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ORIGINAL ARTICLE

Epidemiological analysis of patients with latent tuberculosis infection treated at a tertiary pediatric hospital in Florianópolis

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Tuberculosis,
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Abstract

Objective: Clinical and epidemiological analysis of pediatric patients with LTBI (latent tuberculosis infection). **Method:** Observational, descriptive, analytical and retrospective research, with data collection from medical records of patients suspected of having LTBI treated at a tertiary pediatric hospital in Florianópolis, Brazil from January 2011 to May 2020. **Results:** 203 medical records were analyzed. A total of 112 patients confirmed to have LTBI. The main source case was the mother and household infection was predominant. The treatment time from the source case to the diagnosis in the child was less than 6 months in 87% of the cases. An investigation of the other source case contacts was realized in 60% of the cases. 84% received isoniazid and 15% received rifampicin. Two patients had adverse event to isoniazid. There was a monthly consultations frequency in 51% of cases. 50% of the patients finished the treatment. **Conclusions:** LTBI was found in more than half of the investigated patients, but the number could be even higher considering the frequent loss of follow-up regarding cases in the initial medical analysis. Approximately 10% had tuberculin conversion. Household transmission was the predominant one, and the main source case was the mother. The investigation of the patients was carried out early, but in more than a third of the medical records there was no description of investigation of other household contacts. Half of the patients lost follow-up throughout treatment. The therapy was safe and the socioeconomic analysis was impaired because there was no data in the medical record.

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INTRODUCTION

Approximately a quarter of the world's population has latent tuberculosis infection (LTBI), meaning that they are infected with tuberculosis (TB) bacteria, but have no symptoms or are unable to transmit the disease. People with LTBI are at risk of developing active TB.[1] The pediatric age group is particularly vulnerable to becoming ill from the disease, untreated infected children have a 40% to 50% chance of starting to develop symptoms within 6 to 9 months after exposure.[2,3] Household TB contacts under 5 years of age have a greater chance of rapidly progressing to active disease, with a high risk of morbidity and mortality.[4] TB is considered the sixth leading cause of death in the age group 1 to 5 years, constituting a serious public health problem.[5]

The World Health Organization (WHO) launched the "END TB" strategy in 2014, with the vision of "a world free of TB: zero deaths, zero new cases and zero suffering due to TB". Among the priorities for achieving the goal is the treatment of LTBI, recommended primarily for those under 5 years of age.[6]

Studying the contacts of TB cases is essential to reduce the chain of disease transmission and illness among these contacts.[6] LTBI treatment is expanding, but the majority of patients who have the strongly recommended treatment still do not have access to this care. According to WHO data, only 27% of children under 5 years of age are eligible for LTBI treatment started treatment in 2018.[1,6,7] Furthermore, loss of treatment follow-up is still a serious problem.[8]

This study aims to carry out an epidemiological analysis of children with LTBI treated in a tertiary pediatric hospital, in order to seek data that can assist in earlier diagnosis and more effective treatment, reducing morbidity and mortality rates.

MATERIALS AND METHOD

This is an observational, descriptive and retrospective study. The population evaluated are patients aged 0 to 15 years of age, treated at the infectious disease outpatient clinic of a tertiary pediatric hospital in Florianópolis, Santa Catarina, with suspected LTBI, through a search for ICD Z20.1 (contact with and exposure to TB) in an electronic medical record search through the Micromed® system, from January 2011 to May 2020.

According to the 2011 Manual of Recommendations for TB control in Brazil from the Ministry of Health, for children vaccinated with BCG less than two years ago, the tuberculin skin test (PT) was considered reactive when greater than or equal to 10mm;[9] however, this recommendation changed from 2019, TT being considered reactive greater than or equal to 5mm regardless of the BCG[10] vaccination time. In the present study, the diagnosis of LTBI was made in participants, contacts of the disease and those who had TT equal to or greater than 5mm. Patients who confirmed active TB during the investigation were excluded from the study; patients with an excluded diagnosis of LTBI after undergoing two negative TT 8 weeks apart, ruling out tuberculin conversion; patients who were lost to outpatient follow-up before the diagnosis of LTBI was confirmed; newborns who underwent primary prophylaxis treatment for TB due to household contact with bacilliferous TB.

Among the data analyzed are

Demographic - age, sex, color/race, nationality, origin;

Epidemiological - location of infection, source case, time interval between the start of treatment of the source case and the diagnosis of LTBI, type of TB in the source case, whether the source case has drug-resistant TB, assessment of other contacts:

Diagnosis – performing BCG; carrying out the following tests and results: HIV serology, TT, Interferon Gamma Release Assay (IGRA), chest x-ray.

Treatment data – administration of isoniazid or rifampicin and duration of treatment, adverse event to the medication, identification of who administers the medication;

Follow-up – time to return for consultation after starting treatment, attendance at consultations;

Case closure - completion of treatment, loss of follow--up. A patient who did not return for a previously scheduled appointment was considered lost to follow-up, with the exception of those who attended the appointment monthly, returned until the next-to-the-last month of treatment, and did not return in the last month after the end of treatment.

The information obtained was exported from the Micromed® system, arranged in an electronic spreadsheet (Microsoft Excel® Software) and exported for statistical analysis. The data were organized into descriptive tables. The variables were described as mean and standard deviation in the form of 95% confidence intervals, considering frequency and percentage of variables.

This study was approved by the institution's Research Ethics Committee under protocol number 3,851,341.

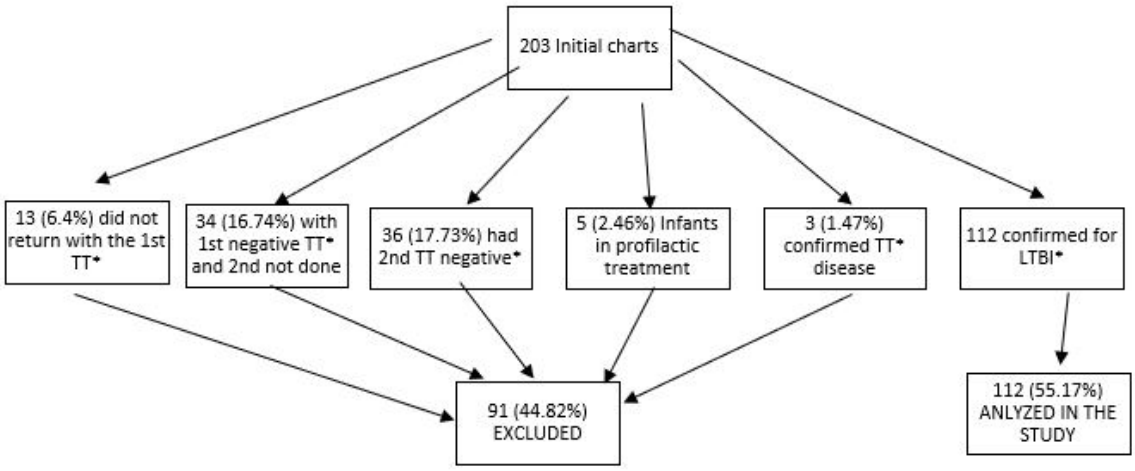
RESULTS

Initially, 203 medical records were analyzed, after applying the exclusion criteria, the sample for this study consisted of 112 medical records. Below is flowchart I with a detailed description of the cases included and excluded in the study (Flowchart I).

Demographic data

Females predominated in 52% of cases (n = 58). The predominant age group was 6 to 10 years of age in 38% of cases (n = 43); followed by 3 to 5 years of age in 28% of cases (n = 27); 0 to 2 years of age in 21 % of cases (n = 24) and lastly from 11 to 14 years old in 16% of cases (n = 18).

One patient was from Haiti. The vast majority of patients belonged to the Greater Florianópolis macroregion in 72% of those analyzed (n = 81); 24% belonged to the city of Florianópolis (n = 27) and 4% belonged to other cities in Santa Catarina (n = 4).



Note: *TT: tuberculine test. *TB Tuberculosis. *TBLI. Turberculosis Latent infection
Flowchart 1. Detailed list of cases with suspected LTBI included and excluded in the study, Florianópolis, 2011-2020.

Socioeconomic data

In 40 records there was information on the number of residents per household, with those with 2 to 5 residents predominating in 73% of cases (n = 29); followed by 28% of cases with more than 5 residents in the same house (n = 11).

Epidemiological data

The description of the source case was present in 111 medical records. In one case there was no record of who was the source case, but only that there was one present; therefore, not being included in the percentage analysis. The mother was the source case in 38% of cases (n = 42), followed by the father and the other category, both with 27% of cases (n = 30). The others category included: grandfather (7 cases), grandmother (2 cases), uncle (8 cases), aunt (5 cases), stepfather (2), stepmother (2), brother-in-law (1), nanny (2 cases) , teacher (1 case). In 8% of cases, the sibling over 10 years old was the source case (n = 9).

In 92 cases (88%) the contagion was intra-household. Of those 12% where the location was categorized as other (n = 12), contact through visits was mentioned in the vast majority of cases, and one case was reported at school. In 8 records, it was not mentioned where the contact was, not being included in the percentage calculation.

Of the 112 medical records analyzed, 47 of them mentioned the type of TB of the source case, with pulmonary TB being prevalent in 91% of cases (n = 43), followed by 9% with laryngeal TB (n = 4). Drug-resistant TB to first-line drugs was described in 4 source cases.

The time interval between the start of treatment of the source case and the diagnosis of LTBI in the child was less than 6 months in 87% of cases (n = 89), followed by 13% of cases in which it occurred within a period of 6 months up to 2 years after the start of treatment of the source case (n = 13). In 10 cases this data was not available in the medical records, being removed from the percentage analysis.

In 60% of the 112 records analyzed, an investigation for LTBI was carried out in the other contacts of the source case (n = 67), in 40% this data was not presented in the records (n = 45).

Diagnostic data

There was a record of BCG being performed in 96% of the medical records (n = 107). In the remaining cases, this data was not mentioned in the medical records.

All patients underwent TT, with 12 having tuberculin conversion. The prevalent TT result was greater than 14mm in 50% of cases (n = 54), followed by 10 to 14mm in 38% of cases (n = 41) and 5 to 9mm in 13% (n = 14). In 3 patients, the TT result was not present in the medical record, but they were described as positive. There were no patients analyzed before 2019 with less than 2 years of BCG vaccination and tuberculin skin test with results in the range between 5 and 10mm. None of the patients underwent IGRA.

In 96% of cases, the chest X-ray was normal (n = 107) and 3% (n = 3) showed changes, but not suggestive of TB. In 2% (n = 2) of patients, there was no record in the system of the chest X-ray or the result.

In relation to HIV, 15% of those analyzed underwent the test (n = 17), all of which tested negative.

Treatment details

Data on the medication of choice for the treatment of LTBI are described in Table I.

Adverse events were described in 2 patients who used isoniazid, including changes in transaminases and abdominal pain. There were no adverse events to rifampicin.

Follow-up data

Of the 112 medical records analyzed, 8 of them were released from the Outpatient Clinic at the beginning of treatment for follow-up with the BHCU in the city of origin and 2

Table 1. Treatment of choice for cases with suspected LTBI included and excluded in the study, Florianópolis, 2011-2020.

	N	%
Isoniazid 180 doses	89	79
Isoniazid 270 doses	6	5
Rifampin 120 doses	17	15
Total	112	100

were followed up in a private network. These patients were not included in the follow-up data analysis.

The frequency of consultations was monthly in 51% of cases (n = 52), followed by bimonthly consultations in 35% of cases (n = 35) and quarterly consultations in 14% of cases (n = 14). One patient did not have this data reported.

The completeness analysis demonstrated that 50% completed the treatment (n = 51).

In Table II, the month in which cases were lost to follow-up for LTBI treatment is described in detail. Loss to follow-up occurred in an unknown month in 2 cases, not included in the analysis.

DISCUSSION

Household contacts of patients with active bacilliferous TB are at high risk of infection. In the present study, cases of confirmed LTBI exceeded more than half of the exposed cases. In a survey carried out in Bahia, in 2004, with 269 household contacts of TB source cases, the prevalence of the disease in the studied population was 3.7% and the prevalence of infection was 63.9%, also exceeding more than 50% of those exposed.[11] It is important to highlight that in the present study the number of LTBI cases may be even higher when considering that 13 cases were excluded because they attended an initial consultation and did not return with the TT results and 34 were excluded because they were negative at the first TT, but do not perform the second one after 8 weeks to rule out tuberculin conversion. The initial data on loss to follow-up before diagnosis is worrying, as these may be cases of undiagnosed LTBI. The active search for these children would provide a way to minimize the problem. There were no patients prior to 2019 (publication of the new recommendation for a TT cutoff value of greater than or equal to 5mm regardless of vaccination time)[10] who met the criteria: less than 2 years of BCG and TT vaccination with results in range of 5-10mm, so there were no diagnostic losses for this reason.

Table 2. Identification of the month in which LTBI cases were lost to follow-up included in the study, Florianópolis, 2011-2020.

	N	%
1st month	5	10
2nd month	10	20
3rd month	12	24
4th month	9	18
5th month	5	10
6th month	8	16
Total	49	100

In a study carried out in 2012 with children in Indonesia who had a case of TB with a positive smear test at home, the pediatric contacts of 210 adults with smear-positive TB were investigated. Of the cases analyzed, 59% confirmed LTBI by positive TT and IGRA. Children whose source case was one of the parents, especially the mother, were four times more likely to be positive for the tests.[12] The mother was the main source case also in the present study. This relationship was also found in a study carried out in Botswana, in 1999, where the mother was identified as the main source case, and in Turkey, in 2005, where the parents were identified as the main source case.[13,14] Another data that favors The greater proximity of the source case to the child is that in the present study, contagion occurred intra-household. In a study carried out in Gambia in 2003, it was demonstrated that the risk of TB infection among household contacts is associated with social proximity within the household, confirming previous conclusions. Furthermore, it was suggested that genetics may play an important role in infection, finding that LTBI tended to cluster in certain families.[15]

In the previously mentioned study carried out on children in Indonesia, economic vulnerability was associated with increased TT positivity. In the present study there was a limitation in relation to socioeconomic data as data such as home ownership and family income were not included in the medical record. Another finding of the Indonesian study was that intra-household crowding was not a significant risk factor.[12] In the present study, the greater number of residents per household was also not related to a greater number of LTBI cases, but only 40 medical records analyzed presented such data, and this may be a limitation of the study. These data suggest that more than the number of people in contact with the case in a limited environment, it is the proximity of contact that is decisive for disease transmission.[15]

Screening of all people who are household contacts of bacilliferous TB cases is recommended.[16] In the epidemiological bulletin on TB in Brazil, published in March 2019 for the years 2017 and 2018, the proportion of examined contacts of new TB cases pulmonary was 53.6%.[17] In the present study, in 60% of the cases analyzed, investigation for LTBI was carried out in other contacts close to the source case, in the others this data was not included in the medical records. Some points that may be related to this result include: not writing down the investigation of other contacts in medical records, difficulty in accessing the health service, including difficulty in transportation and the lack of standardization of services to forward these contacts. In this study, positive data can be seen: in 87% of cases, the investigation of the child was carried out in the first 6 months since the beginning of treatment of the source case, therefore carried out early.

Of the patients confirmed for LTBI, half completed

treatment. The high rate of loss to follow-up is a warning about the importance of greater attention to this disease, seeking to resolve the barriers involved during treatment. In a study carried out in Rocinha in Rio de Janeiro in 2008 and 2009, with children aged 0 to 11 years undergoing treatment for LTBI, the barriers encountered by patients and guardians in relation to LTBI treatment were investigated. Of 85 families, 50 of them reported difficulties in treatment, including lack of money for transportation; distance from residence to the service location; lack of public transport; personal, economic or domestic difficulties.[8] In this study, it was not possible to find the reasons for loss of follow-up, this is a suggestion for future studies, by identifying the barriers involved in follow-up, it becomes easier to know where to act.

The Ministry of Health advises that patients with LTBI should undergo medical consultations at regular intervals of 30 days and those patients who have good compliance and low risk of hepatotoxicity can consult within 60 days.[10] The frequency of consultations in the analysis was monthly in the majority; however, there was a limitation in the analysis of consultation frequency due to the lack of uniformity in relation to returns. For study purposes, the most prevalent return interval for each case was considered. One point that can be considered for non-monthly return is the difficulty in transporting patients. The most frequent month of loss to follow-up was the 3rd month, one of the initial months of treatment. The monthly return of all children would be a strategy to try to reduce loss to follow-up, by strengthening the importance of compliance to therapy. Another possibility is to follow up less complex cases of LTBI in primary care, enabling access to the BHCU closest to home.

In a study carried out by New England in 2018, the treatment of LTBI was compared with 9 months of isoniazid versus 4 months of rifampicin, in adults. It was demonstrated that treatment with rifampicin had a higher completion rate and fewer side effects.[18] In the present study, the majority were treated with isoniazid since rifampicin became the first choice for children under 10 years of age only in 2018, and the data analyzed were collected since 2011.[19] There were no side effects to rifampicin. Two cases presented adverse events to isoniazid, including abdominal pain and increased transaminases, improving after stopping the medication for a period. Around 10% of patients who use isoniazid develop changes in transaminases. In most cases, these changes resolve spontaneously even when the drug is maintained.[20]

There were some limitations to the study, inherent to the retrospective study. Unavailable information and non-standardization of records may have contributed to the limitations. Some variables were not included in the percentage analysis because they were not included in the medical record, such as the patient's color/race, education and owning their own home.

The presence of LTBI was found in more than half of the patients investigated, and it could be more cases when considering the loss of follow-up of cases in the initial analysis. Approximately 10% had tuberculin conversion. Intra-household transmission was predominant and the main source case was the mother. The investigation of patients was carried out early, but in more than a third of the records there was no description of investigation of other intra-household contacts. Half of the patients were lost to follow-up throughout treatment. The therapy used was safe and the socioeconomic analysis was hampered by the lack of data in the medical record.

As children under 5 years of age have a high chance of developing severe forms of the disease, measures are needed to change this scenario. Treatment of LTBI is a fundamental step to prevent the progression of the disease. Actions such as reception, ease of care, referral to social assistance and the dissemination of data through accessible means for the population about the risks involved in loss of follow-up, the severity of the disease, can increase compliance to therapy and minimize the evolution of severe cases.

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