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ORIGINAL ARTICLE

Adolescent tuberculosis: A challenge and opportunity to prevent community transmission☆,☆☆

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KEYWORDS
Adolescent;
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Abstract
Introduction: Adolescents may present with *adult-type* pulmonary tuberculosis (TB), including cavity disease in upper lobes and smear-positive sputum, which involves a significant transmission risk for social and family contacts.
Patients and methods: A retrospective (2007–2012) observational study of a case series of TB was conducted in children and adolescents (<18 years) in a paediatric referral centre in Barcelona. Patients aged ≤12 and >12 years at diagnosis were compared.
Results: The series consisted of 124 patients (56.5% males, median age: 4.0 years). In half of the cases, the patient was of immigrant origin and TB was diagnosed after clinical–radiological suspicion, intra-thoracic disease being the most common (91.9%). Cultures yielded positive results in one third of cases (37.9%) and isolates were sensitive to oral first-line anti-TB agents in 100%. Median (interquartile range) duration of treatment was 6 (6–9) months, directly observed therapy was needed in 10 patients, and there was a satisfactory outcome after treatment in 98.4%. Among adolescents, TB was more prevalent in females (63.2%) and immigrant patients (68.4%), comorbidity at diagnosis and lung cavity forms were more common, and the source case was identified only in 21.1% of the patients.

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Conclusion: Adult-type pulmonary TB is common among adolescents, may be associated with underlying medical conditions, and is often diagnosed late, posing a significant transmission risk to the community.

PALABRAS CLAVE
Adolescente;
Enfermedad *tipo adulto*;
Pediatría;
Contagio;
Tuberculosis

Tuberculosis en el adolescente; reto y oportunidad de evitar el contagio a la comunidad

Resumen
Introducción: La tuberculosis (TB) en el adolescente puede presentar formas radiológicas cavitadas en los lóbulos superiores, con esputos bacilíferos, en lo que se ha llamado TB pulmonar *tipo adulto*, que implica un importante riesgo de contagio en el entorno social y familiar del paciente.
Pacientes y métodos: Estudio observacional retrospectivo (2007-2012) en una serie pediátrica (< 18 años) con TB en un hospital pediátrico de referencia en Barcelona. Se compara a los pacientes $\leq$ 12 y > 12 años.
Resultados: Se incluyeron 124 pacientes (56,5% hombres, edad mediana: 4,0 años). En la mitad, la TB afectó a pacientes de origen inmigrante y se diagnosticó por sospecha clínico-radiológica. La TB intratorácica fue la forma clínica predominante (91,9%), los cultivos fueron positivos en un tercio de los casos (37,9%) y sensibles a los fármacos orales de primera línea en su totalidad. El tiempo mediano (rango intercuartil) de tratamiento fue de 6 (6-9) meses; solo 10 pacientes precisaron tratamiento directamente observado y la evolución fue satisfactoria en la mayoría (98,4%). Entre los adolescentes, la TB fue más prevalente en mujeres (63,2%) e inmigrantes (68,4%), la comorbilidad al diagnóstico y las formas pulmonares cavitadas fueron más comunes y se identificó el caso índice solo en el 21,1% de los pacientes.
Conclusión: En el adolescente, la TB pulmonar *tipo adulto* es común, y a menudo asocia comorbilidad y se diagnostica más tarde, implicando un mayor riesgo de contagio a la comunidad.

Introduction

According to data from the Red Española de Estudio de la Tuberculosis Pediátrica (Spanish Network for the Study of Paediatric Tuberculosis)[1] which comprises 73 institutions that treat paediatric patients with tuberculosis (TB) in Spain, 43% of them treat patients aged more than 14 years. This Network is still open to the incorporation of new institutions and researchers (contact infoptbred@gmail.com), and has prospectively collected data for 340 paediatric patients with TB disease from January to December 2015, of who 65 (19.1%) were older than 12 years at the time of diagnosis. Pulmonary TB in adolescents is sometimes characterised by radiological evidence of cavitation in the upper lung and smear-positive sputum in what has been termed adult-type pulmonary TB (ATpTB).[2,3] This study describes the characteristics of a large paediatric series of cases of TB disease, with particular emphasis on adolescent patients.

Methods

We conducted a retrospective observational study between January 2007 and December 2012 of a paediatric series (up to 18 years of age) of cases of TB disease in the Hospital Sant Joan de Déu (Barcelona), the tertiary referral hospital for paediatric TB infection in the Barcelona Sud Health Area (population, 1,346,050 inhabitants; 16.5% aged less than 15 years). The study was approved by the Ethics Committee of the Hospital Sant Joan de Déu.

We identified TB cases by searching the hospital diagnosis records and the registry of notifiable diseases of the Department of Public Health. We collected demographic, clinical, radiologic, microbiologic, treatment and outcome data from patient medical records. We classified TB disease based on the scheme proposed by Wiseman et al,[4] taking into account not only location (intrathoracic or extrathoracic), but also severity based on disease extent and the associated complications. In our centre, the induction phase (2 months) of anti-TB treatment comprised three drugs (isoniazid, rifampicin and pyrazinamide) until March 2009, after which ethambutol was added to the combination. Maintenance treatment consisted of two drugs (isoniazid and rifampicin) administered for 4 months in most patients (with the exception of those with meningeal or osteoarticular TB) for the entire period under study.

We stored and processed the data in a Microsoft Office Excel relational database. We summarised qualitative variables as proportions, and quantitative variables as median and interquartile range. We classified patients based on their

Table 1 Main demographic, clinical, radiologic, microbiological characteristics and treatment and outcome of TB disease in the overall case series and in the under-12 and over-12 years age groups.

	Total ($n = 124$)	Age $\leq$ 12 years ($n = 105$)	Age > 12 years ($n = 19$)	*P*
Male sex	70 (56.5)	63 (60.0)	7 (36.8)	0.006
Age at diagnosis; median (IQR), in years	4.0 (2.4–9.6)	3.5 (2.0–5.7)	14.9 (13.8–16.3)	<0.0001
Immigrant patient	39 (31.4)	26 (24.8)	13 (68.4)	<0.0001
Patient of immigrant descent born in Spain[a]	66 (53.2)	53 (50.5)	13 (68.4)	NS
Presence of BCG vaccine scar	19 (15.3)	8 (7.6)	11 (57.9)	<0.0001
Reason for diagnosis				
Clinical-radiological suspicion	73 (58.9)	55 (52.4)	18 (94.7)	0.004
Contact investigation	42 (34.7)	41 (39.0)	1 (5.3)	
Immigrant patient protocol	9 (7.2)	9 (8.6)	0 (0.0)	
Comorbidity at diagnosis	5 (4.0)	2 (1.9)	3 (15.8)	0.028
Known index case	64 (51.6)	60 (57.1)	4 (21.1)	0.004
Induration of TB skin test; median (IQR), in mm	19 (12–20)	20 (16–20)	15 (11–20)	NS
Positive tuberculin skin test	111 (89.5)	95 (90.5)	16 (84.2)	NS
Intrathoracic disease	114 (91.9)	97 (92.4)	17 (89.5)	NS
Cavitary TB	4 (3.2)	1 (0.9)	3 (15.8)	0.002
Extrathoracic disease	18 (14.5)	16 (15.2)	2 (10.5)	NS
Severe disease[b]	10 (8.0)	9 (8.6)	1 (5.3)	NS
Required corticosteroid therapy	14 (11.3)	14 (13.3)	0 (0)	NS
Required DOT	10 (8.1)	9 (8.6)	1 (5.3)	NS
Total treatment duration; median (IQR), en months	6 (6.0–9.0)	6 (6.0–6.0)	6 (6.0–9.0)	NS
Cure outcome	122 (98.4)	103 (98.1)	19 (100)	NS

BCG, bacillus Calmette-Guérin; IQR, interquartile range; DOT, directly observed therapy; MTB, *Mycobacterium tuberculosis*; NS, not significant.
Results expressed as *n* (%) unless noted otherwise.
[a] Includes immigrant patients.
[b] According to Wiseman et al.,[4] severe intrathoracic disease includes expansile alveolar opacification, cavitation, empyema or pericarditis, while all forms of extrathoracic disease are severe except tuberculous adenitis or immune-mediated responses such as erythema nodosum.

age at diagnosis: 12 years or less, and older than 12 years. In the bivariate analysis, we studied the association of qualitative variables by means of the chi square test or Fisher's exact test (SPSS version 17.0); we defined statistical significance as a *P*-value of less than 0.05.

Results

We did a retrospective study of 124 cases of TB disease (male, 56.5%; median age [interquartile range] at diagnosis, 4.0 [2.4–9.6] years), out of which 19 (male, 36.8%) corresponded to patients aged more than 12 years at the time of diagnosis. Table 1 summarises the main characteristics of both groups of patients ($\leq$12 years and >12 years).

In patients born to immigrants ($n = 66$), the predominant regions of origin were Morocco (43.1%) and Latin America (30.8%). The diagnosis was made following clinical or radiological suspicion in 58.9% of the cases; the index case was identified in 64 patients (51.6%), in 22 through the investigation of contacts of the secondary paediatric case. Five patients had significant comorbidities at the time of TB diagnosis: Down syndrome, acute lymphoblastic leukaemia under ongoing treatment, homozygous mutation of protein MyD88, cystic fibrosis and superinfection by *Pseudomonas aeruginosa* of a synthetic prosthesis in the buttock. Primary TB infection was the predominant clinical and radiological presentation ($n = 95$, 76.6%). Cultures were positive to *Mycobacterium tuberculosis* in only 37.9% of the patients, and in all cases, the isolated strain was sensitive to first-line antibiotics, but for one patient of Peruvian ancestry, who was infected by a strain with single-drug resistance to streptomycin. Fourteen patients (11.3%) also received corticosteroids, most of them on account of neurologic involvement ($n = 6$) or paradoxical reaction after initiation of anti-TB treatment ($n = 6$). Only two patients did not recover in full: one boy aged 4 years with Down syndrome and tuberculous meningitis that developed raised intracranial pressure and extensive brain lesions, who died; and a girl aged 9 years with no relevant medical history with tuberculous meningitis and residual visual field defects secondary to a hypothalamic chiasmatic tuberculoma, who remains in followup.

Compared to patients aged 12 years or less (Table 1), TB disease in adolescents was more prevalent in women (63.2%) and immigrants (68.4%), and 21.1% had comorbidities at the time of diagnosis. Furthermore, the diagnosis was made following clinical or radiological suspicion in most cases, and

cavitary pulmonary forms were most prevalent. On the other hand, the index case was identified in only 21.1% of these patients.

Discussion

The incidence of TB in Spain in 2013 was 11.9 cases per 100,000 inhabitants, 8.3% less than in 2012. The notified cases included 383 patients aged less than 14 years and 498 patients aged 15 to 24 years.[5] In the Health Area of Barcelona Sud, the mean incidence of TB in individuals aged 12 years or less and individuals aged 12–18 years in the 2010–2014 period was 8.4 and 8.6 cases per 100,000 inhabitants, respectively. However, the incidence of sputum-smear positive TB in these same age groups was 0.4 and 3.5 cases per 100,000 inhabitants.

The main characteristics of this case series were similar to those described in recent studies in low-incidence TB countries of national[6] as well as international[7] scope. In our study, paediatric TB predominantly affected previously healthy preschoolers, with an immigrant background in 50–70% of cases, and was diagnosed in the context of a contact investigation or following clinical or radiological suspicion in similar proportions. Most patients had intrathoracic forms of disease that in most cases, fortunately, responded to first-line anti-TB agents and were cured with appropriate treatment.[6] Children with TB are considered sentinel cases of community outbreaks; in our series, the diagnosis of TB in children allowed the subsequent identification of 22 (17.7%) contagious index cases.

In adolescents, TB can develop over one to three years following primary infection, or due to reactivation of childhood TB.[2,3,8] Recent studies of school outbreaks have demonstrated that primary TB infection can also manifest with upper lung involvement with consolidation, nodules and cavitation[9] in the form of disease known as ATpTB. Compared to young children, ATpTB in adolescents usually manifests with overt respiratory symptoms and detection of bacilli in sputum.[2,3] Although the number of adolescents with cavitary TB in our study was small, the differences between groups were significant; furthermore, the only patient with cavitary disease in the 12-and-under group was 10.9 years of age at the time of diagnosis. Our series demonstrates that contagious cavitary TB can occur in school-aged children and adolescents, which carries important repercussions at the public health level.

In our case series, two-third of adolescent patients had an immigrant background, which also explains the significant differences in the BCG vaccination status and the rate of identification of index cases in adolescents compared to younger children. The other key difference is that diagnosis in nearly all adolescents resulted from clinical or radiological suspicion. These two aspects are highly relevant to public health. First of all, it can be assumed that adolescents with ATpTB have already put their household and school contacts at risk of infection by the time of diagnosis, as has already been described in other studies conducted in low-incidence countries.[10] Furthermore, the social networks of adolescents tend to be broader than those of children, so the number of contacts at risk of infection is also higher.[11] Secondly, if we assume that some of these patients became infected in their countries of origin, the subsequent development of TB disease reveals flaws in the health screening system for new immigrants, as it failed to detect cases of latent TB.

Another common characteristic of TB in adolescents and adults is the higher prevalence of comorbidities at the time of diagnosis, which also carries a higher risk of TB-related morbidity and mortality.[5] In our case series we did find significant differences in prevalence between the groups, but found no association between comorbidity and disease outcome. In Spain, TB of any location is the most prevalent AIDS-defining disease in the adult population along with *Pneumocystis jirovecii* pneumonia.[12] In the absence of other risk factors, HIV antibody tests are not commonly requested in paediatric patients with TB; recently, de Pontual et al.[13] reported a 13% rate of HIV coinfection, especially in adolescents of African origin or with extrapulmonary or severe forms of TB. Although concurrent HIV infection is rare, given the enormous improvements in outcome associated with its early diagnosis, it would be advisable to test TB patients of immigrant backgrounds or with severe forms of disease for HIV.

In the absence of directly observed therapy, adolescence is one of the classic risk factors for poor adherence to anti-TB treatment.[14] In our study, we did not have access to specific data on adherence to anti-TB treatment. Nevertheless, the TB cure percentages after completion of treatment exceeded 95% in both age groups, which demonstrates that adherence was adequate in adolescents, as has been reported recently by other case series.[10,11,13,15]

There are various limitations to our retrospective study. The low number of adolescent patients included in the study may have decreased the possibility of finding an existing association. In addition, a culture of respiratory secretions was not performed in all patients, either due to its low yield or because the drug sensitivity of the index-case strain was known. Both of these circumstances are more common in patients aged 12 years or less, which may have resulted in performance bias. The tuberculin skin test, which continues to be the main tool used in the diagnosis of TB in children, was negative in 13 out of 124 patients (10.5%). During the period under study, interferon-gamma release assays and molecular diagnostic tests, which have increased the probability of obtaining a certain diagnosis of TB in the paediatric age group in recent years, were not yet available in our hospital.

In conclusion, in low-incidence countries, TB in adolescents usually presents as ATpTB, is associated with comorbidities, and is often diagnosed late, which carries a higher risk of transmission to contacts of the patient. Early diagnosis and treatment monitoring, as well as community-based interventions to prevent the transmission of adolescent TB, are the joint responsibility of the health authorities and paediatricians, who should be aware of the particular characteristics of ATpTB.

Conflict of interests

The authors have no conflict of interests to declare.

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