Health Organization in its regional report of 2013 in which extrapulmonary TB in children represented 23% of the cases. In this case, the proportion of extrapulmonary TB is higher, which is probably caused by selection bias since the sample was obtained from a national pediatric referral center.

The search for adult contacts with active disease is an effective strategy for the detection of pediatric cases. In similar...
Table 2: Evidence used for diagnosis

| Localization | n   | Clinical, n (%) | Bacteriology*, n (%) | Histopathology**, n (%) | Epidemiology, n (%) | Tuberculin test, n (%) | Radiology***, n (%) |
|--------------|-----|-----------------|----------------------|-------------------------|---------------------|------------------------|--------------------|
| Lymph node   | 13  | 13 (100)        | 2 (15.3)             | 10 (76.9)               | 5 (38.5)            | 5 (38.5)               | 0                  |
| CNS          | 7   | 7 (100)         | 5 (71.4)             | 0                       | 2 (28.6)            | 2 (28.6)               | 3 (42.8)           |
| Ocular       | 6   | 6 (100)         | 0                    | 0                       | 1 (16.7)            | 6 (100.0)              | 0                  |
| Pleural      | 3   | 3 (100)         | 0                    | 1 (33.3)                | 0                   | 1 (33.3)               | 0                  |
| Joint        | 2   | 2 (100)         | 0                    | 0                       | 0                   | 2 (100)                | 0                  |
| Renal        | 1   | 1 (100)         | 1 (100)              | 0                       | 0                   | 0                      | 0                  |

*Included as bacteriological criteria: smear microscopy, culture or molecular detection tests (polymerase chain reaction), **Histopathological criteria were considered: Biopsy of any tissue that demonstrates epithelioid cell granulomas and caseous necrosis with (active) or Ziehl–Neelsen positive, ***Radiological criteria were considered: Findings on chest radiography, chest tomography with compatible lesions, and CNS images with evidence of basal meningeal enhancement or suspected tuberculomas. CNS: Central nervous system.

Table 3: Evaluation of the history of tuberculosis treatment

| Variable                        | n  | (%)   |
|---------------------------------|----|-------|
| Treatment                       |    |       |
| No*                             | 1  | (3.1) |
| Yes                             | 31 | (96.9)|
| Results                         |    |       |
| Treatment in course             | 5  | (15.6)|
| Joint                           | 1  | (20)  |
| Lymph node                      | 2  | (40)  |
| Ocular                          | 2  | (40)  |
| No institutional follow-up      | 10 | (31.2)|
| Lymph node                      | 5  | (50)  |
| CNS                             | 2  | (20)  |
| Pleural                         | 2  | (20)  |
| Renal                           | 1  | (10)  |
| Cured and completed treatment   | 15 | (46.8)|
| Lymph node                      | 6  | (40)  |
| CNS                             | 4  | (26.6)|
| Ocular                          | 4  | (26.6)|
| Articular                       | 1  | (6.6) |
| Death**                         | 2  | (6.2) |
| CNS                             | 1  | (50)  |
| Pleural                         | 1  | (50)  |
| Adverse effects                 |    |       |
| Mild neutropenia                | 2  | (6.2) |
| Hearing loss                    | 1  | (3.1) |
| Hepatotoxicity                  | 1  | (3.1) |
| Dyspepsia                       | 1  | (3.1) |
| No report                       | 27 | (84.3)|

*See details in the text, **No mortality related to TB. TB: Tuberculosis, CNS: Central nervous system.

by Matos et al.,[10] who reported a positive PPD in 52% of participants with extrapulmonary TB. Considering the limitations (administration technique, interpretation, and biological variables) that restrict the use of this test as the only diagnostic tool is necessary, which is why other tests, such as Interferon-Gamma Release Assays (IGRAs), have emerged for the detection of infection. However, evidence of the use of these tests in the pediatric population is scarce, and its cost is higher than PPD, hence the limitation in its use.[11] In 2011, the WHO recommended to continue using PPDs in low- and middle-income countries,[12] so it continues to be a complementary tool for the diagnosis of TB in our region.

The tuberculous lymphadenitis was the most frequent extrapulmonary presentation, which coincides with the findings of other similar studies conducted in Latin America.[10,11] The most used diagnostic criteria in this series were histological, used in a way similar to that described in the literature.[13] The diagnostic performance of biopsies depends on the method used to take the sample; in our population, all studies were performed through a scission biopsy, whose sensitivity ranges between 84% and 100%, since the performance of other methods, such as the fine-needle aspiration biopsy, has a lower accuracy (55%–85%).[13] The use of ZN and lymph node culture increases the rates of microbiological isolation and is recommended by the literature; nevertheless, in this study, microbiological isolations were not achieved through these methods.

Due to the low performance of conventional bacteriological methods, the use of molecular diagnostic techniques, which have shown heterogeneous results, has increased; in this work, 5 cases were confirmed by molecular biology. In a systematic review carried out in 2007 by Daley et al.,[16] sensitivity ranging between 2% and 100% was reported, depending on the type of molecular test used. No recent systematic reviews that included modalities such as Xpert MTB/RIF were found; however, evidence suggests its usefulness, particularly in cases where cultures are negative.[17-19]

The frequency of TB in CNS differs according to the population evaluated; Wolzak et al.[20] in a study of the South African population (a region that is among the
22 countries with the highest burden of TB according to WHO) report tuberculous meningitis as the main etiology of bacterial meningitis in patients aged between 0 and 13 years (22% n = 126); Turel et al.\(^{[21]}\) report a lower prevalence (6.1%, n = 6) in a series of TB in children in Turkey (region with intermediate prevalence of TB); Sánchez et al.\(^{[14]}\) reviewed 49 cases of TB in pediatric patients in a referral hospital in Chile (country with a low prevalence of TB) and reported 1 case of meningeal TB. Although the TB burden in one region determines the frequency of TB in the CNS, it is striking that, in this research, the prevalence of TB in the CNS was higher than that reported in Turkey, a region with a disease burden similar to ours, which suggests that multiple social, cultural, and environmental factors may modify the frequency of the disease.

Microbiological performance in this research was high in the case of CNS TB, which was higher than the figures reported in other studies.\(^{[22,23]}\) It should be noted that the yields of ZN and culture in CSF for *Mycobacterium tuberculosis* vary between 10% and 71%, which is associated with the technical and clinical difficulties involved when performing repetitive lumbar punctures in the pediatric population (4 lumbar punctures can increase the sensitivity of the culture from 52% to 86%) and the small amount of CSF that can be collected in each procedure. Consequently, the use of molecular tests to increase yields and microbiological isolates has occurred, which has also shortened the time for the identification of the microorganism with a sensitivity higher than that of the CSF culture (sensitivity within a 2%–100% range for culture and 75%–100% for PCR).\(^{[24]}\) This has led to conclude that although the combination of cultures and molecular tests increases the rate of detection of the microorganism, its performance is widely variable, so diagnosis and microbiological confirmation of CNS TB remains an issue.

For this series, ocular TB is the third most frequent extrapulmonary form, which represents a high prevalence in contrast to that reported in the literature, where its prevalence is generally unknown. The difficulties in its diagnosis are reflected on the wide variations of the incidence and frequency between regions.\(^{[25]}\) In the reviewed cases, diagnosis was made based on clinical manifestations and a positive tuberculin criterion (only one case had an additional criterion: epidemiological nexus) and after discarding other infectious and immunological entities. The criteria for diagnosing ocular TB are not well established,\(^{[25,26]}\) and given the difficulties of microbiological confirmation,\(^{[27]}\) a high index of suspicion is required; epidemiological nexus, ocular suggestive findings, exclusion of other known causes of uveitis, and indirect evidence of infection such as PPD and IGRA should also be taken into account.

Llorenç et al.\(^{[28]}\) evaluated the use of PPD and QuantiFERON-TB Gold\(^{®}\) as a complementary test for the diagnosis of tuberculous uveitis, finding sensitivity (87% vs. 90%) and specificity (E = 85% vs. 82%) for both tests; however, it was not performed in the pediatric population, and there are no studies evaluating its usefulness in this age group, so ocular TB should be considered a diagnosis of exclusion. Less frequent forms of extrapulmonary TB found in this research include pleural, joint, and renal TB, which, in general, are difficult to diagnose and rarely occur in children.\(^{[29]}\) There were two deaths although none was attributable to TB; both cases showed associated hematological comorbidity (myelodysplastic syndrome and acute myeloid leukemia).

This work has several limitations. First, the population included in the analysis comes from a single reference center; hence, the results are not extrapolable. Due to the retrospective design of the study, the variables evaluated were taken from medical records, which limited the collection of a greater amount of data about the behavior of the disease and the demographic characteristics of the patients. It is not possible to draw conclusions about the outcome of the treatment because there was no institutional follow-up in a significant proportion of cases. Since there are no cases of extrapulmonary TB in which tests such as IGRA and Xpert MTB/RIF\(^{®}\) were performed, an approximation about their usefulness in the diagnosis of TB in children was not accomplished.

This research allows clinical and demographic knowledge of children diagnosed with extrapulmonary TB in a national reference hospital in Colombia. Histological study is a viable approach to the diagnosis of the infection, particularly in the form of the most frequent localization registered (lymph node). Ocular TB showed a high frequency and should be considered as a differential diagnosis. The clinical criterion was decisive to establish the diagnosis. Molecular biology tools increase microbiological performance although its extended use is limited by its cost. Regional multicenter studies are required to identify the target population and the tools needed for timely management and treatment.

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Conflicts of interest

There are no conflicts of interest.

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