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ORIGINAL ARTICLE

Evaluation of QuantiFERON tuberculosis Gold In-Tube assay for diagnosis of active tuberculosis in children

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Aim: Tuberculin skin test (TST) is still used in diagnostic algorithms of childhood tuberculosis (TB). QuantiFERON TB Gold In-Tube assay (QFT-GIT) is an alternative test to TST based on the detection of interferon-gamma release upon *in vitro* induction of peripheral mononuclear cells by TB antigens. In this study, we aimed to determine the diagnostic value and performance of QFT-GIT for active childhood TB.

Methods: This retrospective study was conducted between January 2005 and December 2011 in three referral hospitals in Turkey with 124 children who were diagnosed with definite active TB. Sensitivity values of TST and QFT-GIT were determined by accepting the microbiological confirmation as the gold standard of diagnosis of TB.

Results: In our study, sensitivity of QFT-GIT and TST was found to be 65 and 66% respectively. However, combined usage of QFT-GIT and TST was found to be more sensitive (85%) than TST or QFT-GIT alone ($P < 0.0001$). Although negative results of QFT-GIT or TST did not exclude the diagnosis of active TB in children, their positivity supported the diagnosis. Specificity could not be measured as only microbiologically confirmed cases of *Mycobacterium tuberculosis* disease were enrolled in the study.

Conclusion: Although sensitivities of TST and QFT-GIT are too low to exclude active TB, their positivity supports diagnosis of active TB in children concomitant with signs and symptoms. QFT-GIT and TST should be used together to enhance diagnostic sensitivity and could help exclude a diagnosis of TB if the pretest probability is low.

Key words: childhood tuberculosis; diagnosis; interferon-gamma; QuantiFERON-TB Gold In-Tube assay.

What is already known on this topic

1 Making the definite diagnosis of microbiologically confirmed active tuberculosis (TB) in childhood period is challenging; immunological testes have been developed to overcome this difficulty, and most of the studies have been performed on probable TB cases.
2 Tuberculin skin test (TST) is the first immunological test that has been used mainly for the diagnosis of latent TB infections despite its low sensitivity and cross-reactivity with Bacille Calmette Guariné vaccine and non-TB mycobacteria.
3 QuantiFERON TB Gold In-Tube Assay (QFT-GIT) is one of the *in vitro* IFN-gamma-releasing assays that have been developed as an alternative screening tool for both latent TB infections and active TB; however, its performance is shown to be decreased in patients under 5 years of age who are accepted to be a risk group for TB infections.

What this paper adds

1 In our study, only confirmed paediatric TB cases were included, which caused our study to be one of the most extensive paediatric series of active TB cases in literature; performance of TST and QFT-GIT was determined in confirmed active TB patients.
2 Our results showed that QFT-GIT performance is not significantly altered by age, and it was shown that the test can be used as a screening tool in patients under 5 years of age who are believed to be a risk group for TB infections.
3 An alternative diagnostic approach using both QFT-GIT and TST simultaneously was offered to enhance diagnostic sensitivity in active childhood TB.

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Conflict of interest: T Zubarioglu, B Bayraktar, N Dalgic, M Sancar, E Cakir, A Togay, H Gencer, E Bulut and A Yalciner declare that they have no conflict of interest. The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors. All procedures followed were in accordance with the ethical standards of the local Ethical Committee of Cerrahpasa Medical faculty and with the Helsinki Declaration of 1975, as revised in 2013.

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Tuberculosis (TB) is one of the most common causes of death among children world-wide; however, childhood TB is neglected in control programmes presumably due to its insignificant role in transmission.[1,2] Definite diagnosis of childhood TB is a major challenge.[1] Culture confirmation in childhood is limited because of the paucibacillary nature of the disease and difficulties in obtaining sputum by expectoration.[1,3] Tuberculin skin test (TST), performed using a purified protein derivative, is the most preferred immunodiagnostic test for the determination of latent TB infections (LTBIs) in the world. However, difficulties in making a definite diagnosis of active TB in childhood have led to the inclusion of TST as a part of the diagnostic algorithm besides clinical symptoms and findings, TB contact history and chest radiography.[1,4]

TST is the first immunological test that has been used for the diagnosis of active TB disease despite its low sensitivity.[4,5] Cross-reactions between purified protein derivative and Bacille Calmette Guariné (BCG) vaccine and non-TB mycobacteria (NTM) are the major drawbacks of TST, which affect specificity.[4–6]

In the most recent global TB report of the World Health Organization, the estimated rate of TB incidence was reported to be 14:1000, whereas the rate for Turkey was reported to be 17:100 000.[7] Although detailed data regarding TB incidence are available, there is no multicentre study about the incidences of NTM infections in Turkey. In a limited group of single-centre studies, microbiological evaluation of the samples with suspected TB cases demonstrated that the frequency of NTM was lower than *Mycobacterium tuberculosis* (MTB), but different strains of NTM could also be reproduced.[8] In view of the high frequency of TB in Turkey and the existence of NTM strains in addition to MTB, the necessity of both specific and sensitive tests is noted for the definite diagnosis of TB.

In vitro IFN-gamma-releasing assays (IGRAs) have been developed as an alternative screening tool for both LTBI and active TB. QuantiFERON TB Gold In-Tube assay (QFT-GIT) is one of the IGRAs that were approved by the U.S. Food and Drug Administration for detection of LTBI. The method is based on measurement of *in vitro* release of interferon-gamma (IFN-γ) from peripheral mononuclear cells in whole blood upon stimulation by TB-specific antigens.[9]

Although IGRA is more specific than TST, there is still a need for investigation about its sensitivity, especially in children with special considerations, such as malnutrition and immunosuppression.[10] Its use in immunocompetent adults for LTBI and active TB has been widely studied, but the role of IGRAs in determination of active TB, especially in children, has not been clarified.[11] The objective of this study was to define sensitivity of QFT-GIT and its contribution to the diagnosis of active TB in immunocompetent children. Comparison of QFT-GIT and TST regarding active childhood TB is also one of the aims of our study.

Methods

Study population

This retrospective study was conducted between January 2005 and December 2011 in three referral hospitals in Istanbul: Sisli Etfal Training and Research Hospital, Sureyyapasa Chest Disease Hospital and Bezmialem Vakıf University Hospital. A total of 124 children diagnosed as having definite active TB were enrolled in the study. Diagnostic criteria for definitive TB disease were defined as the presence of bacteriological confirmation of disease with a positive MTB smear and/or culture of sputum or gastric aspirate, bronchial lavage and/or pleural fluid, as well as samples from organ systems other than the lung. Children with a history of recent vaccination and/or viral infection and children who had an immunosuppressive disease and those with indeterminate QTF-GIT results were excluded from the study.

Tuberculin skin test

In our study, history of a BCG vaccine was recorded by both detection of the BCG scar and family questionnaire. Positive TST criteria were defined as (i) induration ≥15 mm for children with a BCG vaccination without history of active pulmonary TB exposure and (ii) induration ≥10 mm for children with a history of adult active pulmonary TB exposure.[12]

QuantiFERON TB-Gold In-Tube assay

QFT-GIT Analysis Software, which performs a quality control assessment of assay, generates a standard curve and provides quantitative test results as IU/mL for each subject and was used to analyse raw data and calculate results. A software Tb antigen minus nil value ≥0.35 IU/mL and ≥25% of nil value was accepted as a positive result.

Statistical analysis

The data were analysed using SPSS software, version 16.0 (SPSS, Chicago, IL, USA). Comparisons of the portion positive were made between different tests and different subgroups using the χ^2 test or Fisher's exact test when appropriate. $P < 0.05$ was considered significant at 95% confidence intervals (CIs). Concordance between QFT-GIT and TST was assessed using kappa coefficients. Agreement was quantified by the kappa coefficient of agreement with K values ranging from 0.81 to 1.00 indicating very good concordance, 0.61–0.80 good concordance, 0.41–0.60 moderate concordance, 0.21–0.40 fair concordance, and < 0.20 poor concordance. The correlation between two parameters was calculated using Spearman's test.

The study protocol was approved by Ethical Committee, and informed consent was obtained from families of all individual participants included in study.

Results

Demographic and clinical characteristics of patients

A total of 124 children who were diagnosed with definite active TB were included; 68 patients were male, and 56 were female. The median age of patients was 11 years (2 months to 16.7 years). In 50% of patients, an index case could be identified. All patients had a history of BCG vaccine except the youngest patient who was 2 months of old.

In all patients, bacteriological confirmation of a positive MTB smear and/or culture was obtained. Considering the type of bacteriological confirmation, six patients had only positive smear samples, and 27 patients had only positive culture. In 91 patients,

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MTB was shown in both smear and culture samples. Microbiological confirmation was shown in the sample of gastric aspirate in 54, sputum in 24, lymph node material in 12, pleural fluid in 11, peritoneal fluid in 8, cerebrospinal fluid in 5, bronchial lavage material in 4, urine in 2, synovial fluid in 2 and both gastric aspirate and sputum in 2 patients.

Classification of patients according to involvement sites demonstrated that 60.5% of patients had pulmonary, 26.6% of patients had extrapulmonary and 12.9% of patients had both pulmonary and extrapulmonary TB. Main subtypes of pulmonary TB were primary (n = 55), secondary cavitary (n = 18) and TB pleurisy (n = 14), whereas TB lymphadenitis (n = 18) was the dominant subtype of extrapulmonary cases.

There were four patients with indeterminate results. One of these patients was 4 months old. He had miliary TB with central nervous system involvement. He had fever, remarkable leukocytosis and thrombocytopenia with increased C-reactive protein level. Increased acute phase reaction and young age were thought to be responsible for the indeterminate results. Data of all the indeterminate cases could not be obtained. These four cases were excluded from the study.

TST and QFT-GIT results

Sensitivities of TST and QFT-GIT were found to be 66.6 and 65.6%, respectively. Sensitivity reached 85% (77–90 95% CI) by using a combination of two tests simultaneously, and a statistically significant improvement was noted in sensitivity with this diagnostic strategy ($P < 0.0001$). Mean (standard deviation) values for QFT-GIT for nil, Tb antigen minus nil and mitogen minus nil were 0.315 (0.561) IU/mL, 6.416 (8.065) IU/mL and 15.842 (8.996) IU/mL, respectively. Analysis was performed according to different groups of age. No difference was detected for the mitogen-nil values in four separate age groups: (i) younger than 2 years of age; (ii) between 3 and 5 years of age; (iii) between 6 and 10 years of age; and (iv) between 11 and 15 years of age ($P = 0.165$). No difference was found between TbAg-Nil and mitogen-nil values between children who were younger and older than 5 years. QFT-GIT positivity did not show any difference between children who were younger and older than 36 months. Response to TB antigen did not differ according to the clinical presentations (i) between two subgroups: pulmonary and extrapulmonary ($P = 0.818$) and (ii) between three subgroups: pulmonary, extrapulmonary and both pulmonary and extrapulmonary ($P = 0.114$). QFT-GIT positivity according to clinical presentation did not change significantly between three subgroups (pulmonary, extrapulmonary, pulmonary+ extrapulmonary; $P = 0.207$) and between two subgroups (pulmonary, extrapulmonary; $P = 0.081$). Differences between the sensitivity of QFT-GIT and TST according to clinical presentation, gender and age are shown in Table 1. QFT-GIT and TST results among subgroups of clinical presentations are summarised in Table 2.

There was a poor concordance between the QFT-GIT test and TST according to kappa coefficient agreement (concordance 61.3%, K coefficient 0.146, $P = 0.104$) (Table 3). There was also a poor correlation between these tests (Spearman's rho = 0.146, $P = 0.106$).

Indeterminate result frequency was detected to be 0.03%. High nil values were repeatedly detected in three of the four patients.

Table 1 Differences between sensitivity of the QuantiFERON TB Gold In-Tube assay (QFT-GIT) and tuberculin skin test (TST) according to clinical presentation, gender and age among 124 children with definite tuberculosis

Patient population (n)	QFT-GIT positive %, 95% CI	TST positive %, 95% CI	P value
All patients (124)	65, 56–73	66, 58–75	0.154
Type of confirmed tuberculosis			
Pulmonary TB (75)	71, 60–81	72, 62–82	0.848
Extrapulmonary TB (33)	55, 37–72	64, 46–81	0.447
Pulmonary+ extrapulmonary TB (16)	56, 29–84	44, 16–71	0.358
Gender			
Male (68)	60, 48–72	65, 53–76	1
Female (56)	70, 57–82	68, 55–80	0.059
Age groups			
<2 years (14)	79, 54–103	50, 20–80	0.192
3–5 years (11)	55, 19–90	64, 30–98	0.242
6–10 years (29)	55, 36–74	72, 55–90	0.406
11–15 years (70)	67, 56–78	67, 56–78	1

No significant differences were observed between tests ($P > 0.05$). CI, confidence interval; TB, tuberculosis.

Table 2 QuantiFERON TB Gold In-Tube assay (QFT-GIT) and tuberculin skin test (TST) results among subgroup of pulmonary and extrapulmonary tuberculosis patients

Type of tuberculosis (n)	QFT-GIT positive, n (%)	TST positive, n (%)
Pulmonary TB		
Primary TB (55)	35 (64)	35 (64)
Secondary cavitary TB (18)	14 (78)	14 (78)
Progressive primary TB (2)	1 (50)	1 (50)
TB pleurisy (14)	11 (79)	9 (64)
Primary TB plus TB pleurisy (2)	2 (100)	2 (100)
Primary TB plus endobronchial TB (1)	0	1 (100)
Extrapulmonary TB		
Central nervous system TB (10)	8 (80)	7 (70)
Skeletal TB (3)	1 (33)	1 (33)
Urinary TB (3)	1 (33)	2 (67)
Lymphadenitis (18)	8 (44)	11 (61)
Abdominal TB (10)	5 (50)	6 (60)
Miliary TB (4)	4 (100)	1 (25)

No significant differences were observed between tests ($P > 0.05$). TB, tuberculosis.

Discussion

Until 2001, TST had been the only immunological test that was commercially available and approved for MTB infections. In the following years, IGRAs had been developed as an alternative for

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Table 3 Concordance of QuantiFERON TB Gold In-Tube assay (QFT-GIT) and tuberculin skin test (TST) for all definitive tuberculosis patients

		TST				
		Negative	Positive	Concordance, %	K coefficient	*P* value
QFT-TB-GIT	Negative	19 (15.4)	25 (20.2)	61.3	0.146	0.104
	Positive	23 (18.5)	57 (46)			

Concordance is significant at the 0.05 level. There is a poor concordance between two tests according to kappa coefficient agreement.

TST, which were based on the measurement of IFN-γ response to MTB antigens. QFT-GIT, as well as other IGRAs, has been largely studied in adults. However, knowledge about the role of QTF-GIT in the diagnosis of paediatric TB is mainly limited and based on a small series. In this study with a large sample, we aimed to describe the role of QTF-GIT in the diagnosis of active childhood TB in Turkey.

In recent studies, sensitivity of QFT-GIT has usually been evaluated in populations with probable TB cases, including a limited number of bacteriologically confirmed TB cases. Usage of variable definitions to characterise probable TB cases and inclusion of individuals who actually had both active and latent TB disease caused bias in reported sensitivities and complicated the comparison of results between different studies. However, in our study, only confirmed paediatric TB cases were included and caused our study to be one of the most extensive paediatric series of active TB cases in literature.

Studies with a small sample that evaluated the performance of QFT-GIT in definite paediatric TB cases reported sensitivities of QFT-GIT between 65 and 100%.[3,11,13–18] TST was reported to be more sensitive than QFT-GIT (82–100%) in most of the studies.[11,13,14,18] In contrast, there are different studies that suggest TST sensitivity was approximately in the range of 43.8–62.5%, lower than QFT-GIT.[3,15,19,20] In a study with 49 immunocompetent children, sensitivities of TST and QFT-GIT were reported to be 82 and 78%, respectively.[11] In our study, we found no significant difference between the sensitivity of QFT-GIT (65.6%) and TST (66.6%). However, combined usage of both QFT-GIT and TST led to a remarkable increase in sensitivity that reached up to 85% (77–90 95% CI), and this testing approach was found to be statistically significant. Bamford *et al*. reported moderate concordance between the QFT-GIT and TST, which differs from our study but, with a combined usage of both tests, led an improvement in sensitivity (91%).[11]

In Turkey, the BCG vaccine is routinely applied to all infants in the first year of life according to the National Immunization Program. In Morocco, where a similar BCG vaccination programme has been used, combined usage of QFT-GIT and TST was shown to improve the sensitivity of diagnosis in childhood active TB.[19] It has also been suggested that, in BCG-vaccinated populations[18] and NTM-infected children,[13] using both the QFT-GIT and TST could prevent unnecessary treatment through the misdiagnosis of TB due to TST false positivity in latent TB. Those studies highlighted the specificity of QTF-GIT over TST. In concordance with the data above, our results suggested that simultaneous usage of QFT-GIT and TST would be the best testing approach for diagnosis of active TB in children.

Young children are at high risk of developing active disease after exposure to an index case of pulmonary TB.[14] As a result, accurate detection of MTB infection in children under 5 years of age has a crucial role.[16] It is assumed that the performance of IGRAs in those younger than 5 years of age was poor mainly because of an immature immune system.[14,17] However, in our study, QFT-GIT showed no significant difference in terms of sensitivity in patients younger than 5 years of age. There are several reports in the literature to support our finding that the sensitivity of QFT-GIT is not affected by age, and QFT-GIT is a useful tool in the diagnosis of TB even in infants.[17,19,21] Moreover, neither mitogen nor TB antigen response was lower in this age group, which supports the finding that the immune system of children under 5 years of age is mature enough to use QFT-GIT. QFT-GIT performance also showed no difference in age-dependent analysis. Poor response to mitogen and TB antigen at younger ages were detected in studies that mainly used QFT-G.[17,18] In the QFT-GIT test, T-cell stimulation was carried out in antigen-coated tubes. Assay format and presence of third antigen (TB7.7) in QFT-GIT might be responsible for the better performance in younger ages.

Frequency of indeterminate results was 3% (n = 4) in our study and was well correlated with the literature (0.46–8%).[11,13,14,21,22] Few studies reported very high indeterminate results such as 21, 4–31%.[5,23] It has been proposed that proper specimen handling and procedural training may decrease the high percentage of indeterminate results.[23] In addition, immunosuppressive treatments have been associated with a higher number of indeterminate results in which TST was also negative.[5] In a systematic review and a meta-analysis that was performed with paediatric TB cases, no statistically significant difference was noted in indeterminate results between different age groups. However, in studies performed in Africa and in non-human immunodeficiency virus-infected immunocompromised patients, analyses with T-SPOT.TB were shown to have a lower frequency of indeterminate results compared to QuantiFERON-TB analyses.[24] In a study with 2173 subjects, 10 patients were found to have indeterminate QTF-GIT results. Indeterminate results were not shown to be affected by age and/or gender. However, six patients had elevated C reactive protein (CRP) levels, and eight patients had lymphocytosis.[25] In another retrospective study with a large sample, acute infections were emphasised to be responsible for indeterminate results due to inadequate mitogen response.[26] In our study, one patient with an indeterminate QTF-GIT result had an increased acute phase response. We assumed that, in this patient, who demonstrated the presence of high MTB antigenemia due to the active state of infection, lymphocytes might have already been stimulated

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in vivo before *in vitro* testing, or another non-specific stimulation possibly hindered the results of test. Future studies are needed to clarify these remaining points.

The first limitation of our study was that only microbiologically confirmed cases of MTB disease were enrolled. Sensitivity of a positive result from either assay was 0.85; therefore, a negative result from both assays could help exclude a diagnosis of TB if the pretest probability was low. However, specificity could not be measured due to our study design. The second limitation of the study was that patients who only had TST or only IGRA were excluded from the study. This may have led to bias in the sensitivity estimates for the two individual assays.

Conclusion

Our results showed that QFT-GIT performance is not significantly altered by age. Although sensitivities of TST and QFT-GIT are too low to exclude active TB, their positivity supports the diagnosis of active childhood TB concomitant with signs and symptoms. QFT-GIT and TST should be used together to enhance diagnostic sensitivity.

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