

The prevalence of tuberculin skin test positivity and the effect of BCG vaccinations on tuberculin induration size in the eastern Mediterranean region of Turkey

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Aim: To evaluate the prevalence of tuberculin skin test (TST) positivity in Kahramanmaraş and interpret the size of purified protein derivative (PPD) induration with respect to the number of Bacillus Calmette-Guerin (BCG) scars and other factors.

Materials and methods: A total of 2979 school children between the ages of 7 and 17 years were evaluated. On the basis of socioeconomic levels, 11 schools were selected and categorized into 3 subgroups: schools in the suburbs of the city (Group 1), schools in the city center (Group 2), and private schools (Group 3). Children were injected with 5 TU/0.1 mL of PPD and the sizes of induration were measured after 72 h. The number of BCG scars and the sizes of induration were recorded for each pupil.

Results: The TST was positive in 6.3% of the nonvaccinated students and in 7.5% of the vaccinated students ($P > 0.05$). The number of BCG vaccination scars was 0 in 174 children (5.8%), 1 in 1232 children (41.4%), 2 in 1516 children (50.9%), 3 in 54 children (1.8%), and 4 in 3 children (0.1%). The mean diameter of the size of the PPD induration for 0, 1, 2, 3, and 4 BCG vaccinations was 2.50 ± 4.05 mm, 5.60 ± 5.11 mm, 8.49 ± 5.09 mm, 8.46 ± 4.38 mm, and 7.66 ± 6.80 mm, respectively. The size of the induration was greatest in students vaccinated twice ($P < 0.05$). The TST positivity rate was highest in children 11-13 years of age ($P < 0.05$).

Conclusion: The BCG vaccination rate was higher in Kahramanmaraş, whereas the TST positivity rate was lower. The factors that affected the size of the PPD induration were the number of vaccination scars and the age of the subject.

Key words: Bacillus Calmette-Guerin vaccination, tuberculin skin test, tuberculosis

Kahramanmaraş il merkezinde tüberkülin deri testi pozitifliği prevalansı ve BCG aşılmasının tüberkülin deri testi endürasyonu üzerine etkisi

Amaç: Bu çalışmanın amacı Kahramanmaraş il merkezinde tüberkülin deri testi (TDT) pozitifliğini değerlendirmek ve TDT endürasyon büyüklüğünün Bacillus Calmette-Guerin (BCG) skar sayısı ve diğer faktörlere göre değişimini yorumlamaktır.

Yöntem ve gereç: Çalışmada yaşları 7 ve 17 arasında değişen toplam 2979 okul çocuğu değerlendirildi. Sosyoekonomik seviyeye göre 11 okul seçildi ve bu okullar gecekondü (grup 1), şehir merkezi (grup 2) ve ilkokullar (grup 3) olarak alt gruplara ayrıldı. Öğrencilerin BCG skar sayıları kaydedildi ve 5 TU 0,1 ml PPD enjekte edildikten 72 saat sonra endürasyon büyüklüğünün ölçümü yapıldı.

Received: 17.08.2010 – Accepted: 12.10.2010

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Bulgular: BCG'siz öğrencilerde TDT pozitiflik oranı % 6,3, BCG'lilerde ise % 7,5 olarak bulundu ($P > 0,05$). Çalışmaya alınan öğrencilerden 174'ünde (% 5,8) BCG skarı yoktu, 1232'sinde (% 41,4) bir adet, 1516'sinde (% 50,9) iki adet, 54'ünde (% 1,8) üç adet, 3'ünde (% 0,1) dört adet BCG skarı mevcut idi. Ortalama TDT endürasyon reaksiyonu aşısız öğrencilerde $2,50 \pm 4,05$ mm, tek aşılı öğrencilerde $5,60 \pm 5,11$ mm, iki aşılılarda $8,49 \pm 5,09$ mm, üç aşılılarda $8,46 \pm 4,38$ mm ve dört aşılılarda ise $7,66 \pm 6,80$ olarak tespit edildi. TDT'nin endürasyon çapı iki BCG aşısı bulunanlarda belirgin genişti ($P < 0,05$). TDT pozitifliği 11-13 yaş grubunda daha yüksekti ($P < 0,05$).

Sonuç: Kahramanmaraş ilinde BCG ile aşılama oranı ülke genelinden daha yüksekti ve TDT pozitiflik oranları da oldukça düşüktü. BCG skar sayısı ve yaş TDT endürasyon büyüklüğünü etkileyen faktörlerdi.

Anahtar sözcükler: Bacillus Calmette-Guerin aşılması, tüberkülin deri testi, tüberküloz

Introduction

Tuberculosis (TB) remains a major health problem, especially in developing countries. The World Health Organization (WHO) estimates that 8 million adults and 1.3 million children are diagnosed with TB annually and 3 million adults and 450,000 children die from TB. Estimating the number of TB patients and implementing effective treatments are the major goals of TB eradication programs. The major role of the Bacillus Calmette-Guerin (BCG) vaccination is the prevention of serious and life-threatening diseases such as disseminated tuberculosis and tubercular meningitis in children (1-3). The BCG vaccine does not prevent infection with *M. tuberculosis* (4). A metaanalysis suggested that BCG is 50% effective in preventing pulmonary TB in adults and children, while the protective effect for disseminated and meningeal TB appears to be 50%-80% (5). There is no evidence that BCG prevents infection with *Mycobacterium tuberculosis*. Vaccination with BCG is compulsory for all infants in Turkey. The first vaccine is administered in the third month and the second vaccine is administered at the age of 7 years. The Turkish Health Ministry also recommends BCG vaccination when tuberculin induration is < 5 mm. The WHO recommends a single dose of BCG vaccine after birth in all countries with a high incidence of TB infection (2).

The tuberculin skin test (TST) is an important tool for the detection of TB infection (6). It is especially significant for detecting TB-infected pupils in countries with a low incidence of TB where the BCG vaccine is not regularly used as part of TB control (7). Although previous vaccination with BCG in childhood decreases the value of the procedure in Turkey, the TST is still used for diagnosing childhood

TB infection (8). The TST indicates TB infection, but does not indicate TB disease (9). It is an easy technique for showing latent infection in pupils that have had contact with a TB patient and is also ideal for screening large numbers of people (10). However, there is no clear indication whether TST positivity is due to BCG use or atypical mycobacteria. The TST reaction is directly correlated with the number of BCG vaccination scars, but it is inversely correlated with the period of BCG vaccination (11).

In this study, we aimed to evaluate the prevalence of TST positivity among school children between 7 and 17 years of age and interpret the size of purified protein derivative (PPD) induration with respect to the number of BCG scars and other factors.

Materials and methods

The study was conducted among school children between 7 and 17 years of age in the city of Kahramanmaraş (located in the eastern Mediterranean region of Turkey) between November and December 2006. The sample size of children was based on an assumed TST positivity rate of 40% (95% confidence interval). A sample size of 2979 children was sufficient to establish whether TST positivity was present. Schools were grouped into 3 clusters according to socioeconomic levels, with categorization as follows: schools in the suburbs of the city (Group 1), schools in the city center (Group 2), and private schools (Group 3). A random selection method was used in order to choose 11 schools from each cluster.

Prior to the beginning of our study, approval was granted by the Ministry of National Education and the ethics committee, and signed informed consents

were obtained from the parents of all children. Parents were also given a set of questionnaires regarding the health background and history of their children and were asked to submit written documents and statements.

PPD was administered to children by 2 experienced physicians using the Mantoux method, regardless of whether the subjects had BCG scars or not. The PPD solution was injected intradermally into the upper two-thirds of the volar surface of the left forearm. Children were injected with 5 TU/0.1 mL of PPD-RT23 (Tween-80) and the sizes of the induration were determined within 72 h of the injection. The diameter of the PPD induration was measured along and transverse to the longitudinal axis of the arm 72 h after the injection by a physician using the ball-point technique and a transparent millimeter-scale plastic ruler. Those children who had viral infections, such as varicella, measles, mumps, and influenza, or who had been given live-virus vaccines within the last 20 days, were not considered in this study. Children who had had symptoms after the PPD injection or the BCG vaccination within the last 6 months were also excluded. In accordance with the national TB guidelines, a 10-mm cut-off point was used in children with no BCG scar and a 15-mm cut-off point was used in children with a BCG scar (9). Pupils who had a positive TST were referred to the Kahramanmaraş TB Prevention and Treatment Center for further TB evaluation.

For all measured parameters, statistical analyses of between-group differences were performed using ANOVA, followed by a post hoc Tukey test. The Pearson correlation coefficient was used to evaluate the degree of correlation between the parameters. Proportions were compared using the chi-square test. $P < 0.05$ was considered statistically significant and all analyses were performed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Of the 2979 students, 1495 (50.2%) were boys and 1484 (49.8%) were girls. In terms of regional distribution, there were 939 (31.5%) students in Group 1, 1226 (41.2%) in Group 2, and 814 (27.3%) in Group 3. The mean age of girls and boys was 12.23

± 3.13 and 12.12 ± 3.17 years, respectively. Children were classified as having no BCG vaccination scars, 1 BCG vaccination scar, 2 BCG vaccination scars, 3 BCG vaccination scars, or 4 BCG vaccination scars. The number of children having 0, 1, 2, 3, and 4 vaccination scars was 174 (5.8%), 1232 (41.4%), 1516 (50.9%), 54 (1.8%), and 3 (0.1%), respectively. The BCG scars of children were also compared according to regions. The percentage of children without BCG scars was 8.1% in Group 1, 5.4% in Group 2, and 3.9% in Group 3. The number of BCG scars was compared with respect to these groups and the rate of children with no BCG scars in Group 1 was higher than in Groups 2 and 3 ($P < 0.01$). The mean diameter of the PPD induration for Groups 1, 2, and 3 was 6.13 ± 5.23 mm, 7.51 ± 5.42 mm, and 7.03 ± 5.21 mm, respectively (Table 1). The mean diameter of the PPD induration was found to be significantly different among the 3 groups using variance analysis and Tukey's post hoc test ($P < 0.05$).

The number of children with TST positivity was 52 (5.5%) in Group 1, 128 (10.4%) in Group 2, and 39 (4.8%) in Group 3. In comparing TST positivity with respect to regions, the rate was significantly higher in Group 2 ($P < 0.001$).

Overall TST positivity was found in 219 (7.4%) children and, when compared with respect to gender, the rate was 7.8% in boys and 6.8% in girls ($P > 0.05$).

The TST was positive in 208 (7.5%) children with at least 1 BCG scar, while the TST was positive in 11 (6.3%) of 174 children who had no BCG scars ($P > 0.05$). When comparing TST positivity with respect to the number of BCG scars, the TST positivity rate was higher in children with 2 scars ($P < 0.001$).

The number of BCG vaccination scars was 0 in 174 children (5.8%), 1 in 1232 children (41.4%), 2 in 1516 children (50.9%), 3 in 54 children (1.8%), and 4 in 3 children (0.1%) The mean diameter of the size of the PPD induration for 0, 1, 2, 3, and 4 BCG vaccinations was 2.50 ± 4.05 mm, 5.60 ± 5.11 mm, 8.49 ± 5.09 mm, 8.46 ± 4.38 mm, and 7.66 ± 6.80 mm, respectively. The size of the induration was greatest in pupils that had been vaccinated twice ($P < 0.05$; Figure 1). The mean diameter of the PPD induration in children with 1, 2, or more BCG scars was significantly different using variance analysis and post hoc testing ($P < 0.001$). Information on the

Table 1. Mean diameters of PPD induration according to regional groups and number of scars.

Regional group	Number of scars	Number of persons (n)	Mean diameter of PPD (mm)
Group 1	0 BCG	76	1.56 ± 3.42 mm
	1 BCG	400	5.15 ± 5.13 mm
	2 BCG	447	7.79 ± 4.92 mm
	3 BCG + 4 BCG	16	6.00 ± 4.25 mm
Group 2	0 BCG	66	3.18 ± 4.43 mm
	1 BCG	489	6.25 ± 5.31 mm
	2 BCG	651	8.85 ± 5.16 mm
	3 BCG	20	8.75 ± 4.98 mm
Group 3	0 BCG	32	3.31 ± 4.27 mm
	1 BCG	343	5.18 ± 4.70 mm
	2 BCG	418	8.69 ± 5.096 mm
	3 BCG + 4 BCG	21	9.95 ± 3.35 mm

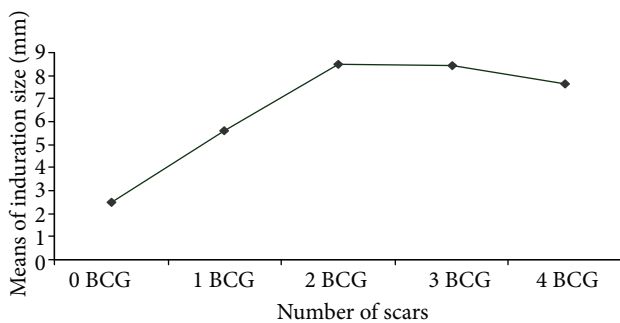


Figure 1. Mean diameters of indurations with regard to the number of scars.

number of scars and the size of the PPD induration was evaluated by correlation analysis; a moderate correlation existed ($r = 0.324$, $P < 0.001$). The mean PPD induration diameter was 16.51 ± 2.46 mm in 260 children who were TST-positive.

Children were further classified into the following 3 age groups: 7-10 years of age, 11-13 years of age, and 14-17 years of age. The mean size of the PPD induration was measured for each group and was

determined to be 5.62 ± 5.05 mm for the group 7-10 years of age, 8.32 ± 5.33 mm for the group 11-13 years of age, and 7.11 ± 5.31 mm for the group 14-17 years of age. The mean PPD diameter was shown to be significantly different between the 3 groups using variance analysis ($P < 0.001$; Figure 2). A positive correlation was detected between age and TST positivity ($P < 0.001$). After being identified as TST-positive, one child was diagnosed with TB and antituberculosis treatment was initiated.

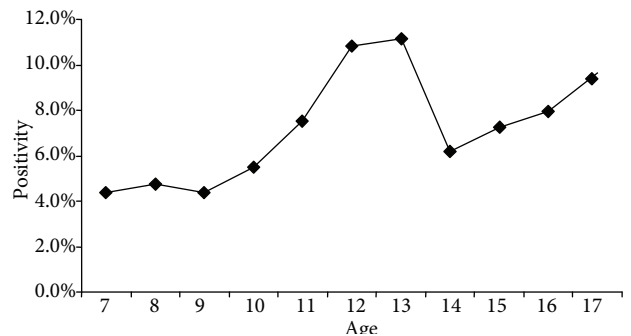


Figure 2. Distribution of TST-positive children in terms of age.

Discussion

Treatment and vaccination programs, population screening, and diagnosis of TB in childhood are very important tools for public health studies (3). TST is a valuable test used to predict the incidence of TB; however, there is no clear indication whether increased PPD values in children are due to BCG vaccination or TB infection (12,13). It is also not clear how many millimeters of induration should be considered positive. Repeated BCG vaccinations, age, PPD solution content, repeated doses of vaccine, personal nutrition, and immunologic status may confound the interpretations of the TST (9). In Turkey, it is difficult to interpret PPD indurations in different groups and this remains a subject for further research.

In Turkey, no standard approaches exist for managing TST positivity. The TST is generally considered positive if the induration size is >10 mm in children having a BCG scar; in some studies, however, an induration size >15 mm is considered positive (14). Şakar et al. (13) found a TST positivity rate of 21.2% in school children between the ages of 7 and 18 years in Manisa. The PPD was considered positive if the induration size was >10 mm. Other studies that considered PPD-positive results to be >6 mm in pupils with no BCG scar and >10 mm in

pupils with a recent BCG scar reported TST positivity rates of 4.1%-9.1% and 43.2%-56.2%, respectively (15,16). Another study that used a 10-mm cut-off point reported TST positivity rates of 1.5%-13.5% in pupils with no BCG scar and 20.2%-67% in pupils with a BCG scar (14). Most of these studies included first- and fifth-grade elementary school students (15-18). The TST positivity rates in Turkey are shown in Table 2.

In the current study, a 10-mm cut-off point was used in children with no BCG scar and a 15-mm cut-off point was used in children with a BCG scar, in accordance with the national TB guidelines. TST positivity was found in 6.3% of children with no BCG scar, 7.5% of children with at least 1 BCG scar, and 7.4% of the general population of the study. The TST positivity rate was lower than that reported in other studies (12-28,29). This may be a result of using a 15-mm cut-off point for a positive TST.

TST positivity rates show variation based on the regions studied. Kolsuz et al. (14) reported a TST positivity rate of 2% in a region of low socioeconomic and cultural development in the city of Eskişehir. In a study that Uzun et al. (22) conducted with children who migrated to the city center from villages, the rate of children having no BCG scar was reported as 66% and the TST

Table 2. Prevalence of TST positivity in different studies.

Study	Number of persons included	Region	Age group	TST Positivity	Cut-off point of PPD
Akkaya et al. 1994 (12)	2133	Isparta	0-15 and >15	63%	≥10 mm
Uzun et al. 1998 (22)	377	Van	0-17	48%	≥10 mm
Uçan et al. 1998-1999 (21)	2835	İzmir, Nazilli, Artvin	6-82	69.3%	≥10 mm
Kolsuz et al. 2000 (14)	2417	Eskişehir	7	6.5%	BCG(-): >10 mm BCG(+): >15 mm
Şakar et al. 2001 (13)	438	Manisa	7-18	21.2%	≥10 mm
Çakıcı et al. 2003 (23)	1491	Çanakkale	7	4.4%	BCG(-): >10 mm BCG(+): >15 mm
Our study 2006	2979	Kahramanmaraş	7-17	7.4%	BCG(-): >10 mm BCG(+): >15 mm

positivity rate was found to be 3.9% among the nonvaccinated children. A major reason for the low TST positivity rate cited in that study may be related to the children's isolated lifestyles. In our study, TST positivity was 5.5% in Group 1, 10.4% in Group 2, and 4.8% in Group 3. The results demonstrate that BCG vaccination is insufficient in rural areas; however, a low TST positivity rate in these areas indicates that natural infection does not increase in poor living conditions. In our study, Group 1 consisted of children from different villages who went to a regional elementary boarding school. The low TST rate in this group may be due to the isolated lifestyle of the families of the children (22).

BCG vaccinations are compulsory for all infants in Turkey. The Ministry of Health recommends the first vaccine in the second month and the second at 7 years of age (9,24). Vaccination programs in the country seem inefficient, however, because studies have detected children at 7 years of age with no BCG scar. The BCG scar rate of 7-year-old school children in different regions of Turkey shows variations due to different socioeconomic conditions (13,14,22,24). The rate of BCG scars among migrants was 26.3% in Van (a city in eastern Turkey) while it was 99.5% in Manisa (a city in the Aegean region of Turkey) (13,22). Table 3 summarizes the rates found in different studies in Turkey. In the current study, the rate of children with a BCG scar was found to be 94.2%, suggesting that

Kahramanmaraş (a city in the Mediterranean region) is a city of efficient vaccination.

There are studies suggesting that the size of the PPD induration may increase significantly with the number of BCG scars (13,14,25). In studies performed by Uçan et al. and Ildirim et al., PPD diameters increased and reactions had a high correlation with the increasing number of BCG scars (21,30). Gundogdu et al. (29) showed an increase in the diameter of the PPD induration with the number of BCG scars in a study conducted on 1879 school children between 7 and 14 years of age in Kocaeli. In our study, it was found that the presence of 1 or 2 BCG scars induced higher tuberculin reactivity than did the presence of no scars (Figure 2).

In the United States, the prevalence of TST positivity among children newly enrolled in primary school was 1%-2%, a figure that increased to 10% in those entering secondary school. The factors associated with TST positivity were age, BCG coverage, and birth outside of the US (31-33). Studies show that overall TST positivity is lower in Turkey than in the USA. High TST positivity rates in parts of Turkey may be explained by routine BCG vaccination and low socioeconomic conditions.

BCG vaccination is considered an important protective measure with regards to TB disease and there are studies discussing its protection capability;

Table 3. BCG scar rates in Turkish studies.

Study	Place	Year	Age group	BCG scar positivity
Özdemir et al. (18)	Eskişehir	1987	7-11	84.4%
Uzun et al. (22)	Van	1998	0-17	66%
Kolsuz et al. (14)	Eskişehir	2000	7	89.9%
Şakar et al. (13)	Manisa	2001	7-18	99.5%
Çakıcı et al. (23)	Çanakkale	2003	7	88.6%
Özşahin et al. (27)	Sivas	2003	7	83.1%
Bozkanat et al. (28)	İstanbul	2003	18-21	92.7%
Tanrıkulu et al. (26)	Şırnak	2005	7	25.3%
Our study	Kahramanmaraş	2006	7-17	94.2%

however, repeated vaccination after the first vaccine is not recommended as a way of increasing its effectiveness (26,34-36). The mean size of the PPD induration of the study group was 6.9 ± 5.3 mm, 6.9 ± 5.2 mm for girls and 6.9 ± 5.4 mm for boys. TST positivity was found in 6.8% of girls and 7.8% of boys. There were no significant differences determined between boys and girls, which may be due to the fact that our study consisted of a childhood population.

Children were classified into 1 of the 3 following age groups: 7-10 years of age, 11-13 years of age, and 14-17 years of age. The mean size of PPD induration was measured for each group; it was 5.62 ± 5.05 mm for the group 7-10 years of age, 8.32 ± 5.33 mm for the group 11-13 years of age, and 7.11 ± 5.31 mm for the group 14-17 years of age. The main factor for the lower PPD size in the third group may be the decreasing effect of BCG with time.

In our study, TST positivity increased and had a positive correlation with age. The results from other studies performed in Turkey are also concordant with the claim made in our study that PPD reaction has a correlation with age (13-21). This may be related to the increase in the number of BCG scars and the increase in the risk of TB infection due to exposure after childhood.

Due to the high number of participants in our study, we were not able to study the booster effect; this shortcoming represents the weakness of the present research.

In conclusion, the BCG vaccination rate in Kahramanmaraş was high, with an overall rate of 94.2%, and TST positivity was low, with a rate of 7.4%. The number of vaccinations (up to 3 scars) and age of the study subjects were the factors that affected the size of PPD induration.

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