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Effect of Neonatal BCG Vaccination and other Risk Factors on Tuberculin Skin Test Reactivity among South Indians

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Abstract: *The tuberculin skin test (Mantoux) is widely used in the diagnosis of M. tuberculosis infection and epidemiological surveys to estimate the prevalence of infection. But, still there is no clear understanding on other various risk factors such as that cause skin test positivity. This work was carried-out in a South Indian population to reveal the association of those other risk factors through medical examination with a questionnaire. Results reveal that the risk factor of 'Family member (or close contact) with TB' was significantly associated with the tuberculin reactivity.*

Keywords: *BCG, Mycobacterium tuberculosis, Questionnaire, Risk Factor, Tuberculin skin test*

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I. Introduction

Tuberculosis is an air borne infectious disease caused by *Mycobacterium tuberculosis.* Approximately two billion people are infected with this causative agent and continues to be a major worldwide health problem. It is the leading killer of youth and adults in developing countries, being responsible for more deaths than any other single infectious organism [1]. Limited access to organized health care, Inadequacies of tuberculosis control programs and the HIV pandemic have contributed significantly to the increase in tuberculosis case rates [2]. Earlier and prompt diagnosis of TB is a priority for TB control, both for treating the individual and for public health intervention to reduce further spread in the community [3]. The tuberculin skin test is one of the few investigations dating from the 19 century that are still widely used as an important test for diagnosing tuberculosis [4].

This Tuberculin skin test is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm. The injection is administered with a tuberculin syringe, with the needle bevel facing upward. The skin test reaction is usually read between 48 and 72 hours after administration. It is a delayed type of hypersensitivity reaction in the form of induration at the test site in sensitized host [5]. The reaction is measured in millimeters of the induration (palpable, raised, hardened area or swelling) only and not the erythema (redness). The diameter of the indurated area is measured across the forearm [6]. Apart from diagnosis, the test is also used in surveys to monitor *M. tuberculosis* infection in a community in order to plan the activities of tuberculosis control programs, by identifying areas of high prevalence of infection and revealing potential cases [7] [8].

However, during surveys all persons with positive tuberculin skin test reactions need not to be infected with *Mycobacterium tuberculosis* [9]. There are several other factors such as previous Bacille Calmette-Guerin (BCG) vaccination [10], Close contact with TB patient, Healthcare profession etc are also responsible for TST positivity. So, present study was carried out to assess the proportion of tuberculin response among the study population in South India with and without prior BCG vaccination in three different geographical locations (Urban, Sub-urban and Rural) and to analyze the influence of various risk factors associated with tuberculin skin test reactivity in the study population.

II. Ethical Committee Approval

The design and methodology of the entire study was approved by the institutional ethical committee of The Tamilnadu Dr. M.G.R. Medical University, Chennai, India.

III. Materials And Methods

3.1 Study Area – I : Urban Chennai

Chennai, formerly known as Madras, is the capital of the South Indian state of Tamil Nadu. It is one of the metropolitan cities in India. Chennai is the third largest commercial and industrial centre in India. The city faces problems with water shortage, traffic congestion and air pollution. Chennai has a diversified economic base anchored by the automobile industry, software services, hardware manufacturing, healthcare and financial services industries.

3.2 Study Area – II : Sub-urban Pallavaram

The second study area Pallavaram is a sub-urb of Chennai city and a municipality in Kancheepuram district of Tamilnadu. It is a residential cum industrial area with numerous leather tanneries and chemical industries.

3.3 Study Area – III : Rural Tirupandiyur (BCG trial area)

This rural study area Tirupandiyur is in Tiruvallur district (formerly part of Chingleput district) of Tamilnadu where the major South Indian BCG trial was conducted (Chingleput BCG trial). This study area is about 50 kilometers from Chennai. The main occupation of the people includes agriculture, weaving and small house-hold industries. The major BCG efficacy trial conducted by World Health Organization and ICMR in this region revealed 0% efficacy for the vaccine [11].

3.4 Sampling and Statistical Analysis

Considering the convenience, feasibility and resources available the convenient sampling method was applied for this study [12]. All the statistical analysis of the present study was carried out in SPSS statistical software system. All the descriptive statistics were expressed as mean ± standard deviation. Logistic regression was used to ascertain the association of risk factors with tuberculin reactivity.

3.5 Recruitment of Study Population

The population enrolled for the present study (from all the three study area) included both male and female adolescent and adult volunteers. The individuals were enrolled by door-to-door visits and by conducting local field campaigns. Interested individuals/volunteers were only registered for the study. Study objectives and other related information were explained and the written informed consent was obtained from each of these volunteers.

A detailed medical examination which included information on BCG scar status and risk factors associated with tuberculin sensitivity were carried out by a qualified/experienced medical and nursing team. After examination, healthy volunteers who were willing to give consent to tuberculin skin test and blood collection were included for the study.

The individuals were classified into BCG vaccinated and BCG-non vaccinated subjects. The vaccinated group included only subjects with a post vaccine scar, the only sure sign of vaccination. This scar is different from that of small pox; it is smaller in size and is identified by the skin which it covers it, which is smooth, pearly and forms fine folds when squeezed [13]. Those with no scar and a definite history of not having received vaccination were grouped as BCG-non vaccinated subjects. Those who gave a history of vaccination but did not have a scar were excluded.

3.6 Tuberculin skin Test (Mantoux)

All the recruited volunteers were subjected to tuberculin skin test (Mantoux intradermal test). The test was performed as per the guidelines given by Centre for Disease Control [14]. Tuberculin skin tests were performed by well trained medical laboratory technicians. Proper instructions were orally given to the individuals. 0.1ml of tuberculin PPD 1TU (Span diagnostics, India) was administrated on the forearm of volunteers. The transverse diameters of the indurations were measured between 72 and 96 hours and were recorded in millimeters. While reading, erythema was not considered and only the induration was measured.

IV. Results

4.1 General Characteristics of the study population

A total number of 196 volunteers between the ages of 13 and 34 from the three different study areas were registered for the present study. Twenty three of them were excluded after medical examination (underweight, malnourished, and with chronic infections etc) and their un-willingness to participate in the study. So a total number of 173 healthy subjects were recruited and subjected to tuberculin skin test. The health status

of the individuals was examined by the physicians. All the volunteers were healthy and free from HIV, hepatitis and other chronic infections. Forty three percent of the subjects (74/173) were BCG vaccinated as assessed by the presence of BCG scar. Skin testing and reading were done by the same team of experienced health care workers. The summary of the study population for each of the study area is given below and shown in TABLE 1.

Table – 1. Descriptive summary of the study population

Characteristics	Study area			Total
	Urban Chennai	Sub-urban Pallavaram	Rural BCG trial area	
No. of enrolled volunteers	60	84	52	196
No. of withdrawn/ excluded volunteers	8	9	6	23
No. of tuberculin tested and read	52	75	46	173
Gender ratio (M:F)%	56 : 44	63 : 37	48 : 52	57 : 43
Mean age ± SD (in years)	22 ± 3.3	19.9 ± 5.3	19.8 ± 3.1	20.6 ± 4.4
No. with BCG scar	27 (52%)	33 (44%)	14 (30%)	74 (43%)
Mean scar size(mm) ± SD	6.8 ± 2.3	8.3 ± 3.9	5.93 ± 1.5	7.3 ± 3.1

4.2 Study Area 1: Urban Chennai

A total number of 60 volunteers were evaluated for the study. Eight of the volunteers were excluded from the study after medical examination and their un- willingness to participate in the study. So, a total number of 52 young adults with mean age (±SD) of 22.3 ± 3.3 were recruited and subjected to tuberculin skin test. Twenty nine of them were male and 23 of them were female volunteers. Of them 52 percent (27/52) had a BCG scar (Fig. 1).

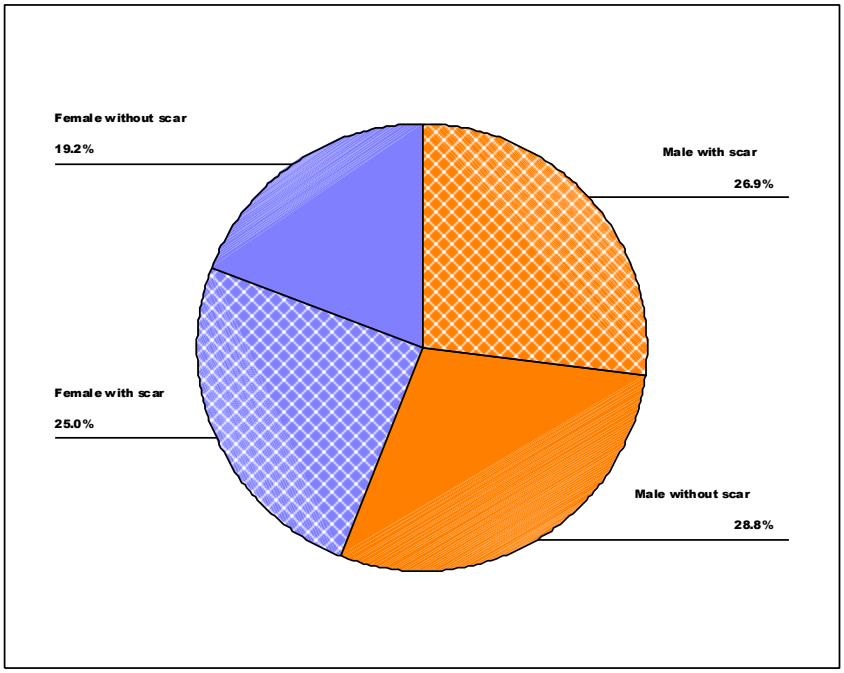

Fig. 1 BCG scar status according to gender in urban Chennai study subjects

4.3 Study Area 2: Sub-urban Pallavaram

A total number of 84 volunteers were evaluated for the study. Nine of the volunteers were excluded from the study after medical examination and their un- willingness to participate in the study. So, a total number of 75 young adults with mean age (±SD) of 19.9 ± 5.3 were recruited and subjected to tuberculin skin test. Forty seven of them were male and 28 of them were female volunteers. Of them 44 percent (33/75) had a BCG scar (Fig. 2).

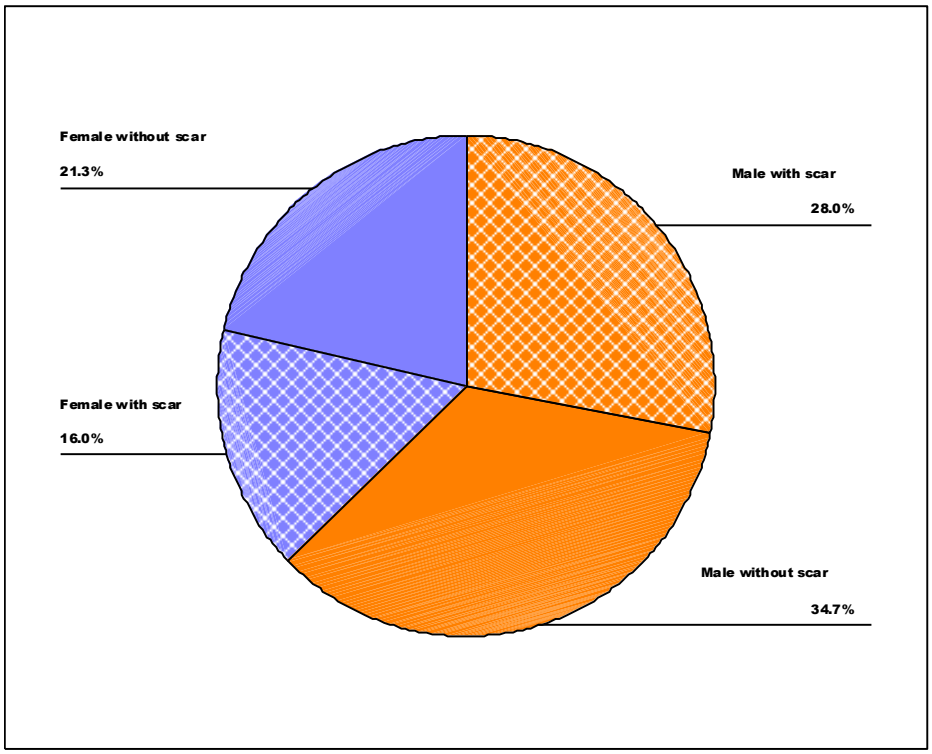

Fig. 2 BCG scar status according to gender in sub-urban Pallavaram study subjects

4.4 Study Area 3: Rural BCG trial area

A total number of 52 volunteers were evaluated for the study. Six of the volunteers were excluded from the study after medical examination and their un- willingness to participate in the study. So, a total number of 46 young adults with mean age (±SD) of 19.8 ± 3.1 were recruited and subjected to tuberculin skin test. Twenty two of them were male and 24 of them were female volunteers. Of them 30 percent (14/46) had a BCG scar (Fig. 3).

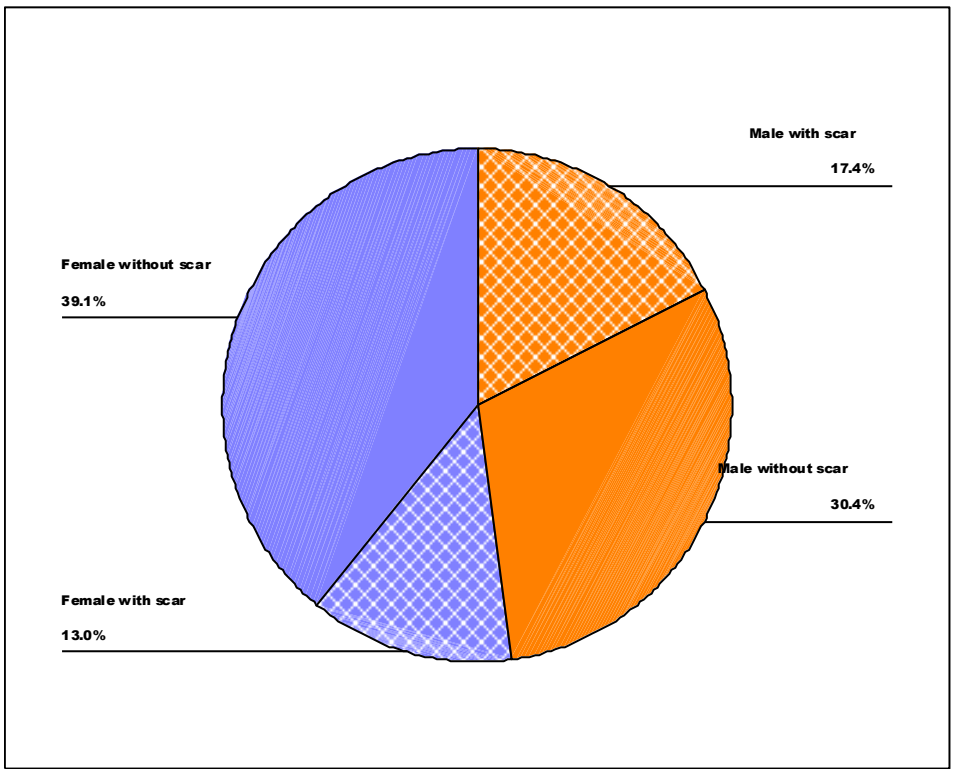

Fig. 3 BCG scar status according to gender in rural BCG trial area study subjects

4.5 Risk factors associated with tuberculin reactivity

The present study has evaluated the association of certain common risk factors with the tuberculin response by logistic regression analysis using tuberculin response result as the dependent variable. The association was expressed in OR (Odds ratio) with 95% confident intervals.

Out of 173 tested study subjects, 53 of them were reactors. The risk factors included in the questionnaire and their association with the tuberculin reactivity is shown in TABLE 2. The questionnaire included 'The status of BCG scar' as a question to associate BCG scar with tuberculin response. Out of 74 subjects with scar, only 29 of them were reactors (OR 1.7; 95% CI 0.8-3.4). The impact was not statistically significant. The questionnaire has revealed 12 TB contacts, out of 173 study subjects. Seven of them were tuberculin reactors and five of them were non-reactors (OR 3.4; 95% CI 0.9-12.1). This risk factor of 'Family member (or close contact) with TB' was significantly associated (*P*=0.05) with the tuberculin reactivity.

Twenty health care workers were included as study subjects who were nurses, clinical lab technicians and other hospital paramedical staff. Among them only six (OR 0.9; 95% CI 0.3-2.8) were reactors. So the risk factor of 'Health care worker' did not have any statistical significance.

All the other risk factors such as Asthma, Smoking, Alcohol & tobacco use, prolonged fever, persistent cough, Wheezing, Fatigue and Sudden weight loss included in the questionnaire were also not significantly associated with the tuberculin response.

Table - 2. Risk Factors Associated with Tuberculin Reactivity

Risk factor	Total No. of subjects in all Study Area			Unadjusted OR (95% CI)
	TST non-reactors (n=120)	TST reactors (n=53)	Total (n=173)	
Presence of BCG scar	**45 (37.5)**	**29 (54.7)**	**74 (42.7)**	**1.7 (0.8-3.4)**
Family member (close contact) with TB	**5 (4.1)**	**7 (13.2)**	**12 (6.9)**	**3.4 (0.9-12.1)***
Health care worker	**14 (11.6)**	**6 (11.3)**	**20 (11.5)**	**0.9 (0.3-2.8)**
Asthma	**3 (2.5)**	**2 (3.7)**	**5 (2.8)**	**1.7 (0.1-16.5)**
Smoking, Alcohol & tobacco use	**9 (7.5)**	**9 (16.9)**	**18 (10.4)**	**2.4 (0.8-6.9)**
Prolonged Fever	**8 (6.6)**	**7 (13.2)**	**15 (8.6)**	**1.7 (0.5-5.5)**
Persistent Cough	**17 (14.1)**	**11 (20.7)**	**28 (16.1)**	**1.8 (0.7-4.3)**
Wheezing	**3 (2.5)**	**1 (1.8)**	**4 (2.3)**	**0.7 (0.04-11.8)**
Fatigue	**0 (0)**	**0 (0)**	**0 (0)**	**NA (NA)**
Lack of appetite	**0 (0)**	**0 (0)**	**0 (0)**	**NA (NA)**
Sudden weight loss	**4 (3.3)**	**1 (1.8)**	**5 (2.8)**	**0.5 (0.06-5.1)**

Numbers in the parenthesis represent the percentage of the total.

NA - Not applicable ; ***** - Statistically significant (P = 0.05)

V. Discussion

Previous studies carried out to analyze the relationship between BCG vaccination and tuberculin response have showed variable results; some showed a relationship and some studies did not [15] [16] [17]. The effect of BCG vaccination on tuberculin response was analyzed in eleven different surveys by Menzies D *et al* and revealed no relationship between the tuberculin response after BCG vaccination and the protective efficacy of the vaccine [18]. Other studies conducted at different parts of the world have also showed no relationship between BCG vaccination and tuberculin response [19] [20] [21]. In our study also the presence of BCG scar does not reveal any association with tuberculin response.

Similarly a previous study that assessed the association of risk factors with tuberculin reactivity through a 'risk assessment questionnaire' was carried out by Koppaka *et al* and have showed that 'Close contact with a TB patient' and 'Birth in a high risk country' were associated with the tuberculin reactivity [22]. In this study also Family member (Close contact with TB patient) has revealed a significant association.

VI. Conclusion

Tuberculin response depends upon numerous factors apart from Latent tuberculosis infection. This study has evaluated the association of those other risk factors with the tuberculin response in a South Indian population. The risk factor of 'Family member (or close contact) with TB' was significantly associated (*P*=0.05) with the tuberculin reactivity. All the other risk factors such as prolonged fever, persistent cough etc were not significantly associated with the tuberculin reactivity in the present study.

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