Diagnosis of Latent Tuberculosis Infection: Comparison between the Tuberculin Test and Quantiferon-TB Gold Plus in Household Contacts from the City of Buenos Aires

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Abstract

The epidemiological control strategy of tuberculosis (TB) includes both the diagnosis and early treatment of baciliferous patients and the identification of individuals with latent tuberculosis infection (LTBI), who represent the pathogen reservoir within the population.
Objective: To compare the results obtained using the tuberculin test (PPD, Purified Protein Derivative) and the QuantiFERON-TB Gold Plus (QTF) in a group of household contacts of patients with bacillary pulmonary TB in the city of Buenos Aires. We used two cutoff points to consider PPD as positive: ≥ 5 mm (PPD-5) and ≥ 10 mm (PPD-10).
Materials and Methods: Blood samples for QTF were taken from household contacts of patients with bacillary TB, followed immediately by the application of PPD. The QTF was considered as the reference test from which to compare the PPD by calculating sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV) and Kappa correlation coefficient.
Results: 48 contacts were included (33 women, 69%), age 38.8 ± 19 years, 27 (56%) Argentinean, 18 (38%) Bolivians and 3 (6%) Peruvians, 37 were cases of TB. Only one contact informed She/she hadn't received the BCG; and 44 subjects showed the BCG scar. The QTF was positive in 23 individuals (47.9%) and undetermined in 2 cases (4.2%). Excluding the indeterminate cases from the analysis, there were no significant differences between positive and negative QTF contacts regarding age (33.8 ± 16 vs. 42.1 ± 20 years), nationality: Argentinean (12 of 26.46%) vs. foreigners (11 of 20.55%) and sex: women (18 of 32, 56%) vs. men (5 of 14, 36%). There were 28 (60.9%) positive cases with PPD-5 and 13 (28.3%) with PPD-10. Comparison between PPD-5 vs. PPD-10: S = 73.9 vs. 34.8%, E = 52.2 vs. 78.3%, PPV = 60.1 vs. 61.5% and NPV = 66.7 vs. 54.5%. The coincident results (positive and negative) between QTF and PPD were 29 (63%) for PPD-5 and 26 (56.5%) for PPD-10. Expressed with the Kappa coefficient, they show weak (0.261) and insignificant (0.130) concordance, respectively.
Conclusions: Considering the QTF as the reference method for its higher specificity, PPD-5, although less specific, was more sensitive than PPD-10 for the diagnosis of latent tuberculosis infection in the group of household contacts under study.

Key words: Tuberculosis, Latent tuberculosis, Tuberculin test, Interferon-γ test, Quantiferon

Introduction

The epidemiological control strategy of tuberculosis (TB) includes both the early diagnosis and treatment of baciliferous patients and the identification of individuals with latent tuberculosis infection (LTBI). The latter represent the bacillary reservoir in the population, and although most of them will remain asymptomatic, we estimate that 10% of them will develop the disease: generally within two years after the contagion, perpetuating the infectious cycle[1].

There isn't any test to effectively diagnose the presence of LTBI or distinguish which of the infected patients will develop the disease.

Historically, the Tuberculin Test (TT) is used basing on the detection of the late sensitivity immune response to antigens of tuberculous mycobacteria from a Purified Protein Derivative (PPD). This test is limited by the fact that it shows cross-reactions with non-tuberculous mycobacteria and with the BCG (Bacillus Calmette-Guérin) (in Argentina, it is applied to newborn babies).

In recent years, an alternative test began to be used: the measurement of interferon-γ released by sensitized lymphocytes (Interferon-Gamma Release Assay, IGRA) exposed to TB antigens. Among these tests, the QuantiFERON-TB Gold Plus (QTF) exposes lymphocytes to antigens ESAT-6 and CFP-10, which are specific for *Mycobacterium tuberculosis*, and the results are not influenced by the BCG and don't show cross-reactions with most atypical mycobacteria (except for *Mycobacterium kansasii, szulgai* and *microti*)[2].

Since most studies about LTBI indicate higher specificity of the QTF in comparison with the tuberculin test[3], in this work we proposed the evaluation of the sensitivity and specificity of the PPD considering the QTF as the reference test, using two PPD cutoff points (5 and 10 mm) in a group of household contacts of patients with bacillary pulmonary TB.

Materials and Methods

The study included household contacts (teenagers and adults) of patients with bacillary TB treated in our Center. We define the household contact as the person living in the same house as the patient (> 6 hours/day) for at least three months before the TB diagnosis. The inclusion of contacts was limited to a maximum of two per index case.

All of the contacts underwent a clinical evaluation and chest x-ray (CxR), and the BCG vaccine application was recorded (skin scar). Subjects with positive serologic test for HIV or another immunosuppression cause, history of TB, finding of TB in the CxR (active or residual) or with history of positive PPD or its application in the last 10 years[4] were excluded from the study.

After signing the informed consent, blood was extracted for the QTF (QuantiFERON-TB Gold Plus, QUIAGEN, Germany), and hemogram and serologic tests were conducted for HIV, followed immediately by the application of PPD by means of the tuberculin test. We used PPD LM-08 tuberculin (Malbrán Institute, Argentina), applied and read by trained personnel.

Results obtained about sensitivity (S), specificity (E) and positive and negative predictive values (PPV, NPV) were compared for the cutoff points of PPD ≥ 5mm (PPD-5) and ≥ 10mm (PPD-10) using the QTF as reference method, and the agreement between tests by kappa coefficient was assessed. Data are presented as mean ± standard deviation for numerical variables and percentages for categorical variables. χ^2 and t tests were used for comparisons between groups, considering $p < 0.05$ as a significant value.

Results

48 contacts were included (33 women, 69%): mean age 38.8 ± 19 years; distribution by nationality was 27 (56%) Argentinean, 18 (38%) Bolivians and 3 (6%) Peruvians, corresponding to 37 TB cases. Except for one patient, all the individuals had received the BCG vaccine, but 3 of them didn't have a visible scar. Results of the comparison between groups with positive and negative QTF are shown in **Table 1**. In two cases (4.2%), the result was indeterminate and so the cases were excluded from the analysis.

The QTF was positive in 23 (47.9%) cases; there weren't significant differences between positive and negative cases when considering age (33.8±16 vs. 42.1 ± 20 years), nationality: Argentinean 12 of 26 (46%) vs. foreigners 11 of 20 (55%) and sex: women (18 of 32, 56%) vs. men (5 of 14, 36%).

There were 28 (60.9%) positive cases with PPD-5 and 13 (28.3%) with PPD-10. Comparison between PPD-5 and PPD-10: S = 73.9 vs. 34.8%, E = 52.2 vs. 78.3%, PPV = 60.1 vs. 61.5% and NPV = 66.7 vs. 54.5%, respectively. The coincident results (both positive and negative) between QTF and PPD were

TABLE 1. Comparison between groups with positive and negative QTF

	Positive QTF n = 23	Negative QTF n = 23	
Age (years)	33.8 ± 16	42.1 ± 20	p NS
Sex			
Women	18 (56%)	14	p NS
Men	5 (36%)	9	
Nationality			
Argentinean	12 (46%)	14	p NS
Foreigners	11 (55%)	9	
PPD results			
PPD ≥ 5 mm	17	11	
PPD < 5 mm	6	12	
PPD ≥ 10 mm	8	5	
PPD < 10 mm	15	18	

29 (63%) for PPD-5 and 26 (56.5%) for PPD-10. Expressed with the Kappa coefficient, they show weak (0.261) and insignificant (0.130) concordance, respectively.

Discussion

Medical practice in Argentina uses the cutoff point of PPD ≥ 10mm for the diagnosis of LTBI, even though the Argentine consensus proposes the "use of ≥ 5mm in household contacts, in order to sensitize the test giving priority to the detection of individuals with weak tuberculin responses"[5]. In our work, we compare both PPD cutoff points considering the QTF as reference method, and we observe that within the group of patients under study, the PPD-5 turned out to be more sensitive than the PPD-10 for the diagnosis of LTBI (73.9 vs. 34.8%, respectively) despite a decrease in specificity.

Due to the lack of a gold standard for the diagnosis of LTBI, many studies use the IGRAs as reference tests for their very high specificity. The LTBI is evaluated by studying patients with active TB and non-exposed healthy volunteers by means of the IGRA. The obtained specificity values are 99% (CI 98-100%) for patients who did not receive the BCG and 96% (CI 94-98%) for vaccinated patients[6]. So, using the QTF as a reference method, the sensitivity values we found are close to the range expressed in similar studies (49 to 68% for PPD-5 and 25 to 50% for PPD-10)[3, 7-9] and support the use of PPD-5 as cutoff point in household contacts to reduce the probability of leaving recently infected individuals without chemoprophylaxis. In our study, when using PPD-5, the contacts identified as positive increased from 28.3 to 60.9%.

Though concordance between the QTF and the tuberculin test was low, it was better with PPD-5 than with PPD-10. The low degree of correlation may be related to the fact that the included population is mostly vaccinated, thus increasing positive results with PPD. The BCG is described as the cause of false positive results in the tuberculin test, but, from the clinical point of view, its history shall not be taken into account when interpreting the PPD during the evaluation of household contacts. On the other hand, it has been described that its effect to generate a positive PPD is lost 10 years after its application[4].

When comparing the positive and negative QTF groups, we didn't find significant differences in relation to age, sex or the fact of being a foreigner. The QTF result was indeterminate in two cases (4.2%): a value that was slightly higher than the globally expressed average (3.4%)[11].

One limitation to this work, apart from the small sample size of individuals under study, was the fact that a second PPD was not included between 8-12 weeks of the first PPD, to identify conversions in contacts with baseline PPD < 5mm and positive QTF.

A methodological point to emphasize, as regards the reading of the PPD, is that it was performed only by trained personnel (the reference area of our hospital has a TB prevalence of 116/100.000 inhabitants)[10]. As described in the WHO guides, in countries that do not use IGRA tests as extensively as in our country, the use of the tuberculin test is considered an equivalent method for the diagnosis of LTBI[12].

To conclude, we consider that the results obtained in our study support the use of 5 mm as a cutoff point of the PPD for the study of household contacts, due to the higher sensibility of this cutoff point and despite the decrease in specificity. Its concrete use will allow for a greater identification of contacts with recently acquired LTBI, whose treatment is part of the prevention of TB development and one of the pillars to reduce the prevalence of this disease.

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