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Tuberculin Skin Test Size after Prolong Time of Bacille Calmette Guérin Vaccination

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The aim of this study was to evaluate the effect of Bacille Calmette Guérin vaccination after long time on tuberculin skin test in adults, because the long-term effect of BCG vaccination is not known in Iran. We carried out a cross-sectional study on 464 on-duty soldiers in a systematic random selection in 2008. Purified protein derivative was injected intradermally with quantity 0.1 mL into the forearm and induration size of skin test was measured after 48-72 h. Induration more than 10 mm was taken as positive reaction. In here all soldiers were man with mean age of 23.28±1 years. All of them had Bacille Calmette Guérin scar in their arms and about 31 (6.7%) had positive tuberculin skin test and 8 (1.7%) of them had positive test size 20-30 mm. One subject had sub-clinical pulmonary tuberculosis. We conclude, that adult with the history of Bacille Calmette Guérin vaccination in their neonatal age that had positive tuberculin skin test should be considered as new tuberculosis infection.

Key words: BCG, PPD, tuberculosis, soldiers

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INTRODUCTION

Tuberculosis is still a major global health problem (Gunneberg *et al*., 2008) and renewed interest in human tuberculosis has been stimulated due to predisposition of patients with HIV infection to mycobacterium infections and the development of multiple drug resistant strains (Wang *et al*., 2008). Every year, Mycobacterium tuberculosis causes approximately 8 million new cases of tuberculosis and 2 million deaths (Lonnroth and Raviglione, 2008), making it the most lethal infectious agent in the world (Corbett *et al*., 2003).

Bacille Calmette Guérin (BCG) is a live attenuated vaccine derived from *Mycobacterium bovis* by Albert Calmette and Camille Guerin between 1906 and 1919 and more than 3 billion doses of the BCG vaccine have been administered worldwide (Kallenius *et al*., 2007). The concern of the public health community about the resurgence and changing nature of tuberculosis prompted an evaluation of the role of BCG vaccination in the prevention and control of tuberculosis (Weir *et al*., 2008). Protective efficacy of BCG for preventing serious forms of tuberculosis in children is about 80%; however, its protective efficacy for the prevention of pulmonary tuberculosis in adolescents and adults is variable, equivocal and remains to be determined (Kunst, 2006). In developing countries BCG vaccination is used as a strategy for the prevention of tuberculosis infection. However, the exact duration of its preventive effect is not known and it is possible that it may interfere with the Purified Protein Derivative (PPD) skin test and leads to confusion in the diagnosis of tuberculosis (Xu *et al*., 2006). Although the delayed-type hypersensitivity skin test reaction to PPD is used worldwide for the detection of tuberculosis, it is incapable of distinguishing mycobacterium tuberculosis infection from BCG vaccination from the infection caused by non-tuberculosis mycobacteria (Wu *et al*., 2008). On other hand, clinical manifestations of tuberculosis aren't specific (Ghorbani *et al*., 2007) and tuberculin skin test serves only as a guide for the tuberculosis diagnosis (Alavi and Sefidgaran, 2008). The aim of this study was the evaluation of PPD skin test in adult that were vaccinated with BCG during their neonatal life.

MATERIALS AND METHODS

This was a cross-sectional study conducted on 464 on-duty soldiers in systematic random sampling from 2000 on-duty soldiers from their computer list name that selected one from each five persons until reach to required sample size consider to exclusion and inclusion criteria in capital city of Iran in February-March 2008. This project was approved by the Ethics Committee of Health Research Center, Baqiyatallah University of Medical Sciences in its approval letter No. 85-379/2008. Demographic data included age (median age of these group was 23 years old and this factor based of divided of age to two groups, ≤23 and >23 years old), education level, marital status, living city and familial tuberculosis was take from each one. Other variables included scar of BCG vaccination, history of smoking by self demonstration (a least one smoke per each day for more than three months) and chronic cough (more than three weeks) and night fever (oral fever more than 38.5°C for more than three weeks) took from each one. All participants gave written informed consent and also filled and signed the questionnaire. The participants were then given tuberculin skin test. PPD was applied to them and single use, 26 gauge sterile injectors were used and 0.1 mL of PPD 5TU solution (Pasteur Institute of Iran) was injected intradermal into top two-thirds of the volar face of the left forearm to create a 6-10 mm swelling. One experienced physician measured the transverse diameters of PPD induration to the longitudinal axis of the arm after 48-72 h with transparent, plastic, millimeter scale rulers. An induration size of more than 10 mm was regarded as positive reaction. Individuals that had chronic cough were examined with infectious specialist doctor in clinic of Baqiyatallah Hospital and evaluated with chest X-ray or lung CT scan and sputum exam if they were in need. The inclusion criteria was BCG scar on the arm and exclusion criteria were past history of clinical tuberculosis, HIV infection, use of immunosuppressive drugs and steroids, history of malignancy, acute viral infection and recent history of PPD test within last six months. Data were analyzed with SPSS version 13 software. Chi-square, Fisher exact test and multivariate analysis were used with logistic regression for confounding factors. p-value of <0.05 was considered as significant.

RESULTS

All the study participants were on-duty soldiers were man with mean age of 23.28±1.8 and range between 20 to 31 years old. All of them had BCG vaccination in neonatal age and therefore all of them had BCG scar in theirs arms. The highest education level of the participants was diploma in 305 (66.3%), about 426 (91.8%) were single, 430 (93.1%) lived in Tehran city and remaining from other provinces of Iran. Chronic cough (more than three weeks) was positive in 51 (10.9%) and history of smoking was positive in 35 (7.5%) participants. About 31 (6.7%) had positive PPD skin test and 8 (1.7%) of them had positive

Table 1: Demographic data and PPD skin test in soldiers

Data	Number	Percent
Age		
≤23	281	60.56
>23	183	39.44
Marital status		
Single	426	91.80
Married	38	8.20
Education level		
<Diploma	87	18.90
Diploma	305	66.30
>Diploma	68	14.80
Province living		
Capital city	430	92.60
Non capital	32	7.40
Smoking		
Positive	35	7.50
Negative	429	92.50
Chronic cough		
Positive	51	11.00
Negative	413	89.00
Night fever		
Positive	13	2.80
Negative	451	97.20
Tuberculosis in family		
Positive	4	0.90
Negative	460	99.10
PPD test		
Positive	31	6.70
Negative	433	93.30

Table 2: Data and PPD skin test reaction in soldiers

	PPD		
Data	Positive	Negative	p-value
Education level			
<Diploma	6(6.9%)	81(93.1%)	0.29**
Diploma	16(5.3%)	288(94.7%)	
>Diploma	7(10.3%)	61(89.7%)	
Smoking			
Positive	13(37.1%)	22(62.9%)	0.0001*
Negative	17(4.0%)	411(96.0%)	
Family tuberculosis			
Positive	1(25.0%)	3(75.0%)	0.24*
Negative	29(6.3%)	430(93.7%)	
Chronic cough			
Positive	7(13.7%)	44(86.3%)	0.04*
Negative	23(5.6%)	389(94.4%)	
Night fever			
Positive	7(53.8%)	6(46.2%)	0.0001*
Negative	23(5.1%)	427(94.9%)	
Age			
23 and less	16(5.7%)	264(94.3%)	0.35*
>23	14(7.9%)	163(92.1%)	
Married condition			
Married	5(13.2%)	33(86.8%)	0.08*
Single	22(5.9%)	404(94.1%)	
Living in city			
Capital city	37(6.3%)	402(93.7%)	0.45*
Other provinces	3(9.4%)	29(90.6%)	

**: Chi-square, *: Fisher exact test

test induration size 20-30 mm and one of them that had history of chronic cough was diagnosed with pulmonary tuberculosis by spiral lung CT scan. He was referred for anti tuberculosis treatment. Demographic data are shown in Table 1. Association between PPD reaction was not significantly related with age (p>0.35), education level (p = 0.29) and history of tuberculosis in their family (p = 0.24), but PPD positive test was significantly related with smoking (p<0.0001), chronic cough (p = 0.04) and night fever (p = 0.0001) that is shown in Table 2.

Logistic regression analysis for confounding factors showed that smoking by OR = 12 with 95% CI 4.6-31.3, p<0.0001 and fever by OR = 20.96 with 95% CI 2.7-162.51, p<0.004) had significant association but other variables such as age, marital status, living in city, education level, TB in family and chronic cough had not significant association with tuberculin skin test and these factors could have confounding effect on PPD skin test.

DISCUSSION

In this study, all the participants had BCG scar and about 6.6% of the individuals had positive tuberculin skin test and one of them had sub clinical pulmonary tuberculosis at the time of study.

Tuberculosis is endemic in I.R. Iran and BCG vaccination is used routinely in the program of vaccination in neonates (Ghorbani *et al*., 2007). Therefore, all the participants had history of BCG vaccination in their neonatal age and the scar of BCG also was seen in their arms (Alavi and Sefidgaran, 2008). The accurate diagnosis of latent tuberculosis infection is an important component of any tuberculosis control program and depends largely on the results of skin testing and because of it we diagnosed asymptotic active tuberculosis in one of the participants. Thus, PPD skin test in adults can help diagnosis of latent tuberculosis; however, the appropriate interpretation of skin test results requires knowledge of the possible confounding factors such as previous Bacille Calmette Guérin (BCG) vaccination (Sleiman *et al*., 2007). In here we suggest that PPD skin test was positive in 6.6% of soldiers as other study with cut-off (PPD>10 mm) of skin test (Kallenius *et al*., 2007). Positive tuberculin skin test result has been reported to vary from 0 to 90% in individuals (Chadha *et al*., 2007) with prior BCG vaccination and reactivity and can vary depending on the interval between vaccination and testing (Chadha *et al*., 2007). Perhaps because of this reasons that we saw less number of participants with positive tuberculin skin test (Rowland *et al*., 2006).

A relatively shorter after BCG vaccination can lead to confusion in the correct interpretation of tuberculin skin test. However, PPD skin test giving a positive result after long time should be considered as tuberculosis infection (Rowland *et al*., 2006) as seen in this study (Rowland *et al*., 2006). As 95.4% of soldiers in our study had negative PPD skin test after long time that resembles another study, it suggests that BCG vaccine protection

could have waned after 10-15 years and PPD skin test giving more than 10 mm reaction should be considered as indicative of tuberculosis infection (Alavi and Sefidgaran, 2008).

Tuberculin skin test that gives strongly positive reaction of more than 15 mm is more likely to be caused by tuberculosis infection rather than the effect of previous BCG vaccination. Results of a earlier study (Wang *et al*., 2008) that resembled ours had more than 1.7% of soldiers with positive skin test of more than 20 mm and one of them (12.5%) had active tuberculosis. It is therefore recommended that any case even with the history of BCG vaccination that gives positive skin test of more than 20 mm reaction should be strictly evaluated for the diagnosis of tuberculosis disease (Wang *et al*., 2008). Tuberculin skin test reactions wane more slowly in those that had infection than who had BCG vaccine. That is why in our study some of participants had PPD positive skin test after 20 years of BCG vaccination and that may be due to past tuberculosis infection in them (Storla *et al*., 2008).

In parts of the world where the disease is most prevalent, BCG vaccination in neonatal age is ineffective against adult tuberculosis (Ramin *et al*., 2008).

In present study it was seen that more than 12% of persons with history of BCG vaccination had previous tuberculosis disease. One of the reasons for this is the endemic occurrence of Tuberculosis in Iran (Ramin *et al*., 2008).

Cigarette smoking is known to be a risk factor for the development of pulmonary diseases. In present study, smoking was significantly related to positive PPD skin test and this may be due to the fact that chronic cough in smokers can be mistaken and delayed diagnosis of tuberculosis (Ramin *et al*., 2008).

Differential diagnosis of the unknown origin fever often varies with age and tuberculosis is the most common infectious disease associated with unknown origin fever. In present study, fever had significant relation with the PPD skin test positivity. It has therefore being suggested that the patients with fever of unknown origin should be ruled out for tuberculosis infection (Kucukardali *et al*., 2008).

Cough is a cardinal feature of pulmonary tuberculosis and acute or chronic infection that involves the sinuses, upper airway, lower airway and lungs may lead to acute or chronic cough (Ngang *et al*., 2007). Latent and active tuberculosis often remain undiagnosed in individuals with chronic cough until it is far advanced such as seen in our study that showed one undiagnosed patient with chronic cough and positive PPD skin test that had pulmonary tuberculosis and PPD skin test helped in its diagnosis (Mark *et al*., 2006).

In this study, most of the participants lived in the capital city of Iran and we couldn't confirm relation between PPD skin test reaction and the place of living. However, it is known that early diagnosis and treatment of tuberculosis is usually delayed in rural areas and further studies are required to exactly know its role in the rural areas (Ohkado *et al*., 2008; Romaszko *et al*., 2008).

Present study couldn't find significant relation of positive PPD skin test reaction with education level of the participants. However, a recent study confirmed that low education level can adversely effect early diagnosis and treatment and thereby allow the disease to spread (Armijos *et al*., 2008).

The risk of interfamily tuberculosis transmission is high. Information from familial tuberculosis contact can help to greatly reduce the number of new tuberculosis cases and speed eradication of the disease. However, in our study interfamilial tuberculosis couldn't be confirmed (Wang *et al*., 2008).

This study had several limitations including similar conditions such as urban city living, BCG scar, marital status, narrow range of age and association between these variables. Thus PPD skin test may not be the actual indicator of previous tuberculosis infection or protection offered by BCG vaccination in this study. Further investigation with in different age and socioeconomic groups and variables is recommended for its exact status in tuberculosis infection and diagnosis.

CONCLUSION

This study showed that more than 6.7% of adults with history of BCG vaccination in their neonatal age had positive PPD skin test and 12% of them with PPD more than 20 mm had tuberculosis disease. Therefore, positive PPD in adults with history of BCG vaccination in their neonatal age should be considered as new tuberculosis infection. On the other hand, adults with PPD skin test more than 20 mm must be evaluated for tuberculosis disease and if need be, they should be treated with anti tuberculosis drugs.

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