Diagnostic utility of QuantiFERON test in comparison with Skin tuberculin test in children with nephrotic syndrome or candidate for renal transplantation

ABSTRACT

Background: QuantiFERON Test (QFT) has been approved as a new in vitro test to diagnose active tuberculosis infection. However, the diagnostic value of this testdepends onvarious population-based factors in each community and thus the assessment of its diagnostic performance in each population is necessary. The present study aimed to assess the diagnostic value of QFT in comparison with skin tuberculin test (TST) to detect tuberculosis infection among Iranian children with nephrotic syndrome or those who were candidate for renal transplantation.

Methods: This cross-sectional study was performed on 31 children who were candidate for renal transplantation needing immunosuppressive medication or diagnosed as a new case for nephrotic syndrome that admitted to Ali Asghar hospital in Tehran in 2013 to 2014.In all patients, both TST and QFT tests were performed according to standard methods.

Results: QFT test was negative in all patients in both groups, while positive PPD test was positive only in a patient suffered nephrotic syndrome with no significant difference (p = 0.35). None of the participant had simultaneous positive TST and QFT test, whereas both tests were both negative in 30 patients yielding a negative predictive value of 96.7% and an accuracy of 96.7% for QFT to diagnose tuberculosis when compared to TST.

Conclusion: QFT is introduced as a diagnostic tool with high negative predictive value and a high accuracy for diagnosis of tuberculosis in children with nephrotic syndrome or those who are candidate for renal transplantation. Despite high cost; it can be used as an accurate alternative for screening tuberculosis.

INTRODUCTION

Nowadays, among different microbial disorders, tuberculosis has remained as the most common life-threatening among adults affecting one-third of all people whole of the world (1). Among different episodes of the disease, 10% appear as active form (2). Only in 2003, 8.8 million cases of tuberculosis were reported by the World Health Organization. Overall, about 40 million new cases of tuberculosis occur annually in the world. Due to the long incubation period of latent tuberculosis infection, adding new infections to previous infections led to creating a major source of latent TB infection. A strategy for global TB control is to create an effective screening tool for identifying high risk patients (3). Preventive treatment can effectively reduce the risk of developing active tuberculosis by more than 90% (4).

Approximately, 95% of the incidence of tuberculosis and 98% of its-related mortality occur in developing countries, while 75% of those appear in the economically active age groups (5). One of the main reasons for global developing tuberculosis is unsuccessful control of disease or lack of appropriate control program leading lack of success in screening, prevention and reduction of improvement rate. Skin tuberculin test (TST) is a standard tool for diagnosing patients with latent tuberculosis, however its positive result cannot definitively approve tuberculosis infection and also its negativity cannot rule out the infection. Furthermore, the positivity of the test may be affected by cross reactions that reduce the specificity of the test from 99% to lower than 95% (6). In this regard, introduction of diagnostic tools with higher specificity and sensitivity had been a special concern (6) in 2005; QuantiFERON-TB Gold In-Tube Test (QFT) was approved as a new in vitro test by the United States Food and Drug Administration (FDA) that is now applied in different centers for disease control and prevention (7). It seems that QFT can be more specific than TST to diagnose active tuberculosis infection. However, the predictive value of QFT is directly dependent to the prevalence of tuberculosis in each community and thus the assessment of its diagnostic performance in each population is necessary. The present study aimed to assess the diagnostic value of QFT in comparison with TST to detect tuberculosis infection among Iranian people.

MATERIALS AND METHODS

This cross-sectional study was performed on 31 children who were candidate for renal transplantation needing immunosuppressive medication or diagnosed as a new case for nephrotic syndrome that admitted to Ali Asghar hospital in Tehran in 2013 to 2014. The exclusion criteria were lack of referring timely for interpretation of TST results, performing TST during the last 6 months, performing TST before QFT, history of PPD sensitivity, history of using immunosuppressive drug, history of active tuberculosis, malignancies, and cardiopulmonary instability. In all patients, both TST and QFT tests were performed. The TST was performed by injecting a 0.1 mL volume containing 5 TU (tuberculin units) PPD into the top layers of skin of the forearm and the skin test was read 48-72 hours after the injection. The induration more than 10 mm was considered as the positive. The QFT assay also was performed as per the manufacturer’s instructions. The assay involved two stages: the first stage involved incubation of whole blood with antigens, and the second stage involved measurement of IFN-g production in harvested plasma by ELISA. Venous blood was directly collected, prior to TST administration, into three 1-ml heparin-containing tubes. One tube contained only heparin as negative control, another also contained mitogen as positive control, and the third tube had overlapping peptides representing the entire sequences of ESAT-6 and CFP-10 and another peptide from a portion of the TB antigen TB7.7 (Rv2654). Within 2–6 h of blood draw, the tubes were incubated at 37°C. After exactly 24 h of incubation, the tubes were centrifuged and plasma was harvested and frozen at −70°C until the ELISA was performed (on average, ELISA was performed within 4– 6 weeks of blood collection). The γ-INF response was quantified using ELISA (Cellestis Ltd, Carnegie, Victoria, Australia). γ-INF values (in international units per milliliter) for TB-specific antigens and mitogen were corrected for back ground by subtracting the value obtained for the respective negative control. As recommended by the manufacturer, and based on previous studies, the cut-off value for a positive test was γ-INF≥0.35 IU/ml (8,9).The patients with positive TST or GFT were physically examined as well as assessed by imaging to rule out active tuberculosis. Those with positive TST, nut without evidences of active tuberculosis were treated with isoniazid (300 mg) plus vitamin B6 for 9 months and then were followed by the completion of study.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t test or Mann- Whitney U test. Negative predictive value was calculated using the crosstabulation method and by comparing the number of true negatives to the total number of true and false negatives.  The accuracy was also calculated by dividing number of correct true positive and negatives by the number of all results. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

Of total 31 children assessed, 17 (54.8%) were diagnosed as the new cases of nephrotic syndrome, while 14 (45.2%) were candidate for renal transplantation needing immunosuppressive medication. The mean age of participants was 6.86 ± 4.0 years ranged 9 month to 15 years (5.29 ± 3.69 years in nephrotic syndrome group and 8.78 ± 3.59 years in renal transplantation group, p = 0.013). Totally, 58.8% in nephrotic syndrome group and 78.6% in another group were male (p = 0.244). The mean duration of nephrotic syndrome was 1.3 weeks± 1weeks and the mean duration of ESRD in renal transplantation group was also 6.35 ± 2.83 years with a mean time of 1.72 ± 1.25 years for dialysis. Regarding underlying disorders in those who were candidate for renal transplantation, 14.3% had Congenital neophrotic syndrome, 7.1% had Cystinuria, 21.4% had FSGS, 7.1% suffered Nephrosis, 21.4% suffered Norogenic Bladder, 14.3% had Norogenic Bladder plus Reflux Nephropathy, and 7.1% had Systinosis. All patients received BCG vaccine at birthday that 93.5% had the scar of this incubation. None of the patients had previous exposure to tuberculosis. All patients in renal transplantation group and 88.2% of those in nephrotic syndrome group were treated with routine medication. Chest X-Ray was positive in 5.9% of those with nephrotic syndrome.

QFT test was negative in all patients in both groups, while positive PPD test was positive only in a patient suffered nephrotic syndrome with no significant difference (p = 0.35). None of the participant had simultaneous positive TST and QFT test, whereas both tests were both negative in 30 patients yielding a negative predictive value of 96.7% and an accuracy of 96.7% for QFT to diagnose tuberculosis when compared to TST.

DISCUSSION

Based on the present results, a closed association was revealed between TST and QFT tools with respect to diagnose tuberculosis. In fact, compared to TST considered as the conventional diagnostic method, QFT was shown to be predictive for diagnosis of tuberculosis with a high negative predictive value and a high accuracy. Reviewing the literature (10-19) similarly showed a negative predictive value ranged 86% to 95% that was near to our results. Although we could not assess the sensitivity or specificity of QFT compared to TST for diagnosing tuberculosis due to the nature of our study, the previous studies could show a range of 60% to 93% for sensitivity and 91% to 100% for specificity of QFT. In fact, it seems that the results obtained by QFT is similar to those obtained by TST, however because of higher cost-benefit of the latter method, TST is more preferred to apply in clinical settings.In a study by Vinton et al (20) and contrary to our results, there were fewer positive QFT test results than positive TST results (6.7% versus 33.0%), while agreement between the tests was poor. As previously pointed, the results of QFT test can be influenced by various population-based factors and thus the results of this test can be widely different in various populations. As shown by Vinton et al (20), a positive QFT result was associated with birth in a country with a high prevalence of TB, the number of years an individual had lived in a country with a high prevalence of TB and high-risk occupational contact. Interestingly, a positive TST result was also associated with older age, receipt of BCG vaccination, and working in an occupation that involved patient contact. In another study by Franken et al (21), the TST was compared with QuantiFERON test for the diagnosis of tuberculosis that among subjects positive by TST, 44.4% of recruits were positive by QFT compared with 11.5% subjects tested after missions abroad. More interestingly, some other studies could show significantly higher sensitivity and specificity for QFT when compared to TST. In Bartu et al survey (22), the sensitivity of the test was 86% in those with valid results, significantly higher than that for the TST (62%), and the correlation between the two tests was not high (55%). Wong et al (23) also showed that the sensitivity of QFG was 100%, versus sensitivity of 62.5% for TST. The positive predictive value of QFG was 100, while the negative predictive value for TST was 86.9%. Cesur et al (24) in Turkey similarly indicated that QFT assay was superior to TST in its ability to detect latent and active tuberculosis infection, not to be affected with BCG vaccination, to discriminate responses due to non-tuberculosis mycobacteria, and to avoid variability and subjectivity associated with application and reading the TST. In fact, QFT can guide more targeted treatment of individuals with actual latent tuberculosis and risk of tuberculosis; however the limited use of QFT due to cost led to preferring TST to QFT in diagnosing tuberculosis especially latent disease conditions. However, in total, despite higher costs for QFG than TST, they have additional value for the diagnosis of active tuberculosisand should be performed when a diagnosis of tuberculosisremains in doubt.

In conclusion, QFT is introduced as a diagnostic tool with high negative predictive value and a high accuracy for diagnosis of tuberculosis in children with nephrotic syndrome or those who are candidate for renal transplantation and despite high cost; it can be used as an accurate alternative for screening tuberculosis.

REFERENCES

1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA. 1999 Aug 18; 282(7):677-86.

2. Styblo K. Recent advances in epidemiological research in tuberculosis. Adv Tuberc Res. 1980;20:1-63. 3. Raviglione MC, O'Brien RJ. Tuberculosis. In: Fauci AS, Braunwald EB, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 17th . Philadelphia: McGraw-Hill Professional. 2008; pp:1014-5.

4. Ravinglion MC, O’Brien RJ. Tuberculosis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al. Harrison's Principles of Internal Medicine. 17th . Philadelphia: McGraw-Hill Professional. 2008; pp:950-94.

5. Nasehi M, Mihaghani L. [National tuberculosis management guidense]. 2ed . Tehran: Sadra Publication Center. 2002;pp:1-32.

6. Glassroth J, Crnich CJ. Pulmonary Infections Caused by Mycobacterial Species. In: Crapo JD, Glassroth JL, Karlinsky J, King TE. Baum's Textbook of Pulmonary Diseases. 7 th . Philadelphia: Lippincott Williams & Wilkins. 2004; pp:379-80.

7. Mazurek GH, Jereb J, Lobue Ph, Iademarco MF, Metchock B, Vernon A. Guidelines for Using the QuantiFERON-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States. Recommendations and Reports MMWR. 2005; 54(RR-15):49.

8. Khan, E.A., and J.R. Strake. 1995. Diagnosis of tuberculosis in children: increased need for better methods. Emerging Infectious Diseases 1: 115–123.

9. Chadha, V.K., P.S. Jagannatha, and P. Kumar. 2004. Can BCG vaccinated children be included in tuberculin surveys to estimate the annual risk of tuberculosis infection in India. The International Journal of Tuberculosis and Lung Disease 8: 1437–1442.

10. Adetifa IM, Lugos MD, Hammond A, Jeffries D, Donkor S, Adegbola RA, et al Comparison of two interferon gamma release assays in the diagnosis of Mycobacterium tuberculosis infection and disease in the Gambia. BMC Infect Dis 2007; 7: 122.

11. Detjen AK, Keil T, Roll S, Hauer B, Mauch H, Wahn U, et al.Interferonrelease assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of Tuberculosis, CID 2007; 45: 322-8.

12. Dewan PK, Grinsdale J, Kawamura LM. Low Sensitivity of a Whole-Blood Interferonrelease assay for detection of active tuberculosis, CID 2007; 44: 69-73.

13. Pai M, Zwerling A, Menzies D, Systematic Review: T-Cell based assays for the diagnosis of latent Tuberculosis infection: an update, Ann Intern Med 2008; 149.

14. Harada N., Higuchi K, Yoshiyama T, Kawabe Y, Fujita A,Sasaki Y, et al, Comparison of the sensitivity and specificity of two whole blood interferon-gamma assays for M. tuberculosis infection, J Infect 2008; 56: 348-53.

15. Pai M, Menzies D, Interferon-Release Assays: What is their role in the diagnosis of active Tuberculosis? CID 2007; 44: 74-77.

16. Ravn P, Munk ME, Andersen AB, Lundgren B, Lundgren JD, Nielsen LN, et al, Prospective evaluation of whole-blood test using Mycobacterium tuberculosis-specific antigens ESAT-6 and CFP-10 for diagnosis of active Tuberculosis, CDLI 2005; 12, 491-6.

17. Britton WJ, Gilbert GL, Wheatley J, Leslie D, Rothel JS, Jones SL, et al. Sensitivity of human gamma interferon assay and tuberculin skin testing for detecting infection with Mycobacterium tuberculosis in patients with culture positive tuberculosis, Tuberculosis 2005; 85, 137-45.

18. Lee JY, Choi HJ, Park IN, Hong SB, Oh Y-M, Lim C-M, et al.Comparison of two commercial interferonassays for diagnosing Mycobacterium tuberculosis infection, Eur Respir J 2006; 28: 24-30.

19. Kang YA, Lee HW, Hwang SS, Um S-W, Han SK, Shim Y S, et al. Usefulness of Whole-Blood interferonassay and interferon-Enzyme-Linked Immunospot assay in the diagnosis of active pulmonary Tuberculosis, CHEST 2007; 132: 959-65.

20. [Vinton P](http://www.ncbi.nlm.nih.gov/pubmed/?term=Vinton%20P%5BAuthor%5D&cauthor=true&cauthor_uid=19191484)1, [Mihrshahi S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Mihrshahi%20S%5BAuthor%5D&cauthor=true&cauthor_uid=19191484), [Johnson P](http://www.ncbi.nlm.nih.gov/pubmed/?term=Johnson%20P%5BAuthor%5D&cauthor=true&cauthor_uid=19191484), [Jenkin GA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Jenkin%20GA%5BAuthor%5D&cauthor=true&cauthor_uid=19191484), [Jolley D](http://www.ncbi.nlm.nih.gov/pubmed/?term=Jolley%20D%5BAuthor%5D&cauthor=true&cauthor_uid=19191484), [Biggs BA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Biggs%20BA%5BAuthor%5D&cauthor=true&cauthor_uid=19191484). Comparison of QuantiFERON-TB Gold In-Tube Test and tuberculin skin test for identification of latent Mycobacterium tuberculosis infection in healthcare staff and association between positive test results and known risk factors for infection. [Infect Control Hosp Epidemiol.](http://www.ncbi.nlm.nih.gov/pubmed/19191484) 2009 Mar;30(3):215-21. doi: 10.1086/595695.

21. Franken WPJ, et al. Comparison of Mantoux and QuantiFERON TB Gold Tests for Diagnosis of Latent Tuberculosis Infection in Army Personnel. Clin Vaccine Immunol. 2007 Apr; 14(4): 477–480.

22. [Bartu V](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bartu%20V%5BAuthor%5D&cauthor=true&cauthor_uid=18534124)1, [Havelkova M](http://www.ncbi.nlm.nih.gov/pubmed/?term=Havelkova%20M%5BAuthor%5D&cauthor=true&cauthor_uid=18534124), [Kopecka E](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kopecka%20E%5BAuthor%5D&cauthor=true&cauthor_uid=18534124). QuantiFERON-TB Gold in the diagnosis of active tuberculosis. [J Int Med Res.](http://www.ncbi.nlm.nih.gov/pubmed/18534124) 2008 May-Jun;36(3):434-7.

23. [Wong KS](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wong%20KS%5BAuthor%5D&cauthor=true&cauthor_uid=26362753)1, [Huang YC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Huang%20YC%5BAuthor%5D&cauthor=true&cauthor_uid=26362753)2, [Hu HC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hu%20HC%5BAuthor%5D&cauthor=true&cauthor_uid=26362753)3, [Huang YC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Huang%20YC%5BAuthor%5D&cauthor=true&cauthor_uid=26362753)4, [Wen CH](http://www.ncbi.nlm.nih.gov/pubmed/?term=Wen%20CH%5BAuthor%5D&cauthor=true&cauthor_uid=26362753)4, [Lin TY](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lin%20TY%5BAuthor%5D&cauthor=true&cauthor_uid=26362753)4Diagnostic utility of QuantiFERON-TB Gold In-Tube test in pediatric tuberculosis disease in Taiwanese children.[J Microbiol Immunol Infect.](http://www.ncbi.nlm.nih.gov/pubmed/26362753) 2015 Aug 28. pii: S1684-1182(15)00820-8. doi: 10.1016/j.jmii.2015.07.012.

24. [Cesur S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Cesur%20S%5BAuthor%5D&cauthor=true&cauthor_uid=21063967)1, [Hoca NT](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hoca%20NT%5BAuthor%5D&cauthor=true&cauthor_uid=21063967), [Tarhan G](http://www.ncbi.nlm.nih.gov/pubmed/?term=Tarhan%20G%5BAuthor%5D&cauthor=true&cauthor_uid=21063967), [Cimen F](http://www.ncbi.nlm.nih.gov/pubmed/?term=Cimen%20F%5BAuthor%5D&cauthor=true&cauthor_uid=21063967), [Ceyhan I](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ceyhan%20I%5BAuthor%5D&cauthor=true&cauthor_uid=21063967), [Annakkaya AN](http://www.ncbi.nlm.nih.gov/pubmed/?term=Annakkaya%20AN%5BAuthor%5D&cauthor=true&cauthor_uid=21063967), [Aslan T](http://www.ncbi.nlm.nih.gov/pubmed/?term=Aslan%20T%5BAuthor%5D&cauthor=true&cauthor_uid=21063967), [Birengel S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Birengel%20S%5BAuthor%5D&cauthor=true&cauthor_uid=21063967).Evaluation of Quantiferon-TB Gold and tuberculin skin test in patients with tuberculosis, close contact of patients, health care workers and tuberculosis laboratory personnel.[Mikrobiyol Bul.](http://www.ncbi.nlm.nih.gov/pubmed/21063967) 2010 Oct;44(4):553-60.