Tuberculin survey among school-aged children in Ahvaz, Iran, 2006

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Tuberculin test; BCG vaccine; Latent tuberculosis; ARI

Summary
Background and objective: The tuberculin test is widely used for the diagnosis of tuberculosis (TB) in children, as it is the only one to provide evidence of infection with Mycobacterium tuberculosis. Our objective was to estimate the prevalence of TB infection, the annual risk of infection (ARI), and the incidence of active TB in school children.

Methods: A cross-sectional study was carried out in Ahvaz, a city of southern Iran, in 2006. A questionnaire was used to collect information, including demographic characteristics, bacillus Calmette–Gue´rin (BCG) vaccination history, and household contact with active TB. Tuberculin testing was performed. Reactivity that measured <5 mm was considered negative, between 5 and 9 mm was considered doubtful, and ≥10 mm was considered positive. Chest radiographs were obtained as part of the evaluation for children with a positive result.

Results: A total of 3906 children with a mean ± standard deviation (SD) age of 10.59 ± 2.63 years (51% female, 49% male) were entered into our study. Of these, 3338 children (85.5%) did not develop a reaction (0 mm), 243 (6.2%) had reactivity of 1—4 mm, 238 (6.1%) had reactivity of 5—9 mm, and 87 (2.2%) had reactivity of ≥10 mm. More than 90% of the children had received the BCG vaccine in the first week of life. The ARI rate was 0.5% and the estimated case of smear-positive TB was approximately 25 per 100 000 population. Only three children were diagnosed with active TB, a prevalence of 75 per 100 000 population.

Conclusions: Tuberculin testing using 5TU-PPD (5 tuberculin units of purified protein derivative) is a valuable diagnostic test for latent TB and active TB in childhood. BCG vaccination has no remarkable effect on the interpretation of tuberculin reactivity. The incidence rate of active pulmonary TB in children in the region of study is of concern.

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Introduction

*Mycobacterium tuberculosis* infects one third of the world’s population and causes millions of cases of tuberculosis (TB) worldwide each year. TB remains common throughout the world with an estimated 9 million new cases (incidence) and 3 million deaths per year worldwide. The great majority of these cases (95%) and deaths (98%) are in developing countries. In 1993, the World Health Organization (WHO) declared it a global public health emergency.

TB continues to be a major public health problem in Iran despite the implementation of a national tuberculosis program (NTP); this may be attributed to risk factors such as drug addiction, imprisonment, and HIV infection. In 1999 the highest and lowest rates of TB in the provinces of Iran were reported to be 137 per 100,000 and 10 per 100,000 population, respectively, with an average of 26 per 100,000 population for the country.

The tuberculin skin test (TST) is still widely used for the detection of *M. tuberculosis* infection, although several novel diagnostic assays have been developed in recent years. However, TST reactivity may also be observed after bacillus Calmette–Guérin (BCG) vaccination or Mycobacterium other than tuberculosis (MOTT) infection. Unless vaccination has taken place recently, a TST reaction of greater than 10 mm should not be attributed to the BCG.

Most TB epidemiological studies, including tuberculin surveys, have been conducted over limited geographical areas. Hence, information on the prevailing epidemiological situation of TB is lacking for most parts of Iran, such as Khuzestan. It was therefore planned to assess the prevailing epidemiological situation of TB by conducting a tuberculin survey during the period 2006–2007 in Ahvaz (the capital of Khuzestan). The objectives of the survey were to estimate the prevalence of TB infection, the annual risk of infection (ARI), and the incidence of active TB in children aged 6–15 years.

Patients and methods

This cross-sectional study was carried out in Ahvaz in Khuzestan, a province in the southwest of Iran, from 2006 to 2007, using a modified WHO Expanded Program for Immunization (EPI) random cluster methodology for sampling. The sample size was estimated on the basis of an assumed minimum prevalence of infection of 1%, which was itself based on results obtained during earlier surveys in different parts of Iran. The sample size needed was estimated to be 5000 children, for investigation in 210 clusters. For the purpose of the survey, a primary school was considered as a primary cluster and a guidance school as a guidance cluster. The clusters were distributed between two strata: guidance (n = 70) and primary (n = 140), in proportion to their populations. A two-stage sampling procedure was used to select clusters within a stratum. In the first stage, two districts were selected by systematic sampling: western district and eastern district. Within a stratum, the number of clusters assigned to districts was in proportion to the population. In the second stage, clusters in each district were selected with the population proportional-to-size method. Twenty-five were to be registered in each cluster.

In the two districts, east and west Ahvaz, 5000 children aged 6–15 years were tested. Demographic data and survey-related data were obtained by questionnaire. We selected tuberculin testers from the experienced health care workers at the Ahvaz Health Center, who were trained by the investigating team. Permission for the survey was obtained from health and educational officers. The survey proposal was approved by the Infectious and Tropical Diseases Research Center of Jondishapoor University of Medical Sciences.

For each child we recorded the name of the school, the primary/guidance school grade, history of contact with an active TB patient, and BCG vaccination status. All children were tested with 0.1 ml 5TU-PPD (5 tuberculin units of purified protein derivative; Razi institute, Tehran, Iran). The tests were read after approximately 72 hours. For each child, the maximum transverse diameter of indurations in mm was measured with a ruler by pen-rolled method and recorded. Reactions of <5 mm were considered negative, 5–9 mm doubtful, and all reactions of 10 mm or more were considered positive. Those with a positive TST were evaluated for active TB by chest radiography and clinical examination. Active TB was considered if at least three of five criteria (TST, history of contact with active disease, abnormal chest X-ray, clinical finding, and acid-fast bacilli (AFB) in sputum or gastric washing) were found.

The ARI was calculated using the formula 1 – PX = (1 – R)X, in which R = ARI, P = prevalence of tuberculin positivity, and X = age in years. The total estimated incidence of new smear-positive pulmonary tuberculosis (SPPTB) per 100,000 population was calculated by multiplying the ARI by 50. The ratios of observed and estimated incidence were calculated.

Data were analyzed with SPSS software. The Chi-square test with continuity correction was used to test the significance of differences between proportions. The calculated values of the test criteria were compared with the tabular value at the 95% level to ascertain the significance of the test (p < 0.05 was considered significant).

Results

A total of 5000 primary school children were enrolled in this study. Of these, 1094 (21.9%) were excluded from the analysis for the following reasons: 856 (17.1%) of the children because of parental avoidance, 220 (4.4%) of the children ran away from the team before they could be tested, and 18 (0.4%) because of concurrent infectious diseases. Of the 3906 children eligible for analysis, 3518 (90%) had evidence of prior BCG vaccination. The mean ± standard deviation (SD) age of unvaccinated children was 10.2 ± 2.6 years and of vaccinated children was 10.9 ± 2.9 years. There was no significant difference between girls and boys in vaccination coverage (p > 0.05).

Of the 3906 children, 3338 (85.5%) had no reaction (0 mm) to the TST, 243 (6.2%) had reactivity of 1–4 mm (giving a total of 91.7% negative TST results), 238 (6.1%) had ‘doubtful’ reactivity of 5–9 mm, and 87 (2.2%) were considered to have a positive TST. The mean ± SD induration size in girls was 1.11 ± 2.87 mm and in boys was 0.59 ± 2.08 mm. There was a significant relationship between induration size and gender (p < 0.001). There was no significant difference between girls and boys for TST positivity (p = 0.579). There was also no relationship between a positive TST and age (p = 0.313). The computed ARI rate was 0.5% (based on infection among...
unvaccinated children) and the estimated case of smear-positive TB was approximately \((0.5 \times 50) = 25\) per 100 000 population. Three of the positive TST subjects had active TB with a prevalence of \(75\) per 100 000. The ratio of observed and estimated incidence was \(75/25 = 3\). Other results are shown in Tables 1 and 2.

**Discussion**

In the present study, the mean size of indurations in tuberculin reactivity to 5TU-PPD was lower than that reported by Lao and De Guia (0.85 \(\pm\) 2.48 vs. 4.5 \(\pm\) 6) and Tanrikulu et al. (0.85 \(\pm\) 2.48 vs. 2.1 \(\pm\) 2.7). This difference is probably due to the age at which vaccination takes place; according to the EPI, in Iran, BCG is administered in the first week of life and there is no revaccination program.

The present study showed that more than 85% of children had no reaction to the tuberculin test. There have been many previous studies showing no reaction (0 mm) to TST in children of school age, with rates of >50% being reported in high prevalence countries. Sleiman et al. (2007, Lebanon) reported no reaction to tuberculin with a rate of 76.3%, and Escobar et al. (2004, Brazil) found that 58.4% of school children had no reaction to the tuberculin test. These findings show that the BCG, despite high vaccine coverage (more than 90%), has no remarkable effect on the TST. The present study observed no influence of BCG on TST response in the different age and gender groups, which may indicate that TST positivity in the school children was related to natural infection rather than previous vaccination. Therefore, detection of TST positivity in children living in countries with routine vaccination should not necessarily be attributed to previous BCG vaccination, and the individual should be evaluated for TB.

There have been many previous studies of TST positivity in school-aged children, with rates of 7.8% to 32% reported in high prevalence countries. Gopi et al. (2006, India) with 7.8%, Sleiman et al. (2007, Lebanon) with 7.8%, Garcia-Sancho et al. (2006, Mexico) with 12.4%, Serane et al. (2001, India) with 18.6%, and Escobar et al. (2004, Brazil) with 32%. The present study detected a low positive rate in school-aged children of 2.2%, which is closest to that found in the Tanrikulu et al. study (2006, Turkey) with a rate of 3.4%. However, the prevalence of active TB was 75 per 100 000 population, and, as found in other studies, household contact with active pulmonary TB (AFB smear-positive) was the main source of transmission. These data suggest that although the low positive TST response rate is linked with the epidemiological status of TB infection in Iran, it also predicts the development of active TB in children in contact with active TB.

The ARI is often derived from a tuberculin survey among children not vaccinated with BCG. The ARI in our study among unvaccinated children was 0.5%; this leads to an estimate of the annual incidence of active TB of 25 per 100 000 in the entire population of the study region. This rate is higher than that reported by Leung et al. and lower than that of Sleiman et al. In the Leung et al. case—control study in Hong Kong among school children, the prevalence of

**Table 1** Tuberculin test results in school children in Ahvaz, Iran, 2006—2007

<table>
<thead>
<tr>
<th>Tuberculin reactivity (mm)</th>
<th>Girls (N = 1995)</th>
<th>Boys (N = 1911)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary school n (%)</td>
<td>Guidance school n (%)</td>
</tr>
<tr>
<td>0</td>
<td>819 (21)</td>
<td>817 (21)</td>
</tr>
<tr>
<td>1—4</td>
<td>90 (2.3)</td>
<td>44 (1.1)</td>
</tr>
<tr>
<td>5—9</td>
<td>77 (2)</td>
<td>86 (2.2)</td>
</tr>
<tr>
<td>10—15</td>
<td>20 (0.5)</td>
<td>29 (0.7)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>8 (0.2)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Total</td>
<td>1014 (26)</td>
<td>981 (25.1)</td>
</tr>
</tbody>
</table>

**Table 2** Frequency of induration size with 5TU-PPD in BCG-vaccinated and BCG-unvaccinated children, Ahvaz, Iran, 2006—2007

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>Vaccinated</th>
<th>Unvaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;5 mm</td>
<td>5—9 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>6</td>
<td>231</td>
<td>198 (91.7)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>7</td>
<td>427</td>
<td>363 (91.4)</td>
<td>25 (6.3)</td>
</tr>
<tr>
<td>8</td>
<td>448</td>
<td>368 (90.8)</td>
<td>27 (6.7)</td>
</tr>
<tr>
<td>9</td>
<td>479</td>
<td>401 (91.8)</td>
<td>26 (5.9)</td>
</tr>
<tr>
<td>10</td>
<td>468</td>
<td>397 (93.4)</td>
<td>20 (4.7)</td>
</tr>
<tr>
<td>11</td>
<td>458</td>
<td>419 (94.5)</td>
<td>16 (3.8)</td>
</tr>
<tr>
<td>12</td>
<td>422</td>
<td>380 (92.4)</td>
<td>21 (5.5)</td>
</tr>
<tr>
<td>13</td>
<td>418</td>
<td>349 (93.3)</td>
<td>16 (4.3)</td>
</tr>
<tr>
<td>14</td>
<td>308</td>
<td>233 (87.6)</td>
<td>24 (9.0)</td>
</tr>
<tr>
<td>15</td>
<td>247</td>
<td>171 (86.8)</td>
<td>23 (11.7)</td>
</tr>
</tbody>
</table>
active TB was estimated to be 16 per 100,000 population. \(^{17}\)
Sleiman et al., in a tuberculin survey among children aged 3–
19 years, found that 12 children had active TB, a prevalence
of 280 per 100,000 population. \(^{11}\) But, this rate is nearly equal
to the lowest rate for developing countries (25/100,000) and
one-third the highest rate for developing countries (240/
100,000). \(^{3,4}\) In the present study the case incidence was three
times that expected. These findings show that, although the
region of study is of moderate TB epidemiological status, TB
is still a major health problem in pediatrics in Ahvaz, and
maybe in Iran. This situation may be due to difficulties in TB
contact follow-up, especially for children, and this problem
must be resolved.

Conclusions

Tuberculin testing with 5TU-PPD is a valuable diagnostic test
for latent TB and active TB in childhood. BCG vaccination has
no remarkable effect on the interpretation of tuberculin reactivity. The incidence rate of active pulmonary TB in
children in the region of study is of concern.

Recommendations

(1) Every 5 years, a tuberculin survey on a large scale should
be carried out to define the trends in TB. (2) A revision of
child follow-up in TB households must be considered.

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