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Evaluation of Interferon-Gamma Release Assay Testing and Tuberculin Skin Test for Early Diagnosis of Tuberculosis in Children and Adolescents

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Abstract

Background: This study aimed to evaluate the diagnostic value of interferon-γ release assay (IGRA), a sensitive microbiological diagnostic method, in children and adolescents with suspected tuberculosis in a country with a high burden of tuberculosis. Method: This study included 581 children and adolescents aged 4 - 19 years who were suspected of having tuberculosis, were latently infected with Mycobacterium tuberculosis, and had received at least one dose of BCG vaccine between April 17, 2019, and February 24, 2021. The study evaluated the TST results of 106 patients who had a positive Quantiferon test and were suspected of having tuberculosis. Results: The study included 581 patients aged between 4 and 19 years. Of these, 106 patients tested positive for the Quantiferon test, while 19 were indeterminate and 456 were negative. The Quantiferon test positivity rate was 18.24%. Among the 106 QFT-Plus-positive cases, 23 patients also tested positive for TST. The difference in distribution was found to be statistically significant. Conclusion: The QFT-Plus test is considered an alternative to TST and other microbiological diagnostic methods for early tuberculosis diagnosis, particularly in children and adolescents.

Keywords

Interferon Gamma Release Assay, Children, Tuberculin Test, Children, Latent Tuberculosis

1. Introduction

Tuberculosis, caused by *Mycobacterium tuberculosis*, is an infectious disease that has affected people for thousands of years. It directly impacts social life and public health due to the challenges encountered in diagnosis and treatment. Despite variations in its incidence over the years, it has become necessary to develop new diagnostic and treatment strategies due to reasons such as complex immunological response, chronic progression and the need for long-term treatment, and therefore Tuberculosis (TB) has never lost its currency.

TB is commonly simplified as having only two clinical states: latent TB infection (LTBI) or active disease [1].

Latent tuberculosis infection (LTBI) is a condition characterized by a persistent immune response to *Mycobacterium tuberculosis* (MTB) antigens, without any clinical symptoms of active tuberculosis (TB) [2].

Most cases of active TB result from the reactivation of LTBI, making it theoretically preventable. To develop effective prevention strategies, it is necessary to have a detailed understanding of the epidemiology of both LTBI and active TB [3].

The diagnostic methods used aim to reduce the global TB burden by distinguishing between active and latent tuberculosis. However, there is no test that definitively establishes a diagnosis of LTBI.

The Mantoux technique is used to perform the TST, which involves the intradermal injection of 5 tuberculin units (TU) of PPD-S purified protein derivative (PPD) [4].

On the other hand, the IGRA test evaluates the cell-mediated immune response *in vitro*. The readout is based on the level of IFN-γ produced by circulating effector memory cells [5].

Several studies have shown that TST has poor sensitivity and specificity in the diagnosis of TB infection [6]. The IGRA tests have a high level of specificity when compared to TST. IGRA tests are also advantageous as they significantly eliminate false positive results in BCG vaccinated individuals, as is the case in our country, thus eliminating the cost and toxicity associated with unnecessary treatment.

Although interferon-gamma release assays (IGRAs) cannot distinguish between active tuberculosis (TB) and latent TB infection (LTBI), IGRA results are not affected by Bacillus Calmette-Guérin (BCG) vaccination and are less likely to be affected by exposure to non-tuberculous mycobacteria (NTM) [7].

Screening for LTBI is recommended only for individuals with known risk factors for progression to disease, such as recent infection, young age, and immune suppression. Clinicians may encounter discordant TST and IGRA results and may be uncertain about how to manage these patients [8].

Currently, candidate biomarkers are assessed in TST/IGRA-based categories. Such markers have the potential to prioritize patients for preventive treatment and spare uninfected people from treatments that may not benefit

them [9].

Despite a decline in TB incidence to 14.6 per 100,000 in 2017, Turkey is still one of the high-priority countries for TB control [10] [11]. According to Turkish Ministry of Health guidelines, TST is the recommended method for LTBI screening, and with IGRA being used only in exceptional circumstances such as immunosuppression and TST negativity in individuals with clinically high suspicion of TB disease [10]. However, diagnosing LTBI in both adults and children remains complex due to the lack of a gold standard. The development of interferon-gamma release assays represents a significant breakthrough in LTBI diagnosis. Evaluating IGRAs for diagnosing LTBI in children is challenging due to the differences in immune responses between children and adults. On the other hand, in countries where neonatal BCG vaccination is routine, as in our country, IGRA seems to be more advantageous than TST in the diagnosis of latent TB because it has more specific antigens [12].

This study aimed to evaluate the value of tuberculosis (TB) diagnostic methods, including the tuberculin skin test (TST) and interferon-gamma release assay (IGRA), when used alone or in combination for children and adolescents suspected of having TB.

2. Materıals and Methods

This study was conducted at the University of Health Sciences Dr. Behçet Uz Children's Hospital in İzmir, Turkey between May 2012 and October 2021. The hospital is a reference center for contagious diseases in the Aegean region. This retrospective study included 581 patients aged 4 - 19 years. Data on their demographic characteristics (age, gender, and medical history), history of TB contact, presence of BCG scar, and screening results for TB infection or disease were collected from medical records.

To determine the sample size, we searched the literature and found a study with 289 patients from Turkey and another article in which the Interferon-γ Release Test was studied in 3593 patients under 15 years of age. Considering our hospital capacity, we limited the study to 581 cases in patients between 4 and 19 years of age [13] [14].

Also included were children with any risk factor for LTBI, measles vaccination less than 1 month ago, or in any category that could affect PPD results, a history of an underlying disease, such as corticosteroid therapy, or underlying disease history.

This study focused on the diagnosis of both latent and active tuberculosis (TB) in the pediatric population in Turkey, which has a high TB burden.

Each patient underwent a standard TST and an IGRA test (Quantiferon-TB Gold Plus® test, QFT-G; Cellestis, Carnegie, Australia) to evaluate for signs of active or previous TB infection, in addition to a chest radiograph (CXR).

Microbiological confirmation was performed by culturing ARB, performing PCR, and testing for *Mycobacterium tuberculosis*. Four out of 106 patients with

a positive Quantiferon test were confirmed with one or more of the laboratory diagnostic methods, including the BacT/Alert 3D system, Kinyoun staining, and PCR.

Tuberculin Skin Test

A physician with training measured the diameter of cutaneous induration 72 hours after the test. Prior to therapy, a positive test for immunocompetent patients was considered when the transverse diameter of induration was ≥15 mm for BCG-vaccinated patients and ≥10 mm for BCG-unvaccinated patients [10].

Interferon-Gamma Release Assay

The Quantiferon-TB Gold Plus® test was conducted following the manufacturer's instructions. Blood samples were analyzed in four separate tubes: the Nil tube, TB antigen tube 1, TB antigen tube 2, and Mitogen tube, which served as a positive control. Both TB antigen tubes contained peptide antigens derived from the Mycobacterium tuberculosis complex-associated antigens, ESAT-6, and CFP-10. The tubes were incubated at 37˚C for 16 - 24 hours. The plasma was separated through centrifugation, and the concentration of interferon-gamma (IFN-ɣ) (IU/ml) was determined using enzyme-linked immunosorbent assay. A QFT-G assay was considered positive for an IFN-ɣ response to either TB antigen tube that was significantly above the Nil IFN-ɣ (IU/ml) value. Tests were interpreted as indeterminate if the Mitogen minus Nil was <0.5, or the Nil was >8.0; tests were interpreted as negative if the TB antigen minus Nil was <0.35, or if the TB antigen minus Nil was ≥0.35 but was <25% of the Nil value; tests were interpreted as positive if the TB antigen minus Nil was ≥0.35 and was ≥25% of the Nil value [8].

Statistical Analysis

Statistical analysis was performed using SPSS software version 20.0 (IBM Corp., Somers, NY). Categorical variables were analyzed using either a chi-square or Fisher exact test. The compatibility between tests was examined using the kappa coefficient.

The chi-square test was used to examine the distribution relationship between categorical variables in the data. The compatibility between tests was evaluated using the kappa coefficient. A p-value of less than 0.05 was considered statistically significant, and the data were analyzed using the IBM SPSS 22 program. The QFT test was recorded as positive or negative based on the IFN-γ concentration cut-off value of 0.35 IU/mL. The study's results were presented as percentages for categorical variables and means ± SD or medians for continuous variables. Differences between groups were assessed using the Mann Whitney test. The odds ratio was used to examine the relationship between TST and QFT-test positivity. The Kappa value was 0.2. A p-value of ≤0.05 was considered significant ($\chi^2 = 7.101$; p = 0.01 - 0.025).

Sensitivity, specificity and accuracy values were calculated. The statistical significance level (p) was accepted as <0.05.

The study protocol received approval from the local hospital ethics committee with 756 protocol and decision number 2022l18-09.

3. Results

The study population comprised of 55 boys (51.88%) and 51 girls (48.12%) with a mean age of 13.4 years (ranging from 4 to 19 years). Out of the total patient samples, 19 were indeterminate, 456 were negative, and 106 were positive for the Quantiferon test.

The positivity rate for the Quantiferon test was 18.24%. The patients who received Bacillus Calmette-Guérin (BCG) vaccination were also included in this study. Out of the 106 patients who tested positive in the study, 51.88% were male and 48.12% were female. The mean age at diagnosis was 13.4 years.

Among the 106 patients, 23 (21.69%) tested positive for PPD. Of the 106 patients who tested positive for QFT, 5 (21.7%) had TST induration ≥ 20 mm and 18 (78.2%) had TST induration of <19 mm.

Although all patients had negative PPD results, 63.5% (40/63) of them tested positive for QFT (Table 1).

Of the 106 patients, 26 were PPD positive and 60 were negative. Among the 71 patients with a positive Quantiferon test, 63.3% (45/71) were PPD negative and 36.6% (26/71) were PPD positive. All 15 patients with a negative Quantiferon test were also PPD negative. Of the 20 patients with an intermediate Quantiferon test result, 90% (18/20) were PPD negative and 10% (2/20) were PPD positive (Table 1).

This study evaluated the consistency between PPD positivity and QFT-Gold IT test positivity. The analysis revealed a consistency of 36.5% and a kappa value of 0.2 (p value: 0.01 - 0.025) for QFT-Gold IT test with tuberculin skin test positivity. It was concluded that the consistency between the two types of positivity was very weak.

According to PPD results, the sensitivity of the interferon-gamma release assay (IGRA) test was 92.85%.The specificity was 19.23% .This very low rate suggests that the PPD test is an inadequate test, especially in determining the absence of tuberculosis. We concluded that studies with more cases are needed for specificity assessment.

Sensitivity, specificity and accuracy values were calculated. The statistical significance level (p) was accepted as <0.05.

Table 1. Negativity, positivity, and intermediate distribution of cases.

Quantiferon test	PPD (+)	PPD (−)	Total
Positive	26 (36.6%)	45 (63.3%)	71
Negative	0	15 (100%)	15
Intermediate	2 (10%)	18 (90%)	20
Total	28 (26.4%)	8 (73.5%)	106

Table 2. General characteristics of the patients.

	Quantiferon positive	PPD positive
Clinical findings (Fever, Cough, Lymphadenopathy, Night sweats)	35	5
Family contact	19	9
Radiological findings (Atelectasis, Consolidation, Caviter lesions, Ground glass image)	15	5
Tbc Lymphadenitis	8	1
Active Tuberculosis	5	2
Miliary TB	1	_
Microbiological Diagnosis	4	_
An underlying disease history	52	4

Out of 106 patients with Quantiferon positive, 35 exhibited symptoms such as fever, cough, lymphadenopathy, and night sweats. Among them, 8 were diagnosed with Tbc lymphadenitis, 5 with Active Tuberculosis, 3 with Latent Tuberculosis, and only 1 with Miliary Tbc. The microbiological diagnosis was made in 4 of the Quantiferon-positive patients (Table 2).

Additionally, 19 out of 106 patients with a positive Quantiferon test had a family history of contact. All study participants underwent chest X-ray investigations, with a chest CT scan performed if necessary. (Of the 35 patients who received a CT scan, 15 were found to have radiological images showing consolidation, cavitary lesions, ground glass opacity, and atelectasis) (Table 2).

As shown in Table 2, clinical findings were observed in 5 of the PPD-positive patients, while the history of family contact was limited to 9 patients. 1 patient was followed up with a diagnosis of TB lymphadenitis and 2 patients with active Tbc. Radiologic images of 5 patients were compatible with Tbc.

Clinical evaluation revealed a history of underlying disease in 56 of the patients. These diseases include ulcerative colitis, Crohn's disease, juvenile idiopathic arthritis (polyarticular, systemic, and oligoarthritis types of JIA), asthma, allergic asthma, FMF, nephrotic syndrome, membranous nephropathy (MGN), erythema nodosum, and ankylosing spondylitis. Many diseases disrupt the regulation of the immune system, such as CAPS, Lymphangioleiomyomatosis (LAM), CD137 deficiency, ALL, hypothyroidism, epilepsy, Hodgkin's lymphoma, Gilbert's syndrome, hypogammaglobulinemia, pancreatitis, mevalonate kinase deficiency, hyper IgE syndrome (Job's syndrome), uveitis.

4. Discussion

Tuberculosis (TB) remains a significant health concern due to diagnostic challenges. The gold standard for diagnosing TB is detecting Mycobacteria in clinical specimens. However, demonstrating bacilli in pediatric TB is not always possible. Infected children are crucial in spreading TB due to the difficulty of microbiologic diagnosis and fewer positive bacteriologic tests resulting from the presence of fewer bacilli in children.

Early detection of latent TB infection in infected children is crucial as they are at risk of developing adult TB in the future. Microbiologic methods have a low chance of detecting TB bacilli in children, and PPD may have a false negative rate of 17%. Therefore, the Quantiferon TB Gold test is a useful tool for detecting latent TB infection cases and supporting the diagnosis of TB disease.

Diagnosing childhood TB is challenging due to the difficulty of children to produce sputum samples, the low growth rate of TB bacilli in culture, the limited usefulness of nucleic acid amplification tests, and the lack of an ideal biomarker for TB cases in children.

The patients who received the Bacillus Calmette-Guérin (BCG) vaccination were also included in this study. Out of the total patient samples, 19 were indeterminate, 456 were negative, and 106 were positive for the Quantiferon test. The positivity rate for the Quantiferon test was 18.24%.

According to PPD results, the sensitivity of the interferon-gamma release assay (IGRA) test was 92.85%. This rate was close to the target value recommended by the WHO (optimal requirement > 95%) for QFT-Plus tests [15].

The specificity was 19.23%. This very low rate suggests that the PPD test is an inadequate test, especially in determining the absence of tuberculosis.

Buonsenso *et al*. found that the overall sensitivity and specificity of QFT-Plus for active TB were 83.3% and 90.1%, respectively [16].

When the 106 Quantiferon-positive patients were evaluated in terms of parameters such as family contact history, clinical and radiological findings, microbiological diagnosis, underlying disease history, Tbc lymphadenitis, active tuberculosis, latent tuberculosis, or miliary Tbc, the PPD-positive group was significantly higher than the PPD-positive group. The QFT-Plus test shows better sensitivity than PPD in the evaluation of pediatric patients with suspected TB. In the light of these data, we can say that QFT-Plus can be a good alternative to TST in children.

In our study, out of 106 patients with a positive Quantiferon test, only 4 (3.7%) had a definitive microbiological diagnosis of tuberculosis. The low rate of culture positivity in our study can be attributed to the fact that our patients were in the pediatric age group, where age is one of the main factors associated with the positivity of culture results. While culture is the primary diagnostic tool for active tuberculosis, Tuberculin Skin Test (TST) and gamma interferon tests are used to diagnose latent tuberculosis infection (LTBI). When we evaluate our results, we can say that the Quantiferon test has shown a strong performance, given the difficulty of microbiological confirmation of TB in children and adolescents.

In our study, we found a significant difference in the correlation between tuberculosis contact and Quantiferon positivity compared to PPD positivity.

When evaluating the probability of progression to active tuberculosis in Quantiferon-positive cases, the Quantiferon TB Gold test was found to be significantly more effective than the PPD test in detecting tuberculosis clinically and radiologically, as well as in determining active tuberculosis, miliary TB, and TB lym-

phadenitis forms.

The addition of the Quantiferon TB Gold test to PPD can aid in the diagnosis of Tuberculosis in children and adolescents presenting with symptoms such as fever, cough, night sweats, lymphadenopathy, atelectasis, consolidation, cavitary lesions, and ground glass image findings in the lungs, as well as those diagnosed with active Tuberculosis, Miliary TB, and Tbc Lymphadenitis, and with a history of contact with adults with Tbc.

In our study, we found that the response to IFNgamma may be reduced by immunosuppressive treatment and medical conditions. This is supported by the "intermediate value" results observed in these patients.

In our study, 8 out of 19 patients (42%) who were considered to have an intermediate value had an immunosuppressive disease. In another study, 14.2% of 198 children tested for latent tuberculosis infection tested positive for QFT-Plus, while the indeterminate rate was only 2.5%. Of the 198 children tested for LTBI screening [16].

A total of 64 patients received prophylaxis and treatment. Clinical criteria, such as contact history, active tuberculosis findings, diagnosis of tuberculosis lymphadenitis, latent and miliary tuberculosis, radiologic lung findings, immunosuppression status, steroid use, and PPD were evaluated to make this decision. In our study, we included the positivity of the Quantiferon test as one of the criteria for determining the global prevalence of latent tuberculosis, potential patient pool, and initiation of prophylaxis. This is because IGRA results and TST positivity are also considered important for these purposes.

Seventeen patients diagnosed with tuberculosis were treated with combinations of INH, rifampicin (RIF), pyrazinamide (PZA), and ethambutol. Only three patients were found to have INH resistance. One limitation of our study was the lack of further follow-up of patients who received isoniazid prophylaxis and had a positive QFT-Plus or TST result, and were likely to have TB disease. However, the study's strength lies in its inclusion of data on a large group of 581 children and adolescents aged 4 - 19 years.

Based on these data, the use of the Interferon-Gamma Release Assay Test may increase the effectiveness of screening for latent tuberculosis infection in children and adolescents presenting with different complaints and findings in high-risk regions, such as our country, where TB incidence is high and BCG vaccination is mandatory. Therefore, we believe that the use of IGRA is effective in planning childhood TB treatment.

The biggest limitation of our study was the lack of control over factors that may affect the diagnosis of TB, such as HIV status and malnutrition. Although there are studies indicating that there is no concordance between TST and IGRA positivity in immunocompromised patients, IGRA may be useful for the detection of LTBI in patients with negative TST due to immunosuppression [14].

Although we consider IGRA as an alternative to TST and other microbiologic methods, we think that the lack of long-term data on the clinic of the patients who participated in the study is an issue that should be taken into consideration.

In conclusion, it is suggested that tests based on IFN-γ research demonstrate higher specificity than TST, are more associated with *M. tuberculosis* contact, and are superior in supporting clinical and radiologic findings. It is believed that IFN-γ tests will aid in the diagnosis of immunocompromised children and adolescent patients, particularly in groups prone to false negative TST results in terms of specificity and sensitivity, as observed in our study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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