

ORIGINAL ARTICLE

High Rate of Negative Results of Tuberculin and QuantiFERON Tests Among Individuals With a History of Positive Skin Test Results

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OBJECTIVES. To evaluate individuals at high risk for tuberculosis exposure who had a history of a positive tuberculin skin test (TST) result in order to determine the prevalence of unsuspected negative TST results. To confirm these findings with the QuantiFERON-TB test (QFT), an in vitro whole-blood assay that measures tuberculin-induced secretion of interferon- γ .

METHODS. This survey was conducted from November 2001 through December 2003 at 3 sites where TST screening is regularly done. Detailed histories and reviews of medical records were performed. TSTs were placed and read by 2 experienced healthcare workers, and blood was drawn for QFT. Any subject with a negative result of an initial TST during the study (induration diameter, <10 mm) underwent a second TST and a second QFT. The TST-negative group comprised individuals for whom both TSTs had an induration diameter of <10 mm. The confirmed-negative group comprised individuals for whom both TSTs yielded no detectable induration and results of both QFTs were negative.

RESULTS. A total of 67 immunocompetent subjects with positive results of a previous TST were enrolled in the study. Of 56 subjects who completed the TST protocol, 25 (44.6%; 95% confidence interval [CI], 31.6%-57.6%) were TST negative ($P < .001$). Of 31 subjects who completed the TST protocol and the QFT protocol, 8 (25.8%; 95% CI, 10.4%-41.2%) were confirmed negative ($P < .005$).

CONCLUSIONS. A significant proportion of subjects with positive results of a previous TST were TST negative in this study, and a subset of these were confirmed negative. These individuals' TST status may have reverted or may never have been positive. It will be important in future studies to determine whether such individuals lack immunity to tuberculosis and whether they should be considered for reentry into tuberculosis screening programs.

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Current clinical practice holds that, once a person has a positive tuberculin skin test (TST) result, he remains TST positive for life, making retesting unnecessary.^{1,2} However, a number of studies have investigated the rate of reversion of TST status, with documented reversion rates ranging from 5% to 100%.³⁻¹⁴ It is not clear whether these rates reflected true reversion or whether, for some subjects, initial TSTs incorrectly indicated positivity.

The QuantiFERON-TB test (QFT) (Cellestis)—a whole-blood assay for documenting cell-mediated immunity to tuberculosis—is available for the detection of *Mycobacterium tuberculosis* infection in circumstances specified by the Centers for Disease Control and Prevention.¹⁵ This first-generation QFT measures tuberculin-induced secretion of interferon- γ by peripheral white blood cells in vitro. Although

there is support for use of the QFT,¹⁶⁻¹⁸ there is controversy about whether it should replace the TST.¹⁹⁻²¹ The TST and QFT may be identifying separate but overlapping aspects of tuberculosis immunity.

In this study, we hypothesized that there is a population of individuals with a history of a positive TST result who would subsequently have a negative result or no induration after an initial and a second (ie, 2-step) TST and would also have negative results of an initial and a second QFT.

METHODS

Human Subjects

The study was approved by the Yale University School of Medicine Human Investigation Committee; all participants

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gave written informed consent. Subjects with a previous positive TST result were enrolled from November 2001 through December 2003 at 3 sites where TSTs are performed: the VA Connecticut Healthcare System Employee Health Unit (West Haven, CT); the Central Medical Unit/APT Foundation (New Haven, CT), a clinic that manages the medical problems of substance abusers and also screens its own employees; and the Winchester Chest Clinic at Yale–New Haven Hospital (New Haven), a clinic that, among other functions, screens for latent tuberculosis infection and evaluates individuals referred from Yale–New Haven Hospital Occupational Health Services. Exclusion criteria included the presence of an immunosuppressive condition (results of recent serological tests for detection of human immunodeficiency virus were available for all at-risk subjects), receipt of immunosuppressive therapy, pregnancy, receipt of live-virus vaccination within the preceding 3 months, necrotic response to purified protein derivative, known history of tuberculosis, history of unstable TST responses (ie, a remote history of a positive TST result followed by a negative TST result), or recent (ie, within 2 years) close, unprotected contact with an individual with tuberculosis. A detailed analysis of medical records and responses on a questionnaire provided information about demographic characteristics, country of origin, significant time spent in a foreign country, employment history, bacille Calmette–Guérin vaccination status, tuberculosis exposure risks, drug or alcohol abuse, medical risk factors, and results of previous TSTs. Guidelines on acceptable treatment and completion of therapy were derived from a recent statement.²²

Interventions

TSTs were placed in accordance with standard practice described elsewhere,²³ and blood was drawn for QFT within several minutes of the TST placement. The subject was scheduled to return to the testing site in 48 hours, and the TST was read using the palpation method by 2 nonblinded experienced healthcare workers, at least one of whom was a coinvestigator. The initial reading was the average of the induration diameters recorded by the 2 readers (in only one instance was there significant disagreement). A positive TST result was defined as an induration diameter of 10 mm or larger. If the TST result was negative (induration diameter, <10 mm) but the size of the induration increased during the week after TST placement, the subject was instructed to return so that we could determine whether the induration diameter was 10 mm or larger. Subjects with negative TST results were scheduled to return within 1–3 weeks after placement of the initial test to have a second TST placed and to have blood drawn for a second QFT.

The QFT was performed according to the manufacturer's instructions. Criteria from the package insert were used to categorize a QFT result as negative if a tuberculin response was either less than 15% of the mitogen response or <1.5 IU/mL above the nil response (the mitogen response had to be >1.5 IU/mL above the nil response). Our interpretation of

the results was more stringent than the instructions specified in the package insert, because we did not consider a QFT result to be negative if there was a significant tuberculin response to both *Mycobacterium tuberculosis* and *Mycobacterium avium*.

Outcomes

Subjects with a history of a positive TST result were considered to be "TST negative" if both study TSTs were performed and the induration diameter was less than 10 mm for both. Subjects with a history of a positive TST result were considered to be "TST positive" if the induration was 10 mm or larger for the first or second (if done) TST. Subjects with a history of a positive TST result were considered to be "confirmed negative" if they underwent a 2-step TST in this study and had no detectable induration after each TST and had negative results of both QFTs.

Statistical Analysis

The study design was cross-sectional, and we used the Fisher exact test (except as noted below) to calculate whether differences in proportions were statistically significant; the Student *t* test to compare parametric data; and the Mann Whitney *U* test to compare nonparametric data. The following software programs were used: Epi Info 2000 (Centers for Disease Control and Prevention) and SPSS, version 11.5 (SPSS). The binomial distribution was used to calculate 95% confidence intervals (CIs) for proportions for the prevalence of TST negativity and confirmed negativity. A sample size of 28 subjects was needed to evaluate the possibility of a 25% versus a 0% reversion rate at a *P* value of .05 and a power of 80%.

RESULTS

Overall, 67 subjects with a history of a positive TST result were enrolled; 11 were excluded from the analysis after study entry because the TST protocol was not completed (5 subjects), because exclusion criteria were discovered after entry (5 subjects), or because of another reason (1 subject). Of the remaining 56 subjects, 31 (55.4%) were TST positive (28 had an induration of 10 mm or larger after the initial TST, and 3 had such an induration after the second TST). The remaining 25 subjects (44.6%; 95% CI, 31.6%–57.6%) were TST negative (ie, the initial and second TSTs yielded induration diameters of <10 mm). A comparison with a hypothetical TST-positive population of the same size in which no one became TST negative yielded a *P* value of .001 by the Fisher exact test. In our population of TST-negative subjects, 17 (68%) had no detectable induration after each test.

Previous induration measurements had been recorded in the medical records of 18 (84%) of the 25 TST-negative subjects. Within this group, a past induration diameter of less than 15 mm was a significant predictor of TST negativity (Table 1), but notably, TST negativity was observed for 4 (23.5%) of 17 subjects with previously documented indu-

TABLE 1. Comparison of Characteristics of Tuberculin Skin Test (TST)-Negative Subjects With Those of Subjects Whose TST Results Remained Positive

Characteristic	All subjects (<i>n</i> = 56)	TST-negative subjects (<i>n</i> = 25)	TST-positive subjects (<i>n</i> = 31)	Odds ratio for TST negativity (95% CI)	<i>P</i>
Age, mean years (range)	46.2 (29-73)	46.6 (29-66)	45.8 (29-73)76
Sex					
Female	27 (48.2)	14 (56.0)	13 (41.9)	1.0 (referent)	
Male	29 (51.8)	11 (44.0)	18 (58.1)	0.6 (0.2-1.9)	.42
Race					
White	28 (50.0)	15 (60.0)	13 (41.9)	1.0 (referent)	
Black	18 (32.1)	8 (32.0)	10 (32.3)	0.7 (0.2-2.7)	.55
Hispanic	4 (7.1)	1 (4.0)	3 (9.7)	0.3 (0.0-4.3)	.60
Asian (includes Indians)	6 (10.7)	1 (4.0)	5 (16.1)	0.2 (0.0-1.9)	.18
Study site location					
VA hospital	28 (50.0)	10 (40.0)	18 (58.1)	1.0 (referent)	
Central Medical	23 (41.1)	13 (52.0)	10 (32.3)	2.3 (0.7- 8.4)	.14
Winchester	5 (8.9)	2 (8.0)	3 (9.7)	1.2 (0.1-12.4)	>.99
History of BCG vaccination	6 (10.7)	1 (4.0)	5 (16.1)	0.2 (0.0-2.2)	.21
History of TB exposure risk	12 (21.4)	3 (12.0)	9 (29.0)	0.3 (0.1-1.6)	.19
Born outside of the U.S.	6 (10.7)	0 (0.0)	6 (19.4)	0.0 (0.0-0.96)	.03
Medical risk factor present	8 (14.3)	3 (12.0)	5 (16.1)	0.7 (0.1-4.2)	.72
Worked at a study clinic	5 (8.9)	5 (20.0)	0 (0.0)	∞ ^a	.01
History of injection drug use	18 (32.1)	9 (36.0)	9 (29.0)	1.4 (0.4-4.9)	.77
Previously treated for latent TB infection	43 (76.8)	21 (84.0)	22 (71.0)	2.2 (0.5-10.9)	.34
Past TST induration of <15 mm	21/38 ^b (55.3)	14/18 ^b (77.8)	7/20 ^b (35.0)	6.5 (1.3-36.4)	.02

NOTE. Data are no. (%) of subjects, unless otherwise indicated. See "Outcomes" in Methods for the definitions of TST negativity and TST positivity. BCG = bacille Calmette-Guérin; TB = tuberculosis.

^a Odds ratio is undefined (∞), because of a 0 in the denominator.

^b The denominator is the number of subjects for whom the size of the induration had been recorded.

ration of greater than 15 mm. We assessed the speed with which treatment had been initiated for subjects who had converted to a positive TST result, and we found that there was no difference between TST-negative subjects and TST-positive subjects in the median number of months between the last negative TST result and the beginning of treatment initiated after conversion to a positive TST result (13 months vs 15 months; *P* = .83).

Of the 56 subjects who completed the TST protocol and were not excluded from the study, 31 also completed the QFT protocol and either remained TST positive or were determined to be confirmed negative (ie, had no detectable induration on either TST, as well as negative results on initial and second QFTs). Of these 31 subjects, 8 (25.8%; 95% CI, 10.4%-41.2%) were confirmed negative. A comparison with a hypothetical TST-positive population of the same size in which no one became confirmed negative yielded a *P* value of .005 by the Fisher exact test.

Previous induration measurements had been recorded in the medical records of 7 (87.5%) of these 8 confirmed-negative subjects. There was a trend towards confirmed negativity in individuals with past induration diameters of less than 15 mm (Table 2), although notably, confirmed negativity was observed for 2 (16.7%) of 12 individuals with previously documented induration diameter of greater than 15 mm. Of note,

all 8 confirmed-negative subjects had received treatment for latent tuberculosis infection (Table 2). There was no difference between confirmed-negative subjects and TST-positive subjects in the median number of months between the last negative TST result and the beginning of treatment initiated after conversion to a positive TST result (13 months vs. 14 months; *P* = .87).

DISCUSSION

Our data demonstrated that 45% of individuals in our screening population with a positive result of a previous TST had a negative result of a 2-step TST in this study, the majority of whom had no detectable induration after either TST. Furthermore, 26% of a subset of subjects who also had QFTs performed had no detectable induration after either TST and had negative results of both QFTs. Thus, we have established that there was a population of individuals in our screening programs who are registered as having had a positive result of previous TST but had negative results for 2 different tests for tuberculosis immunity performed in our study. Although we cannot confirm the accuracy of the positive results of previous TSTs because the tests were not done under study conditions, 17 (68%) of the TST-negative subjects and 7 (87.5%) of the confirmed-negative subjects had previous TSTs

performed at the same healthcare facilities and by the same healthcare professionals involved in this study. Although there are reasons (discussed below) why the positive results of the previous TSTs might have been erroneous, it does not change the fact that the results were recorded as positive and that individuals with these results would not have been tested again if they had not participated in this study. The primary questions for TST-negative subjects and confirmed-negative subjects that must be answered are: Were their TST results ever positive? Did their TST results truly revert from positive to negative? And if the status did truly revert, does it follow that the subjects are no longer immune to tuberculosis?

This is not the first study to document reversion of TST results.³⁻¹⁴ However, it is the first study to combine this finding with negative QFT results in a very rigorous fashion (ie, our criteria for confirmed negativity required a TST finding with no detectable induration on 2-step testing and negative results of both QFTs).

TST negativity and confirmed negativity were more common in subjects with a past induration diameter of less than 15 mm,^{5,24,25} which has been reported elsewhere to be a significant predictor of false-positive TST results.^{26,27} However,

among individuals with a previous induration of greater than 15 mm (a group more likely to have true tuberculosis infection), we still found that 23.5% were TST negative and 16.7% were confirmed negative.

In individuals who undergo serial TSTs, it is possible that, after a negative result of the initial TST, a positive result in the second year of testing may have been the result of a boosted reaction. TST results for persons with a boosted reaction may be more likely to revert,²⁸ but because most of our subjects were part of a tuberculosis screening program, and all of our confirmed-negative subjects had had at least 3 previous negative TST results before conversion to positivity, it is unlikely that previous boosting played a major role in the previously positive TST results in the confirmed-negative subjects.

Reports of reversion of TST results are fairly frequent.³⁻¹⁴ One study showed that the reversion rate correlated with the speed with which treatment was initiated: the TST result for 100% of 45 individuals reverted after initiation of treatment within 3 months after the positive TST result.³ Another study of 20 recent conversions (interval between TSTs, ≤ 1 year) among healthcare workers in a hospital showed that, after

TABLE 2. Comparison of Characteristics of Confirmed-Negative Subjects Who Completed Both the Tuberculin Skin Test (TST) Protocol and the QuantiFERON-TB Test Protocol With Those of Subjects Whose TST Results Remained Positive

Characteristic	All subjects (n = 31)	Confirmed- negative subjects (n = 8)	TST-positive subjects (n = 23)	Odds ratio for confirmed negativity (95% CI)	P
Age, mean years (range)	47.3 (29-73)	48.5 (29-61)	46.9 (29-73)72
Sex					
Female	16 (51.6)	6 (75.0)	10 (43.5)	1.0 (referent)	
Male	15 (48.4)	2 (25.0)	13 (56.5)	0.3 (0.0-1.9)	.22
Race					
White	13 (41.9)	4 (50.0)	9 (39.1)	1.0 (referent)	
Black	10 (32.3)	3 (37.5)	7 (30.4)	1.0 (0.1-8.0)	>.99
Hispanic	3 (9.7)	1 (12.5)	2 (8.7)	1.1 (0.0-28.1)	>.99
Asian (includes Indians)	5 (16.1)	0 (0.0)	5 (21.7)	0.0 (0.0-4.0)	.28
Study site location					
VA hospital	15 (48.4)	3 (37.5)	12 (52.2)	1.0 (referent)	
Central Medical	11 (35.5)	3 (37.5)	8 (34.8)	1.5 (0.2-14.1)	>.99
Winchester	5 (16.1)	2 (25.0)	3 (13.0)	2.7 (0.2-36.3)	.56
History of BCG vaccination	6 (19.4)	1 (12.5)	5 (21.7)	0.5 (0.0-6.1)	>.99
History of TB exposure risk	9 (29.0)	1 (12.5)	8 (34.8)	0.3 (0.0-2.9)	.38
Born outside of U.S.	6 (19.4)	0 (0.0)	6 (26.1)	0.0 (0.0-2.4)	.30
Medical risk factor present	6 (19.4)	1 (12.5)	5 (21.7)	0.5 (0.0-6.1)	>.99
Worked at a study clinic	4 (12.9)	4 (50.0)	0 (0.0)	∞^a	.002
History of injection drug use	7 (22.6)	0 (0.0)	7 (30.4)	0.0 (0.0-1.8)	.15
Previously treated for latent TB infection	24 (77.4)	8 (100.0)	16 (69.6)	∞^a	.15
Past TST induration of <15 mm	11/23 ^b (47.8)	5/7 ^b (71.4)	6/16 ^b (37.5)	4.2 (0.5-53.6)	.19

NOTE. Data are no. (%) of subjects, unless otherwise indicated. See "Outcomes" in Methods for the definitions of confirmed negativity and TST positivity. BCG = bacille Calmette-Guérin; TB = tuberculosis.

^a Odds ratio is undefined (∞), because of a 0 in the denominator.

^b The denominator is the number of subjects for whom the size of the induration had been recorded.

treatment with isoniazid, 50% had a TST result that reverted, and an additional 25% had a marked diminution in their induration.⁴ These dramatic findings are in concert with ours.

Regardless of whether one believes that the TST-negative subjects and confirmed-negative subjects ever had positive TST results, that they are subject to a boosted reaction at a later date,²⁸ or that they remain immune to tuberculosis after treatment of infection,^{29,30} it still is necessary to make a recommendation about future testing of individuals with positive results of past tests who now have negative results of recent tests. It might be important to analyze such individuals for tuberculosis immunity with additional tests^{24,31-37} in order to make an informed decision about the need for future screening. If the number of "surprise" negative TST results in high-risk screening programs is as high as that observed in our study, the need to discover these individuals and develop a plan for them is apparent.

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Some of the results of this study have been reported previously in the form of an abstract (Friedman LN, Khaled G, Nash EN, et al. High rate of tuberculosis skin test (TST) reversion in screening programs, and its association with the Quantiferon-TB (QFN) assay. *Am J Respir Crit Care Med* 2004; 169:A259).

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