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RESEARCH ARTICLE

Factors associated with tuberculosis disease in children from a hospital in Western Mexico

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Abstract

Background: *This study aimed to describe the clinical and demographic characteristics of children with confirmed tuberculosis disease and identify associated factors.* **Methods:** *We conducted a retrospective and observational study at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca. Inpatient and outpatient children under 18 years of age who were reported to the National Epidemiological Surveillance System (SINAVE, for its Spanish acronym) for suspected tuberculosis and who had molecular or microbiological tests for mycobacteria were included in the study. Multivariate analysis with logistic regression was used to analyze associated factors.* **Results:** *One hundred and nine patients under 18 years of age with suspected tuberculosis were included in the study. About 50.5% (55/109) were male, and the median age was 11 years. Tuberculosis was confirmed in 55% (n = 60): 15% (9/60) had a pulmonary infection, and the rest (51/60) had an extrapulmonary infection. The diagnostic tests used were histopathological study (n = 26), expectoration or gastric aspirate stains (n = 17), polymerase chain reaction (n = 12), and cultures (n = 5). Positive purified protein derivative (PPD) or interferon-gamma release assay (IGRA) tests were found in 33.9%. Malnutrition (odds ratio [OR] 15.9, 95% confidence interval [CI]: 2.3-109), and consumption of unpasteurized products (OR 7.45, 95% CI: 1.02-54.3) were associated with tuberculosis disease in children.* **Conclusions:** *Malnutrition and consumption of unpasteurized dairy products are associated with tuberculosis.*

Keywords: *Tuberculosis. Latent tuberculosis. Miliary tuberculosis.*

Factores asociados con enfermedad tuberculosa en niños de un hospital del occidente de México

Resumen

Introducción: *El objetivo de este estudio fue describir las características clínicas y demográficas de niños con enfermedad tuberculosa confirmada e identificar los factores asociados.* **Métodos:** *Se realizó un estudio observacional retrolectivo en el Hospital Civil de Guadalajara Dr. Juan I. Menchaca. Se incluyeron menores de 18 años hospitalizados y ambulatorios que se notificaron al Sistema Nacional de Vigilancia Epidemiológica (SINAVE) por sospecha de tuberculosis y que contaron con pruebas moleculares o microbiológicas para micobacterias. El estudio de los factores asociados se realizó mediante análisis multivariado con regresión logística.* **Resultados:** *Se incluyeron en el estudio 109 menores de 18 años con sospecha de*

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tuberculosis. El 50.5% (55/109) fueron de sexo masculino y la mediana de edad fue de 11 años. Se confirmó enfermedad tuberculosa en el 55% (n = 60) de los casos: el 15% (9/60) presentaron infección pulmonar y el resto extrapulmonar. Las pruebas diagnósticas utilizadas fueron el estudio histopatológico (n = 26), tinciones de expectoración o aspirado gástrico (n = 17), reacción en cadena de la polimerasa (n = 12) y cultivos (n= 5). 33.9% de los pacientes presentaron prueba de derivado proteico purificado (PPD) o ensayo de liberación de interferón gamma (IGRA) positiva. Se observó que la desnutrición (razón de momios (RM) 15.9, intervalo de confianza (IC) 95% 2.3 – 109) y el consumo de productos no pasteurizados (RM 7.45, IC 95% 1.02 – 54.3) se asociaron con enfermedad tuberculosa en niños. **Conclusiones:** *La desnutrición y el consumo de lácteos no pasteurizados se asocian con la enfermedad tuberculosa.*

Palabras clave: *Tuberculosis. Tuberculosis latente. Tuberculosis miliar.*

Introduction

In recent decades, global mortality due to tuberculosis has decreased by 31.4%[1]; however, in 2019, the disease caused 1.4 million deaths, and one-third were due to rifampicin-resistant bacteria[2]. In Mexico, the rate of tuberculosis varies from 8.5 to 13.8 cases/100 thousand inhabitants, and 24% of cases are children under 18 years of age[3]; in this age group, tuberculosis has a higher morbidity and mortality rate[4].

The demographic and social characteristics of the pediatric population in Mexico have changed in recent years, which could lead to epidemiological changes in infections such as tuberculosis. Between 1950 and 2020, residency in urban areas in Mexico increased from 43% to 79%[5]; in addition, chronic conditions such as obesity affect 35.6% of preschoolers and 40% of adolescents[6].

It has been reported that in children, the absence of bacillus Calmette-Guerin (BCG) vaccination, contact with bacilliferous patients, and a state of primary or secondary immunosuppression increase the risk of tuberculosis. However, it is pertinent to investigate other factors that are associated with a higher probability of infection.

This study aimed to describe the clinical and demographic characteristics of children with confirmed tuberculosis and compare those with children with discarded infections.

Methods

A retrospective and observational study was conducted at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca (HCGJIM), Mexico. The institution is a referral hospital that serves the general population, mainly with limited economic resources.

In patients who meet the operational definition of a probable case of tuberculosis[7], the Department of Epidemiology is notified to report the case to the National Epidemiological Surveillance System (SINAVE, for its Spanish acronym). Simultaneously samples are collected for molecular, histopathological, and microbiological tests to identify bacteria of the *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canettii, and M. caprae y M. pinnipedii*).

This study included inpatients and outpatients under 18 years of age who were reported to SINAVE from January 2015 to January 2020 and had diagnostic tests to identify mycobacteriae.

In samples of cerebrospinal fluid, sputum, abscess secretion or gastric aspirate, Ziehl Neelsen (ZN) staining, culture in Löwenstein-Jensen medium and, since 2018, automated polymerase chain reaction (PCR) (GeneXpert MTB/RIF®) were performed. Information about clinical and demographic variables was obtained from the clinical records.

For this study, the following definitions were considered:

Confirmed tuberculosis: The presence of signs and symptoms related to tuberculosis infection corroborated by identification of *M. tuberculosis* in stains, culture, or PCR. For extrapulmonary, lymph node, peritoneal, and intestinal infections, histopathological findings characteristic of tuberculosis (caseous granulomas or positive stains for acid-fast bacilli) was also considered confirmatory[7,8].

Probable tuberculosis: Clinical data suggestive of tuberculosis with negative stains, culture, or PCR; however, with exposure to a confirmed contact with tuberculosis or who showed radiographic studies suggestive of infection such as miliary infiltrate or pulmonary caverns[7,8].

Unproven tuberculosis: Patient admitted to the study who presented negative microbiological and/or histopathological tests for the detection of mycobacteria and who was not classified as a probable case[7,8].

Tuberculosis infection: Reactive tuberculin skin test (> 10 mm in immunocompetent patients or > 5 mm in immunocompromised patients) or positive interferon-gamma release assay (IGRA) test[7,9].

Malnutrition: In children of 5 years of age or older, malnutrition was diagnosed if the body mass index (BMI) was less than the 3rd percentile, and for children under 5 years of age, the presence of weight for height < 90%.

The definitions of other symptoms studied were as follows: chronic cough (daily cough lasting more than 4 weeks), adenomegaly (increase in lymph node size > 1.5 in a previously normal region), and fever (temperature > 38°C), with the rectal recording being the most appropriate; for this study, axillary measurement was also considered adequate. Gastrointestinal symptoms included abdominal pain, vomiting, diarrhea, abdominal distension, and constipation[10-12].

Statistical analysis

The frequency of tuberculosis in children reported to SINAVE was estimated. Frequencies and percentages were estimated for qualitative variables, and median and interquartile ranges (IQR) for quantitative variables. For the comparison of proportions to contrast hypotheses, we used a χ^2 test or Fisher's exact test, and for the comparison of medians, we used the Mann–Whitney U test. For the study of factors associated with tuberculosis (dependent variable), patients with a confirmed diagnosis were compared with those with unproven disease (patients with negative microbiological or molecular tests and who did not present suggestive radiographic data or contact with a bacilliferous patient). In a second phase, those with confirmed infection were compared with the rest of the patients, including probable cases. In both phases, bi-variate analysis was performed, and variables with $p < 0.2$ were subjected to multivariate analysis with logistic regression. IBM SPSS® Statistics version 25 was used. The project was approved by the Ethics and Research Committees of the HCGJIM.

Results

During the study period, 732 patients with suspected tuberculosis were registered in SINAVE, of whom 14.9% (109/732) were under 18 years of age. Among those included in the study, 50.5% were male, and 49.5% female; the median age was 11 years (minimum 0.16, maximum 17.0, IQR 11.5). 25.7% were younger than 5 years, and only nine were < 1 year.

About 55% of the patients were classified as having tuberculosis (n = 60), 19.3% as probable (n = 21), and 25.7% with unproven tuberculosis (n = 28). Among patients with the confirmed disease, 15% (9/60) had a pulmonary infection; the rest were extrapulmonary infections (27 lymph node, 12 intestinal, eight miliary, two meningeal, one event of articular, and one cutaneous tuberculosis). The tests that allowed confirming the diagnosis were histopathological study 43.3% (n = 26), sputum or gastric aspirate stains 28.3% (n = 17), PCR 20% (n = 12), and cultures 8.3% (n = 5).

About 33.9% (37/109) of pediatric patients had positive PPD or IGRA skin test results. This result was significantly more frequent in patients with tuberculosis than patients with unproven tuberculosis (43.3% vs. 3.6%, p = 0.006).

The most frequent clinical manifestations in those with confirmed tuberculosis were adenomegaly, fever, and weight loss; however, those symptoms were only observed in slightly more than half of the patients. Less frequent manifestations were asthenia and gastrointestinal symptoms (Table 1).

For the study of the factors associated with tuberculosis in the first phase, patients with confirmed tuberculosis were compared to those with unproven disease. The variables analyzed were sex, age, contact with a person with tuberculosis, BCG vaccination, consumption of unpasteurized dairy products, nutritional status, and human immunodeficiency virus (HIV) infection. In the bivariate analysis, the conditions associated with confirmed tuberculosis were malnutrition, consumption of unpasteurized dairy products, and BCG vaccination. However, in the multivariate analysis, only malnutrition and unpasteurized dairy consumption showed independent association (malnutrition: odds ratio [OR] 15.9, 95% confidence interval [CI] (2.3-109) p = 0.005; unpasteurized dairy consumption: OR = 7.45, 95% CI: 1.02-54.3 p = 0.04). The multivariate analysis compared patients with tuberculosis (dependent variable) and those with unproven disease.

The same factors were analyzed in the second phase, but children with confirmed tuberculosis and those with probable or unproven infection were compared. In the bivariate analysis, an association was observed with age < 5 years, positive PPD or IGRA, and malnutrition; however, in the multivariate analysis, only the last two were independent factors (Table 2).

The results of the PPD skin test or IGRA were compared with any of the methods considered confirmatory for tuberculosis (BAAR staining, culture, PCR, or histopathological study). It was observed that PPD and IGRA showed sensitivity, specificity, and positive and negative predictive values of 43.3%, 96.3%, 96% and 44.2%, respectively. Thus, negative results do not rule out infection, but the probability of tuberculosis infection was > 90% when the results were positive.

Table 1. Comparison of clinical and demographic characteristics of children with tuberculosis, probable tuberculosis, and unproven disease

Clinical and demographic characteristics	Tuberculosis (n = 60)	Probable tuberculosis (n = 21)	Unproven disease 28	p*
Clinical manifestations (%)				
Age < 5 years	18.3	33.3	35.7	0.6
Chronic cough	28.3	28.6	39.3	0.31
Asthenia or hypoactivity	28.3	23.8	53.6	0.01
Adenomegaly	55.0	14.3	42.9	0.29
Weight loss	50.0	42.9	46.4	0.75
Hemoptysis	1.7	0.0	3.6	0.58
Dyspnea/breathing difficulty	11.1 (6/54)	5.0 (1/20)	25.0 (5/20)	0.12
Fever	51.7	71.4	67.9	0.15
Diaphoresis	21.7	19.0	35.7	0.16
Intestinal symptoms	25.5 (15/59)	28.6	48.1 (13/27)	0.04
Positive PPD/IGRA	43.3	47.6	3.6	0.001
Diagnostic tests (%)				
AFB stains	28.3 (17/60)	0	0	-
Löwenstein-Jensen culture	8.3 (5/60)	0	0	-
PCR (GeneXpert MTB/RIF®)	20.0 (12/60)	0	0	-
Histopathological study	43.3 (26/60)	0	0	-
Characteristics included (%)				
Male	43.3	61.9	57.1	0.23
Age in years (median)	11.0	11.0	9.5	0.61
Exposure to a contact with TB	16.1 (9/56)	20.0 (4/20)	6.7 (1/15)	0.32
BCG vaccine	89.6 (52/58)	95.2 (20/21)	71.4 (20/28)	0.03
NP dairy consumption	51.2 (21/41)	46.7 (7/15)	20.0 (2/10)	0.07
Overweight or obesity	4.2 (2/48)	6.7 (1/15)	14.2 (4/28)	0.26
Malnutrition	72.9 (35/48)	73.3 (11/15)	32.1 (9/28)	< 0.001
HIV infection	5.0	9.5	3.6	0.76
Previous TB	3.3	0.0	10.7	0.7

*The P value corresponds to the comparison between patients with confirmed tuberculosis disease and those with unproven disease. In qualitative variables, the hypothesis contrast test was χ^2 or Fisher's exact and in quantitative variables Mann–Whitney U test.
AFB: acid-fast bacillus, BCG: bacillus Calmette-Guerin, HIV: human immunodeficiency virus, IGRA: interferon-gamma release assay, NP: non-pasteurized, PCR: polymerase chain reaction, PPD: purified protein derivative, TB: tuberculosis.

Discussion

In this study, we observed that 14.9% of the total number of patients registered in the SINAVE were under 18 years of age, and among these, 55% presented confirmed tuberculosis. Although culture is considered the reference test, it has limitations since it does not provide immediate results. Therefore, it is recommended to perform staining or PCR as well to establish timely diagnoses.

In adults, a higher risk of tuberculosis has been described in those with chronic degenerative diseases[13]; however, the risk is lower in those with obesity without diabetes[14]. Aibana et al.[15] reported that, in children exposed to adults with tuberculosis, 26.1% presented subsequent infection and noted that the risk was lower if the contact was an adult with obesity.

In HCGJIM patients, no association between overweight or obesity and tuberculosis was observed; however, similar to what has been described in different studies[16-18], a relationship between tuberculosis and malnutrition was identified. It has been described that poor nutritional status is the most frequent comorbidity in infected children (24.3%)[19]. Although being underweight may precede tuberculosis[16,19], weight loss may also be a consequence, given the chronic and progressive evolution of the infection.

At the HCGJIM, we observed that malnutrition was the only independent factor related to tuberculosis in the two phases of the study when comparing children with confirmed tuberculosis and those with probable or ruled-out infections. We also noted that in the initial analysis, the BCG vaccine had a lower frequency of application in uninfected children, but in the multivariate analysis, no association was found. We considered this a confounding effect of the variable and possibly attributable to an overestimation of the infection risk when clinicians were aware of the unvaccinated status or to the socioeconomic characteristics of our population studied.

Similar to the findings of this study, Cohn et al.[20] described a prevalence of tuberculosis of 20.8% in

Table 2. Comparison of clinical and demographic characteristics of children with confirmed tuberculosis and those with probable or unproven infection

Clinical and demographic characteristics	Tuberculosis (n = 60)	Probable tuberculosis or unproven infection (n = 49)	p*	OR (95% CI) Multivariate analysis
Clinical manifestations (%)				
Chronic cough	28.3	34.7	0.48	-
Asthenia or hypoactivity	28.3	40.8	0.19	-
Adenomegaly	55.0	30.6	0.01	-
Weight loss	50.0	44.9	0.6	-
Hemoptysis	1.7	2.0	0.88	-
Dyspnea/breathing difficulty	10.7 (6/56)	15.0 (6/40)	0.14	-
Fever	51.7	69.4	0.06	-
Diaphoresis	21.7	28.6	0.41	-
Intestinal symptoms	25.5 (15/59)	39.6 (19/48)	0.3	-
Characteristics included (%)				
Age < 5 years	18.3	34.7	0.05	0.43 (0.14-1.25)
Male	43.3	59.2	0.1	2.24 (0.85-5.91)
Exposure to a contact with TB	16.1 (9/56)	14.3 (5/35)	0.81	-
BCG vaccination	89.6 (52/58)	81.6 (40/49)	0.21	-
Positive PPD or IGRA	43.3	22.4	0.02	2.9 (1.04-8.39)**
NP dairy consumption	51.2 (21/41)	36.0 (9/25)	0.22	-
Overweight or obesity	4.2 (2/48)	11.6 (5/43)	0.18	0.59 (0.09-4.0)
Malnutrition	72.9 (35/48)	46.5 (20/43)	0.01	3.04 (1.11-8.34) **
HIV infection	5.0	6.1	0.8	-
Previous TB	3.3	6.1	0.49	-

*The p value corresponds to the comparison between patients with confirmed tuberculosis disease and those with unproven disease. In qualitative variables, the hypothesis contrast test was χ^2 or Fisher's exact and in quantitative variables Mann–Whitney U test.
**Statistically significant association.
BCG: bacillus Calmette-Guerin, CI: confidence interval, HIV: human immunodeficiency virus, IGRA: interferon-gamma release assay, NP: non-pasteurized, OR: odds ratio, PPD: purified protein derivative, TB: tuberculosis.

migrant children, the frequency of malnutrition was 29%, and consumption of unpasteurized milk (or dairy pruducts) was found to be associated with tuberculosis (OR: 3.2; 95% CI: 1.4-7.4)[20].

In Mexico, consuming unpasteurized dairy products or their derivatives is frequent. The results of this study highlight the importance of surveillance and control of zoonotic infections related to the consumption of these foods. In the country, up to 7.6% of tuberculosis cases are attributable to *M. bovis*; in states such as Jalisco, it can be up to 28%[21]. A study conducted by Escárcega et al. described that the prevalence of bovine tuberculosis was 15.1%[22].

Consistent with our results, Bapat et al.[23] observed that consumption of unpasteurized dairy products significantly increased the risk of tuberculosis[12]. Gompo et al. also noted an increased disease risk in those exposed to cattle[24].

O'Connor et al.[25] described human infections caused by *M. bovis* originating from species outside cattle. Other authors have emphasized that animal-related occupations increase the risk of tuberculosis[26,27].

The proportion of extrapulmonary tuberculosis varies from 9% to 78% and represents a challenge for the clinician because it requires invasive diagnostic methods. Diriba et al.[28] described that factors associated with extrapulmonary infections include age < 14 years, male sex, and consumption of unpasteurized milk. In HCGJIM patients, 85% of children with tuberculosis showed extrapulmonary involvement and predominately lymph node localization. This high proportion is likely related to the factors described or associated with the institution being a referral center for severe cases of the disease.

According to different guidelines for the diagnosis and treatment of tuberculosis in children[29], the skin test with PPD and IGRA should not be considered the reference tests for the diagnosis of latent infection since different conditions favor false negative or positive results; the recommendation is to consider clinical criteria, risk factors, and the history of BCG vaccination or exposure. The reference test for the diagnosis of tuberculosis is the culture of sputum, gastric aspirate, pleural fluid, cerebrospinal fluid, urine, or tissue biopsies. Nucleic acid identification tests are not a substitute for cultures but allow a rapid diagnosis.

Tuberculosis in children is at greater risk of progressing to severe forms such as miliary or meningeal tuberculosis.

Therefore, universal application of the BCG vaccine, detection and treatment of bacilliferous adults, surveillance and control of zoonoses associated with dairy products, and implementation of prophylactic treatment in children with latent tuberculosis are pertinent.

The limitations of this study are the small number of patients and the low sensitivity of microbiological and molecular tests to identify mycobacteria.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflicts of interest.

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