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Spotlight on latent tuberculosis infection screening for juvenile idiopathic arthritis in two countries, comparing high and low risk patients

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Abstract

Background: Rheumatic diseases are associated with an increase in overall risks of tuberculosis (TB). The aim of this study was to evaluate the frequency of TB and the frequency of latent TB infection (LTBI), in clinical practice, for juvenile idiopathic arthritis (JIA) patients from high and low risk of TB incidence endemic countries.

Methods: This is an international, multicenter, cross-sectional, observational study of data collection from Brazil and Registry of Portugal at REUMA.PT. The inclusion criteria were patients with Juvenile Idiopathic Arthritis (JIA) with age ≤ 18 years who underwent screening for Mycobacterium tuberculosis infection [tuberculin skin test (TST) and/or interferon gamma release assay (IGRA)]. Chest X-rays and history of exposure to TB were also assessed.

Results: 292 JIA patients were included; mean age 14.3 years, mean disease duration 7.5 years, 194 patients (66.4%) performed only TST, 14 (4.8%) only IGRA and 84 (28.8%) both. The frequency of LTBI (10.6%) and TB was similar between the two countries. The reasons for TB screening were different; in Brazil it was performed more often at JIA onset while in Portugal it was performed when starting Disease Modified Anti-Rheumatic Drugs (DMARD) treatment ($p < 0.001$). Isoniazid therapy was prescribed in 40 (13.7%) patients (31 with LTBI and 9 with epidemiologic risks and/or due to contact with sick people). Only three patients (1%) developed active TB.

Conclusion: We found nearly 10% of patients with LTBI, a small percentage of patients with treatment due to epidemiologic risks and only 1% with active TB. Distinct reasons and screening methods for LTBI were observed between the two countries.

Keywords: Tuberculosis, Latent tuberculosis infection, Juvenile idiopathic arthritis, Rheumatic diseases, Children

Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MT), is a major cause of morbidity and mortality among children and adolescents globally, with a mortality rate of around 1.6 million people every year [1]. In 2018, Brazil registered 37.4 new cases of TB per 100,000 habitants according to the Ministry of Health, remaining a highly endemic country, whereas Portugal registered 16.6

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cases per 100,000 habitants, thus being considered a low TB risk country [2, 3].

Juvenile idiopathic arthritis (JIA) is the most common pediatric autoimmune rheumatic disease. Despite JIA outcome improvement, infections, particularly TB, remain a major concern for pediatric rheumatologists [4]. Indeed, rheumatic diseases are associated with a 2- to 4-fold increased TB risk, due to immune dysregulation and immunosuppressive treatments [5–7]. The frequency of latent tuberculosis infection (LTBI) has been described as twice as high in JIA patients after one year of methotrexate (MTX) treatment, compared to the healthy pediatric population [8, 9]. After starting biologic agents, the risk of LTBI reactivation and new TB infections in adults increased from 2 to 30 times, depending on the clinical setting and the type of tumor necrosis factor (TNF) inhibitor used, being particularly higher for monoclonal antibodies [10–15].

Therefore, it is recommended that all candidates for biologic Disease Modified Anti-Rheumatic Drugs (bDMARDs) treatment should be screened for MT infection before starting the treatment [16]. Long-term evaluation revealed that LTBI screening and primary prophylaxis before anti-TNF treatment is effective in preventing TB in a highrisk JIA population. Tuberculin skin test (TST) is the most used test to assess previous TB exposure [17]. Cellular response to MT-specific antigens such as interferon gamma release assay (IGRA) and enzyme linked immune absorbent spot (Elispot), could also be used, with the advantage of lower occurrence of false negative results, due to the use of immunosuppressors, but with the disadvantage of a higher cost [18]. To our knowledge, there is no previous study assessing the frequency of TB and LTBI screening in JIA patients, comparing high and low risk TB incidence endemic countries.

The aim of this study was to evaluate the frequency of TB and the frequency of latent TB infection (LTBI) in clinical practice for juvenile idiopathic arthritis (JIA) patients from high and low risk of TB incidence endemic countries.

Methods

An international, multicenter, cross-sectional, observational, study was carried out on JIA patients from Portugal and Brazil according to the revised International League of Associations for Rheumatology (ILAR) criteria [19], and ruling out other causes of chronic arthritis, registered at REUMA.PT. REUMA.PT is a prospective longitudinal real-world registry developed by the Portuguese Society of Rheumatology to record data from patients with several rheumatic diseases, including JIA. Partnerships have been formed with other countries, specifically with Brazil, that uses the same Portuguese version of the database, kindly provided for their own use [20]. All patients aged ≤ 18 years who had available data from TST and/or IGRA were included. From Sao Paulo state, the centers included were two in Sao Paulo city, one in Ribeirao Preto city, one in Botucatu city (with an incidence rate of tuberculosis of 31–50/100,000 habitants, considered as high risk), and from Rio de Janeiro state, one in Rio de Janeiro city was included (with an incidence of 51–65/100,000 habitants, considered as high risk). On the other hand, Portugal presented a rate of 16.6 cases per 100,000 habitants (considered as low risk) [2, 3].

The electronic registry data collection was performed up to May 2019, with a total of 1549 JIA patients included, of those, 292 patients with JIA diagnoses met the inclusion criteria, including sociodemographic, clinical description and treatment during follow up in tertiary centers clinics, being from twelve centers in Portugal and five in Brazil.

The TB screening, the use of conventional Disease Modified Anti-Rheumatic Drugs (cDMARDs) and biologic DMARDs (bDMARDs), and the TB events were systematically assessed. TST and/or IGRA were performed at JIA onset or before starting cDMARDs use, and always prior to the introduction of bDMARDs therapy to screen for LTBI, in accordance with Brazilian and Portuguese guidelines for biological therapies for children and adolescents with JIA [21, 22]. In both countries, 2TU units were used to perform TST. We only considered the information from the first performance of the TST and IGRA.

Screening tests included TST, IGRA, chest X-ray and history of exposure to TB. A positive TST was defined as the papule diameter as being equal to or greater than 5 mm. The chest X-ray findings looking for previous signs of TB were also considered. IGRA test values were also recorded. TB exposure was defined as current or past family history of close contact, professional contact, or school contact with an individual with known TB at any time. LTBI is defined clinically by a reactive TST and/or positive IGRA, in the absence of clinical and radiological findings, and LTBI treatment was recommended [23]. In the case of active TB (by clinical and/or radiological findings), treatment referral and follow up was offered.

Anti-bacillar treatment was indicated if a diagnosis of LTBI was established, in case of close contact with TB diagnosed individuals, or if TB was diagnosed. LTBI treatment was administered with isoniazid (INH) at 5 mg/kg (up to 300 mg/day) for six consecutive months or longer according to local guidelines [20, 21]. Anti-TNF therapy could be prescribed after one month of starting INH.

Sociodemographic data (current age, sex, educational level,) were also collected. Variables related to the disease such as its duration and treatment received, were obtained by direct interview with patients and from medical records. The types and doses of cDMARDs and bDMARDs treatment were registered. Patients receiving biological therapy with TNF inhibitors (TNFi) (etanercept, adalimumab, infliximab, certolizumab or golimumab), interleukin 6 (IL6) inhibitor (tocilizumab), or inhibitor of the T-lymphocyte co-stimulatory signal by CTLA4 (abatacept) were included.

Local Ethics Committee approval was obtained, and Reuma.PT was approved by the Portuguese data protection authority (Comissão Nacional de Proteção de Dados). Parents provided a written informed consent and children signed an assent form provided by Reuma.PT.

Statistical analysis

Descriptive statistics were used to calculate the mean (standard deviations) or median (range) for continuous variables, and frequencies (percentages) for categorical variables. Normal distribution was assessed using Kolmogorov–Smirnov test. Comparisons between countries were performed using Student's t-tests, chi-square, or Fisher's exact tests, as deemed appropriate. In order to detect differences between groups, comparisons in JIA patients performing TB screening tests for different reasons, Fisher's exact test, chi-square test or one-way analysis of variance (ANOVA) were used. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 292 JIA patients (188 Portuguese and 104 Brazilian), 61.3% female, with a mean age of 14.3 ± 6.7 years and mean disease duration of 7.5 ± 6.2 years, were included in the study. Table 1 shows demographic data and clinical descriptors. The Portuguese population was older and presented a longer disease duration.

Table 2 shows TB screening tests, treatment, and risk factors for TB in Portuguese and Brazilian populations. The reasons for TB screening were different for the two countries; it was performed more often at JIA onset in Brazil, whereas in Portugal it was performed when starting DMARD treatment, especially before starting biological treatment ($p < 0.001$). The use of chest X-ray and IGRA as screening tools were significantly more frequent in Portugal than in Brazil (77.1% and 55.8%, $p < 0.001$; and 51.1% and 1.92%, $p < 0.001$, respectively). Forty patients (13.7%) were treated with INH as a prophylactic therapy. From these, 31 had criteria for LTBI and 9 received the medication due to being considered at high risk of TB and/or due to contact with active TB cases. Patients with criteria for LTBI treatment were similar in Portuguese and Brazilian JIA patients (10.6% in both countries). Only three patients (1%) were identified as having active TB (1 in Portugal and 2 in Brazil, corresponding in both cases to 1% of the patients screened).

Table 3 shows the demographic data, clinical characteristics, TB screening tests and treatment for TB in patients performing the test at JIA onset or prior to the use of DMARDs.

Table 1 Demographic data and clinical descriptors of Portuguese and Brazilian juvenile idiopathic arthritis populations

	Portuguese	Brazilian	*p* value	Total
Number of patients (%)	188 (64.4)	104 (35.6)	–	292 (100)
Current age (mean ± SD) (years)	16.3 ± 7.1	10.7 ± 3.9	**< 0.001**	14.3 ± 6.7
Disease duration (mean ± SD) (years)	9.1 ± 6.8	4.5 ± 2.9	**< 0.001**	7.5 ± 6.2
Female (%)	108 (57.4)	71 (68.3)	0.069	179 (61.3)
JIA categories (%)*				
Persistent oligoarticular	35 (18.6)	24 (23.1)	0.36	59 (20.2)
Extended oligoarticular	26 (13.8)	9 (8.7)	0.19	35 (12)
Polyarticular RF negative	35 (18.6)	34 (32.7)	**0.006**	69 (23.6)
Polyarticular RF positive	14 (7.4)	6 (5.8)	0.58	20 (6.8)
Enthesitis related arthritis	40 (21.3)	11 (10.6)	**0.02**	51 (17.5)
Systemic onset	14 (7.4)	13 (12.5)	0.15	27 (9.2)
Psoriatic arthritis	11 (5.9)	4 (3.8)	0.45	15 (5.1)
Undifferentiated or unclassified	2 (1.1)	2 (1.9)	0.54	4 (1.4)
Not reported	11 (5.9)	1 (1)	–	12 (4.1)

p-value < 0.05 are shown in bold

JIA, Juvenile Idiopathic Arthritis; RF, rheumatoid factor

Table 2 Tuberculosis screening tests, treatment, and risk factors for tuberculosis in Portuguese and Brazilian juvenile idiopathic arthritis populations

	Portuguese	Brazilian	*p* value	Total
Number of patients (%)	188 (64.4)	104 (35.6)	–	292 (100)
Reason for screening (%)			**< 0.001**	
At disease onset	55 (29.3)	63 (60.6)		118 (0.4)
Before treatment	127 (67.7)	36 (34.6)		163 (5.8)
Other*[1]	6 (3.2)	5 (4.8)		11 (3.8)
Age at screening				
At JIA onset	8.9 ± 5.4	7.2 ± 4.2	0.064	± 4.9
At treatment start				
Before bDMARDs (years of age)	11.9 ± 5.8	9.5 ± 2.8	0.162	11.5 ± 5.6
Number (%)	72 (38.3)	15 (14.4)	**< 0.001**	87 (29.8)
Before cDMARDs (years of age)	9.6 ± 5.1	9.2 ± 3.7	0.692	9.5 ± 4.7
Number (%)	55 (29.3)	21 (20.2)	0.091	76 (26)
Other*[1]	18.5 ± 2.1	5.4 ± 3.5	**< 0.001**	11.2 ± 7.4
TST performed as single test (%)	92 (48.9)	102 (98.1)	**< 0.001**	194 (66.4)
TST ≥ 5 mm (%)	8 (8.7)	11 (10.8)	0.625	19 (9.8)
IGRA performed as single test (%)	13 (6.9)	1 (1)	**0.023**	14 (4.8)
IGRA positive (%)	0 (0)	1 (100)	0.071	1 (7.1)
TST and IGRA performed (%)	83 (44.1)	1 (1)	**< 0.001**	84 (28.8)
TST ≥ 5 mm (%)	10 (12)	0	0.999	10 (11.9)
IGRA positive (%)	3 (3.6)	0	0.999	3 (3.6)
TST and IGRA positive (%)	0	0	–	0
LTBI therapy (Isoniazid) (%)	20 (10.6)	11 (10.6)	0.999	31 (10.6)
Chest X-ray performed (%)	145 (77.1)	58 (55.8)	**< 0.001**	203 (69.5)
Abnormal chest X-ray (%)*[2]	4 (2.8)	4 (6.9)	0.171	8 (3.9)
Immigrant from highrisk countries (%)	3 (1.6)	1 (1)	0.547	4 (1.4)
Exposure by contact TB cases (%)	3 (1.6)	3 (2.9)	0.592	6 (2.1)
Tuberculosis treatment (%)	1 (0.5)	2 (1.9)	0.290	3 (1)
Background of low socio-educational level	37 (19.7)	21 (20.2)	0.916	58 (19.9)

p-value < 0.05 are shown in bold

JIA, Juvenile Idiopathic Arthritis; bDMARDs, biologic Disease Modifying Anti-Rheumatic Drugs; cDMARDs, conventional Disease Modifying Anti-Rheumatic Drugs; TST, Tuberculin skin test; IGRA, Interferon ɣ release assay; LTBI, latent tuberculosis infection; TB, tuberculosis

* [1]Patients underwent the tuberculin skin test for different reasons (9), contact with sick relative (1) and suspected Tuberculosis case (1)

* [2]Nonspecific pulmonary infiltrates and interstitial pulmonary infiltrates

Twelve out of 76 patients (15.8%) that performed TST and/or IGRA before initiating cDMARD presented a positive TB screening test; and 5 out of 87 patients (5.7%) that performed TST and/or IGRA before initiating bDMARD presented a positive TB screening test.

At the time the patients underwent LTBI test, 212 patients were off immunomodulators/immunosuppressants and the others were on immunomodulators/immunosuppressants (65 on methotrexate, 3 on sulfasalazine, one on leflunomide). The medications of the eleven patients who had performed the TB screening for other reasons were: 6 on treatment with methotrexate (the others were off medication).

Discussion

We found 10.6% JIA patients with criteria for LTBI and 1% classified as having active TB. Distinct reasons and methods to perform LTBI screening occurred in both countries.

TB is still a public health problem in developing or developed countries. The disease is even more worrisome in patients with systemic rheumatic diseases, such as JIA, especially in those under anti-TNF agents [4]. In our study, the reason for TB screening in Brazil was most often at JIA onset, whereas in Portugal the screening was mostly due to DMARD treatment onset, especially biological treatment. Screening using chest radiography and IGRA was more frequently performed in Portugal. Anti-bacillar therapy was indicated in cases classified as

Table 3 Demographic data, clinical characteristics, tuberculosis screening tests, and treatment for tuberculosis in Portuguese and Brazilian juvenile idiopathic arthritis populations undergoing the test at disease onset or prior to the use of conventional and biologic Disease Modified Anti-Rheumatic Drugs (DMARDs)

	Test performed at JIA onset	Test performed before starting cDMARD	Test performed before starting bDMARD	*p* value
Number of patients (%)	118 (42)	76 (27)	87 (31)	–
Current age (mean ± SD) (years)	12.1 ± 6.5	15.4 ± 6.3	16.3 ± 6.8	**< 0.001**
Disease duration (mean ± SD) (years)	5.6 ± 5.0	7.7 ± 5.7	9.7 ± 7.4	**< 0.001**
Female (%)	73 (61.9)	44 (57.9)	56 (64.4)	0.696
TST performed (%)	114 (96.6)	67 (88.2)	87 (100)	**0.001**
TST ≥ 5 mm (%)	13 (11.4)	9 (13.4)	5 (5.7)	0.240
Chest X-ray performed (%)	65 (55.1)	61 (80.3)	72 (82.8)	**< 0.001**
Abnormal chest X-ray (%)	6 (9.2)	0	2 (2.8)	0.064
IGRA performed (%)*[1]	17 (14.4)	39 (51.3)	38 (43.7)	**< 0.001**
IGRA positive (%)	0	3 (7.9)	0	0.106
LTBI therapy (isoniazid) (%)	12 (10.2)	11 (14.5)	5 (5.7)	0.178
Tuberculosis therapy (%)	3 (2.5)	0	0	0.123

p-value < 0.05 are shown in bold

bDMARDs, biologic Disease Modifying Anti-Rheumatic Drugs; cDMARDs, conventional Disease Modifying Anti-Rheumatic Drugs; TST, Tuberculin skin test; IGRA, Interferon γ release assay; LTBI, latent tuberculosis infection

* [1]Three patients underwent IGRA due to other reasons (TB suspicion)

LTBI and/or history of contact with active TB patients, and/or in the case of the existence of high epidemiological risk factors for TB. LTBI treatment was performed more frequently in patients who underwent TST prior to the beginning of cDMARDs than prior to the use of bDMARDs or at disease onset. The frequency of indication for LTBI treatment was similar in Portuguese and Brazilian JIA patients. Only 3 patients had criteria for active TB.

The incidence of TB in Brazil is markedly higher than in Portugal. Non-mandatory BCG vaccination has occurred in Portugal since 2017, consistent with a TB low-risk country, whereas in Brazil it is included in the vaccination calendar during the first months of life [24, 25]. Recent studies have shown that the influence of BCG vaccination on TST depends more on the age at which the vaccine is administered than on the interval between BCG vaccination and TST performance [26]. This effect decreases over time, especially if the vaccine is administered before the age of two, the period during which it is administered in the Brazilian population [26]. Therefore, we imagine that the TST was not influenced by the BCG vaccination in our study population.

TST was performed either in the context of JIA diagnosis or post- diagnostic. TB is a major concern in the differential of diagnosis of chronic arthritis, especially in a highrisk setting. This justifies the higher frequency of TST performance at JIA onset in Brazil. In contrast, Portuguese patients had a TST performed mainly post-diagnostic, before the beginning of bDMARDs. A previously reported small JIA case series showed a high frequency of LTBI performed prior to MTX therapy, in Brazil. This study may suggest the recommendation of LTBI screening not only before the use of biological agents but also prior to the use of cDMARDs [9].

In a retrospective cohort of sixty-nine JIA patients on anti-TNF treatment, LTBI screening was positive in three patients (4.3%) and no active TB was diagnosed during a median follow up time of 3.8 years [17]. We also observed a low incidence of TST positivity (5.7%) in patients submitted to LTBI screening prior to bDMARDS therapy.

Importantly, although TB risk is much higher in Brazil than in Portugal, the rate of TST positivity was roughly the same (8.7% in Portugal vs 10.8% in Brazil). The prevention of active TB through the treatment of LTBI is one of the main strategies for reducing the incidence of this disease [27].

The introduction of biological agents during the 2000s for the treatment of JIA has dramatically changed the prognosis of children and adolescents with this chronic disease, but it has also raised concerns about possible risk of infections and other events in these patients. In a recent report of the Pharmachild registry, in 32 countries, a significant number of opportunistic infections was found, including 27.4% of TB and 4.1% of LTBI in JIA patients under immunosuppressive therapy, across different geographic areas [28].

The overall incidence rate of active mycobacterial infection in our previous Brazilian study including children, adolescents, and adults with chronic inflammatory arthritis, after using TNFi, was 86.9/100.000 person-years for patients and 35.8/100.000 person-years for the control group, with significant differences between both groups [29]. This data reinforces the indication of LTBI screening in this population.

In this study, chest X-rays showed non-specific pulmonary infiltrates and interstitial pulmonary infiltrates in very few JIA patients. These imaging findings were unrelated to TB disease, as confirmed by a pediatric pulmonologist.

We presume that the better economic situation facilitates access to exams such as chest X-rays and IGRA. Recently, WHO recommended that IGRA should not be used in low and middle-income countries (generally those with a higher TB burden), as there is insufficient data and evidence about the performance of IGRA in these populations [30]. IGRA has similar performance to TST but is more expensive and more complex to perform, therefore TST should be preferential in these countries. Studies on infection detection supported the use of TST [31]. IGRA may have an advantage over TST in patients under corticosteroids therapy and during a short period of time immediately after BCG vaccination. However, data from pediatric population and immunosuppressed individuals who could benefit from IGRA is limited and more studies with a large sample size would be desirable [32].

The indications for treatment of LTBI according to the recommendations in Brazil and Portugal are quite similar and include TST positivity (≥ 5 mm) and/or IGRA positivity in cases without previous LTBI treatment, or chest X-ray showing disease sequels of previous untreated TB, or presence of epidemiological data suggestive of TB contact (history of TB exposure in the last two years, previous TB illness, immigrants and residents from high prevalence/incidence areas of TB, comorbidities associated with increased risk of TB, and travel to endemic areas) after exclusion of active TB [21, 22].

LTBI treatment includes INH with different treatment protocols for the two countries (in Brazil for six months, in Portugal for nine months) [21, 22]. We observed in our study that LTBI therapy was indicated more frequently in patients due to positive TST before using cDMARDs than before bDMARDs.

The main limitations of the present study are the retrospective design (registry based) and a small number of JIA patients submitted for IGRA test. Another limitation was the use of glucocorticoids or DMARDs that may have affected the accuracy of the TST [33]. Furthermore, we do not think that the sample is representative, as it only included five Brazilian cities from one region, and two Portuguese cities.

Conclusion

This international multicenter study evaluated the frequency of TB and the value of LTBI screening in clinical practice of JIA patients at high and low risk of TB incidence in two endemic countries. We observed no differences in the occurrence of patients with criteria for LTBI and TB treatment in both countries.

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Author contributions
All authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethical approval and consent to participate
This study was approved by the Local Ethics Committee, and Reuma.PT was approved by the Portuguese data protection authority (Comissão Nacional de Proteção de Dados). Parents provided a written informed consent and children signed an assent form provided by Reuma.PT.

Consent for publication
All coauthors have agreed to have seen and approved the manuscript for submission.

Competing interests
The authors declare that they have no conflict of interest.

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