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The changing epidemiology of spinal tuberculosis: the influence of international immigration in Catalonia, 1993–2014

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SUMMARY

The overall incidence of spinal tuberculosis (TB) appears to be stable or declining in most European countries, but with an increasing proportion of cases in the foreign-born populations. We performed a retrospective observational study (1993–2014), including all cases of spinal TB diagnosed at a Barcelona hospital to assess the epidemiological changes. Fifty-four episodes (48·1% males, median age 52 years) of spinal TB were diagnosed. The percentage of foreign-born residents with spinal TB increased from 14% to 45·2% in the last 10 years ($P = 0{\cdot}017$). Positive *Mycobacterium tuberculosis* testing in vertebral specimens was 88·2% (15/17) for GeneXpert MTB/RIF. Compared with natives, foreign-born patients were younger ($P < 0{\cdot}01$) and required surgery more often ($P = 0{\cdot}003$) because of higher percentages of paravertebral abscess ($P = 0{\cdot}038$), cord compression ($P = 0{\cdot}05$), and persistent neurological sequelae ($P = 0{\cdot}05$). In our setting, one-third of spinal TB cases occurred in non-native residents. Compared with natives, foreign-born patients were younger and had greater severity of the disease. The GeneXpert MTB/RIF test may be of value for diagnosing spinal TB.

Key words: GeneXpert MTB/RIF, immigration, Pott disease, spinal tuberculosis, tuberculosis.

INTRODUCTION

The epidemiology and clinical pattern of tuberculosis (TB) are changing throughout the world, with the number of cases remaining stable or slowly declining every year in both developing and industrialised countries (http://www.who.int/tb/publications/global_report/en/). However, in low–medium TB incidence European countries an increasing proportion of TB cases in the foreign-born populations originating from high-burden countries has been described [1]. In addition, in Europe and the USA, the percentage of extrapulmonary TB cases has increased from 7·8% of all TB infections in the 1960s to up to 40%

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in recent studies (http://www.who.int/tb/publications/global_report/en/WTr) [2, 3].

Musculoskeletal TB accounts for 10–35% of extrapulmonary TB infections and 2·2–4·7% of TB cases overall (http://www.who.int/tb/publications/global_report/en/WTr) [2, 3]. Spinal TB (Pott's disease) is the most common form of skeletal TB (50%). Although the overall incidence of spinal TB worldwide is unknown, a significant increase has been described in some areas in relation to immigration 2 and the HIV epidemic [4]. Catalonia (Spain) is a region with a low incidence of TB [5] that has experienced a considerable increase in the percentage of foreign-born inhabitants over the last two decades (from 2·9% in 1993 to 14·5% in 2014) [6]. From 1996 to 2013, there was a steady downward trend in native and foreign-born TB cases, with an average annual decline of 6·6% over the last 6 years [5, 7]. However, in European countries, an increasing proportion of cases in the foreign-born populations has been described and the number of extrapulmonary TB cases has risen [1, 3]. This includes vertebral TB, which accounted for 2·1% of all TB cases in 2004 and 5·8% in 2013 [5, 7].

The diagnosis of extrapulmonary TB remains challenging because of the suboptimal sensitivity of conventional bacteriological methods. New strategies are being incorporated into *Mycobacterium tuberculosis* detection, and techniques involving DNA amplification by polymerase chain reaction (PCR) are being increasingly used. Published data on the role of PCR in the diagnosis of osteoarticular TB are limited, but the available results are promising and suggest that the technique may have considerable value for this purpose [8, 9].

The aim of this study was to assess the epidemiologic changes associated with spinal TB and the clinical characteristics of patients with this condition diagnosed in our centre over the last 21 years, to explore the clinical characteristics of the disease in foreign patients compared with autochthonous population. In addition, we aimed to describe our experience on the yield of PCR for the early diagnosis of spinal TB, since a higher index of suspicion and prompt diagnosis may improve the prognosis of this entity.

METHODS

Study setting and patient population

A retrospective, observational study was performed on all consecutive adult (>18 years old) patients with confirmed or probable spinal TB. Patients were identified by searching the Hospital Universitari Vall d'Hebron (Barcelona, Catalonia) Infectious Diseases Registry for consecutive spinal TB cases recorded from 1993 to 2014. Informed consent was not required because of the retrospective nature of the study. The study protocol was approved by the Vall d'Hebron Ethics Committee for Clinical Research. Because of the retrospective nature of the study, the requirement for informed consent was waived.

Disease definitions

The diagnosis of confirmed spinal TB was established on positive culture of biopsy specimens and/or positive PCR for *M. tuberculosis* or on the presence of compatible vertebral lesions together with documented microbiological isolation of TB in another location. The diagnosis of probable spinal TB was established by a consistent clinical presentation, consistent radiologic patterns and/or histopathological features, negative *Brucella* spp. serology and culture, and clinical improvement after antituberculous treatment.

We examined factors that have been associated with spinal TB in previous studies: country of birth, HIV status, diabetes mellitus, alcoholism, drug addiction, chronic renal failure, administration of corticosteroids or other immunosuppressive treatments (including monoclonal antibody therapy), solid organ neoplasm, and transplantation [10].

Mortality was considered TB-related if TB was the cause or played a major role in the patient's death and TB-unrelated if TB had no role in the patient's death.

Vertebral osteomyelitis diagnostic work up

In our centre, in patients with suspected vertebral osteomyelitis erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), WBC (white blood cell) count, *Brucella* spp serological study, Mantoux test, blood cultures and radiological contrast imaging (computed tomography (CT) scan or preferably magnetic resonance) were routinely recommended. If a microbiological diagnoses was not established, samples were collected under strict aseptic conditions by percutaneous needle aspiration cytology-biopsy under CT guidance or by open surgical biopsy. Vertebral specimens were sent for Ziehl–Neelsen staining, conventional and mycobacterial culture, histological examination, and GeneXpert MTB/RIF molecular test (from 2009).

Microbiological techniques

Fresh tissue was digested and decontaminated using the method described by Kent and Kubica [11]. All specimens underwent microscopic examination (fluorochrome [auramine-O] staining and Ziehl–Neelsen staining when fluorochrome stain was positive) and were inoculated and incubated in a BACTEC MGIT 960 system (Becton Dickinson Diagnostic Instrument System, Baltimore, MD). *M. tuberculosis* antimycobacterial susceptibility testing was performed with the BACTEC MGIT 960 SIRE Kit for first-line drugs (streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide) and with BACTEC MGIT 960 for second-line drugs (amikacin, capreomycin, ethionamide, moxifloxacin and ofloxacin). Use of the GeneXpert MTB/RIF molecular test (Cepheid, Sunnyvale, CA), which detects *M. tuberculosis* DNA and rifampicin resistance, was started in our centre in June, 2009.

Treatment and follow-up

Due to the low incidence of isoniazid resistance (<4%) and of multidrug-resistant TB in our setting, prior to the publication of WHO recommendations, some patients (mostly autochthonous) were initially treated with only three drugs at the discretion of the attending physician. According to our hospital protocol, in the current clinical practice, we routinely start with four drugs in all patients until microbiological sensitivity data are available.

All patients received daily therapy. Patients with appropriate treatment adherence were followed monthly on an outpatient basis. Patients with suspected non-adherence received directly observed therapy (DOT) at home or were hospitalised in a social sanitary centre specialized in the tuberculostatic treatment with a 24 h medical attention. All patients were treated and followed-up by a multidisciplinary team including infectious disease specialists, radiologists, surgical spine specialists, and nurses responsible for DOT when indicated.

Statistical analysis

A descriptive analysis was performed. Continuous variables are expressed as the median and interquartile range. All proportions were calculated as percentages of patients with available data. Categorical variables were analysed using the χ^2 test and continuous variables using the Mann–Whitney U test or Student's t test. Differences were considered significant at a P value of <0·05. SPSS software (Version 19·0; SPSS Inc, Chicago, IL) was used for the statistical analyses.

RESULTS

Patient demographics and baseline characteristics

Over the 21-year study period, 54 patients with spinal TB were identified (Table 1). Overall, 31·5% (17/54) of cases occurred in foreign-born patients: nine (52·9%) were from sub-Saharan Africa, three from Pakistan (17·6%), two from Morocco (11·8%), two (11·8%) from Bolivia and one (5·9%) from China. Over the last 10 years, there has been a more than threefold increase in the percentage of non-native patients among the total with spinal TB (1993–2003, 3/22, 13·6% *vs.* August 2004–2014, 14/32, 43·8%; P = 0·017). Nearly one-third of patients (33·3%) had one or more risk factors predisposing to spinal TB. The most common underlying diseases are listed in Table 1.

Clinical presentation and complications

Clinical presentation an associated complication stratified by patient origin are shown in Table 2. Median duration of symptoms before the diagnosis was 5·3 months (interquartile range (IQR) 1·7–7·9). Focusing on the neurological findings, cauda equina syndrome, nerve root pain, and paraparesis were present in seven (12·9%) patients each, tetraparesis in three (5·6%), paraplegia in one (1·8%) and isolated paralysis of the upper extremities in one (1·8%).

Forty-five (83·3%) of the 54 patients presented at least one acute local complication (Table 2). Simultaneous extra-spinal active TB was diagnosed in 15 (27·8%) patients: nine (16·6%) had pulmonary or pleural TB, three (5·6%) miliary TB, two (3·7%) genitourinary tract TB and one (1·8%) mandibular TB.

Diagnostic test findings and imaging studies

Diagnostic procedures and microbiological studies results stratified by patient origin are shown in Table 3. Overall, 46 (85·1%) patients met the diagnostic criteria of confirmed spinal TB and eight (14·8%) of probable TB. In addition, 15 (27·7%) patients had positive extra-vertebral cultures and seven (12·9%)

Table 1. *Demographic variables and baseline underlying conditions of patients with spinal tuberculosis*

	All patients, *n* = 54	Natives, *n* = 37 (68·5%)	*Foreign born*, *n* = 17 (31·5%)	*P* value
Demographic variables				
Age, y, median (IQR)	52 (27·7–72)	65 (32·5–74·5)	31 (26·5–41·5)	<0·01
Sex, male, *n* (%)	26 (48·1)	16 (43·2)	10 (58·8)	0·38
Comorbidities, *n* (%)	18 (33·3)	15 (40·5)	3 (17·6)	0·12
Alcoholism	6 (11·1)	5 (13·5)	3 (5·9)	0·65
Diabetes mellitus	5 (9·3)	5 (13·5)	0	0·16
Chronic renal failure	4 (7·4)	2 (5·2)	2 (11·8)	0·58
Liver transplant	3 (5·6)	3 (8·1)	0	0·54
HIV infection	3 (5·6)	3 (8·1)	0	0·54
Systemic steroids	2 (3·7)	2 (5·4)	0	1
Monoclonal antibody*	1 (1·9)	1 (2·7)	0	1

IQR, interquartile range; y, years.
* Infliximab.

Table 2. *Clinical presentation and acute complications in patients with spinal tuberculosis*

	All episodes (*n* = 54)	Natives (*n* = 37)	Foreign born (*n* = 17)	*P* value
Diagnostic delay, months, median (IQR)	5·3 (1·7–7·9)	4·9 (1·4–7·9)	6·1 (3–8·2)	0·96
Clinical findings at diagnosis, *n* (%)				
Back pain	47 (87)	32 (86·5)	15 (88·2)	1
Neurological symptoms	26 (48·1)	15 (40·5)	11 (64·7)	0·14
Constitutional syndrome	14 (25·9)	10 (27)	4 (23·5)	1
Fever	11 (20·4)	7 (18·9)	4 (23·5)	0·72
Spinal site affected, *n* (%)				
Cervical	2 (3·7)	2 (5·4)	0	1
Cervicothoracic	2 (3·7)	1 (2·7)	1 (5·9)	0·53
Thoracic	22 (40·7)	15 (40·5)	7 (41·2)	0·56
Thoracolumbar	6 (11·1)	4 (10·8)	2 (11·8)	1
Lumbar	17 (31·5)	13 (35·1)	4 (23·5)	0·53
Lumbosacral	1 (1·9)	0	1 (5·9)	0·31
Sacral	2 (3·7)	2 (5·4)	0	1
Multifocal	2 (3·7)	0	2 (11·8)	0·09
Extra-spinal tuberculosis, *n* (%)	15 (27·8)	9 (24·3)	6 (35·3)	0·51
Acute local complications, *n* (%)				
Paravertebral abscess	33 (61·1)	19 (51·4)	14 (82·4)	0·038
Spinal cord compression	15 (27·8)	7 (18·9)	8 (47·1)	0·05
Spinal deformity	11 (20·4)	8 (21·6)	3 (17·6)	1
Epidural abscess	5 (9·3)	3 (8·1)	2 (11·8)	0·64

IQR, interquartile range.

positive histological results that supported the TB diagnosis. GeneXpert MTB/RIF has been performed in our hospital since 2009, with a positivity rate of 88·2% (15/17) in vertebral specimens. When culture was used as the reference standard, the GeneXpert MTB/RIF test had a sensitivity of 100% and specificity of 88·9% for *M. tuberculosis* detection.

On laboratory testing, the median ESR (normal value (NV) <5 mm/h) and CRP value (NV <0·5 mg/dl) were elevated in all patients (Table 3). *M. tuberculosis* antimycobacterial susceptibility testing was available for 44 patients. In seven (15·9%), the microorganism showed primary resistance to only one agent: four (7·4%) to isoniazid, three (5·5%) to streptomycin and one (1·8%) to rifampin. There were no cases of multidrug-resistant TB.

Abnormalities related to spinal osteomyelitis were found in all 46 (100%) patients who underwent CT of the spine and all 42 (100%) who had MRI (magnetic resonance imaging). Technetium-99 m bone

Table 3. *Diagnostic procedures and microbiological studies of patients with spinal tuberculosis*

	All episodes ($n = 54$)	Natives ($n = 37$)	Foreign born ($n = 17$)	P value
Positive Ziehl–Neelsen stain*	27/43 (62·8)	19/27 (70·4)	8/16 (50)	0·20
Positive mycobacterial culture*	38/52 (73·1)	26/35 (64·3)	12/17 (70·6)	1
Positive GeneXpert MTB/RIF test*	15/17 (88·2)	5/6 (83·3)	10/11 (90·9)	1
Compatible histology*	27/43 (62·8)	15/28 (43·6)	12/15 (80)	0·11
Positive TST*	16/25 (64)	11/16 (68·8)	5/9 (55·6)	0·67
WCC count, $\times 10^9$/L, median (IQR)	7·6 (5·9–9·6)	7·4 (5·4–9·3)	8·2 (6·5–10·8)	0·13
ESR, mm/h, median (IQR)	65 (19–86)	65 (29–89)	60 (10·5–78·5)	0·37
CRP, mg/dL, median (IQR)	7·9 (3–19·5)	5 (3–11)	19·5 (3·7–47)	0·03

TST, tuberculin skin test; WCC, white cell count; IQR, interquartile range; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
* Data are number of positive results/total number studied and (%) and refer to vertebral specimens.

scanning was mainly used during the 1990s, with a positivity rate of 85·7% (18/21).

Treatment and outcome

Treatments used and outcomes are shown in Table 4. All patients were treated with an empirical combination of first-line antituberculous drugs adjusted to a definitive treatment schedule based on microbiological results with three (51·9%) or four (48·1%) drugs, with a median duration of 12·1 months (IQR 9·8–14·2). Only six out of 54 patients (88·9%) received therapy for <9 months and treatment was shortened mainly because of hepatic toxicity.

In addition to chemotherapy, surgical treatment was performed in 16 (29·6%) patients at a median of 20 days after the diagnosis (IQR 14–127) (Table 4). Eleven (68·7%) of 16 patients had one or more indications for surgery: a large paravertebral abscess or fistula (16, 100%), spinal cord compression (9, 56·2%) or spinal deformity (5, 31·2%).

Fifteen (27·8%) of the 54 patients experienced side effects associated with the antituberculous treatment: nine (16·7%) hepatotoxicity, two (3·7%) gastrointestinal intolerance, two (3·7%) drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), one (1·8%) skin rash and one (1·8%) *Clostridium difficile*-associated diarrhoea.

No significant differences were detected between patients with different empirical combination of first-line antituberculous drugs (three *vs.* four drugs) and between patients with different courses of therapy (<9 *vs.* >9 months) regarding need for surgical treatment, clinical evolution and mortality.

However, we observed a trend for lower side effects in patients with three first-line drugs regimen (45·5% *vs.* 25·8%, $P = 0·07$). Within patients initially treated with three first-line therapy, only one native patient showed isoniazid and rifampin resistance at definitive antimycobacterial susceptibility testing.

The infection cured in all but three patients (5·55%), who died from TB-related causes: two patients with miliary TB (one AIDS patient and one liver transplant recipient, both treated with three drugs first-line therapy) and one patient (with four drugs first-line therapy) with DRESS syndrome.

Comparison between foreign-born patients and natives

As compared with native Spanish patients, foreign-born patients were significantly younger (31 *vs.* 65 years, $P<0·01$), had a non-significantly lower incidence of baseline diseases (17·6% *vs.* 40·5%, $P = 0·12$), and no immunosuppressive baseline conditions (liver transplant, monoclonal antibody therapy, and systemic steroid therapy) (0% *vs.* 13·5%, $P = 0·16$) (Table 1). There were no differences in the diagnostic delay since the onset of symptoms (4·9 *vs.* 6·1 months, $P = 0·96$), but foreign-born patients required surgery more often than natives (58·8% *vs.* 16·2%, $P = 0·003$), due to a higher percentage of large paravertebral abscesses (82·4% *vs.* 51·4%, $P = 0·038$) or spinal cord compression (47·1% *vs.* 18·9%, $P = 0·05$) (Table 2). Positive findings on microbiological and histological diagnostic testing and laboratory analyses were not significantly different, except for plasma CRP, which showed higher values in foreign-born patients than in natives (19·5 *vs.* 5 mg/dl, $P = 0·031$) (Table 3). Treatment was started with four drugs more often in foreign-born patients than in natives (82·4% *vs.* 32·4%, $P = 0·01$). Antimycobacterial susceptibility testing did not confirm significantly higher

Table 4. *Treatment and outcome of patients with spinal tuberculosis*

	All episodes ($n = 54$)	Natives ($n = 37$)	Foreign born ($n = 17$)	P value
Treatment, months, median (IQR)	12·1 (9·8–14·2)	12·1 (9·1–18·3)	12·1 (11·6–12·3)	0·33
Treatment with four first-line drugs, *n* (%)	26 (48·1)	12 (32·4)	14 (82·4)	0·01
Time to spinal surgery, days, median (IQR)	20 (14–127)	30 (8·5–155)	19 (11–94)	0·98
Antimycobacterial drug resistance*	8/44 (18·2)	4/30 (13·3)	4/14 (28·6)	0·24
Surgery, *n* (%)	16 (29·6)	6 (16·2)	10 (58·8)	0·003
Long-term complications, *n* (%)	23 (42·6)	13 (35·1)	10 (58·8)	0·14
Persistent back pain	14 (25·9)	8(21·6)	6 (35·3)	0·32
Neurological deficit	10 (18·5)	4 (10·8)	6 (35·3)	0·05
Spinal deformity	6 (10·1)	5 (13·5)	1 (5·9)	0·65
Tuberculosis-related deaths, *n* (%)	3 (5·6)	2 (5·4)	1 (5·9)	1
Follow-up, months, median (IQR)	25·5 (12–63)	24·9 (11·8–84·3)	22·7 (11·9–57)	0·14

IQR, interquartile range.
* Data are expressed as number of affected patients/total number studied and (%).

resistance rates in the foreign-born patient group (28·6% *vs.* 18·3%, $P = 0·24$). Treatment adherence and duration of follow-up were similar in the two groups. Foreign-born patients did not have a significantly higher rate of persistent sequelae (58·8% *vs.* 35·1%, $P = 0·14$), although those related to permanent neurological complications approached significance (35·3% *vs.* 10·8%, $P = 0·05$) (Table 4).

DISCUSSION

This study provides a better understanding of the changing epidemiology and clinical pattern of spinal TB and adds information on use of GeneXpert MTB/RIF in spinal specimens to the growing literature on the management of extra-pulmonary TB [8, 9].

Over the last decade, the number of foreign-born residents has increased in Catalonia, and the percentage of non-native patients in our series of spinal TB cases also showed a significant increase (13·6% *vs.* 43·8%, $P = 0·017$). As compared with native patients, foreign-born patients were younger, a finding consistent with the reported bimodal age distribution of extra-pulmonary TB [2]. In recent years, the HIV epidemic has coincided with an important rise in extra-pulmonary TB in several developing countries [4]. Only three (5·6%) of the native patients in our study were infected by HIV, which is in line with the notion that HIV infection has little impact on the epidemiology of spinal TB in industrialised countries [2]. In addition, five (13·5%) native patients had systemic factors other than HIV, including induced immunosuppression (liver transplant, monoclonal antibody therapy, and systemic steroid therapy). In contrast, there were no baseline immunosuppressive conditions in foreign patients. These data are likely related to aging and the increased prevalence of immunosuppressive conditions in individuals from developed countries.

Although the percentage of patients with comorbidities was higher among the native population than among the immigrant (40·5% *vs.* 17·4%) and the diagnostic delay was similar in both (probably because in our country, migrant population has universal and free of charge access to healthcare system) the prognosis of the disease was worse among immigrant patients. Non-native patients presented higher PCR values and a higher rate of local complications, required surgery more often and led to a higher incidence of persistent sequelae, suggesting greater disease severity in this group. However, there are several possible explanations for these findings. Foreign-born patients from developing areas may have impaired immunity caused by factors such as vitamin D deficiency [12], inadequate diet, social vulnerabilities [13], or an abnormal innate immune response [14], which can favour extra-pulmonary TB reactivation and affect the clinical course of the infection. Furthermore, strains circulating in developing countries may be genetically different from each other and from those circulating in Europe. Patients of Asian origin are known to have a higher incidence of lymphatic TB infection, whereas individuals from sub-Saharan Africa (52·9% of immigrants in our study) are more likely to develop osteoarticular TB [15–17]. The results of our study are consistent with the notion that *M. tuberculosis* subpopulations may have differing virulence and pathogenicity and that

the interaction between the mycobacterium and the host immune response may contribute to differences in the anatomical site affected, the characteristics of the disease, and the inflammatory response [15–17].

Pott disease continues to be an insidious infection with a diagnostic delay ranging from weeks to months, manifesting with a variable and non-specific clinical presentation. In our cohort and in previous studies, back pain was the most common symptom, reported in 83–100% of patients [18, 19]. The presence of fever and constitutional symptoms are not remarkable but local neurologic symptoms of varying severity are common and clinicians should be familiar with the clinical features of Pott disease, as prompt initiation of therapy is needed to reduce severe complications. Persistent back or neck pain associated with abnormal laboratory findings (elevated PCR or ESR) even in the absence of fever or constitutional symptoms should alert to the need for an imaging evaluation, especially in patients with risk factors for TB.

Conventional *M. tuberculosis* detection techniques are still in widespread use for establishing the diagnosis, but extra-pulmonary TB has a paucibacillary nature and these tests lack the required sensitivity and specificity for this scenario [19]. In our series, the sensitivity of Ziehl–Neelsen stain (62·8%), histology (62·8%) and culture (73·1%) performed on vertebral specimens was consistent with the reported rates in some retrospective epidemiologic studies, with values of 15–50%, 65–95% and 50–80%, respectively [19].

Molecular tests have proven to be fast, accurate diagnostic tools for laboratory diagnosis of TB. GeneXpert MTB/RIF has been recommended as the first-line test for suspected pulmonary TB in areas with a high prevalence of HIV or drug resistance. In extra-pulmonary specimens this test has a reported sensitivity 80·4–81·3% and specificity of 86·1–99·8% [8, 9]. Although GeneXpert MTB/RIF has not been validated for the diagnosis of osteoarticular TB, we found high-positivity rates, in keeping with previous studies reporting high sensitivity (90–95·6%) and specificity (96·2–100%) in spinal specimens [8, 9]. Moreover, as Held *et al.* reported, the results of GeneXpert in vertebral samples are available within 48 h compared with a median of 35 days (IQR 15–43) for culture [9]. Although mycobacterium culture is the reference standard for the diagnosis of TB and enables establishment of a full antibiogram, GeneXpert provides several useful advantages. It can be directly applied to clinical specimens and is more accurate than Ziehl–Neelsen smear, faster than culturing, and allows rapid detection of rifampicin resistance, which has therapeutic implications when starting treatment. In our current clinical practice, antituberculous therapy is administered earlier than in the past because of GeneXpert MTB/RIF use for detection of TB spinal infection. In keeping with recent Infectious Diseases Society of America guidelines, we believe that molecular tests should be performed when extra-pulmonary TB is suspected to guide decision making, because false-positive results are unlikely. However, a negative molecular test result may not be used to exclude TB [20].

Regarding pharmacological treatment, the median duration of antituberculous chemotherapy was 12 months and there were no relapses in our series. Therapy duration of 6–9 months has been recommended but we believe longer treatment (12 months) is preferable because recurrence has been reported after short-course regimens [21–23]. The duration of therapy could be shortened in patients with no local complications or drug resistance, and after successful spinal surgery [24–26]. About one-third of our patients required surgery, mainly for neurological complications or spinal deformity/instability. Previous studies have reported variable rates of 25–98% of surgical requirements, which likely depends on the patients' characteristics and the diagnostic delay [19].

Adverse drug reactions to first-line antituberculous drugs are common and have important implications. Of the 54 patients treated with antituberculous drugs, 15 (27·8%) had at least one side effect. Although non-native patients did not have a higher incidence of adverse drug reactions, two patients from Bolivia had DRESS syndrome, a severe hypersensitivity reaction to antituberculous drugs characterized by skin rash, hepatitis, eosinophilia, and fever, and one of these patients died [27]. These data highlight the importance of surveillance for early detection and treatment of adverse drug reactions. Despite the side effects associated with pharmacological treatment, the compliance rate is very high thanks to the programmes of supervised treatment and strict clinical control of these patients.

The strengths of this study are that it covers a lengthy period (21 years), includes a prolonged follow-up, and patients have been treated by the same team of infectious disease specialists. The limitations include its retrospective, single-centre,

observational nature, the changes that have occurred over time in the diagnosis, clinical management and therapy for TB infection, and the relatively small sample size of foreign-born patients, which may have introduced a type II error in the statistical analysis. The fact that genotypic and phenotypic testing of TB strains was not performed can be considered another limitation. Lastly, the percentage of patients with local complications undergoing surgical treatment may be higher than would be expected, because our centre is a reference hospital for spine surgery in Catalonia.

In summary, spinal TB remains an insidious infection associated with a considerable diagnostic delay. During the last decade in our setting, there has been a significant increase in the number of non-native patients with spinal TB, who show a higher rate of local complications, surgery requirements, and persistent sequelae than native Spanish patients with this condition. In our clinical practice, the GeneXpert MTB/RIF test seems to have had a favourable repercussion on spinal TB detection. Based on our results, we firmly recommend to perform an imaging test to rule out spinal TB in the presence of persistent back or neck pain associated with elevated PCR or ESR, particularly in patients with risk factors for TB and to use GeneXpert MTB/RIF as a first-line test for suspected spinal TB.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at https://doi.org/10.1017/S0950268817000863

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ETHICAL STANDARDS

The study protocol was approved by the Vall d'Hebron Ethics Committee for Clinical Research.

INFORMED CONSENT

Because of the retrospective nature of the study, the requirement for informed consent was waived.

DECLARATION OF INTEREST

None.

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