Sensitivity to sensitins and tuberculin in Swedish children. IV. The influence of BCG-vaccination

L.O. Larsson*, M. Magnusson**, B.-E. Skoogh*, A. Lind***


ABSTRACT: BCG-vaccinated schoolchildren, 8-9 yrs of age, were simultaneously tested on separate arms with tuberculin and a sensitin.

Using the 6 mm cut-off they reacted in 49% to two tuberculin units purified protein derivative (PPD RT23), in 67% to 0.1 μg Mycobacterium avium sensitin RS10, and in 58% to 0.1 μg M. scrofulaceum sensitin RS95. The corresponding figures for non-BCG-vaccinated schoolchildren of the same age tested at the same time were 3, 25 and 32%, respectively.

The results indicate a stimulating influence of BCG-vaccination on tuberculin and sensitin reactivity. Since the sensitin reactions were the larger ones, these reactions were not only due to the vaccination. The BCG-vaccinated schoolchildren seem to have acquired infections by atypical mycobacteria despite vaccination.


Vaccination of man with BCG induces varying degrees of delayed type hypersensitivity (cell-mediated immunity), depending on the composition and dose of the vaccine as well as on several other factors. It has been discussed whether sensitivity induced by BCG vaccine could be better demonstrated with the use of sensitins than with tuberculins based on M. tuberculosis [1, 2].

From the 1940s until the mid 1970s, practically all newborns in Sweden were BCG-vaccinated. In April 1975, the general BCG-vaccination was discontinued due to an improved tuberculosis situation and because of an observed increase of BCG complications in this country [3-5].

Since 1986, studies concerning sensitin and tuberculin reactivity in children have been performed in Sweden [6, 7]. One of the premises of these studies was that the final analyses should not include results of BCG-vaccinated children because of possible cross-reactions induced by BCG. The first of our studies comprised non-vaccinated schoolchildren, 8-9 yrs of age, living in Göteborg, a city on the west coast of Sweden. There were some BCG-vaccinated children in the classes chosen for these studies and they were also tested. We sought to discover whether these BCG-vaccinated children had been protected against infections by atypical mycobacteria and, therefore, had a lower reactivity to the sensitins used in this study than their non-vaccinated class-mates. The present report shows the differences in prevalence of sensitin and tuberculin reactors between BCG-vaccinated and non-BCG-vaccinated schoolchildren in Göteborg.

Subjects and methods

Subjects

The material comprised 164 schoolchildren, 8-9 yrs of age. The children were without doubt BCG-vaccinated since all had a vaccination scar. A confirmed record of year of vaccination was available for 107 children. The majority of them had been vaccinated in the first two years of life. The interval between vaccination and testing was less than three years for two children only.

The BCG vaccine was produced by Statens Seruminstitut, Copenhagen, and was given intracutaneously. Since in 1978, Sweden changed from freeze-dried vaccine based on the Swedish strain to vaccine based on the Danish strain, some children obtained the former while others obtained the latter. However, for some children born and BCG-vaccinated abroad there is no information concerning source and composition of the vaccine used.

Information about earlier purified protein derivative (PPD)-testing was obtained for 144 children, whilst such information was lacking in 20 cases. Among these 144 children, 31 had been PPD-tested earlier, whilst 113 had not. None of the children had had any known contact to a tuberculous patient.

The group of 2,819 non-BCG-vaccinated schoolchildren used for comparison has been described previously [6].

The children and their parents were provided with oral and written information, and the study was approved by the Scientific Ethical Committee of the Faculty of Medicine, University of Göteborg.
Table 1. Indurations ≥6 mm caused by tuberculin PPD RT23, M. avium and M. scrofulaceum sensitins in BCG-vaccinated and non-BCG-vaccinated children

<table>
<thead>
<tr>
<th></th>
<th>PPD RT23</th>
<th>M. avium sensitin</th>
<th>M. scrofulaceum sensitin</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG-vaccinated</td>
<td>Reacting %</td>
<td>49</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Tested n</td>
<td>164</td>
<td>72</td>
</tr>
<tr>
<td>Non-BCG-vaccinated</td>
<td>Reacting %</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Tested n</td>
<td>2819</td>
<td>1368</td>
</tr>
<tr>
<td>p</td>
<td>≤0.001</td>
<td>≤0.001</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

PPD: purified protein derivative.

Table 2. Indurations ≥6 mm caused by tuberculin PPD RT23, M. avium and M. scrofulaceum sensitins in children who had previously been PPD tested and children not previously tested

<table>
<thead>
<tr>
<th></th>
<th>PPD RT23</th>
<th>M. avium sensitin</th>
<th>M. scrofulaceum sensitin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously PPD tested</td>
<td>Reacting %</td>
<td>61</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Tested n</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Not previously PPD tested</td>
<td>Reacting %</td>
<td>43</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Tested n</td>
<td>113</td>
<td>53</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

PPD: purified protein derivative

Skin tests

The standard Mantoux test was applied. Two simultaneous injections were given on the middle part of the dorsal surface on the right and left forearm, respectively. One injection consisted of two tuberculin units (TU) PPD RT23 and the other of 0.1 mg M. avium sensitin RS10, or of 0.1 μg M. scrofulaceum sensitin RS95.

The reactions were read after three days by measuring the transverse diameter of the induration in mm. The nurses who read the skin tests were not aware which preparation (PPD RT23 or sensitin) had been injected on the right and left forearm, respectively; this information was reserved for the attending clerk.

Statistical method

The Chi-squared fourfold table method was applied.

Results

All of the 164 schoolchildren were tested with PPD RT23. Seventy-two of them were tested with M. avium sensitin RS10, and 92 with M. scrofulaceum sensitin RS95. Using the 6 mm cut-off, the prevalences of skin reactions were 49% to PPD RT23, 67% to M. avium, sensitin and 58% to M. scrofulaceum sensitin (table 1). The differences between the prevalences of skin reactions (≥6 mm) for PPD RT23 and the used sensitins were insignificant.

For the non-vaccinated children, the prevalences of reactions were significantly lower than those for the vaccinated children (p<0.001). Also, when 3 and 10 mm cut-offs were applied significant differences were demonstrated between non-vaccinated and vaccinated children. In contrast to the BCG-vaccinated children the differences between the prevalence of reaction for PPD RT23 and the sensitins was significant (p<0.001).

The group of BCG-vaccinated children has been partitioned into those who were vaccinated as infants and those vaccinated after one year of age. The mean PPD RT23 value for the first group was 4.9 mm and for the second group 6.9 mm. Using the 6 mm cut-off, there was a slight difference in prevalence of reactions (23 out of 57 vs 31 out of 50) between the two groups (p<0.05).

For children who had previously been tuberculin tested on one single occasion the skin test prevalence did not differ significantly from those for the children not previously tested (table 2).

As many as 50 of the schoolchildren (30%) had no induration at all when tested with PPD RT23; on the other hand, 12 had an induration ≥15 mm. Seven children tested with M. avium sensitin and six tested with M. scrofulaceum sensitin showed reactions >15 mm. The largest PPD reaction was shown by a girl with a 22 mm induration; she was also tested with M. scrofulaceum sensitin and had an induration of 10 mm caused by this sensitin. The time interval between BCG-vaccination and tuberculin testing was 8 yrs for this girl.

Discussion

Infections by atypical mycobacteria seem to be widespread in the area where the tested BCG-vaccinated and non-vaccinated schoolchildren live, and
they have probably been exposed to these bacteria [6, 7]. The BCG-vaccinated children had a higher prevalence of large sensitin reactions than the nonvaccinated ones. However, there is no reason to assume that they had been infected by atypical mycobacteria in a higher degree than the non-vaccinated children. Nor can these high prevalences solely be expressions of cross-reactions caused by BCG, since they are considerably higher than for PPD RT23 (table 1). Most probably the high prevalence of sensitin reactions is due to the combined effect of infections by atypical mycobacteria and BCG. This contradicts earlier results obtained in experimental studies on animals where BCG-vaccination increased the resistance to mycobacterial infections other than those caused by M. tuberculosis and M. bovis [8, 9]. However, neither the BCG-vaccinated children, nor the non-vaccinated ones had any symptoms of disease caused by atypical mycobacteria.

The present study of BCG-vaccinated children showed a much higher prevalence of reactions ≥ 6 mm to tuberculin PPD RT23 compared with the non-BCG-vaccinated schoolchildren (table 1). Furthermore, the preponderance of sensitin reactions over the tuberculin reactions was clearly smaller among BCG-vaccinated than among non-vaccinated children. These data confirm earlier findings that the tuberculin test with two TU PPD RT23 is an appropriate method to evaluate post-vaccination sensitivity [10]. Eighty of the 164 vaccinated children, i.e. 49%, had an induration to tuberculin PPD RT23 ≥ 6 mm. This prevalence is somewhat higher than the 38%, which Sievers [10] obtained in 1975–1976 in Göteborg, when he tested a similar cohort of BCG-vaccinated schoolchildren. One reason for this difference in prevalence may be that all of the children in Sievers' study were vaccinated as newborns, whilst some of the children in the present study had been vaccinated as infants.

In epidemiological studies, simultaneous skin testing with two TU PPD RT23 and, e.g. 0.1 µg M. avium or M. scrofulaceum sensitin may provide information about low-degree tuberculin sensitivity in BCG- as well as in non-BCG-vaccinated populations. Our earlier studies [6, 7] have shown that in Sweden low-degree tuberculin sensitivity is not related to tuberculous infection or disease but rather to infection by atypical mycobacteria. Thus, a single tuberculin test is unsuitable to elucidate the cause of low-degree sensitivity. As an alternative to comparative simultaneous tests, consecutive testing using serial doses of tuberculin PPD with increasing strength may also be applied [11]. Such consecutive testing has, however, some disadvantages, e.g. it involves several test occasions.

In our earlier studies the prevalence of skin reactions ≥ 6 mm to M. avium and M. scrofulaceum sensitins was unexpectedly high in non-BCG-vaccinated schoolchildren [6]. In the present material of BCG-vaccinated schoolchildren the prevalence was still higher; this indicates a stimulating influence of BCG-vaccination on sensitin reactivity.

Acknowledgements: This study was made possible thanks to generous economical support from King Oscar II's Jubilee Fund, Sweden, and to the enthusiasm and skill of the testing team.

References