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SHORT COMMUNICATIONS

Effect of BCG vaccine on tuberculin skin tests in 1–6-year-old children

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Bacillus Calmette Guerin (BCG) vaccination used in the prevention of tuberculosis may cause problems in interpreting the tuberculin skin test (TST), which is commonly used in the diagnosis of infection. A limited number of studies have been undertaken to investigate how length of time after BCG vaccination affects TST results. TST induration values of unvaccinated children were compared with those of children vaccinated once in order to determine the changes in TST responses after BCG vaccination. Mantoux TSTs were administered to 1145 children aged 1–6 y and induration was measured at 72 h. BCG scar status and average TST induration diameters were identified for each age group.

Conclusion: Average TST induration in vaccinated children is significantly higher than that in unvaccinated children, and in the vaccinated group there is no statistically significant difference between induration values in the different age groups. BCG vaccination at the age of 0–2 mo affects TST for a long period and this condition does not change until 6 y of age.

Key words: *Childhood tuberculosis, tuberculin skin test, tuberculosis*

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Dr Robert Koch declared the discovery of *Mycobacterium tuberculosis* as a causative agent of tuberculosis (TB) on 24 March 1882, in Berlin. Up until that time, one person in seven died of TB in Europe and America (1). Effective drugs against *M. tuberculosis* were not found until 1950. Owing to increasing drug resistance and the failure of national programmes, little progress could be achieved from those anti-tuberculosis drugs. As a result, almost 200 million people have died of TB since 1882, and the deaths have continued at the beginning of the 21st century (2). According to WHO's 1998 reports on the struggle against TB, every four seconds one person becomes infected with TB, and one person dies every ten seconds. WHO recommends mass vaccination in countries where the incidence of TB is high. In Turkey, this vaccination programme has been conducted since 1953 by the Ministry of Health, which still recommends two doses of vaccination, at 2 mo of age and again at 7 y of age. BCG vaccination is administered by the TB clinics of the Ministry for the Prevention and Treatment of TB to 2-mo-old babies, and at the age of 7 y all children receive BCG vaccine at school. However, BCG vaccination causes some difficulties in interpretation of tuberculin skin tests (TSTs). There is no reliable method to differentiate the reaction caused by vaccination, infection with TB or atypical mycobacteria. Many authorities accept an induration of 10 mm or more in unvaccinated children as a response to 5 tuberculin units (TU) PPD as the criterion for infection with TB. In vaccinated children, the authorities offer different values such as 10, 15 or 20 mm to be used as the criteria for infection with *M. tuberculosis* (3–6). Only a few studies have investigated how long the vaccination affects TST values and there is no consensus on this subject. In some studies the length of time is reported to be less than 1 y, in others 3.5 or 10 y (7, 8).

This study was conducted in Istanbul, from 1 April to 31 August 2000. Children from three different primary school preparatory classes, one daycare centre and from our hospital outpatient clinics were included in the study. The schools were chosen from different parts of the city in order to maintain the representativeness of the study population versus the whole child population in actual age groups in Istanbul. A total of 1145 children aged 1–6 y were randomly selected and given TSTs using the Mantoux technique. Before application of the TST, the presence of BCG scars was confirmed under

Table 1. BCG scar status and average tuberculin skin test (TST) induration diameters.

BCG scar status	No./percentage	Average value
Without scar	135 (17%)	2.8 ± 2.6
With scar	650 (83%)	6.1 ± 5.1
Total	785	

Table 2. Tuberculin skin test (TST) induration average values of age groups according to BCG status.

	Without scar	With scar
1-y-old	2.3 ± 1.4	6.6 ± 5.2
2-y-old	3.2 ± 2.8	7.2 ± 5.8
3-y-old	3.0 ± 3.0	6.5 ± 5.3
4-y-old	2.5 ± 2.2	4.6 ± 3.9
5-y-old	3.4 ± 4.0	6.2 ± 5.3
6-y-old	2.5 ± 1.9	5.3 ± 5.0

direct light and reported. The test was performed by four experienced physicians, intradermally on the anterior part of the left forearm. Five TU PPD solutions (PPD-S) were used for the test. Parents were instructed to prevent their children from scratching and to keep the test area dry. The PPD solutions used were produced by Canada Inter-vax Biologicals Ltd., and they all had the same serial number. Seventy-two hours after the tests had been given, the borders of the indurations were identified by pen method, and horizontal and vertical diameters were measured by an experienced physician. The diameter of the erythema was not taken into account. Children with a reaction of more than 10 mm were examined, and they were all given chest roentgenograms. Parents were questioned in detail about household contacts. No active TB case was identified. All of the children included in this study were healthy. Out of 1145 children, 360 were excluded from the study because they did not come to the TST evaluations on time. Of these 360 children, 94 were from primary schools, 48 were from daycare centres and 218 were from hospital outpatient clinics. Concerning the vaccination status of the excluded children, 294 had scars and 66 were without scars. For these children, whether with or without scars, no statistical difference was found when their age distribution was compared with that of children who were included in the study. The study was completed with 785 children. Statistical analysis was done using χ^2, one-way ANOVA and Tuhey–Kramer tests.

The subjects were grouped according to age and the presence of BCG scars. Within each group, subgroups were also made according to the response to the TST, defined as induration diameters of 0–5 mm, 6–10 mm, 11–15 mm, 16–20 mm and >20 mm. The mean age of cases was 3.3 ± 1.7 y. Of the 785 children who completed the study, 396 (50.4%) were female and 389 (49.6%) were male. BCG scar status and average TST induration diameters are reported in Table 1.

A statistical difference was found between the groups with and without scars ($p < 0.001$). All of the children making up the group with one scar were those vaccinated at 0–2 mo of age. The distribution values of cases grouped according to age, BCG scar status and TST induration are presented in Tables 2, 3 and 4. Among the children with scars, the TST responses of 124 were between 0 and 5 mm (Table 4), 102 of these children showing a response of 0 mm. Among the children without scars, the TST responses of 388 were between 0 and 5 mm (Table 3), with 279 of these children showing a response of 0 mm.

In all age groups, when the distribution of TST induration values is taken into account, there are

Table 3. Distribution of tuberculin skin test (TST) responses according to age groups among children without scar.

	0–5 mm	6–10 mm	11–15 mm	16–20 mm	>-20 mm	Total
1-y-old	31 (96.8%)	1 (3.2%)	0	0	0	32
2-y-old	21 (87.5%)	2 (8.3%)	1 (4.2%)	0	0	24
3-y-old	17 (89.4%)	1 (5.3%)	1 (5.3%)	0	0	19
4-y-old	20 (95.2%)	0	1 (4.8%)	0	0	21
5-y-old	19 (86.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	0	22
6-y-old	16 (96.1%)	1 (5.9%)	0	0	0	17

Table 4. Distribution of tuberculin skin test (TST) responses according to age groups among children with scar.

	0–5 mm	6–10 mm	11–15 mm	16–20 mm	>20 mm	Total
1-y-old	58 (54.4%)	25 (23.3%)	17 (15.8%)	7 (6.5%)	0	107
2-y-old	60 (50.8%)	25 (22.8%)	23 (19.6%)	4 (3.4%)	4 (3.4%)	118
3-y-old	70 (56%)	24 (19.2%)	22 (17.6%)	9 (7.2%)	0	125
4-y-old	73 (73%)	18 (18%)	7 (7%)	2 (2%)	0	100
5-y-old	59 (59%)	22 (22%)	15 (15%)	2 (2%)	2 (2%)	100
6-y-old	68 (68%)	15 (15%)	13 (13%)	4 (4%)	0	100

Table 5. Comparison of PPD values in age groups.

Age groups (y)	With scars	Statistical evaluation
1–2	$p > 0.5$	Not significant
1–3	$p > 0.5$	Not significant
1–4	$p < 0.01$	Significant
1–5	$p > 0.5$	Not significant
1–6	$p < 0.1$	Slightly significant
2–3	$p > 0.5$	Not significant
2–4	$p < 0.001$	Advanced significant
2–5	$p > 0.1$	Not significant
2–6	$p < 0.01$	Significant
3–4	$p < 0.01$	Significant
3–5	$p > 0.5$	Not significant
3–6	$p < 0.1$	Slightly significant
4–5	$p < 0.05$	Slightly significant
4–6	$p > 0.1$	Not significant
5–6	$p > 0.1$	Not significant

significant statistical differences between children with and those without scars ($p < 0.001$). Age groups were evaluated statistically to determine whether there was any change in TST induration values in the years following BCG vaccination. The results are shown in Table 5.

When all age groups were taken into account, no significant change was found between ages.

Although TB is a curable disease, its diagnosis is difficult and treatment is prolonged. Thus, the compliance of patients is poor and this causes healthy people to come under threat of infection. The increasing number of resistant TB cases not only causes the spread of the disease but also increases the risk of failure of treatment. Although new methods have been developed over the years in the diagnosis of TB, because of the high costs and variations in their sensitivity they are not a superior alternative to TST. Since the culture positivity is low, TST plays an important part in the diagnosis of childhood TB. Turkey, with its high incidence of TB, has a high BCG vaccination coverage. Although BCG vaccination protects against TB meningitis and miliary TB, it can make interpretation of TSTs problematic. According to the American Academy of Pediatrics (AAP), if there is no risk in children over 4 y of age, an induration of 15 mm and more should be regarded as infection. If there is any risk factor, this value is accepted to be 10 or 5 mm. The AAP reports a maximum induration of 10 mm associated with vaccine, whereas some authors accept this value as 12 and 15 mm (4, 6, 10). The American Thorax Association accepts that a maximum induration of 10 mm develops as a response to BCG vaccination. The effect of BCG vaccination on TST induration values disappeared 3–5 y after vaccination (7, 8). In another study conducted in vaccinated children, it has been reported that induration values of 3–19 mm could be accepted (8). In Turkey, there have not been sufficient studies on this subject. In one of the studies it is shown that some changes occurred in TST response after vaccination of between 6.5 mm and 11 mm. Maximum induration value was 10–11 mm and this value has been reached within one year of vaccination (9). These values decreased in the subsequent years. The Ministry of Health has accepted an induration of 10 mm or more as "positive" in unvaccinated children. This value has been accepted as 15 mm and more in vaccinated children (11).

Gulnar and Bulut followed 41 subjects with TST responses of 20 mm and more for one year but found no active TB cases (8). Lockman et al. reported that positive reactions ($\geq$10 mm induration) were not associated with age, time since BCG vaccination, clinical signs or symptoms of TB, nutritional status, overcrowding, recent measles, or polio immunization (12). In unvaccinated and vaccinated children we found average TST induration values of 2.8 ± 2.5 mm and 6.0 ± 5.1 mm, respectively. In each age group, there is a statistically significant difference between vaccinated and unvaccinated children. In the vaccinated group, there is no statistically significant difference between induration values in the different age groups. This leads us to believe that BCG vaccination at the age of 0–2 mo has a long-time effect on TST and this condition does not change until 6 y of age, as found in our study group. However, there are various views on this subject (13, 14). TST reaction may also be influenced by previous vaccination with live viral vaccines. According to the vaccination schedule in Turkey, children are given measles, measles-mumps-rubella (MMR) and polio vaccines at the 9th, 15th and 18th mo, respectively. Children also receive booster doses of polio and MMR at 4–6 y of age. The relatively high proportion of children with scars and with a reaction of less than 6 mm could be explained by the possible influence on vaccination of these viral vaccines in the routine programme. Consequently, TST is affected by many factors such as vaccine type used, dosage of vaccine, application method, the dosage and quality of the TST, the age of the person vaccinated, the immunity and nourishment status of the person vaccinated, experience of the person performing the BCG vaccination and the TST (16). Furthermore, if *Mycobacterium* infection is prevalent in the community, the probability of the high TST response is strong. Thus, different results of different studies could be acceptable.

Studies in which tuberculin reactivity is evaluated in vaccinated children have been done in developed countries in which TB is not a problem. However, it is important to carrry out these kinds of studies in developing countries in which TB is still a challenging health problem. We believe that widespread studies in which TST responses are evaluated in different age groups in different regions should be undertaken. Evaluations would be more appropriate if the epidemiological characteristics of countries were taken into account.

References

1. Grange JM. Mycobacterial diseases in the world: yesterday, today and tomorrow. In: Radladge C, Stanford J, Grange JM, et al. The biology of mycobacteria. London: Academic Press; 1989: 3
2. World Health Organization. TB a global emergency. WHO/TB/98: 177
3. Crofton J, Horne N, Miller F. Clinical tuberculosis. London: Macmillan, 1992: 29–116
4. American Academy of Pediatrics, Tuberculosis. In: Peter G, editor. 1997 red book: report of the Committee on Infectious Diseases. 24th ed. 1997: 541–62
5. Coulter JBS. Tuberculosis. In: Campbell AGM, McIntosh N. Forfar & Arneil's textbook of pediatrics. 5th ed. Edinburgh: Churchill Livingstone, 1998: 134–48
6. Ildirim I, Hacimustafaoglu M, Ediz B. Correlation of tuberculin induration with the number of BCG vaccines. Ped Infect Dis J 1995; 14: 1060–3
7. American Thoracic Society. Diagnostic standards and classification of tuberculosis. Am Rev Respir Dis 1990; 142: 725–35
8. Gulnar SB, Bulut BU. Influence of vaccination on tuberculin reactivity in healthy Turkish school children. Acta Paediatr 1997; 86: 549
9. Ozcan C, Alpar R, Pehlivan E. The examination of the relation between E. tuberculosis incidence and some important variables via stepwise cokim regression. J Izmir Thorax Hosp 1998; 6: 7–10
10. Starke JR, Jacops RF, Jereb J. Resurgence of tuberculosis in children. J Ped 1992; 120: 839–55
11. Ministry of Health, Chief Administration for the Prevention and Treatment of Tuberculosis. Guidelines for the prevention and treatment of tuberculosis: 1998
12. Lockman S, Tappero JW, Kenyon TA, Rumisha D, Huebner RE, Binkin NJ. Tuberculin reactivity in a pediatric population with high BCG vaccination coverage. Int J Tuber Lung Dis 1999; 3: 23–30
13. Al-Kassimi FA, Abdullah A, Al-Orainey IO, Benar AB, Al-Hajjaj MS, Al-Majed S, Al-Wazzan A. The significance of positive Mantoux reactions in BCG vaccinated children. Tubercle 1991; 72: 101–4
14. Eskiocak M, Bay A, Suncak R, Gurses N. Predictive value of a 24 hour tuberculin skin test evaluation. Arch Dis Child 1997; 76: 452–3
15. Del Castello AM, Rook G. Tuberculosis in children. Curr Opin Pediatr 1995; 7: 612

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