Pediatric Tuberculosis: 12 Years of Experience in a Tertiary Referral Center in Portugal

Tuberculose em Idade Pediátrica: Experiência de 12 Anos num Centro Terciário de Referência em Portugal

ARTIGO ORIGINAL

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ABSTRACT

Introduction: The diagnosis of tuberculosis in children is a challenge namely because extrapulmonary tuberculosis and severe disease are more frequent in this age group. The aim of this study was to evaluate and reflect about severe tuberculosis in pediatric age, in a metropolitan area of Lisbon.

Material and Methods: Descriptive study about patients under 18 years of age admitted with tuberculosis disease in a tertiary pediatric hospital, from 2008 to 2019 (12 years).

Results: We report 145 patients, average of 12 cases/year, with an increase in the last three years. Median age of 12.9 years, 42.8% born in Portuguese-speaking African countries and 20% had a chronic disease. The diagnosis was pulmonary tuberculosis in 52.4% (n = 76) and extrapulmonary tuberculosis in 47.6%: lymphatic (n = 26), skeletal (n = 15), miliary (n = 8), meningeal (n = 7), peritoneal/intestinal (n = 6), pleural (n = 4), renal (n = 1), cutaneous (n = 1), thoracic wall (n = 1) and salivary glands (n = 1). The tuberculin test was positive in 78/99 (78.8%) and *interferon gamma release assay* in 61/90 (67.8%). In 20.7% (n = 30) acid-fast bacilli were identified in gastric aspirate/sputum and the agent was identified in 59.3% (n = 86). Tuberculosis was resistant in 11% (n = 16). Patients with extrapulmonary tuberculosis were younger (p = 0.006) and had more prolonged therapy (p < 0.001). Therapy-related complications occurred in 11% (n = 16). One patient died (with terminal cancer).

Conclusion: This study highlights the need for screening of tuberculosis in children from endemic countries, patients with immunosuppression and chronic disease.

Keywords: Child; Tuberculosis; Tuberculosis, Pulmonary

RESUMO

Introdução: Em Pediatria, o diagnóstico de tuberculose constitui um desafio, pois a doença pode frequentemente manifestar-se através de formas graves e extrapulmonares. O objetivo deste estudo foi avaliar e refletir sobre a tuberculose grave com necessidade de internamento, em idade pediátrica, numa área metropolitana de Lisboa.

Material e Métodos: Estudo descritivo de doentes com idade inferior a 18 anos, internados com o diagnóstico de tuberculose num hospital pediátrico terciário, de 2008 a 2019 (12 anos).

Resultados: Identificados 145 doentes, numa média de 12 casos por ano, e um aumento do número de casos nos últimos três anos. A mediana de idades dos doentes era de 12,9 anos, 42,8% nascidos em países africanos de língua oficial portuguesa e 20% tinham doença crónica. Diagnosticou-se tuberculose pulmonar em 52,4% (n = 76) e tuberculose extrapulmonar em 47,6%: ganglionar (n = 26), óssea (n = 15), miliar (n = 8), meníngea (n = 7), peritoneal/intestinal (n = 6), pleural (n = 4), renal (n = 1), cutânea (n = 1), da parede torácica (n = 1) e glândulas salivares (n = 1). A prova tuberculínica foi positiva em 78/99 (78,8%) e o *interferon gamma release assay* em 61/90 (67,8%). Em 20,7% (n = 30) identificaram-se bacilos ácido-álcool resistentes no exame direto do suco gástrico/expetoração e o agente foi identificado em 59,3% (n = 86). A tuberculose resistente ocorreu em 11% (n = 16). Os doentes com tuberculose extrapulmonar eram mais jovens (p = 0,006) e fizeram tratamentos mais prolongados (p < 0,001). Ocorreram complicações da terapêutica em 11% (n = 16). Registou-se um óbito numa doente com neoplasia avançada.

Conclusão: Este estudo alerta para a necessidade do rastreio da infeção em crianças de países endémicos, imunossuprimidos e com doença crónica.

Palavras-chave: Criança; Tuberculose; Tuberculose Pulmonar

INTRODUCTION

Ten million new cases of tuberculosis (TB) and 1.3 million deaths related to this pathology were estimated worldwide in 2017 by the World Health Organization (WHO).[1] An incidence of less than 10 cases per 100,000 population has been found in developed countries, reaching 150 to 500 cases per 100,000 population in endemic countries. One million children were diagnosed with TB within the same year,[1] while the number of cases remained stable between 9 and 11.1 million worldwide in 2018 and 2019, including 11% and 12% involving patients aged under 15, respectively.[2,3]

In Portugal, TB incidence rates of less than 20 cases per 100,000 population were found in 2014, placing the country among the lowest incidence group for the disease. Therefore, and according to WHO recommendations for countries with low incidence, effective surveillance systems and incidence rates of tuberculous meningitis under one case per 10,000,000 population for five consecutive years, bacillus Calmette-Guérin (BCG) vaccination was moved from universal to restricted risk groups from June 2016 (Table 1).[4]

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High incidence rates (> 20 cases and > 50 / 100,000 population) were found in 2014 in the metropolitan areas of Porto, Lisbon, Setúbal and Algarve.[5] Even in 2016, when an incidence of 18 cases per 100,000 has been found, a concentration of cases in Lisbon and Porto was found, showing an uneven distribution of the disease.[6]

At the same time, even though an incidence 4.8 times higher than the estimated national incidence (95.4 / 100,000 in 2014 and 86.7 / 100,000 in 2016) was found in immigrants from other countries, the percentage of immigrant patients diagnosed with TB remained stable at 15.9% and 18.4% within those years.[5,6]

TB is caused by Mycobacterium tuberculosis, an aerobic, acid-alcohol-resistant, airborne bacillus. Inhaled particles reach the mediastinal ganglia and terminal airways, leading to the Ghon complex, which includes the initial focus of infection and regional lymphadenopathy. In this phase, the infection may remain contained, may spread, or later reactivate, leading to three different forms of progression: (i) Latent tuberculosis or infection, affecting asymptomatic patients with normal chest X-ray and showing signs of contact with the bacillus, with positive tuberculin skin test and/or interferon gamma release assay (IGRA); (ii) Pulmonary disease with intrathoracic lymphadenopathies and parenchymal disease, in the presence of signs and symptoms and/or chest X-ray abnormalities. In this case, when mycobacteria are identified by direct examination in sputum or gastric juice, the patient is considered contagious;[7] (iii) Lymph node TB is the most frequent presentation of extrapulmonary tuberculosis (67%), followed by others less frequent presentations including meningeal (13%), pleural (6%), miliary (5%) and bone TB (4%).[8,9]

Paediatric patients unlike adults present with clinical manifestations one to two years following the initial infection.[9,10] In children under 2, clinical progression affects 10% - 40% of the patients,[9] with a higher risk of disseminated and meningeal disease (2% - 20%).[11]

TB is currently considered a rare entity in developed countries, even though remaining an important health issue worldwide, requiring continuous efforts in the development of control strategies.[1] This study was aimed at assessing the forms of disease in paediatric patients diagnosed with severe TB requiring hospitalisation in a metropolitan area in Lisbon.

MATERIAL AND METHODS

This was an observational and descriptive study in patients under age 18 admitted to a tertiary hospital and diagnosed with TB, throughout 12 years (between January 2008 and December 2019). Sociodemographic, epidemiological, BCG vaccination, clinical examinations and testing, therapy, and complications were analysed.

Tuberculin skin test ≥ 5 mm positivity criterium was considered in non-vaccinated and immunosuppressed patients, while ≥ 10 mm was considered in vaccinated patients, as well as the presence of blister formation or ulceration regardless of vaccination status.

Statistical analysis was performed using Statistical Package for Social Sciences® (SPSS) software, version 23.0. The Shapiro-Wilk test was used to check the normality of continuous variables. Student's t-test was used to compare the behaviour of continuous variables with normal distribution between groups of patients with pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (ETB); Mann-Whitney non-parametric test was used for continuous variables that did not show normal distribution. Chi-square test was used for nominal variables, in the comparison of the different defined groups (PTB *versus* ETB). A 5% significance level was considered.

This study was approved by the Ethics Committee of Hospital D. Estefânia, in Lisbon.

RESULTS

A total of 145 patients were included, with an average of 12 cases per year and an increase in the number of cases was found within the past three years (n = 66; 45.5%) (Fig. 1) mostly affecting the Portuguese population (Fig. 2) with a peak in 2017 (12 Portuguese patients/22 cases) and 2019

Table 1 – Risk groups for TB[4]

Children with no BCG record*/ No vaccination scar and:	**Covered situations:**
Coming from countries with a high incidence of TB	- Countries with incidence rate ≥ 40/100,000 - At least 3-month stay
Who have completed screening of contacts and/or prophylaxis	To be assessed by Public Health in liaison with the regional coordinators of the *Programa Nacional para a Tuberculose* and CDP**
Patients whose parents, other cohabitants or co-living people presented with	- HIV/AIDS infection, upon HIV infection in the patient was ruled out (HIV positive mother) - Drug or alcohol dependence - Parents coming from countries with high incidence of TB - History of TB
Coming from communities with high risk of TB	To be assessed by Public Health in liaison with the regional coordinators of the *Programa Nacional para a Tuberculose* and CDP
Travellers from countries with high incidence of TB	- Countries with incidence rate ≥ 40/100,000 - At least 3-month stay - Vaccination could be considered for shorter stays, whenever a high risk of infection is considered

* BCG: *Bacillus* Calmette-Guérin vaccine; ** CDP: *centros de diagnóstico pneumológico* (pulmonary diagnostic centres)
Adapted from: *Direção-Geral da Saúde. Estratégia de vacinação contra a tuberculose com a vacina BCG, NORMA Nº 006/2016. 2016.*

(15 Portuguese patients/23 cases); 50.6% (40/79) of the patients presenting with TB within the first nine years were Portuguese, 43% (34/79) were from PALOP (Portuguese-speaking African Countries), 2.5% (2/79) from Asia, 2.5% (2/79) from South America and 1.3% (1/79) from Eastern Europe, while 53% of the patients (35/66) presenting within

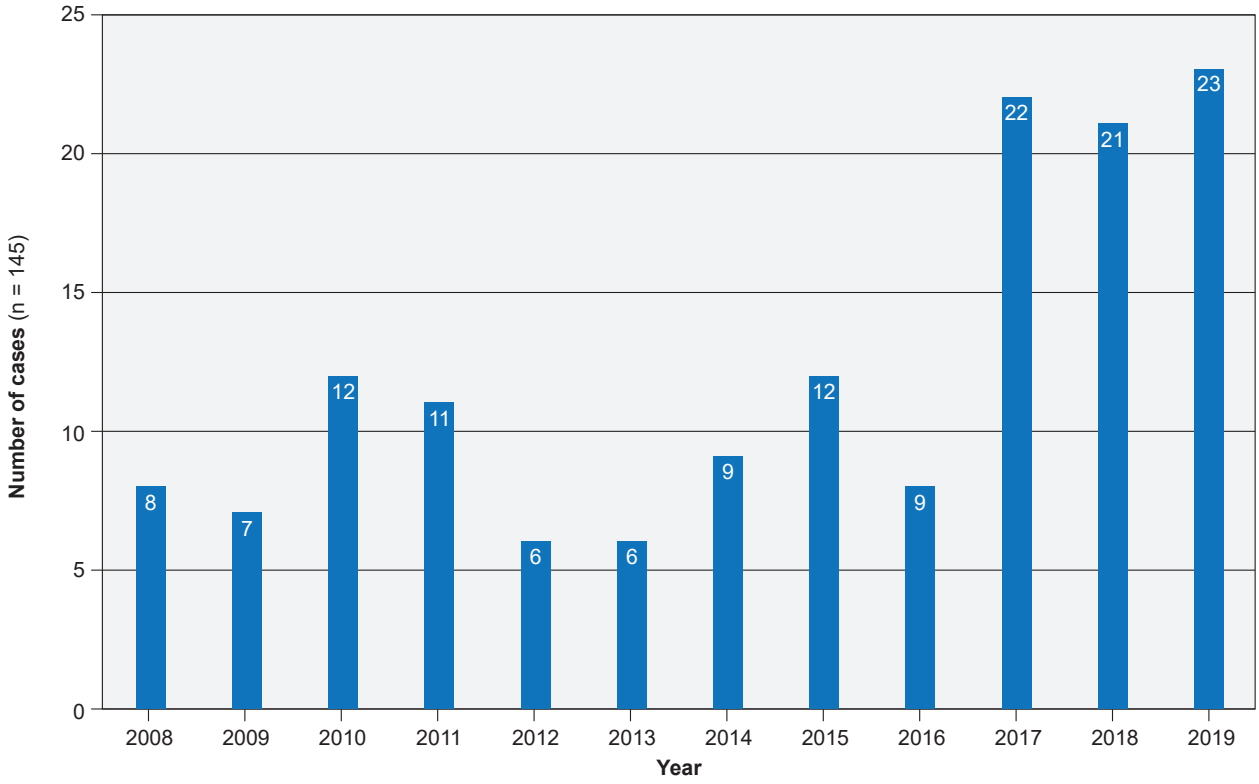

Figure 1 – Distribution of cases of TB

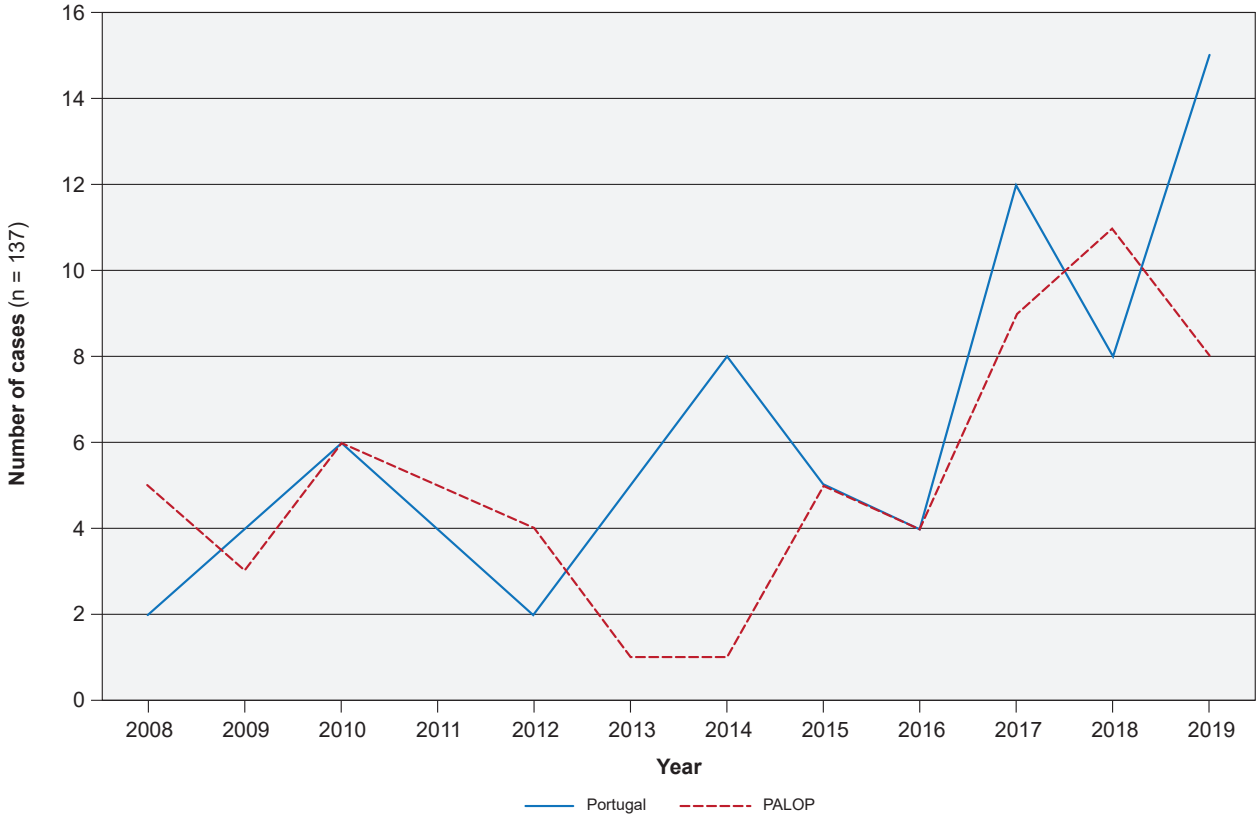

Figure 2 – Distribution of cases of TB among patients born in Portugal *vs*. those from the PALOP

the past three years were Portuguese, 42.4% (28/66) from PALOP countries and 4.5% (3/66) from Asia.

The characterisation of the paediatric TB population is shown in Table 2.

There was a slight male predominance (54.5%), with a median age of 12.9 [3.9 - 16.1 years], mostly affecting patients aged 10 and older [60% (n=87)], 15 and older [36.6% (n=53)] and under 12 months [7.6% (n=11)]. Over half of the patients were born in Portugal (51.7%), 42.8% in PALOP countries. Patients originating from other countries (5.5%) were also found: Asia (n = 5), South America (n = 2) and Eastern Europe (n = 1). At the time of admission, 4.5 months [0 - 15 years] was the median length of residence in Portugal for PALOP patients.

Most children (74.5%) had received the BCG vaccination, confirmed by the individual health record and/or vaccination scar; 14 from the unvaccinated patients (37) were Portuguese (10 born after 2015), 20 were PALOP nationals and three were of Asian origin.

Twenty-nine patients (20%) presented with chronic disease and two with more than one pathology. Two children of African origin were infected with the human immunodeficiency virus (HIV): one patient was diagnosed simultaneously with TB and a second patient was screened at a follow-up visit. Four patients (2.8%) on immunosuppressive therapy (corticoid therapy) had never been screened for TB.

The presence of one contact who had been diagnosed with active TB was related to 50 patients (34.5%). Previous screening had only been obtained in 29 from these 50 cases. No screening had been performed in 21 patients,

Table 2 – Patients diagnosed with TB

Clinical characteristics		n (%)
Age group	0 – 12 months	11 (7.6 %)
	1 – 5 years	31 (21.4 %)
	5 – 10 years	16 (11.0%)
	> 10 years	87 (60.0%)
Nationality	Portugal	75 (51.7%)
	PALOP	62 (42.8%)
	Others	8 (5.5%)
BCG/vaccination scar	Yes	108 (74.5%)
	No	37 (25.5%)
Chronic disease	Endocrine	7 (4.8%)
	Neurological	6 (4.1%)
	Haematological	5 (3.4%)
	Gastro-intestinal	4 (2.8%)
	Rheumatological	2 (1.4%)
	Kidney	2 (1.4%)
	Others	5 (3.4%)
Immunosuppression		4 (2.8%)
Pulmonary TB		76 (52.4%)
Extrapulmonary TB		69 (47.6%)
Forms of ETB	Lymph node	26 (37.7%)
	Bone	15 (21.7%)
	Miliary	8 (11.6%)
	Meningeal	7 (10.2%)
	Peritoneal	4 (5.8%)
	Pleural	4 (5.8%)
	Intestinal	2 (2.9%)
	Kidney	1 (1.4%)
	Cutaneous	1 (1.4%)
	Chest wall	1 (1.4%)
	Salivary gland	1 (1.4%)
TST	Tested	99/145 (68.3%)
	Positive	78/99 (78.8%)
	Negative	2/99 (2.0%)
	Anergic	19/99 (19.2%)
IGRA Quantiferon	Tested	88/145 (60.7%)
	Positive	52/88 (59.1%)
	Negative	26/88 (29.5%)
	Indeterminate	10/88 (11.4%)
IGRA T-SPOT	Tested	24/145 (16.6%)
	Positive	9/24 (37.5%)
	Negative	15/24 (62.5%)

even though the contact was well known. Five patients were diagnosed with latent TB and had therefore only been medicated with isoniazid. In most cases (62%), an index case was found within the patient's household: mother (n = 11), father (n = 8) and another cohabiting relative (n = 12). A non-cohabiting relative was found as regards 11/50 patients. Friends or neighbours (n = 4), a resident at the same institution (n = 3) and one case of nosocomial infection (n = 1) were the contacts related to the remaining eight patients. A 13.7-month median time was found between index case diagnosis and diagnosis of TB in our patients.

A total of 76 patients were diagnosed with PTB (52.4%), with cough (n = 51), fever (n = 31), asthenia (n = 25), weight loss (n = 24) and chest pain (n = 17). Other less frequent clinical presentations included haemoptysis (n = 6) and pneumonia unresponsive to conventional antibiotic therapy (n = 2).

A total of 69 patients (47.6%) presented with ETB and were diagnosed with lymph node (n = 26), bone (n = 15), miliary (n = 8), meningeal (n = 7), peritoneal (n = 4), pleural (n = 4), intestinal (n = 2), kidney (n = 1), cutaneous (n = 1), chest wall (n = 1) and salivary gland (n = 1) TB. One patient presented with both bone and pleural TB. Different symptoms were found, according to the different presentations, even though fever was mostly found (52.2% of the patients). Symptoms related to PTB are shown in Table 3. Patients diagnosed with lymph node TB presented with fever (n = 11), cough (n = 10), asthenia (n = 7), weight loss (n = 7), subacute/chronic cervical lymph node (n = 6) and chest pain (n = 4). Patients diagnosed with bone TB also presented with fever (n = 8), while osteoarticular symptoms mostly included back pain (n = 10), followed by bone swelling (n = 6), and kyphosis (n = 4). Patients with miliary tuberculosis presented with prolonged fever (n = 8) and those with meningeal TB with neurological symptoms (n = 6) and fever (n = 2). The patients diagnosed with intestinal and/or peritoneal TB presented with non-specific symptoms including asthenia (n = 4), weight loss (n = 3), fever (n = 4), abdominal pain (n = 3) and ascites (n = 1). The patients diagnosed with pleural tuberculosis presented with cough (n = 3), fever (n = 3) and chest pain (n = 1). The only patient diagnosed with kidney TB presented with haematuria, asthenia, and weight loss. The patients diagnosed with cutaneous TB presented with a chronic ulcer in the face, with a two-year progression and no improvement with different antimicrobial agents. The rare forms of chest wall TB and with the involvement of salivary glands presented as chronically progressive swellings with no major impact on the general condition of the patients.

Severe forms found in 15/145 (10.3%) patients included seven patients presenting with meningitis and eight with miliary TB. Eight of these patients had been vaccinated with BCG and two were aged under 12 months, one with age 3 and five were adolescents aged over 13. One of the patients diagnosed with miliary TB presented with HIV infection.

Most patients [78/99 (78.8%)] presented with a positive tuberculin sensitivity test (TST - Mantoux), even though

Table 3 – Characteristics of symptoms in patients diagnosed with ETB

Type of ETB (n)	**Symptoms** (n)
Lymph node (26)	Fever (11) Cough (10) Asthenia (7) Weight loss (7) Neck lymph node with subacute/chronic evolution (6) Chest pain (4)
Bone (15)	Fever (8) Back pain (10) Swelling (6) Kyphosis (4)
Miliary (8)	Fever (8)
Meningeal (7)	Neurological symptoms (6) Fever (2)
Peritoneal/intestinal (6)	Asthenia (4) Weight loss (3) Fever (4) Abdominal pain (3) Ascites (1)
Pleural (4)	Cough (3) Fever (3) Chest pain (1)
Kidney (1)	Haematuria with asthenia and weight loss (1)
Cutaneous (1)	Chronic ulcer in the face with two-year progression, unchanged upon different antimicrobials (1)
Chest wall (1)	Swelling with chronic evolution (1)
Salivary gland (1)	Swelling with chronic evolution (1)

19/99 (19.2%) were anergic. Most patients [61/90 (67.8%)] showed a positive IGRA TB test and TST and IGRA were tested simultaneously in 54 patients (37.2%). Eleven of these patients were anergic to TST and showed a negative IGRA test, while one patient showed a positive TST and negative IGRA test. IGRA-Quantiferon Gold Plus was tested as first choice in 88/90 (97.8%) of the patients and was positive in 52/88 (59.1%); 35.2% of these patients were aged under 5 and 15.9% were aged under 2, while a positive test was found in 54.8% and 57.1%, respectively. IGRA T-SPOT was tested in 24/90 (26.7%) patients [(including those with indeterminate IGRA-Quantiferon (n = 6) or with negative IGRA-Quantiferon (n = 11) and as first choice (n = 7)], and was positive in nine (37.5%), including 5 patients aged under 5 and one under 2.

The chest X-ray pattern found in patients diagnosed with PTB showed condensation (n = 24), cavitation (n = 20), hilar lymphadenopathy (n = 15), nodular infiltrates (n = 9) and pleural effusion (n = 5). Chest computed tomography (CT) scan was obtained in 72/76 patients and confirmed or showed *de novo* condensation (n = 46), hilar lymphadenopathy (n = 35), cavitation (n = 31), nodular parenchymal images (n = 21), pleural effusion (n = 8), calcifications (n = 7), and atelectasis (n = 5). Five patients presenting with normal chest X-ray showed abnormalities in chest CT scan, namely parenchymal nodular images, condensation, and calcifications, in support of an accurate diagnosis. Bronchial fibroscopy was performed in 41/76 (53.9%) patients, showing abnormalities in 73.2% with nonspecific inflammation (n = 22) and endobronchial granuloma (n = 8).

Complications were found in 24 (16.6%) patients, including pleural effusion (n = 8), bronchopleural fistula (n = 1), hard palate injury (n = 1), and secondary amyloidosis (n = 1) in patients diagnosed with parenchymal lung disease with cavitations; kyphosis (n = 6), scoliosis (n = 1), lumbar protrusion (n = 1), paravertebral abscess (n = 1), macrophage activation syndrome (n = 1), left middle cerebral artery ischemic stroke (n = 1), epilepsy (n = 1) and worsening of baseline epilepsy (n = 1) in those diagnosed with ETB. Long-term (one year upon diagnosis) sequelae were found in 12 patients (8.3%), including kyphosis (n = 6), scoliosis (n = 1), right hemiparesis and developmental delay (n = 1), epilepsy with neuropathy involving cranial nerves VI and VII (n = 1), refractory epilepsy and developmental delay (n = 1), lobectomy related to granuloma (n = 1), and pulmonary fibrosis (n = 1).

Table 4 – Comparison between patients diagnosed with PTB *vs.* ETB

	TB	PTB	EPTB	*p*-value
Age (median; years)	12.9	14.6	10	**0.006**
Age group	0 – 12 months	6/76 (7.9%)	5/69 (7.2%)	0.883
	1 – 5 years	13/76 (17.1%)	18/69 (26.1%)	0.188
	5 – 10 years	4/76 (5.3%)	12/69 (17.4%)	**0.020**
	> 10 years	53/76 (69.7%)	34/69 (49.3%)	**0.012**
Nationality	Portuguese	43/76 (56.6%)	32/69 (46.4%)	0.22
	Other	33/76 (43.4%)	37/69 (53.6%)	0.22
BCG	108/145 (74.5%)	61/76 (80.3%)	47/69 (68.1%)	0.094
Chronic disease	29/145 (20.0%)	18/76 (23.7%)	11/69 (15.9%)	0.244
TST				
Tested	99/145 (68.3%)			
Positive	78/99 (78.8%)	44/53 (83.0%)	34/46 (73.9%)	0.269
Negative	2/99 (2.0%)	1/53 (1.9%)	1/46 (2.2%)	0.919
Anergic	19/99 (19.2%)	8/53 (15.1%)	11/46 (23.9%)	0.266
IGRA Quantiferon				
Tested	88/145 (60.7%)			
Positive	52/88 (59.1%)	27/41 (65.9%)	25/47 (53.2%)	0.228
Negative	26/88 (29.5%)	9/41 (22.0%)	17/47 (36.2%)	0.145
Indeterminate	10/88 (11.4%)	5/41 (12.2%)	5/47 (10.6%)	0.818
IGRA T-SPOT				
Tested	24/145 (16.6%)			
Positive	9/24 (37.5%)	1/11 (9.1%)	8/13 (61.5%)	**0.008**
Negative	15/24 (62.5%)	10/11 (90.9%)	5/13 (38.5%)	**0.008**
Mycobacteria isolation	86/145 (59.3%)	51/76 (67.1%)	35/69 (50.7%)	**0.045**
Bacilliferous TB	30/145 (20.7%)	26/76 (34.2%)	4/69 (5.8%)	**< 0.001**
Median length of stay (days)	15	12.5	22	**0.011**
Median therapy duration (months)	6	6	9	**< 0.001**
Complications	24/145 (16.6%)	11/76 (14.5%)	13/69 (18.8%)	0.480
Sequelae	12/145 (8.3%)	1/76 (1.3%)	11/69 (15.9%)	**0.001**
Total	**145**	**76**	**69**	

Mycobacteria were isolated from specimens in 86 patients (59.3%). Positive direct examination was found in 21.4%, nucleic acid amplification test (NAT) in 47.6%, and cultural examination in 59.3% of the patients. Mycobacteria were isolated in gastric juice (n = 48), sputum (n = 18), bronchoalveolar lavage (n = 14), in other specimens (n = 18) and specimens from different locations were obtained in 107 patients (73.8%) and mycobacteria were isolated simultaneously from different specimens in 20 patients (13.8%).

Acid-fast bacilli were identified on direct examination from gastric juice/expiration specimens in 30 patients (20.7%). Antimicrobial resistance was found in sixteen patients (11%) [isolated resistance to isoniazid (n = 9) or streptomycin (n = 3), and to isoniazid with an additional drug, including streptomycin (n = 2), ethambutol (n = 1) and pyrazinamide (n = 1)]. A previous history of latent TB with isoniazid therapy was found in 2/16 patients.

Side effects of antimicrobial therapy were found in 11% (n = 16) of the patients, including hyperuricemia (n = 9), toxic hepatitis (n = 6), axonal sensory polyneuropathy (n = 1) and drug-induced lupus (n = 1) (one patient presented with hyperuricemia and drug-induced lupus). These were found in eight patients with chronic disease. A median 21 days (5 - 60) until the onset of hepatitis were found in patients with toxic hepatitis. Treatment was withdrawn in four patients waiting for the improvement of transaminase levels, while treatment remained in one patient (with only a mild elevation; monitoring was maintained). Six patients with hyperuricemia were started on allopurinol. Isoniazid was withdrawn, while rifampicin and levofloxacin were remained in the patient diagnosed with drug-induced lupus. The patient presenting with axonal polyneuropathy was medicated with pyridoxine at a therapeutic dose for neuropathy.

A 0.7% mortality rate was found in our group of patients (one patient presenting with advanced cancer and critical malnutrition on palliative care was transferred from PALOP).

The comparison between patients with PTB *vs.* ETB is shown in Table 4.

Mycobacteria was mostly isolated from specimens in patients presenting with PTB (67.1% *vs.* 50.7%; $p = 0.045$) and these were more frequently bacilliferous patients (34.2% *vs.* 5.8%; $p < 0.001$), while patients presenting with ETB were younger (median of 10 *vs.* 14.6 years; $p = 0.006$), showing more anergic TSTs, although with no statistically significant differences (23.9% *vs.* 15.1%; $p = 0.266$). Anergic tests were mostly found in patients presenting with TB meningitis, aged under 2 and on corticoid therapy. Longer hospital stay was found in patients presenting with ETB (median of 22 *vs.* 12.5 days; $p = 0.011$), as well as longer duration of therapy (median of nine *vs.* six months; $p < 0.001$). Longer hospital stays were found in patients diagnosed with bone (median of 27 days), miliary (29 days), and meningeal (31 days) TB. Longer hospital stay was also found in smear-positive patients (median of 27.5 *vs.* 13.5 days; *p*-value = 0.004).

DISCUSSION

Although rare in developed countries, the incidence of TB in paediatric patients is not negligible and is associated with significant morbidity.[1-3] The cases of TB in paediatric patients born in Portugal, whose index case was not identified, correspond to undiagnosed cases of bacilliferous TB in the community.[5,6] A TB incidence of 6.1 cases per 100,000 under-5 patients was reported in 2017, although data on the disease affecting the paediatric population are scarce.[12] Despite children represent 10% to 20% of the global TB burden, these have been chronically neglected.[13-15] The absence of standardised diagnostic criteria, the variability of the clinical presentation and the fact that children frequently present as non-bacilliferous with negative cultures, lead to the underlying constraints in reaching a diagnosis,[13,16] which in this group requires a high degree of suspicion. The fact that a higher risk of severe disease has been found in children and that childhood infection contributes to the reservoir of new cases in the future[9] shows that this entity should not be neglected.

Most patients in our group were born in Portugal, unlike other studies carried out in developed countries where the population is mainly immigrant.[16,17] The study showed that most children were infected within their family households and even though the disease was known in adults, over one year (13.7 months) was the average time between diagnosis in the index case and in our patients. On the other hand, although 50 patients had a known contact with TB, only 29 were screened. These aspects suggest that the screening of contacts of TB patients may fall far short of what is desired and may need reformulation and improvement.

The increase in the number of cases in 2017 is related to an outbreak of an adult case of bacilliferous TB, with extended time between symptom onset and diagnosis,[12] in addition to failures in identifying the disease in at-risk groups. On the other hand, the stabilisation in the number of patients from PALOP countries, where TB is endemic, highlights the importance of systematic screening in this population.

The withdrawal of the BCG vaccine from the National Vaccination Programme for the general population in 2016 had no influence on the number of cases in this study. Most patients had been submitted to the BCG vaccine, which has no significant interference in the transmission of pulmonary disease, even though in this study also did not prevent severe forms such as tuberculous meningitis and miliary TB in healthy patients (n = 8; five patients diagnosed with meningeal TB and three with miliary TB), confirming the need for new vaccines with impact on group immunity.[18]

Diagnosis has been challenging, particularly due to the lack of specificity of symptoms, constraints in obtaining bacteriological confirmation and a high incidence rate of ETB.[13,16,19]

Nonspecific clinical presentation has been found, including common symptoms such as cough, fever, asthenia, and weight loss.[17,19,20] Mycobacteria were mostly isolated from specimens in 59.3% of the patients presenting with PTB, as it happens in adulthood. This was in line with what has been found in other studies.[16,17] However, a higher rate of patients with positive cultural examination has been found (59.3%

vs. 25% - 50%),[9,13] which may show an optimal technical capacity of the microbiology laboratory at our hospital.

TST and IGRA testing may help diagnosis but do not distinguish active disease from latent infection, and its association with the clinical, imaging findings and epidemiological context is crucial.[21] TST was positive in 78.8% of the patients and slightly higher than in other studies (72.3%[21] and 53.3%).[19] IGRA may be more beneficial in the context of latent TB.[22] Lower IGRA-Quantiferon and T-SPOT positivity was found in this study, when compared to literature, even though these were not performed in all patients, with an influence on the results.[22]

Extrapulmonary TB is a more complex presentation, and strong clinical suspicion is required for diagnosis. The 47.6% rate found in this study was higher than what has been described in other countries including Turkey (35%)[19] and Denmark (24.8%)[16] even though it was more frequent in immigrants and in younger patients, in line with literature.[16,19]

Approximately 210,000 children die from TB complications each year worldwide,[23] with the highest mortality rate related to TB meningitis.[9] In this study, 16.6% of the patients presented with complications and 8.3% with sequelae, while three patients presented with complications and sequelae associated with central nervous system involvement. The significant rate of sequelae in patients with bone TB (7/15; 46.7%) also confirms that the morbidity of the disease remains high even in countries with good treatment resources.

Antimicrobial resistance has been found in 11% of the patients, which is a significant rate and recommends close monitoring and surveillance, in line with other studies. In a study held in Denmark, resistance in paediatric age was 11%,[16] over 4% estimated prevalence in Spain,[24] and 3.7% in Europe (> 10% of cases reported in Estonia and Lithuania).[25]

This was a more comprehensive study than other studies carried out in Portugal[26] and showed a high morbidity and interference in children's health. These aspects should be the object of serious reflection towards the implementation of measures aimed at reducing the paediatric disease in Portugal.

The study presents some limitations, namely the fact that it is unicentric and retrospective, based on the collection of data from clinical files, with the possibility of omitted information.

CONCLUSION

TB is not a frequent presentation in children, even though it has a significant impact on child's health and should not be neglected. Extrapulmonary presentations are more frequent in this age group, involving a more challenging diagnosis and treatment and requiring strong clinical suspicion for diagnosis.

Reducing the time until diagnosis is crucial in children, preventing from severe presentations, in addition to reducing contagiousness. The study also alerts to the importance of systematic screening of the infection in children from PALOP countries, in immunocompromised and chronically ill children.

OBSERVATIONS

Partial data presented as oral communication at the 11th Refresher Conference on Infectious Diseases at the Curry Cabral Hospital of the Coimbra University Hospital, held on 25 and 26 January 2018, Lisbon.

Poster at the 12th Conference on Infectious Diseases of the Hospital de Curry Cabral do CHULC, held on 23 and 24 January 2020, Lisbon, with the Award for Best Poster of the Conference.

AUTHOR'S CONTRIBUTION

MB: Study design, data storage and collection, participation in data analysis and interpretation, writing of the manuscript, result review and discussion.

APR: Study design, data collection, participation in data analysis and interpretation.

CVM: Data collection, participation in data analysis and interpretation.

TMS: Data collection, participation in data analysis and interpretation, version review and critical revision.

CG, FC: Participation version review, critical revision.

MJB: Study design, participation in version review, critical revision and final version approval.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

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

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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