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The influence of BCG immunisation on tuberculin reactivity and booster effect in adults in a country with a high prevalence of tuberculosis

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ABSTRACT

The relationship of age and previous BCG vaccination with tuberculin skin test (TST) reactivity was investigated to assess the interpretation of TST results in the adult population of Turkey, where there is a high prevalence of tuberculosis and a routine BCG vaccination programme. The influences of age and BCG vaccine status on booster reaction were also evaluated. TST was applied (5 tuberculin units of purified protein derivative intradermally) to two healthy adult groups, namely 98 medical students and 187 elderly people in a retirement home. The TST was considered positive if an induration ≥10 mm in diameter was produced. Subjects (41 elderly people and 39 students) with a reaction <10 mm in diameter were retested 1 week later. There was no significant difference between the students (59.1%) and elderly subjects (58.8%) with respect to positive TST response. No influence of BCG scars on TST reactivity was observed in either group. The booster effect was seen more commonly in the elderly, but the presence of a BCG scar did not influence the booster effect in either group. It was concluded that a positive TST response and booster reaction in adults in high-prevalence countries may be caused by latent tuberculosis rather than previous vaccination.

Keywords BCG, booster effect, *Mycobacterium tuberculosis*, tuberculin reactivity, tuberculosis

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INTRODUCTION

Almost one-third of the world's population is infected with *Mycobacterium tuberculosis*, with an increase of up to 1% new cases being reported each year [1]. In 2001, the annual tuberculosis rate in Turkey was *c.* 26/100 000 population [2]. The Turkish Ministry of Health has aimed to prevent tuberculosis since 1953 with a routine national immunisation programme for newborn children. Until 1998, a first BCG vaccination in the newborn period was repeated after 7, 10 and 17 years following a negative (< 10 mm) tuberculin skin test (TST). After 1998, only two doses were used, the first within 2 months of birth and the second at the age of 7 years.

The TST is still used widely for detection of mycobacterial infections, although several novel diagnostic assays have been developed in recent years. However, TST reactivity may also be observed after BCG vaccination. Factors such as the age at vaccination, time interval, number of doses and booster effect of natural infection affect the TST reactivity associated with BCG vaccination [3–9]. There is no reliable way to distinguish between a reaction associated with vaccination and a reaction caused by *M. tuberculosis* infection. Following the challenge of unvaccinated subjects with 5 tuberculin units (TU) of purified protein derivative (PPD), many workers consider that an induration of >10 mm is positive; however, the significance of a positive reaction in previously vaccinated subjects is still debatable [4,5,7,9,10]. There is a particular need to define the significance of TST results in countries, such as Turkey, that have a high prevalence of infection and a routine BCG vaccination programme.

A single TST may not be satisfactory for the assessment of immunity against *M. tuberculosis.* The immune response may gradually weaken in adults who were vaccinated with BCG or exposed

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to *M. tuberculosis* in childhood, resulting in a negative TST response. A repeated test can restore this reactivity. The booster effect of a second test is observed most strongly 1–5 weeks following the first TST, although the effect is thought to continue for as long as 1 year [11]. However, the TST should be repeated within 1–3 weeks in patients with an initial negative TST result [12].

The present study is the first in Turkey to evaluate the TST reactivity and booster effect in two healthy adult populations belonging to discrete age groups. The study aimed to determine the relationship of age and previous BCG vaccination with TST reactivity, and also the influence of age and vaccine status on the booster reaction.

MATERIALS AND METHODS

TSTs were applied in October 2000 to adult subjects divided into two discrete groups, namely first-year medical students and elderly individuals at a retirement home in Ankara. The students completed self-administered questionnaires to record demographic data such as age and history of exposure to tuberculosis. A similar questionnaire for the elderly subjects was completed with the help of investigators. All subjects with a history of tuberculosis treatment, current immunosuppressive treatment, immunisation with live vaccine within the last 8 weeks, or any circumstance causing an immunocompromised state, were excluded. There was no evidence for active tuberculosis or silent carriage in the study subjects. The presence of a typical BCG scar was accepted as an indicator of past vaccination. BCG scars were identified on the upper third of the arm, usually no more than 4 cm below the shoulder vertex. No TST had been performed on study subjects in the preceding year to their knowledge.

The TST was performed by an experienced physician. Five TU of PPD solution (Biocinetest-PPD; Chiron, Siena, Italy) was used for the test. A steel needle of 27 gauge attached to a 1-mL syringe was used to administer 0.1 mL PPD solution intradermally on the volar surface of the forearm. Subjects were instructed not to scratch or moisten the test area. The induration margins were interpreted by the same physician using the pen method. The test was considered positive if a reactive induration exceeded 10 mm in diameter. Subjects with an induration of <10 mm underwent a second test 1 week later. The booster effect was considered positive if the induration on the second test was >10 mm and at least 6 mm greater than that on the original test. The TST results were analysed according to age and the presence of a BCG scar with the chi-square test.

RESULTS

The retirement home had 302 elderly residents. Of these, 25 were unavailable during the study period, 31 suffered from severe dementia and were unable to respond to queries, and 59 did not consent to the test, leaving 187 study subjects aged 60–100 years. The student group comprised 98 first-year medical school residents aged 17–21 years. A positive reaction (≥ 10 mm) was observed in 58 (59.1%) students and 110 (58.8%) elderly subjects ($p > 0.05$). The mean induration diameter was 8.6 ± 6.0 mm (0–20 mm) in students and 8.7 ± 6.9 mm (0–32 mm) in the elderly group. At least one BCG scar was present in 82 (83.6%) students and 37 (19.7%) elderly subjects, and nine students and two elderly subjects possessed double scars. The presence of BCG scars did not influence the TST response in either group (Table 1).

Only one of 40 students with a negative TST response (< 10 mm) and 36 of 77 elderly subjects refused to undergo a second test. Thus, 41 elderly subjects and 39 students received the second test. The booster effect on both groups is shown in Table 2. The 'negative' results included eight elderly subjects and two students who had an induration that was at least 6 mm larger compared to the first test, but which did not exceed 10 mm. Overall, the booster effect was more common in the elderly group, but the presence of a BCG scar did not influence the booster effect significantly in either group. Table 3 shows that the booster effect diminished gradually with increasing age in the elderly group, but this effect was not statistically significant ($p > 0.05$).

Table 1. TST responses according to BCG scar presence

		No. (%) with diameter of PPD induration:			
Group	**Scar**	**0 mm**	**1–9 mm**	**> 10 mm**	**Total**
Students	Absent	2 (12.5)	4 (25.0)	10 (62.5)	16
	Present	15 (18.3)	19 (23.1)	48 (58.5)	82
	Total	17 (17.3)	23 (23.4)	58 (59.1)	98
Elderly	Absent	12 (18.0)	45 (30.0)	93 (62.0)	150
	Present	6 (16.2)	14 (37.8)	17 (45.9)	37
	Total	18 (9.6)	59 (31.5)	110 (58.8)	187

Table 2. Distribution of the booster effect between groups

		No. showing booster effect (%)				
		Elderly		Students		
		Positive	**Negative**	**Positive**	**Negative**	**p value**
Scar	Present	3 (30.0)	7 (70.0)	1 (3.0)	32 (97.0)	< 0.05
	Absent	13 (41.9)	18 (58.1)	–	6 (100)	< 0.05
	Total	16 (39.0)	25 (61.0)	1 (2.6)	38 (97.4)	< 0.05
p value		> 0.05	> 0.05	> 0.05	> 0.05	

Table 3. Frequency of the booster effect according to age groups in the elderly population

Age group (years)	Booster effect (%)		Total
	Negative	Positive	
60–69	3 (37.5)	5 (62.5)	8
70–79	9 (60)	6 (40)	15
80 +	13 (72.2)	5 (27.8)	18
Total	25 (61)	16 (39)	41

No active cases of tuberculosis were reported in the succeeding 3 years in either the elderly subjects in the retirement home or the medical students.

DISCUSSION

There have been many previous studies of TST positivity in adult populations, with rates of >30% being reported in high-prevalence countries [6,9,13]. The present study also detected high positive rates in students and elderly subjects of 59.1% and 58.9%, respectively. However, none of the positive TST subjects had any signs of active tuberculosis during the study period and, as found in other studies [14–16], none developed disease within 3 years. These data suggested that a high positive TST response rate was linked with a high prevalence of infection, but that it did not predict the development of active tuberculosis in the short term.

The positive TST response rate increases with age, whether or not there has been previous vaccination with BCG [6,8]. TST positivity rates were reported to be 42% among subjects aged >75 years, compared with 3.1% in college and university students in the USA [15,17]. In a previous study from Turkey, a TST response of >10 mm was reported for 67.3% of 2835 subjects aged 6–82 years, with a particular increase in the positive rate for subjects aged >18 years [18]. The present study found high positive rates in both age groups studied, with no statistical difference. The high positive rates may be a result of the high prevalence of tuberculosis in Turkey. In addition, TST positivity associated with neonatal BCG vaccination may be superimposed on the immunity that develops following natural infection with increasing age. Cross-reactions caused by the presence of atypical mycobacteria are another possibility, but there are limited data in Turkey regarding the incidence of atypical mycobacterial infections.

A typical scar forms in 90–95% of individuals following BCG vaccination [19]. As in other studies, the presence of a BCG scar was accepted as an indicator of previous vaccination. Among the students, 83.6% had a BCG scar as a result of the routine vaccination programme. However, only 19.7% of the elderly subjects had BCG scars, which might be attributed to limited catch-up vaccination campaigns, or specific events such as military service or work in a health care facility.

Previous BCG vaccination is one of the most common reasons for false-positive TST reactions. A positive TST reaction of >10 mm, which develops in 90% of subjects within 3 months of immunisation, may decrease with time [4]. This period is reported to vary from 1 to 25 years, but BCG-induced positive TST reactivity lasts longer following immunisation in adulthood [9]. Some reports suggest that a TST response of >10 mm in adults cannot be linked reliably with neonatal immunisation in low-prevalence countries [4,20]. In a meta-analysis, it was reported that a TST reaction of >15 mm was unlikely to be the result of BCG vaccination if 15 years had elapsed [10]. However, evaluation of TST reactions in immunised subjects in high-prevalence countries is controversial [9]. The present study observed no influence of BCG scar on TST response in either age group, which may indicate that TST positivity in the adult population was related to natural infection rather than previous vaccination. Therefore, detection of TST positivity in adults living in countries with routine vaccination should not necessarily be attributed to previous BCG vaccination, and the individual should be evaluated for tuberculosis.

Repeating the TST for the diagnosis of latent tuberculosis increases the sensitivity of the test method. An individual should be considered as previously infected if a positive reaction is observed after the second test. The booster effect associated with repeated TSTs is encountered more frequently in elderly subjects [21]. Van den Brande and Demedts [22] observed that 29% of elderly subjects reacted in the first test, increasing to 43% following the second test. In addition, a decreasing booster effect with increasing age was found. The present study also observed a slight decrease in the booster effect with increasing age, but this was not statistically significant.

Another major determinant of the booster effect is a history of previous BCG vaccine exposure

[23,24]. Menzies *et al.* [25] studied a group of students and found a statistically significant difference for the booster reaction between previously vaccinated (10.1%) and unvaccinated students (2.5%). A similar correlation was not found in the present study, possibly because age is a stronger determinant of the booster effect in high-prevalence countries.

In conclusion, interpretation of a positive TST response in an individual should take local epidemiological data into account. In this study, the positive TST reaction rate was found to be high in adult populations, irrespective of BCG immunisation. These findings suggest that a positive TST response and the booster reaction in high-prevalence countries are usually caused by latent tuberculosis rather than previous vaccination. Thus, the results support the WHO recommendations [26] that, while TST is a useful diagnostic method, revaccination is not recommended and TST should not be used for this purpose.

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