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Comparison between Quanti-FERON-TB Gold In-Tube test and tuberculin skin test for diagnosis of latent tuberculosis in children: A cross-section study

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ABSTRACT

Objective: To compare Quanti-FERON-TB Gold In-Tube (QFT-GIT) test and tuberculin skin test (TST) for the diagnosis of latent tuberculosis infection in children.

Methods: In this cross-sectional study, 64 participants who were between 3 months and 14 years old and had close contact with smear-positive pulmonary tuberculosis were included. Both QFT-GIT test and TST were done and the results were analyzed by SPSS software and Kappa test.

Results: The distribution of gender and age according to QFT-GIT and TST results were matched (P>0.05). Overall agreement between QFT-GIT and TST for diagnosis of latent tuberculosis infection in children was 75%. In addition, the contingency coefficient was 0.257, and the Kappa measure of agreement was 0.246 (P=0.034).

Conclusions: Compared to TST, QFT-GIT shows no apparent advantage for diagnosis of latent tuberculosis infection in children.

KEYWORDS: Tuberculosis; Latent tuberculosis infection; Tuberculin skin test; Quanti FERON

1. Introduction

Tuberculosis still remains a major global health problem, and the World Health Organization declared it a global health emergency in 1993[1]. According to the WHO Global Tuberculosis Report in 2012, there were 8.7 million new cases and 1.4 million deaths in 2011. There were 500 000 cases and 64 000 deaths among children[1,2]. Transmission of tuberculosis is person to person, usually by airborne droplets among adolescents or adults[2-5]. Children are rarely infected[6-8] and they may harbor dormant organisms lifelong, which constitute a long-lasting reservoir of tuberculosis in the population. Latent tuberculosis infection (LTBI) occurs after inhalation of mycobacterium tuberculosis organism. Infected people are usually asymptomatic with normal chest radiography but tuberculosis skin test (TST) or interferon-gamma release assay (IGRA) is positive[9-11]. Accurate diagnosis of LTBI is critical for tuberculosis control strategies, especially in children and immune-deficient patients[12-14]. The hallmark of LTBI was positive TST and the absence of clinical and radiologic manifestations[1-2,15-17]. TST or the Mantoux test is the intradermal injection of purified protein derivative (PPD) that is stabilized with Tween 80. After 48-72 h of infection, the diameter of skin induration around the injection spot will be measured. The sensitivity and specificity of TST is variable according to the prevalence of tuberculosis infections[14,18-20]. If the test is applied to a population with low prevalence of infection, its positive predictive value is low. Two new blood tests T-SPOT. TB

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and Quanti FERON-TB (QFT-GIT) have been developed that can diagnose LTBI by measuring the interferon released by patients' T cells in response to mycobacterium tuberculosis antigens (TB7.7, ESAT-6 and CFP-10)[9-10,19,21]. The two new emerging tests have a high specificity in the low prevalence regions but they are more expensive and with limitations for certain groups of patients including children and immune-compromised patients[11,13,20,22]. Although TST has been used for a long time for diagnosis of LTBI, recently IGRA has been developed. This test measures interferon-γ production by the patient's T cells in response to stimulation by *Mycobacterium tuberculosis* antigens[23,24]. Although a number of studies have evaluated the IGRA and TST in adults, the number of studies on children is limited[23,24-25]. The aim of this study was to compare QFT-GIT (one IGRA test) and TST for diagnosis of LTBI in children.

2. Participants and methods

2.1. Participants

A cross-sectional study was carried out on 3 months to 14 years old children at Infectious Diseases Research Center (affiliated with Kermanshah University of Medical Sciences, Kermanshah, Iran). Altogether, 64 children who had close contact for weeks with their families with positive pulmonary tuberculosis were included in this study (Figure 1). Participants had a history of Bacilli Calmette-Guerin (BCG) vaccination at birth. After the complete description of the study protocol and objectives, informed consents were obtained from all participants. This study was approved by the Ethics Committee of the Kermanshah University of Medical Sciences (approval number: 89181).

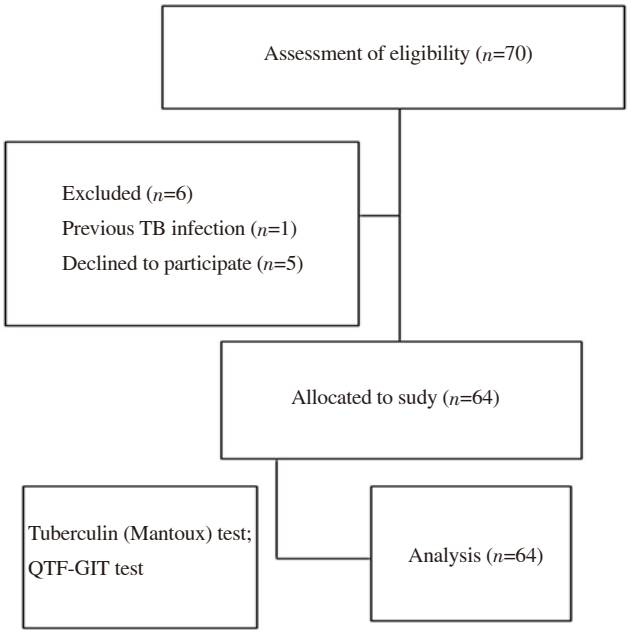

Figure 1. The study flowchart.

2.2. Evaluation and monitoring of children

A standard questionnaire was completed for each patient including gender, age, tuberculosis contact, socioeconomic status, and history of BCG vaccination. All of the participants underwent a normal thorough physical examination, and a normal chest X-ray. Both results were asymptomatic. Latent TBI infection was defined as close contact with smear-positive pulmonary tuberculosis but without clinical or radiological manifestation.

The tuberculin (Mantoux) test was performed by intradermal injection of 0.1 mL of PPD (Razi Institute, Iran) into the most superficial layer of the epidermis on the forearm. The reading was done 48-72 h after the injection, and indurations were measured. According to the manufacturer's instructions (Cellestis Company, Australia), QFT-GIT test was also done for the blood samples of all participants. The test antigens consisted of two mixtures of ESAT6 and CFP10 proteins.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 16 (SPSS Inc, Chicago, IL, USA). *Chi*-square or Fisher exact test was used to compare gender, socioeconomic status and age between the positive or negative results of TST and QFT-GIT test. The measure of agreement Kappa was used to determine the agreement rate between TST and QFT-GIT test. The significance level of the tests was set at α=0.05.

3. Results

A total of 64 participants of 3 months to 14 years old were included in our study. Among them, 33 children (51.6%) were boys and 31 (48.4%) were girls. In addition, 16 participants (25.0%) were under 4 years old, and only 7 participants (10.9%) had good socioeconomic status. There was no significant difference between QFT-GIT results according to the sex (P=0.577) and age (P=0.100). But it is significantly different between socioeconomic status (P=0.018) and QFT-GIT results. Also, there were no significant difference between TST results according to gender (P=0.100) and age (P=0.430). But it was significantly different between SES (P=0.002) and TST results.

Of the total 64 participants, 9 persons had positive QFT-GIT and 17 had PPD greater or equal 10 mm. The concordance (or agreement) percent between TST and QFT-GIT test was 75% and the Kappa rate (measure of agreement) was 0.246 (P=0.034). The 7.8% of the two tests were both positive and 67.2% were negative (Table 1). According to the some categories (2 age groups, 3 levels of SES, and 2 genders), the agreement percent between TST and QFT-GIT test in moderate SES (84.5%), Age $\leqslant$4 years (77.5%), and girls (77.5%) were more than other categories. Also, the agreement measures of Kappa rate were higher in these three categories (0.376, 0.239, & 0.239, respectively) (Table 2).

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Table 1. Comparison between results of TST test and QFT-GIT.

QFT-GIT	TST		Total
	Negative	Positive	
Positive	4 (6.2%)	5 (7.8%)	9 (14.1%)
Negative	43 (67.2%)	12 (18.8%)	55 (85.9%)
Total	47 (73.4%)	17 (26.6%)	64 (100%)

QFT-GIT: Quanti-FERON-TB Gold In-Tube test; TST: tuberculin skin test.

Table 2. Concordance rate and agreement rate between TST test and QFT-GIT test according to age, sex and socioeconomic status categories.

Categories	TST		QFT-GIT	
	Positive	Negative	Positive	Negative
Age≤4 years	1 (6.2%)	15 (93.8%)	4 (25%)	12 (75%)
Age>4 years	8 (16.7%)	40 (83.3%)	13 (27.1%)	35 (72.9%)
SES=low	4 (33.3%)	8 (66.7%)	7 (58.3%)	5 (41.7%)
SES=med	5 (11.1%)	40 (88.9%)	8 (17.8%)	37 (82.2%)
SES=high	0 (0%)	7 (100%)	2 (28.6%)	5 (71.4%)
Boys	5 (15.2%)	28 (84.8%)	10 (30.3%)	23 (69.7%)
Girls	4 (12.9%)	27 (87.1%)	7 (22.6%)	24 (77.4%)
Total	9 (14.1%)	55 (85.9%)	17 (26.6%)	47 (73.4%)

QFT-GIT: Quanti-FERON-TB Gold In-Tube test; TST: tuberculin skin test. SES: Socioeconomic status.

4. Discussion

Iran is a country with a high rate of tuberculosis exposure and BCG vaccination. LTBI patients are not well screened and treated, but in some cases, screening and treatment of LTBI are performed by using TST. Our study showed that there is no superiority of QFT-GIT over TST for the diagnosis of LTBI and overall concordance between the two tests was 75% in children.

Jennifer *et al.* showed that QFT-GIT is a specific test for tuberculosis in children in low endemic areas, but there is a need for prospective long-term evaluation studies[26]. According to their findings, there was an excellent correlation between negative TST results and negative QFT-GIT results, but only 23% of children with positive TST had positive QFT-GIT. In our study, the agreement between the negative results was 67.2% and 29% of children with positive TST had positive QFT-GIT.

Bamford *et al.* by doing a retrospective analysis of data from children investigated for active tuberculosis at six large UK pediatric centers, found that the negative IGRA does not indicate active tuberculosis but using both TST and IGRA can increase the sensitivity for diagnosis of active tuberculosis[27]. In our study, 67.2% of children with negative TST had negative QFT-GIT.

According to an Australian survey done among healthcare workers with a low prevalence of tuberculosis and a significant rate of BCG vaccination, a positive QFT-GIT was associated with the prevalence of known risk factors for tuberculosis exposure while a positive TST was associated with a prior BCG vaccination. The concordance between TST and QFT-GIT was 75% but our study was done in an area with a high prevalence of tuberculosis and all the participants in our study had a positive history of BCG vaccination[28].

Another survey in Spain revealed that the incidence of LTBI in health care workers is 11.2% and there is an agreement between QFT-GIT and TST especially when the results of both tests are negative[29]. Our study also revealed that there is a high agreement when results of both tests are negative (67.2%), but in a study in Brazil, 55.6% of 261 household tuberculosis contacts had positive results tested by TST, while 43.1% of 298 who tested by IGRA, had positive results[30]. They concluded that TST+/IGRA- and TST+/IGRAT groups shared more similar characteristics, so in a tuberculosis-endemic area, TST appears to be more suitable when making the decision to treat latent tuberculosis infection. Their conclusion is similar to our study.

Vaziri *et al.* in a survey among 67 hospital nurses, concluded a 63.7% agreement between QFT-GIT and TST in the diagnosis of LTBI and there is no superiority of QFT-GIT over TST, but, TST is more suitable considering the high cost of QFT-GIT. The result of their study among adults is also similar to our study in children with LTBI[31]. According to Pollock *et al.*, QFT assay may identify those at higher reactivation risk rather than all previously infected co-workers, so a negative QFT assay should be interpreted with caution[32].

Many studies have shown that there is a different concordance among QFT and TST in general and in situations when both are positive. Annie *et al.*[33] showed high overall concordance between the two tests in HIV-infected individuals, but agreement among subjects with positive tests with either modality was low. In addition, Carvalho *et al.*[34] showed that the agreement was 100% for TST negative results but only 34% for TST positive ones. Total agreement between QFT and TST in their study was 71%. In our study, 29% of subjects with positive TST had positive QFT results. When QFT was negative and TST was positive, the disagreement was 18.8%, and when TST was negative and QFT was positive, it was 6.2%

According to this study, it seems that QFT -GIT has no superiority over TST for diagnosis and detection of LTBI in children, and TST seems to be more suitable considering the cost.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contribution

K.G.: Study concept and design; R.C., M.J. and S.M.: Acquisition of data; M.R.: Analysis and interpretation of data; A.A. and R.C.:

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Drafting of the manuscript, critical revision of the manuscript for important intellectual content; M.R.: Statistical analysis; S. A.S.: Administrative, technical, and material support; A.A. and K.G.: Study supervision.

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