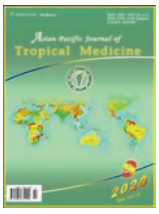

Short Communication

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Performance and correlation of QuantiFERON-TB Gold, T-SPOT.TB and tuberculin skin test in young children with or exposed to tuberculosis

Keswadee Lapphra[1], Paninun Srinuchasart[1], Sansnee Senawong[2], Utane Rungpanich[2], Pinklow Umrod[2], Alan Maleesatharn[1], Nantaka Kongstan[1], Watcharee Lermankul[1], Kulkanya Chokephaibulkit[1]✉

[1]*Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

[2]*Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

ABSTRACT

Objective: To evaluate the performance of interferon gamma release assays and tuberculin skin test in Bacillus Calmette-Guerin vaccinated young children.

Methods: A cross-sectional study was conducted in healthy children younger than 5 years who were recently diagnosed with tuberculosis or had recent exposure to active tuberculosis. QuantiFERON-TB Gold, T-SPOT.TB and tuberculin skin test were performed in each patient.

Results: Of the 60 children, median age 3.3 years, 17 had tuberculosis and 43 had recent tuberculosis exposure. Overall, 15 (25.0%) children had tuberculin skin test reaction ≥10 mm; 8 (13.3%) were positive by QuantiFERON-TB Gold In-Tube test, and 12 (20.0%) by T-SPOT.TB. Nineteen (31.7%) children had at least one positive test. There was a moderate agreement between interferon gamma release assays and tuberculin skin test.

Conclusions: The positive rates of interferon gamma release assays and tuberculin skin test were low in young children who were infected with tuberculosis, supporting the management strategy of not testing children younger than 5 years.

KEYWORDS: Tuberculin skin test; QuantiFERON-TB Gold In-Tube test; T-SPOT.TB; Young children

1. Introduction

Young children are at high risk of developing tuberculosis (TB) following exposure[1]. Tuberculin skin test (TST) is commonly used to support the diagnosis of latent tuberculosis infection (LTBI) and active TB; however, young TB-infected children may not react to TST and a reactive TST may be a consequence of Bacillus Calmette-Guerin (BCG) or infection by non-tuberculous mycobacteria (NTM) prevalent in TB-endemic areas. Interferon gamma release assays (IGRA) do not react to BCG and most NTM[2], are preferred to TST in older children and adults[3], but may be less reactive in young children with immature T-cell function.

Due to the limited knowledge of IGRA in BCG-vaccinated young children, we evaluated the performance and correlation of IGRA tests and TST in young children in a high TB burden setting who received BCG vaccination at birth and recently diagnosed with LTBI, or with active TB.

2. Patients and methods

This was a cross-sectional study in a tertiary care center, Siriraj Hospital, in Bangkok, Thailand. The study was approved by the Siriraj Institution Review Board (Si107/2016). We enrolled children younger than 5 years with a history of recent close contact to adults with active TB, or children who were diagnosed with TB within the last 6 months. Children were excluded if they had any condition that could affect immune status.

The study involved 2 clinic visits: at the first visit, the TST test was performed using an intradermal injection of 0.1 mL PPD RT23 (Staten Serum Institute, Denmark), and a single blood sample was drawn for two separate IGRA tests (1) QuantiFERON-TB Gold In-Tube test (QFT-GIT, Cellestis Limited, Australia) and (2) T-SPOT.

✉To whom correspondence may be addressed. E-mail: kulkanya.cho@mahidol.ac.th

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TB (Oxford Immunotec, UK). A second visit was scheduled 48-72 h later to read the TST reaction (the same person read the TST results throughout the study).

Baseline clinical data were extracted from the medical records. Clinical follow-up was conducted for up to 2 years after TB exposure or TB treatment. Data were analyzed using STATA v11.0 (Stata Corporation, USA). Agreement between tests were determined using Cohen's kappa coefficient (κ)[4].

3. Results

Sixty (48.3% male) children, median age was 3.3 years (interquartile range; IQR 1.6-4.3), were enrolled. Among these, 43/60 (71.7%) had recent TB exposure and 17/60 (28.3%) had TB. No children were HIV positive. All children had received BCG vaccination evidenced by scar or vaccination record. Among the TB-exposed children, the median duration of TB exposure before enrollment was 2.2 (IQR 0.3-4.8) months. The available CXR of the 55 source cases revealed that 38/44 (86.4%) had non-cavitary lesions and 23/46 (50.0%) were sputum smear positive for AFB, and 44/60 (73.3%) were microbiologic confirmed. All children received isoniazid preventive treatment except a child exposed to MDR TB.

All children with TB had pulmonary tuberculosis, plus extrapulmonary infection (2 cases); meningitis and chronic mastoiditis. The median duration from diagnosis of TB to enrollment was 2.2 (IQR 0.1-5.2) months; 5 (29.4%) children were bacteriologically confirmed. All children received anti-TB treatment.

Overall, 15 (25.0%) children had a TST reaction ≥10 mm, and 5 (8.3%) had TST reaction ≥15 mm; 8 (13.3%) children were positive by QFT-GIT and 12 (20.0%) by T-SPOT.TB. Nineteen (31.7%) children had at least one positive IGRA test or a TST reaction at ≥ 10 mm, 14 (32.6%) in TB exposed and 5 (29.4%) in TB children, respectively. Only 3 (7.0%) children with TB exposure and 3 (17.6%) with TB were positive by all three tests. Borderline and indeterminate T-SPOT.TB results were reported in one child each in the LTBI and TB groups, respectively.

The QFT-GIT, T-SPOT.TB, and TST were in moderate agreement overall with κ=0.53 (P<0.01) TST reaction ≥10 mm, and κ=0.58 (P<0.01) TST reaction ≥15 mm (Table 1). The agreement between QFT-GIT and TST was substantial (κ=0.63, P<0.01, with TST reaction ≥10 mm, and κ=0.74, P<0.01, with TST reaction ≥15 mm). The T-SPOT.TB and TST agreement was moderate (κ=0.47, P<0.01, with TST reaction ≥10 mm; and κ=0.53, P<0.01, with TST reaction ≥15 mm). The agreement between QFT-GIT and T-SPOT.TB in all children was moderate (κ=0.52, P<0.01), and was substantial (κ=0.82, P<0.01) in children with TB. There was no statistical difference in positive rates for any test or agreement between IGRA or TST reactions in children aged <2 years (n=20) and when compared with those 2-5 years (n=40) of age at either TST reaction 10 or 15 mm.

Two TB-exposed children progressed to active TB disease during the

Table 1. Agreement and concordance between TST and IGRA tests.

Patient characteristics	QFT-GIT *vs.* TST				T-SPOT.TB *vs.* TST				QFT-GIT *vs.* T-SPOT.TB		Overall concordance among the tests			
	TST≥10 mm		TST ≥15 mm		TST ≥10 mm		TST ≥15 mm				TST≥10 mm		TST ≥15 mm	
	Agreement (%)	κ (P value)	Agreement (%)	κ (P value)	Agreement (%)	κ (P value)	Agreement (%)	κ (P value)	Agreement (%)	κ (P value)	Agreement (%)	κ (P value)	Agreement (%)	κ (P value)
All (n= 60)	88.3	0.63 (<0.01)	95.0	0.74 (<0.01)	80.4	0.47 (<0.01)	87.5	0.53 (<0.01)	85.7	0.52 (<0.01)	76.8	0.53 (<0.01)	83.9	0.58 (<0.01)
TB exposed (n=43)	88.3	0.61 (<0.01)	95.4	0.73 (<0.01)	75.6	0.29 (0.03)	87.8	0.49 (<0.01)	82.9	0.37 (0.01)	73.2	0.41 (<0.01)	82.9	0.50 (<0.01)
TB disease (n=17)	88.2	0.68 (0.00)	94.1	0.77 (<0.01)	93.3	0.84 (<0.01)	86.7	0.60 (0.01)	93.3	0.82 (<0.01)	86.7	0.78 (<0.01)	86.7	0.72 (<0.01)
Bacteriologically confirmed (n=5)	80.0	0.62 (0.09)	80.0	0.55 (0.09)	100.0	1.00 (0.01)	60.0	0.29 (0.18)	80.0	0.62 (0.07)	80.0	0.73 (0.00)	60.0	0.44 (0.04)
Without bacteriologically confirmed (n=12)	91.7	0.63 (0.01)	100.0	1.00 (<0.01)	90.0	0.62 (0.02)	100.0	1.00 (<0.01)	100.0	1.00 (<0.01)	90.0	0.71 (<0.01)	100.0	1.00 (<0.01)
By age group														
< 2 years (n=20)	95.0	0.83 (<0.01)	95.0	0.77 (<0.01)	94.7	0.86 (<0.01)	84.2	0.50 (0.01)	89.5	0.69 (<0.01)	89.5	0.79 (<0.01)	84.2	0.64 (<0.01)
2-5 years (n=40)	85.0	0.55 (<0.01)	95.0	0.72 (<0.01)	73.0	0.28 (0.04)	89.2	0.55 (<0.01)	83.8	0.41 (0.01)	70.3	0.40 (<0.01)	83.8	0.54 (<0.01)

QFT-GIT: QuantiFERON-TB Gold In-Tube test; TST: tuberculin skin test; TB: tuberculosis.

2 year follow-up period. One child had a TST reaction of 10 mm, positive QFT-GIT, but negative T-SPOT.TB; while the other child had a TST of 8 mm and negative IGRA tests.

4. Discussion

Our findings demonstrate the limitations of both IGRA and TST for diagnosis of TB infection in BCG-vaccinated young children. The TST was slightly more likely to be positive than IGRA, but only one third of the children were positive by at least one of the IGRA tests or TST. There was a moderate agreement between QFT-GIT and T-SPOT.TB, and between IGRA and TST, while there was a substantial agreement between QFT-GIT and TST. The positive rates of IGRA in our study were lower than previously reported in young children in western countries and in Italy[5,6]; but slightly lower than that reported in older Thai children[7]. The relatively low positive rates of IGRA in our study could be due to different immunologic responses in our population, and also from the anti-TB treatment received prior to testing[8].

A limitation of our study was the relatively small number of participants. Overall, we found that both TST and IGRA demonstrated poor sensitivity for diagnosis of TB infection in young children in our setting. These results do not support the recently recommendation by the American Academy of Pediatrics to use IGRA in children 2-5 years of age[9]. The data in our study support the current WHO recommendation[10] and the Thai national guidelines to start treatment for LTBI in young children with exposure to TB regardless of the TST test or IGRA results.

Conflicts of interest statement

The authors declare they have no personal or professional conflicts of interest regarding any aspect of this study.

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Authors' contributions

KL, KC, and PS designed study, analysed and interpreted data. SS, UR, and PU performed IGRA (QFT-GIT and T-SPOT.TB). AM analysed data. NK and WL established the cohort including subject finding, invitation, and informed consent process. All the authors contributed significantly to the manuscript.

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