Current Medicine Research and Practice 9 (2019) 1–2

Contents lists available at ScienceDirect

Current Medicine Research and Practice

journal homepage: www.elsevier.com/locate/cmrp

Editorial

Pediatric tuberculosis in India

Tuberculosis (TB) was first called consumption (phthisis) by Hippocrates because the disease caused significant wasting and loss of weight. India has the largest burden of TB in the world, and more than half the cases are associated with malnutrition.[1,2] Stefan Prakash Eicher, born in Maharashtra, India, made this oil painting "What Dreams Lie Within" of an emaciated patient with TB seen on the streets of New Delhi (Image 1).[3]

Stefan P. Eicher made this oil painting

Robert Koch, on March 24, 1882, discovered the transmissible agent *Mycobacterium tuberculosis* as the cause of TB. He was awarded the Nobel Prize in 1905. Waksman et al. identified streptomycin as the first bactericidal agent for TB and was awarded the Nobel Prize in 1952.

TB is a leading cause of death in children in India. There is a critical need for its improved and rapid diagnosis. Diagnosing TB in children is a challenge as they do not produce adequate specimens for microscopy and culture and are often paucibacillary and close to half are extrapulmonary. The clinical algorithms are not sensitive and specific enough. Conventional tuberculin skin test (TST) is a century old, in which purified protein derivative (PPD) derived from *M. tuberculosis* (MTB) is used. But, it has several limitations: poor reproducibility, booster effect, and cross-reactions with Bacille Calmette Guerin (BCG) and environmental *Mycobacteria*.

Interferon-γ release assays (IGRAs) use specific antigens derived from MTB (early secretory antigenic target-6 [ESAT-6], culture filtrate protein-10 [CFP-10], and TB 7.7) and give more specific and sensitive results both in the diagnosis of latent and clinical diseases.

In this issue of the journal, Kaul et al.[4] have used both TST and IGRAs in a prospective study of 125 children with disease and have concluded that sensitivity and specificity of IGRAs are better than those with TST. However, a few issues need consideration.

BCG is routinely given at birth to all children in India, and the BCG coverage is 86%. This can give positive TST without the child actually having infection or clinical disease. Also, TB being endemic in India, children are constantly exposed to tubercular antigens. Data on prevalence of environmental mycobacteria in India are also absent. Both these exposures can continue to increased positivity to TST. Therefore, TST results in India can often be false positive. No data on these issues are available in India so far.

This author conducted a study of skin test responses to a host of mycobacteria in BCG-vaccinated healthy Kuwaiti school children.[5] BCG was routinely given to all children at the age of 5 yrs (school-going age). A multiple skin test survey on 1200 children aged 8–11 yrs and on 1228 children aged 12–16 yrs was conducted. All (except 15 children) had taken Japanese BCG vaccine 5 yrs–9 yrs before the study was conducted. Tuberculin positivity was 90% in both the groups. This was associated with very high responsiveness to many other environmental mycobacterial antigens as well. It was proposed that such high TST positivity several years after BCG vaccination may be due to responsiveness to group II antigen present in all slow-growing species.

Another study was conducted in Canada on 3996 school-going children (51.6% had taken earlier BCG in infancy and 48.4% had no BCG).[6] TST was positive in only 5.7% of previously vaccinated children and in only 0.2% non-BCG–vaccinated children ($p < 0.001$). Of 65 BCG-vaccinated children who were TST positive, only 5 (7.7%) were IGRAs positive (95% confidence interval [CI], 2.5%).[6] Canada has a very low prevalence of human and environmental mycobacteria.

In view of these two studies, India, where BCG at infancy is mandatory and both latent and clinical TB are common, TST can be an unreliable test for diagnosis of TB. India must generate its own data to resolve this issue.

IGRAs have been advocated as better diagnostic tests for TB.[7–9] However, false-negative results are known to occur. In a recent study of 1527 patients with TB in the USA (2013–2015), 87.7% were IGRAs positive and 12.3% were IGRAs negative. The negative results were associated with old age, underweight, extrapulmonary TB, leukocyte antigen DRBI 0701 alleles, and HIV coinfection. Owing to delay in starting treatment in such patients, mortality was higher.[10]

Also, recent studies of serially tested health-care workers in the USA show that false conversions (from positive to negative) or reversions (from positive to false negative) are well reported with IGRAs than with TST.[11]

The two diagnostic tools are in vivo TST and in vitro IGRAs. A meta-analysis of 15 comparative studies shows that there is no significant difference in the sensitivity between TST (88.2%; 95% CI, 79.7–94.2%) and QuantiFERON-TB Gold (QFT) (89.6%; 95% CI, 79.7–95.7%). However, QFT has significantly higher specificity

https://doi.org/10.1016/j.cmrp.2019.01.002

(95.4%; 95% CI, 93.8–96.6%) than TST (86.3%; 95% CI, 83.9–88.6%).

The American Academy of Pediatrics (Committee on Infectious Disease) in 2014 has stated that both IGRAs and TST are imperfect.[8] Only children who have a risk factor for TB infection due to significant immunosuppression or have TB disease should be tested with either method. However, a negative result with either test does not rule out TB.[12] "Furthermore, IGRAs are an advance in the diagnosis of infection or disease in children because these have a greater specificity over TST and greatly reduce false-positive results and unnecessary treatment in children who have earlier received BCG or were exposed to nontuberculous mycobacteria (NTM)."[13]

In a systematic review of TST and IGRAs for diagnosis of latent tuberculosis infection (LTBI) in immigrants from high-endemic to low-TB-incidence countries, IGRAs had a higher specificity than TST and were the standard of care test.[14,15]

India is a high-burden country of TB infection and disease. BCG is given at birth and has a high coverage. Our data of prevalence of environmental mycobacteria are absent. Most children (88%) suffering TB disease are earlier BCG vaccinated. These factors have a heavy influence in the interpretation of TST and IGRAs. There is a need for population-based studies with adequate sample size to generate our own data for comparison of TST and IGRAs for diagnosis of TB infection and disease in adults.

Conflict of interest

The authors have none to declare.

References

1. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis*. 2010;50(Suppl 3):S184–S194.
2. Bhargava A, Benedetti A, Oxlade O, Pai M, Menzies D. Undernutrition and the incidence of tuberculosis in India: national and subnational estimates of the population-attributable fraction related to undernutrition. *Natl Med J India*. 2014;27:128–133.
3. Moonan PK. Tuberculosis - the face of struggles, the struggles we face, and the dreams that lie within. *Emerg Infect Dis*. 2018;24:592–593.
4. Dhillon A, Raveendran R, Saluja S, Kaul D. Evaluation of QuantiFERON-TB Gold test for the diagnosis of asymptomatic tubercular infection in children. *Curr Med Res Prac*. 2018;8.
5. Bahr GM, Chugh TD, Behbehani K, et al. Unexpected findings amongst the skin test responses to mycobacteria of BCG vaccinated Kuwaiti school children. *Tubercle*. 1987;68:105–112.
6. Jacobs S, Warman A, Richardson R, et al. The tuberculin skin test is unreliable in school children BCG-vaccinated in infancy and at low risk of tuberculosis infection. *Pediatr Infect Dis J*. 2011;30:754–758.
7. Laurenti P, Raponi M, de Waure C, Marino M, Ricciardi W, Damiani G. Performance of interferon-γ release assays in the diagnosis of confirmed active tuberculosis in immunocompetent children: a new systematic review and meta-analysis. *BMC Infect Dis*. 2016;16:131.
8. Starke JR, Committee on Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics*. 2014;134:e1763–e1773.
9. Starke JR, Byington CL, Maldonado YA, et al. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. Pediatrics 134: e1763-e1773.
10. Nguyen DT, Teeter LD, Graves J, Graviss EA. Characteristics associated with negative interferon-γ release assay results in culture-confirmed tuberculosis patients, Texas, USA, 2013–2015. *Emerg Infect Dis*. 2018;24:534–540.
11. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. *N Engl J Med*. 2015;372:2127–2135.
12. Nguyen DT, Teeter LD, Graves J, Graviss EA. Characteristics associated with negative interferon-γ release assay results in culture-confirmed tuberculosis patients, Texas, USA, 2013–2015. *Emerg Infect Dis*. 2018;24:534–540.
13. World Health Organization. *Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management*. World Health Organization; 2018. http://www.who.int/iris/handle/10665/260233.
14. Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. *Mol Diagn Ther*. 2015;19: 9–24.
15. Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. *Clin Microbiol Rev*. 2014;27: 3–20.

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19 December 2018
Available online 14 January 2019