Prevalence of reactivity to the tuberculin test and associated factors in the population attended at a drug addiction center in the period 2013-2016

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ABSTRACT

Objective: Epidemiological study of prevalence, carried out at Center for Drug Addiction of the center of addictions of Nou Barris (Barcelona, Spain) during 2013-2016 in order to know the prevalence of tuberculin test reactivity (TTR) and its predictive factors in drug-dependent population.

Material and methods: Epidemiological and clinical variables, associated with the consumption of drugs and the practice of the tuberculin test, were collected. The reading rate and the prevalence of TTR for annual periods, as well as the predictive factors through a bivariate and multivariate logistic regression analysis.

Results: 389 patients were studied (109 in 2013, 84 in 2014, 111 in 2015 and 85 in 2016) and they went to the reading of the TT 337 (86.6%). The prevalence of TTR was 33.2% in the readings. At the bivariate level, TTR was associated with sex, origin and prior history. In the multivariate analysis, the predictive value of age was confirmed (more reactivity in ≥40 years; p <0.001, odds ratio [OR]: 4.85, confidence interval [IC]: 2.68-8.78), being male (p = 0.003, OR: 2.81, IC: 1.43-5.53), and being an immigrant (p <0.001; OR: 7.32, IC: 3.56-15.03).

Discussion: It is concluded that the prevalence of TTR is high, especially in men, in those of more age, and in immigrants and that the drug addiction devices continue to be basic in the detection and monitoring of the latent tuberculosis infection.

Keywords: drug users; surveillance; latent tuberculosis; tuberculin; straining; emigrants and immigrants; heroin; epidemiology.

INTTRODUCTION

Tuberculosis (TB) remains a serious public health issue worldwide. Even though the epidemiological situation of TB has improved, one third of the world's population currently presents latent TB infection (LTI)[1] and the number of patients developing active TB is extremely high. In 2015 there were 10.4 million cases worldwide and 1.8 casualties due to TB: 0.4 million of which were coinfected with human immunodeficiency virus (HIV)[2]. TB is, in fact, one of the ten leading causes of mortality and it results in more deaths than HIV and malaria. Moreover, we should consider that these are evitable cases, since TB is a preventable disease, and in most cases, curable.

Out of the countries in the European Union, Spain remains a country with high LTI and TB rates. In 2014, five thousand and eighteen (2018) new cases of TB were reported in Spain and one thousand one hundred and thirty-two (1132) in Catalonia[3].

The association of TB with heroin use, especially for injecting drug users (IDUs) is well known ever since the pre-AIDS era[4]. In Spain, the number of heroin users dropped from 1990 and for the last years the prevalence has remained stable, although with a reduced injected use. Currently, it is estimated that 0.7% of the adult population has used heroin at some point[5]. Information and health education, the reduction in the number of users during the 90s, a diminished use of the parenteral route, opioid

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agonist therapies and the implementation of har-reduction programs have lead to a modified epidemiology of HIV infection and ever since the mid-90s its Transmission is mainly due to sexual relationships[6]. During this period, the rate of TB in Spain has also dropped[3] and it is possible that it has also done so among drug users, since in 2016, being IDU was the main risk factor in 2.4% of the new diagnoses of TB[7]. Yet, full information was only available in 46 cases. Thus, there is a lack of data, few studies on the issue and we really do not know if the prevalence of LTI in this group has varied thirty-five years after the appearance of HIV. On the other hand, it is also possible that other factors, such as an increased number of immigrant population with drug addiction issues and with high original endemicity for TB may be affecting the situation and leading to an increased prevalence of LTI among drug users in Spain. These data are essential to adapt public health strategies and improve TB control among drug users and hence, in the community. The objective of this study is to know the prevalence of the reactivity to the tuberculin test (TTR) among drug users who initiate Treatment and the Trend of this prevalence throughout recent years as well as predictors associated to TTR.

MATERIAL AND METHODS

Epidemiological descriptive cross-sectional prevalence study carried out in the Drug Addiction Treatment and Follow-Up Centre of Nou Barris (CAS of NB), a facility providing outpatient care to alcohol or drug users who request assistance in this area of Barcelona. The district of Nou Barris has a reference population of 165,718 inhabitants (as of 2007) which accounts for 10.27% of the population of Barcelona.

The CAS of NB, among other provisions, screens TB in all patients initiating treatment there. For that purpose, the tuberculin skin test (TST) also known as Mantoux intradermal test is performed by means of the intradermal injection of 2 U (0.1 ml) of Purified Protein Derivative (PPD RT 23) to all patients who initiate treatment and that fulfil screening criteria according to the medical service (most frequently those with prior negative TST over a year ago). Lecture of the tuberculin test, which measures positivity or negativity by means of the size of the induration and thus, the presence or not of potential infection, is performed 48 to 72 hours later.

This study included all patients requesting assistance in CAS NB from 2013 to 2016 in whom TTR had to be performed. The following were excluded: a) patients with a history of TB; b) patients with previous positive TST; and c) patients with previous negative TST in the last year, as to avoid the booster effect. The exclusion of these patients was already carried out by the medical staff in the establishment and they never underwent the TST.

TST was considered to be positive when:
– An induration of 5 or more millimetres in HIV-infected persons and/or recent contact with a person with pulmonary or laryngeal TB.
– An induration of 10 or more millimetres in non-HIV-infected patients or in the absence of recent contact with pulmonary or laryngeal TB in the absence of BCG vaccination.
– An induration of 15 or more millimetres for BCG-vaccinated patients with no other previous considerations.

The TST was considered negative for indurations under the aforementioned diameters

Positive cases were referred to Drassanes Care Centre in Barcelona, to rule out active TB by means of radiological and bacteriological studies.

The study variables were collected by means of a specifically designed information collection sheet and data from the electronic clinical record. The following variables were collected: a)age; b) age group (15 to 24, 24 5 to 34, 35 to 44, 45 to 54, 55 to 64 and 65 or more); gender (male/female); Spanish (yes/no) and country of origin otherwise; e) main drug of abuse; f) opioid agonist therapy (OAT) (yes/no); g) IDU (yes/no); h) prior imprisonment (yes/no); i) dual pathology (yes/no); j) HIV infection (yes/no); k) Hepatitis C Virus (HCV) infection (yes/no); l) year of last TST; m) result of TST in millimetres; n) assistance for TST reading (yes/no); o) positive TST (yes/no); and p) prior clinical record in CAS (yes/no).

The statistical analysis of data was performed by means of SPSS version 24.0 for Windows. For the description of continuous variables, the mean, standard deviation, minimum, median, maximum and number of valid cases were used. For the description of categorical variables, the number and percentage of patients per category have been used. For all statistical tests, the level of statistical significance (p) was 0.05. A descriptive analysis of sociodemographic and clinical variables of patients has been performed, globally and comparatively according to nationality, to determine whether there were statistically significant differences between the autochthonous population and immigrants. The reading rate of TST and the prevalence of TTR was performed by means of an "intention-to-treat (ITT) analysis" (including all patients with

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inclusion criteria regardless they actually had their TST read) and "per-protocol analysis" (only including those who had their TST read). A bivariate analysis of the results of TST and the presence of TTR with the variables included in the study was performed. To assess factors potentially associated to TST reading as well as predictors for LTI, the variables which proved significant in the bivariate analysis were included in a binary logistic regression multivariate model, and odds ratios (OR) with their corresponding 95% confidence intervals (CI) were calculated.

In order to perform this study, prior authorization from the Directorate of the Drug Prevention and Care Services of the Public Health Agency in Barcelona was sought. Moreover, patients were requested their informed consent, which could not be performed in no longer active members of the Centre, since this study was partly retrospective and partly prospective.

The study was performed in accordance with international ethical recommendations, good clinical practices guidelines, RD 711/2002 and the regulations in force in Spain (Circular 15/2002). Management, communication and transfer of personal data was done according to Organic Law 16/1999 as of December 13th, for the protection of personal data.

RESULTS

The study included all patients who sought assistance in CAS NB from 2013 to 2016 subject to TST. Patients who were excluded were: a) those with a history of TB disease; b) those with previously positive TST; and c) those who had undergone TST in the last year, as to avoid the booster effect: a strong immune response generated by a second exposure to tuberculin. The exclusion was already performed by the medical staff and these patients never underwent TST.

A total of 389 patients were included: 109 in 2013, 84 in 2014, 11 in 2015 and 85 in 2016. 299 (76.9%) were males and 90 (23.1%) were females. The men age was 40.3 ± 7.4 years. Other descriptive features are depicted in Table 1.

Immigrants presented a younger mean age (37.1 vs 41.7; p=0.002) and presented a reduced prevalence of dual pathology (13.8% vs 40.2%; p<0.001) but presented most commonly with a previous history in the CAS NB (80% vs 69.3%; p=0.05), heroin use (18.5% vs 8.4%; p=0.01), OAT (18.5% vs 9% p=0.025), TTR (59.3% vs 28%; p<0.001) and more millimetres of mean induration (10.5 vs 4.4 mm; p<0.001). There were no statistically significant differences for the rest

Table 1. Descriptive features of the study population.

Variable	n	%
Spanish		
– Yes	323	83
– No	66	17
Prior CAS history		
– Yes	277	71.2
– No	112	28.8
Heroin		
– Yes	40	10.3
– No	349	89.7
IDU		
– Yes	27	6.9
– No	361	93.1
OA treatment		
– Yes	41	10.5
– No	348	89.5
Conviction record		
– Yes	46	11.8
– No	340	87.4
– NA	3	0.8
Dual pathology		
– Yes	139	35.7
– No	250	64.3
HIV infection		
– Yes	10	2.6
– No	322	82.8
– NC	57	14.6
HCV infection		
– Yes	26	6.7
– No	305	78.4
– NA	58	14.9

Note. OA: opioid agonists; CAS: centro de atención y seguimiento de drogodependencias; NA: not available; IDU: injecting drug use; HCV: Hepatitis C virus; HIV: human immunodeficiency virus.

of variables. The graphical comparison between immigrants and Spanish patients is depicted in Figure 1.

337 patients (86.6%) came forward for their TST to be read. There were no significant differences in the trend of attendance per year (85.3% in 2013, 89.3% in 2014, 87.4% in 2015 and 83.5% in 2016; p=0.57). TST reading was not associated either to gender, a previous history in Cas, alcohol, heroin or cocaine use, criminal record, OAT, dual pathology, HIV or HCV infections.

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†in millimetres
*Statistically significant (p <0,05).
Apenitenc: conviction record; LTI: latent TB infection; OAT: opioid agonist therapy; IDU: injecting drug use.
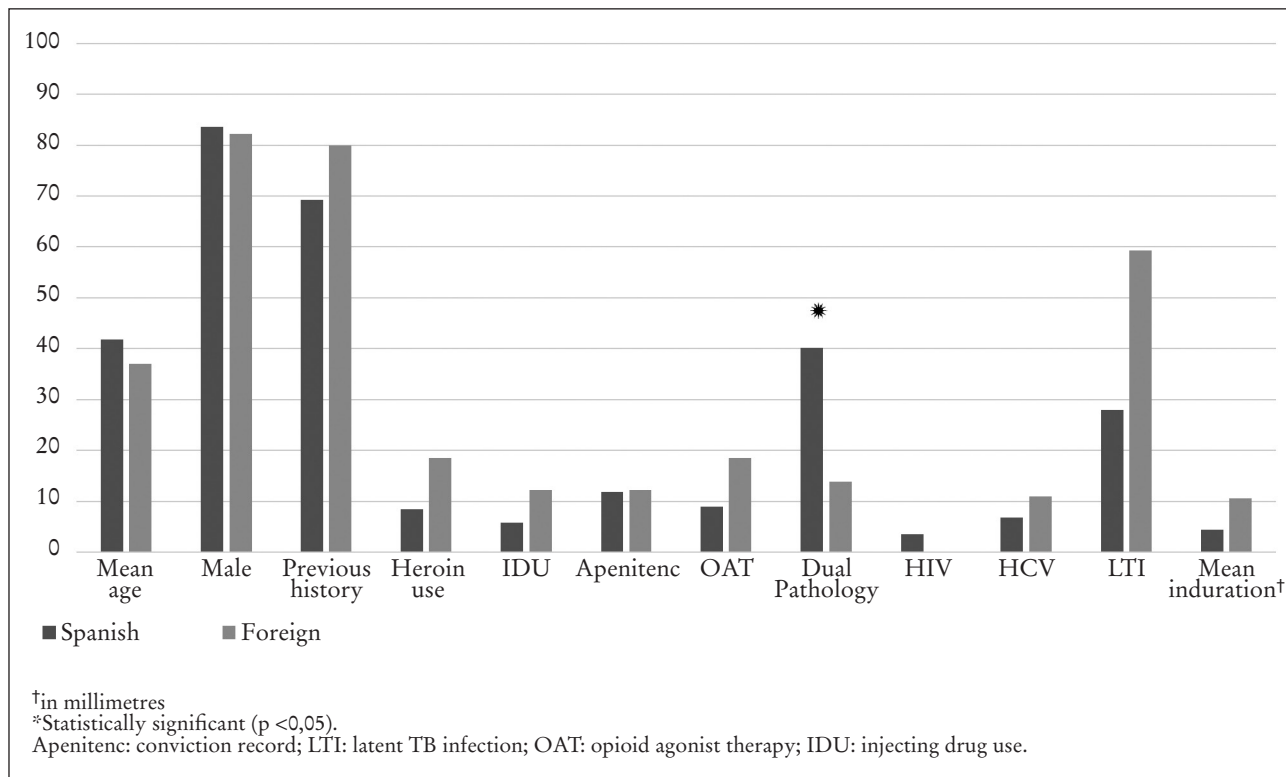
Figure 1. Distribution of variables according to patients' nationality.

By contrast, TST reading did prove to be associated to the age group (91% of attendance for patients ≥ 40 years old vs. 80.8% for younger patients; p=0.001), Spanish nationality (87% of attendance among Spanish patients vs. 83.1% among immigrants; p=0.03) and IDU (63% of attendance among IDUs vs. 88.4% for non-IDUs; p<0.001). Multivariate analysis confirmed the association between TST reading and being 40 years old or older (OR 2.91; 95% CI: 1.54-5-51; p=0.001) and not being an IDU (OR 0.9; CI: 0.08-0.47; p<0.001).

The prevalence of TTR by ITT analysis was 28.2% (112/389) and 33.2% (112/337) per protocol analysis. Induration had a minimum value of 0 mm and a maximum of 32 mm with a mean induration of 5.45 mm ± 8.27. A larger mean induration was observed among immigrants (19.5 mm vs. 4.4 mm in Spanish patients; p<0.001). The trend in the prevalence of TTR during the study years showed no significant differences (p=0.37).

Patients with TTR were older (mean age of 45.3 vs 39.8 among those with no TTR; p<0.001). To a bivariate extent, TTR also was associated to gender (36.9% among men vs. 20.3% among women; p= 0.005), nationality (59.3% among immigrants vs. 28% among Spanish patients) and with a previous history

Table 2. Variables associated to tuberculin skin test reading. Bivariate and multivariate analysis.

Bivariate analysis			Multivariate analysis	
Variable	TST reading n (%)	p	p	OR (95%CI)
Age ≥40 years		0.001	0.001	2.91 (1.54-5.51)
– Yes	190 (91.8)			
– No	147(80.8)			
Spanish		0.03	–	
– Yes	281 (87.0)			
– No	55 (83.1)			
IDU		<0.001	0.001	0.10 (0.08-0.47)
– Yes	17 (63.0)			
– No	319 (88.4)			

Note. Variables considered in the analysis: age, age group, gender, nationality, main drug of abuse, opioid agonist therapies, injecting drug use, history of conviction, dual pathology, HIV infection, HCV infection, attendance to TST reading, year of last TST and previous clinical history in CAS.
CI: confidence interval: OR: odds ratio, TST: tuberculin skin test; IDU: injecting drug use.

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Table 3. Predictors for TST reactivity. Bivariate and Multivariate analysis.

	Bivariate analysis			Multivariate analysis
Variable	Reactive TST n (%)	p	p	OR (95%CI)
Age ≥40 years		<0.001	<0.001	4.85 (2.68-8.78)
– Yes	81 (42.6)			
– No	31(21.1)			
Male		0.005	0.003	2.81 (1.43-5.53)
– Yes	97 (36.9)			
– No	15 (20.3)			
Previous history		0.033	–	–
– Yes	72 (30.0)			
– No	40 (41.2)			
Immigrant		<0.001	<0.001	7.32 (3.56-15.03)
– Yes	32 (59.3)			
– No	79 (28.0)			

Nota. Variables considered in the analysis: age, age group, gender, nationality, main drug of abuse, opioid agonist therapies, injecting drug use, history of conviction, dual pathology, HIV infection, HCV infection, attendance to TST reading, year of last TST and previous clinical history in CAS. CI: confidence interval: OR: odds ratio, TST: tuberculin skin test; IDU: injecting drug use.

in CAS (30% among those with one vs. 41.2% in those who did not; p= 0.03). However, there were no significant differences with previous imprisonment, drug abuse, IDU, OAT, dual pathology or HIV/HCV infections. Multivariate analysis confirmed the independent association of TTR with age (more prevalence for patients of 40 or more years of age; OR: 4.85, CI: 2.68-8.78; p <0.001), gender (more prevalence for men; (OR: 2.81, CI: 1.43-5.53; p = 0.,003) and nationality (more prevalence of TTR among immigrants OR: 2.81, CI: 1.43-5.53; p = 0003) while the predictive value of a previous history was ruled out (Table 3).

DISCUSSION

In Spain, it is estimated that the overall prevalence of TTR in adults in 22.3%[8] and that it goes up to 25.7% among risk groups such as hospital staff[9], although data from Alcaide et al[8] are from 2003 and probably throughout recent years the prevalence of TTR may have dropped. This study, targeted at alco-

hol and illegal drug abusers, who have traditionally been considered a "population at risk" of suffering TB, has proven a higher prevalence (28.8% in the ITT analysis and 33.2% in the PP analysis). This can be considered a high figure within the adult Spanish population, although lower than that observed (40-50%)[10-12] among some population groups, such as the imprisoned population. We have not observed a difference regarding prevalence according to the type of substance of abuse or the route of abuse, probably because the infection rate depends mostly on the incidence of the disease which is more strongly associated to socioeconomic status than to drug abuse itself. Nevertheless, we did observe that the prevalence of TTR was higher among men, older individuals and immigrants. The association of TTR with male gender has been broadly established[8,13-15] and is probably due to the fact than men present higher exposure rates than women. The association between TTR and age has also been cited by many authors[8,9,12,13,16,17] and it has even been stated than between 20 and 54, the risk of infection increases by approximately 5 to 9.4% per every increased year of age[8,13]. Last, the prevalence of TTR in our study also was significantly associated with the immigrant population. Throughout recent years, LTI has raised due to the immigration phenomenon, which has been increasingly ongoing in Spain ever since 2000[18]. This is mainly from developing countries where TB is highly endemic. The arrival of this population has entailed an increased number of TB in our country leading to epidemiological modifications and is therefore impeding TB control[19]. Hence, for example, in January 2015, 4,718,863 immigrants were registered in Spain, with a concurrent increase of TB prevalence, especially in big cities such as Barcelona and Madrid[20]. Some studies have observed[21,22], as we have, that the prevalence of TTR is higher among immigrants, especially males[23,24]. In our study, the prevalence of TTR was 59.3% for immigrants while for the autochthonous population it was 28%. This is already quite striking, but it is even more so if we consider that the immigrant population was younger (up to two thirds were under 40) while 57.3% of the autochthonous population was over 40 years old- which should hypothetically result in a lower rate of infection, which it does not.

On the other hand, it has also been stated that the duality drug-abuse and immigration is more and more common, although this statement is somewhat controversial according to some authors[25]. In this study, only 17% of the sample was immigrant, but substance abuse such as heroin and the probability of OAT were significantly more common in this group

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than in Spanish participants. It is likely that foreign heroin users are more prone to OAT programs, while non-drug users and others who believe that they do not need these treatments are more reluctant to seeking assistance. It is also possible, that overall, access of immigrant population may be impaired due to illegal stays, unawareness of healthcare circuits, cultural or language barriers or even due to the insensitivity of some healthcare professionals[26]. Anyhow, the prevalence of TTR is probably higher among immigrant drug users than among those who do not use drugs, as previously observed in other studies[27-29], although the prevalence greatly varies depending on the country of origin and for some groups, such as those from Maghreb, prevalence rates of up to 70% have been observed regardless of drug use[30]. In opposition, we should consider that immigrants showed larger indurations (10.5 vs 4.4mm; p<0.001) than the Spanish population, which can be due to the influence of vaccination, or the presence of infections by Mycobacteria other than Mycobacterium tuberculosis which may induce booster effects. It seems unlikely that all immigrants with TTR are so due to TB infection.

Something that we should also consider is attendance to TST reading: 86.6% of the patients who actually underwent the test. This is quite satisfying especially if we bear in mind that this is a drug-abuser population, who is usually less adherent and more unstable. In fact, this data differs by over 10% from those obtained by Alcaide et al.[13] in an immigrant population in Barcelona, where 24% of the sample did not attend the TST reading. In this study, immigrants also presented a poorer attendance than Spanish individuals, yet with no statistical significance in the multivariate analysis, Other groups such as younger individuals and IDUs probably need particular attention, since they also were the group with the worse attendance rate.

One of the obstacles of this study was to determine the positivity threshold of the TST in screening this population. There are different opinions regarding the ranges of TST due to its low specificity, high TB vaccination coverage and potential infection by different strains than M. tuberculosis – more prevalent in nearby or tropical countries (cross-reactions). This study has adopted the recommendations of García Pais et al.[31] gathered in Fisterra and widely accepted. A limitation of the study is that is was carried out in only one CAS in Barcelona, which always limits the extrapolation of its conclusions. Nevertheless, we do not believe that overall results would have greatly varied if carried out in other similar facilities across the city. Only the rate of immigrant population and

its country of origin, heterogeneous in each CAS, could entail modified TTR prevalence rates.

Finally, we must highlight that these results prove that although some infections such as HIV have significantly decreased among drug users, other such as TB, most commonly associated to low incomes and poor social conditions, are still extremely high. Therefore, we recommend keeping guard for its prevention and control and insist in implementing strategies aimed at reducing the morbimortality of this infection in our community.

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