

Tuberculin testing of individuals infected with the human immunodeficiency virus: relationship with peripheral T-cell counts and active tuberculosis*

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ABSTRACT

Objective: To evaluate tuberculin test results and relate them to the presence or absence of active tuberculosis, as well as to CD4⁺ and CD8⁺ T-lymphocyte counts. **Method:** The charts of 802 patients with acquired immunodeficiency syndrome treated between August of 1985 and March of 2003 were reviewed. Of the 185 patients submitted to tuberculin tests (23.1%), 107 (57.8%) were male, and 78 (42.2%) were female. Patients were divided into two study groups: tuberculin test reactors (n = 28); and tuberculin test non-reactors (n = 157). Among the reactors, the mean age was 30.60 years, with a standard deviation of 6.62 years, compared with 34.45 years, with a standard deviation of 10.32 years, among the non-reactors. **Results:** Most of the individuals tested presented only a mild response to the tuberculin test. We found that, at the time of the test, the percentage of individuals with active tuberculosis was greater in the reactor group than in the non-reactor group. During the test period, 10 reactor group patients and 11 non-reactor group patients presented some clinical form of active tuberculosis. In addition, CD4⁺ T-lymphocyte counts were lower than 200 cells/mm³ in 6 reactor group patients and in 8 non-reactor group patients. **Conclusion:** Indurations greater than 5 mm were unrelated to higher absolute CD4⁺ T-cell counts.

Keywords: Tuberculin test; Acquired immunodeficiency syndrome; Tuberculosis; CD4-positive T-lymphocytes; CD8-positive T-lymphocytes

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INTRODUCTION

According to the World Health Organization, one-third of the world population, approximately 1.7 billion people, are carriers of *Mycobacterium tuberculosis*, the infectious agent of tuberculosis. Of those, 5% to 10% will develop the disease, which is responsible for three million deaths per year.⁽¹⁾

In Brazil, it is estimated that 35 to 45 million people are infected with *M. tuberculosis*, and there are approximately 100,000 new cases every year. In a study conducted in 1996,⁽²⁾ it was shown that tuberculosis was the most prevalent opportunistic infection among patients with acquired immunodeficiency syndrome (AIDS) in Rio de Janeiro. Between 1988 and 1996 in Brazil, among all the individuals with AIDS, 7.8% were co-infected with *M. tuberculosis*, of which 5.5% occurred among patients 13 years of age or older and 2.3% among those under 13.⁽³⁾

Tuberculosis affects patients in the early stages of infection with the human immunodeficiency virus (HIV), even prior to the development of severe immunosuppression.⁽¹⁾ With the development of AIDS, there are uncommon and severe presentations of the disease, such as disseminated and lymph node forms of tuberculosis.⁽⁴⁻⁶⁾

The purified protein derivative (PPD) test, a delayed-type hypersensitivity skin test, is used as an auxiliary method in the diagnosis of tuberculosis, as well as to identify cases in which chemoprophylaxis with isoniazid is indicated.⁽⁷⁻⁸⁾ This test, if interpreted in isolation, identifies the infection but not active tuberculosis. Among immunocompetent patients, the diameter of the palpable induration distinguishes nonreactors (up to 4 mm) from weak reactors (5 to 9 mm). Induration equal to or greater than 10 mm indicates that the individual is a strong reactor. However, among HIV-positive individuals (including those with AIDS), an induration equal to or greater than 5 mm is considered a strong reaction.⁽⁷⁻⁸⁾

Individuals co-infected with HIV/*M. tuberculosis* normally respond to the PPD skin test as nonreactors, which is different from what one finds among patients with tuberculosis alone. Some authors⁽⁹⁾ who studied individuals with pulmonary tuberculosis without AIDS found that 75% were strong reactors to the PPD test. Others⁽⁵⁾ found that the majority of 339 individuals co-infected with the pulmonary,

extrapulmonary or associated forms of tuberculosis were nonreactors to the PPD, which was in accordance with various other studies.⁽¹⁰⁻¹⁴⁾ Differing from these, some authors⁽¹⁵⁾ found similar proportions of individuals who were HIV seropositive (80%) or seronegative (93%) among those presenting indurations equal to or greater than 10 mm and active tuberculosis. The weaker response to the PPD test among HIV-positive individuals is certainly due to the alterations in the cellular immune response caused by the virus, which, as some other authors⁽¹⁶⁾ have shown, can even lead to anergy. Those authors, who carried out delayed-type hypersensitivity skin tests, including the PPD test, reported anergy among 10% of HIV-positive individuals and found that these individuals had CD4⁺/mm³ T-cell counts equal to or greater than 500 cells/mm³ and that two-thirds of those had counts lower than 200 cells/mm³. In another study,⁽¹⁷⁾ strong PPD test reactivity was observed in 108 (29%) of the 374 HIV-positive patients analyzed. In yet another study,⁽¹⁸⁾ no relationship was found between diameter of the induration and CD4⁺ T-cell count.

The objective of the present study was to evaluate the skin reaction among HIV-positive individuals (including those with AIDS), to the tuberculin test and to relate that response to the number of peripheral T-cells with CD4⁺ and CD8⁺ markers, as well as to the presence or absence of clinically active tuberculosis.

METHODS

In order to select the patients, a retrospective study was conducted to evaluate the medical charts of 802 HIV-positive individuals (including those with AIDS), all of whom were treated in the Tropical Diseases Outpatient Clinic of the Botucatu School of Medicine of the Paulista State University between August of 1985 and March of 2003. The inclusion criterion was having had a PPD skin test.

The 185 patients who had had a PPD skin test were divided into two groups according to the skin reaction to the PPD test: the strong reactor group, composed of 28 patients (induration = 5 mm); and the nonreactor group, composed of 157 patients (induration < 5 mm).

The data collection was carried out during the review of the medical charts. The following variables were considered: age; gender; stage of HIV

infection; current tuberculosis status; results of the PPD test; CD4⁺ T-cells/mm³; and CD8⁺ T-cells/mm³. The PPD tests and the T-cell counts were performed during the same period.

The diagnosis of tuberculosis was established based on positive sputum smear microscopy or positive culture of any biological material, with histopathological examination compatible with or showing the presence of bacilli, as well as on epidemiological history or radiological exams suggestive of the active form of the disease and on a response to specific treatment.

The PPD skin test using PPD-RT23 in the dose equivalent to 2 tuberculin units, which is part of the routine treatment of HIV-positive patients, was carried out by various professionals, all of whom were trained by the São Paulo State Department of Health. The results were read with a millimeter ruler and always by the same professional who had applied the antigen. No patient had performed the PPD skin test within the preceding six months.

The two groups were compared using the methods described below. For binary variables (yes/no and gender), the chi-square test or Fisher's exact test was utilized. For quantitative variables, the t-test for two independent samples was used. The calculated statistics were considered significant when values of $p < 0.05$ were found, p being the probability of drawing an erroneous conclusion regarding the significance.⁽¹⁹⁾

The study design was approved by the Ethics in Research Committee of the Paulista State University Botucatu School of Medicine.

RESULTS

Of the 185 patients who had the PPD test, 28 (15.1%) were strong reactors and 157 (84.9%) were nonreactors. Among the strong reactors, the induration of the tuberculin test varied from 5 to 25 mm. There were 107 male patients (58.6%) and 78 female patients (41.4%). There was a greater proportion of males in the nonreactor group ($\chi^2 = 3.902$; $p < 0.05$) (Table 1).

With respect to age, the mean reported among the strong reactors was 30.6 ± 6.62 years, which was significantly lower than the mean age among the nonreactors, 34.45 ± 10.32 years. ($t = 2.57$; $p < 0.05$) (Table 2).

Concerning the stage of the HIV infection, 25% of the strong reactors were asymptomatic, and the

TABLE 1

Distribution of the 185 individuals infected with the human immunodeficiency virus (including those presenting acquired immunodeficiency syndrome) and submitted to the tuberculin test, by gender

Gender Group	Male Number (%)	Female Number (%)	Total Number (%)
G1	21 (75.0)	7 (25.0)	28 (100.0)
G2	86 (54.8)	71 (45.2)	157 (100.0)
Total	107 (58.6)	78 (41.4)	185 (100.0)

TABLE 2

Distribution of the 185 individuals infected with the human immunodeficiency virus (including those presenting acquired immunodeficiency syndrome) and submitted to the tuberculin test, by age

Age (years) Group	Mean	Standard deviation
G1	30,60	6,62
G2	34,45	10,32

G1: strongly positive tuberculin reactors; G2: nonreactors to the tuberculin test

G1 < G2 with respect to the mean age ($t = 2.57$; $p < 0.05$).

remainder had AIDS. Among the nonreactors, 42.6% were asymptomatic, and 57.4% had AIDS ($\chi^2 = 3.102$; $p > 0.05$).

The proportion of individuals with active tuberculosis at the time of the PPD skin test was significantly greater among the strong reactors. ($\chi^2 = 19.379$; $p < 0.01$) (Table 3).

The mean and standard deviation of the CD4⁺

TABLE 3

Distribution of the 185 individuals infected with the human immunodeficiency virus (including those presenting acquired immunodeficiency syndrome) and submitted to the tuberculin test, by current tuberculosis status

TB Current	Yes Number (%)	No Number (%)	Total Number (%)
G1	10 (35,7)	18 (64,3)	28 (100,0)
G2	11 (7,0)	146 (93,0)	157 (100,0)
Total	21 (11,4)	164 (88,6)	185 (100,0)

TB: tuberculosis; G1: strongly positive tuberculin reactors; G2: nonreactors to the tuberculin test. G1 > G2, in relation to the active form of the disease ($\chi^2 = 19.379$; $p < 0.001$).

T-cell counts were equivalent in both groups ($t = 1.16$; $p > 0.10$). The same occurred in relation to the CD8+ T-cells ($t = 0.17$; $p > 0.50$). For both CD4+ and CD8+ T-cells, the lower limit of the count was always lower among the nonreactors than among the strong reactors (Table 4).

DISCUSSION

In the present study, the groups were not homogeneous with respect to gender and age bracket. In Brazil, males have been predominant in the AIDS population since the onset of the epidemic, although the ratio of males to females has been falling over the years.⁽²⁰⁾

The predominance of the 20-39 age bracket is in accordance with the distribution of AIDS cases reported in Brazil, although an increase in the number of cases in the 40-49 age bracket has been observed.⁽²⁰⁾ The aging of the epidemic has also been observed in the USA, where, over the last decade, the number of cases among adults aged 50 or more has quintupled.⁽²¹⁾ In Brazil, it has increased from 6.2% in the 1980s to 9.4% in 2003,⁽²²⁾ a fact that might be explained by the universal access to antiretroviral treatment, which has resulted in greater life expectancy among individuals with AIDS.

The progressive depletion of CD4+ T-cells due to HIV infection leads to the loss of important immunological functions, favoring the advent of opportunistic infections and neoplastic diseases.⁽²³⁾ However, the functional decline can be observed even before a significant reduction in the number of CD4+ T-cells is detected.⁽²⁴⁻²⁵⁾

Therefore, CD4+ T-cells and the components of the cellular population resident in the lung, including alveolar macrophages and fibroblasts

infected early with HIV, impair pulmonary function, which makes the lung quite vulnerable to opportunistic infections such as tuberculosis.⁽²⁶⁾ The CD8+ T-cells also play a role in immunity against the etiologic agent of tuberculosis. Data from experimental models indicate that animals with low CD8+ T-cell counts are much more susceptible to infection with *M. tuberculosis*, specifically in the lungs.⁽²⁶⁾ These cells appear to be the source of interferon- γ , a cytokine essential in the defense against *M. tuberculosis*, and therefore might be involved in the activation of macrophages.⁽²⁶⁾

In the present study, there was no significant difference between the two groups in terms of mean CD4+ and CD8+ T-cell counts. In both groups, the mean CD4+ T-cell count was above 200 cells/mm³. Among the nonreactors, half of the patients had CD4+ T-cell counts > 200 cells/mm³. In Africa, some authors⁽²⁷⁾ have found CD4+ T-cell counts among patients with AIDS/tuberculosis comorbidity that are quite similar to those found in the present study. These authors suggested that the high frequency of tuberculosis among individuals with AIDS and those with mild immunodeficiency was related to the high prevalence of *M. tuberculosis* infection in the African population. The same occurred in Brazil, where the incidence and prevalence of the infection are rather significant.⁽²²⁾ In addition, due to its relatively high virulence, *M. tuberculosis* manifests itself during the course of the immunosuppression, earlier than do other opportunistic agents.⁽¹⁵⁾ A different situation was found in the USA, where the epidemiology is considerably different from that of Brazil and Africa. Among individuals with AIDS/tuberculosis in the USA, much lower CD4+ T-cell counts were reported.⁽⁶⁾

The relationship between the number of CD4+ T-cells/mm³ and the skin reaction to the PPD test

TABLE 4

Distribution of 171 patients individuals infected with the human immunodeficiency virus (including those presenting acquired immunodeficiency syndrome) and submitted to the tuberculin test, as well as to CD4+ and CD8+ T-cell counts, by the results of the T-cell counts

Group	CD4+ T-cell counts/mm ³		CD8+ T-cell counts/mm ³	
	Mean (Rng)	Standard deviation	Mean (Rng)	Standard deviation
G1	247,04 (39-614)	164,48	860,13(348-1741)	451,57
G2	294,78 (1-1274)	273,65	842,82 (62-2608)	510,94

G1: strongly positive tuberculin reactors; G2: nonreactors to the tuberculin test; Rng: range. In relation to the mean number of CD4+ T-cells, G1 = G2 ($t = 1.16$; $p > 0.10$); In relation to the mean number of CD8+ T-cells, G1 = G2 ($t = 0.17$; $p > 0.50$)

remains an unresolved matter. In the present study, 84.9% of the analyzed patients presented anergy to the tuberculin test, despite 16.6% of them having CD4⁺ T-cell counts = 500/mm³ and 50.3% of them having counts above 200/mm³. Even among reactors to PPD test, among which only 10.7% had CD4⁺ T-cell counts = 500/mm³, the diameter of induration varied from 5 mm to 25 mm. These data are similar to those of another study,⁽¹⁸⁾ in which no relationship was observed between the size of the PPD test induration and CD4⁺ T-cell counts. Despite the mean counts not having differed, it should be emphasized that the minimum CD4⁺ and CD8⁺ T-cell counts were lower among nonreactors than among strong reactors. Another study,⁽¹⁷⁾ which evaluated 374 HIV-positive individuals, found 108 strong reactors with CD4⁺ T-cell counts equivalent to those of nonreactors. In contrast, other authors⁽¹⁶⁾ reported anergy in only 10% of HIV-positive individuals with CD4⁺ T-cell counts = 500 cells/mm³, compared with approximately 60% in those with CD4⁺ T-cell counts = 200 cells/mm³.

In the present study, there might have been a significantly greater proportion of patients with active tuberculosis among HIV-positive strong reactors to the PPD test. However, there is no universal agreement on the value of skin reaction to the PPD test as an indicator of active tuberculosis. Some authors⁽²⁹⁾ have suggested that response not be used as a criterion for identifying cases of HIV seropositivity in which antituberculosis treatment is indicated. Others⁽¹⁷⁾ have reported active tuberculosis among 5.4% of the individuals presenting HIV seropositivity no reaction to the PPD test. Still others⁽¹⁵⁾ have reported induration = 10 mm among 80% of HIV-positive tuberculosis patients, compared with 30% of those with tuberculosis and without HIV. According to some authors,⁽¹⁾ the sensitivity to the tuberculin test among individuals presenting HIV seropositivity is inversely proportional to the degree of immunosuppression. In one study,⁽³⁰⁾ indurations = 10 mm were reported among 40% to 60% of active tuberculosis patients presenting HIV seropositivity and having been previously asymptomatic, compared with 10% to 30% of AIDS patients.

In conclusion, the results of the present study are in agreement with those of other studies showing that most HIV-positive individuals do not respond to the PPD skin test, and that the intensity

of the response is unrelated to CD4⁺ T-cell counts. Although there is no consensus on the role of PPD skin tests in the diagnosis of active tuberculosis among AIDS patients, the results of the present study show that strong reactors to the test were more often diagnosed with tuberculosis.

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