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Revisiting Mantoux test in the era of immunization and Multi-drug resistant tuberculosis

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ABSTRACT

This review reinvents the role of mantoux test/tuberculin skin test (TST) in the laboratory diagnosis of tuberculosis (TB). TB has been the most significant infectious disease responsible for severe morbidity and mortality worldwide. Asia and African continents constitute most of the burden of world TB. Although a treatable infectious disease, the exposed individuals do not always show clinical signs of infection. TB may be present latent in many infected population. Clinical, radiological, cultural and staining methods, molecular techniques and many other advanced laboratory methods are available for the diagnosis of TB. Among the various laboratory techniques available for the diagnosis of TB, Mantoux TST is a low cost and easily done test that if performed and interpreted appropriately can be used for diagnosis of TB.

KEY WORDS: Mantoux test, laboratory diagnosis of tuberculosis, tuberculin skin test

INTRODUCTION

Mantoux test is an intradermal skin test used to demonstrate delayed type of hypersensitivity (DTH) reaction against *Mycobacterium tuberculosis* (TB). TB has been an infectious disease continuingly being identified as responsible for severe morbidity and mortality thorough out the world. The intensity of this disease is more severe in the poor, developing and third world nations owing to various social and demographic factors that include overcrowding, poor hygiene, lack of proper nutrition etc.,. Although the laboratory diagnosis of TB by conventional methods are available in most of the centers that include Ziehl–Neelsen's staining method and culture on Lowenstein–Jensen's medium, the factors that limit accuracy of diagnosis include availability of an efficient microscopist and that the traditional culture takes a long time before confirmation. Availability of advanced techniques like fluorescent staining, culture (*Mycobacterium* growth indicator tube) and nucleic acid detection by polymerase chain reaction have revolutionized the laboratory diagnosis of TB. In the era of emergence of multi-drug resistant TB, laboratory diagnosis of TB, initiation of appropriate anti-tubercular therapy and regular follow-up of infected patients assumes greater significance. Owing to the fact that most of the laboratory methods require sophisticated instruments, skilled manpower and good infrastructure, many poor and financially weak nations cannot afford to utilize them. Among the available laboratory techniques, acid-fast staining and mantoux test are cost-effective and can be easily performed by trained medical personnel [1-3]. The present review focuses on the utility of mantoux test in the laboratory diagnosis of TB.

HISTORICAL ASPECTS

The bacterium *Mycobacterium* TB was first described by Robert Koch in 1882 [4]. Initially, the mantoux test was applied by German physician Felix Mendel in 1908 and later was modified and used by Charles Mantoux in the year 1912. This test is also in use till date on the name of scientist Charles Mantoux. Though mantoux test is used for the demonstration of DTH against *Mycobacterium* TB, its significance as a laboratory diagnostic method for the diagnosis of TB is still in debate. This is mainly due to the introduction of the vaccine Bacillus Calmette Guerin (BCG) and that in the developing countries and the endemic parts of the world most of the individuals are exposed to tubercle bacilli or have been infected sub clinically. Owing to the causes discussed earlier and many other factors,

the sensitivity and specificity of mantoux test in the diagnosis of TB is poor. Also, what appears important is that mantoux test cannot differentiate between nan earlier exposure and current infection [5].

MANTOUX TEST

Mantoux test is also called as tuberculin skin test. This test is performed for the demonstration of DTH reaction against tubercle antigen or a purified protein derivative (PPD). Mantoux test has been in use for more than 100 years now [6]. Initially, the PPD was prepared from *Mycobacterium* TB by Seibert (PPD-S) and also from a research strain of *Mycobacterium* TB (PPD-RT-23), which is now replaced by PPD extracted from human strain of *Mycobacterium* TB grown on a protein-free synthetic medium and inactivated. The immunological basis for tuberculin test is the hypersensitivity reaction involving the cells of T- cell immunity. At the site of injection, the tubercle antigen (PPD) sensitizes T-cells to accumulate and release lymphokines/cytokines. These inflammatory cells induce local reaction by producing vasodilation, edema, induration, vesiculation, fibrin deposition and necrosis of the skin. For tuberculin skin, the test the injection should be given on the volar aspect of left forearm and the injection area should be rounded by using a marker. The patient should be advised to avoid scratching the area and keep the site of injection clean. The Standard dose of antigen includes 5 TU (tuberculin units) of PPD with Polysorbate 80 (0.0006%). By using 26 or 28 gauze needle and tuberculin syringe which can deliver accurate dose of 0.1 ml, 0.1 ml (5TU) is injected intra-dermal/intra-cutaneously with the bevel of the needle facing upwards [Figures 1a and b-3a and b].

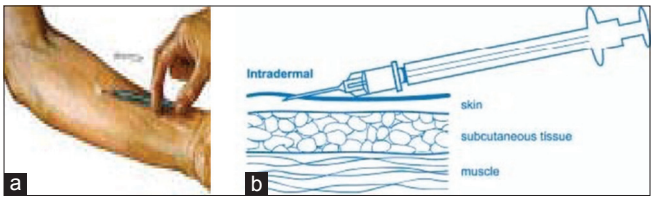

Figure 1: (a and b) How a tuberculin test should be performed

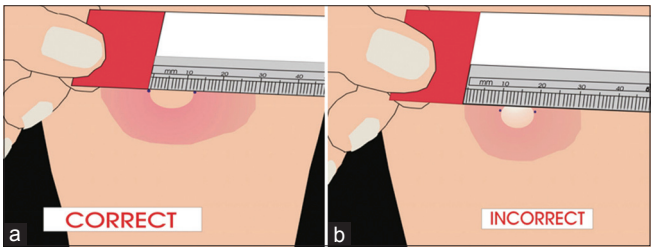

Figure 2: (a and b) How a tuberculin test must be read

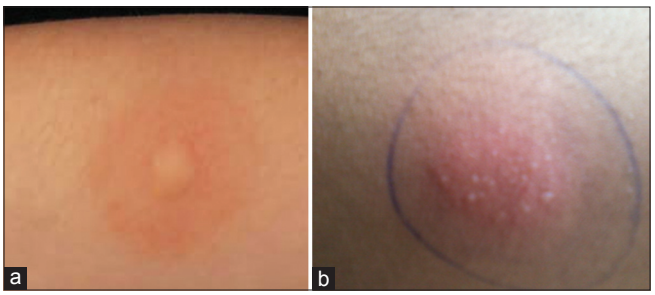

Figure 3: (a and b) A small induration at the injection site and a marked area in which there is a large induration with exaggerated skin reaction

WHO NEEDS A MANTOUX TEST

All individuals who give a history of recent contact with infected population (family, friends and work place), people with radiological signs (chest X-ray) of present/previous infection, immunosuppressed individuals (HIV infected, other conditions, very old age), screening test for employers/school children, test prior BCG vaccination in children less than a year old, individuals going for organ donation and people moving to high risk areas of TB [7,8].

INTERPREATION OF MANTOUX TEST

If the test is negative, no further repeat testing is required at this time, but you may need another test a few months later, depending on the reason for the test. If the test is positive, a chest X-ray and physical examination will be needed to ensure there is no sign of active disease. If there are no signs of active TB the doctor will discuss the possibility of taking medication to prevent the development of TB disease. The benefits of taking the medication depend on the person's age, health and underlying risk of TB disease [9]. Tuberculin test should be read after 48 h and not beyond 72 h after injection. Reading of the tuberculin test must be made in good light visibility, with a forearm slightly flexed at elbow. Appearance of edema and indurations' which can be palpated, redness and signs of necrosis must be noted and measured using a scale in millimeters [10]. Adverse skin reaction showing vesicular or ulcerative changes including regional lymphadenopathy and fever should be noted, which may indicate active TB infection and properly managed. The test result is read by measuring the size of induration/edema in millimeters where in a >5 mm induration should be considered as a positive tuberculin skin test in individuals who are in close contact with active TB patients (Family member already infected), persons with Human immunodeficiency virus (HIV) infection and in individuals with radiological signs of TB. An indurations' of >10 mm diameter should be noted as a positive tuberculin test in drug addicts, diabetes mellitus, individuals on long term corticosteroid therapy, people with chronic kidney diseases and cancer patients. An observation of >10 mm diameter indurations' among individuals who are shelter less, jail inmates, people living in crowded areas, residents of nursing homes, mental health facilities, migrant population and children below 5 years and those who are exposed to infected adults should be considered as mantoux positive. A reaction of >15 mm should be considered as positive in people with low risk, no history of exposure and who have no underlying conditions as described in detail in Table 1. False positive mantoux test can be attributed to underlying infection with *Mycobacteria* other than *Mycobacterium* TB, prior vaccination with BCG, incorrect method of performing and reading the test. A false negative tuberculin skin test should be considered in cases of patients with cutaneous anergy (immune dysfunction),

Table 1: Interpretation of mantoux test

Diameter of induration	Interpretation	Consideration	Action
<5 mm	Negative	Repeat test if necessary	Proceed with BCG vaccination and also consider false negative criteria: Temporary immunosuppression due to steroids, upper respiratory tract infections, infectious mononucleosis, measles, varicella and HIV infection
>5 mm	Positive	Who are in close contact with active TB patients (Family member already infected), persons with HIV infection and in individuals with radiological signs of TB	If not vaccinated , vaccination with BCG is not advised now
>10 mm	Positive	Drug addicts, diabetes mellitus, individuals on long term corticosteroid therapy, people with chronic kidney diseases and cancer patients, people who are shelter less, individuals in jails, people living in crowded areas, residents of nursing homes, mental health facilities, migrant population and children below 5 years and those who are exposed to infected adults	Consider clinical aspects and initiate treatment
>15 mm	Positive	Low risk, no history of exposure and who have no underlying conditions as described earlier	Consider clinical aspects and initiate treatment

HIV: Human immunodeficiency virus, BCG: Bacillus Calmette Guerin, TB: Tuberculosis

recent TB infection/treatment, and children below 1 year age, fulminant disease, current viral infections/vaccinations and non-standard technique of performing the test.

DISCUSSION

Previous studies have noted that BCG vaccination is not a contraindication for a tuberculin skin test but indicated that in such individuals the mantoux test must be cautiously interpreted and a skin reaction of more than 10 mm should be considered as a positive test [11-15].

A condition wherein reversal of mantoux test from a previous positive to the negative reaction can be observed in immunosuppressed individuals. Another type of reaction termed as mantoux conversion which can happen in vaccinated individuals and those who have been infected by typical/atypical *Mycobaterial* species is noted wherein a negative mantoux may turn in to a positive test or an initial mild reaction may increase in the later test [16]. Mantoux test is not recommended in individuals with a previous reaction of more than 15 mm, those having a history of previous infection and infants <6 months of age.

A recent study has observed that mantoux test can be used for the diagnosis of ocular TB, which remains to be least invasive and cost effective procedure. The drawback being that the tuberculin skin test cannot differentiate between infections of *Mycobacterium* TB from that of atypical *Mycobacteria* [17]. An epidemiological report published recently from Korea has indicated that with a reaction of >10 mm diameter taken as a cut off, there has been a decrease in the positivity against tuberculin skin test from 2005 (28%) to 2009 (15%), which was associated to BCG vaccination [18]. A study from developing nation, Peru has noted that in the geographical regions endemic to TB and in the era of vaccination with BCG, a mantoux reaction of >10 mm should be considered as positive [19]. When tuberculin skin tes t was performed with six different doses of PPD in a single male adult aged 35 years, it was observed that the reaction initially increased but later doses showed no significant adverse skin reaction proving the safety and utility of mantoux test in the diagnosis of latent TB [20]. A study from Iran has observed that even in the individuals who were vaccinated, a positive tuberculin skin test of a certain diameter indicates latent TB infection [21]. In a study from Madagascar, performed in 1st year school going children, it has been observed that a positive mantoux test indicated an active/latent TB infection and prior BCG vaccination was not a limiting factor signifying the importance of TST in the vaccinated population [22]. A recent study from Peru has compared the positivity of TST in BCG vaccinated and non-vaccinated population and has noted that BCG vaccination does not contribute to positive TST reaction and that it can still be used for the detection of latent TB cases [23]. Another recent study from south India, which used a two-step tuberculin skin test has noted that a repeat test did not greatly alter the prevalence of TST positivity, but it was noted that the two-step TST identifies individuals who can potentially boost their immune response to a second test, and thus, prevents them from being misclassified as those with newly acquired infection, or tuberculin converters. This study has also noted that two-step tuberculin skin test may be useful where serial tuberculin testing needs to be performed to distinguish those who show an enhanced response or boosters from those who indeed have a new infection, or converters [24]. A very recent study from India, which compared TB Quantiferon (Interferon-γ) detection in blood and TST has noted that micronutrient deficiency of Zinc has reduced the detection of TB by quantiferon method whereas TST performance was not affected [25]. American study published recently has noted that a negative TST may be shown in active TB cases and that if not treated based only on the TST result may suffer severe morbidity and mortality. This study has also observed that persons with a TST >15 mm had 67% lower odds of death than persons with a negative TST (adjusted odds ratio 0.33, 95% confidence interval 0.30-0.36) [26].

CONCLUSION

From the available literature, it is evident that even in the individuals who are vaccinated with BCG, the tuberculin

test can be done for the detection of immunological reaction against the tuberculin antigen. Although tuberculin test does not differentiate between the active infection and the previous infection, a detailed history with current clinical picture combined with radiological suspicion and the size (diameter in mm) of the induration, a decision on whether to initiate antitubercular therapy can be taken by the physician. Critical points to consider while performing the tuberculin test includes the age of the individual, confounding factors, including HIV infected population, malnourished individuals, drug addicts, diabetes mellitus, individuals on long term corticosteroid therapy, people with chronic kidney diseases and cancer patients, people who are shelter less, individuals in jails, people living in crowded areas, residents of nursing homes, mental health facilities, migrant population and children below 5 years and those who are exposed to infected adults. Training personnel/health care workers about the correct technique of performing the tuberculin test and reading the reaction could contribute to better application of tuberculin skin test [27,28].

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