Follow-up Study on Tuberculin Test After B.C.G. Vaccination and the Difference Between Natural Conversion to Tuberculosis and B.C.G. Conversion

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ABSTRACT

As B.C.G. vaccination is being given extensively to uninfected children in this country, it has become important for pediatricians, general practitioners and public health people to differentiate natural conversion of response to tubercle bacilli from B.C.G. conversion. The authors have investigated this problem by studying 993 pupils in a primary school in Seoul. In our investigation, the difference between the conversion rate with 1/2,000 O.T. and 1/10,000 O.T. at various intervals after B.C.G. vaccination in the B.C.G.-converted group is statistically significant, whereas in the naturally converted group, the difference between the two groups is not statistically significant. There also is a difference in local reaction between the naturally converted group and the B.C.G.-converted group, although it is hard to distinguish with a single reaction whether it is due to natural conversion or to B.C.G. conversion. From both the results of our study and a some of the previous articles on this matter, the authors conclude that natural conversion to tuberculosis may be differentiated from B.C.G. conversion by utilizing the tuberculin test, since B.C.G. vaccination is being frequently practiced among children as a measure for preventing tuberculosis. Various reports have appeared on this problem by Kim (1960), Ohkura (1958), Sylla (1937) and Sweany (1947). None of the reports, however have given satisfactory answers to us. The authors investigated this subject from April, 1959, to March, 1960, for one year with some results. It is the purpose of this paper to present the results of our investigation and to review some of the previous literature on this matter.

MATERIALS AND METHOD

Nine hundred and ninety-three first-grade children in the Namdai-Moon primary school, including both male and female aged from 6-5 to 8 years, were selected as examinees for the investigation. Initially, a tuberculin test was done to all selected children with 0.1 cc. of 1/2,000 old tuberculin (Lot
— 68 —

THE DIFFERENTIATION OF B.C.G. CONVERSION AND NATURAL CONVERSION

No. 6781) made in the National Health Institute in Korea; then a second tuberculin test was performed with 1/500 old tuberculin (Lot No. 6784) made in the same institute to the children showing negative reactions to the previous test with 1/2,000 O.T., to determine a truly negative reaction.

B.C.G. vaccine (Lot No. 74), made in the National Health Institute in Korea, was administered to the negative children as tested as above, using 0.1 cc. containing 0.05 mg., intradermally in the region of the left deltoid muscle. Then tuberculin tests were made with 1/2,000 O.T. (Lot No. 6733), and 1/10,000 O.T. (Lot No. 6791), using 0.1 cc. intradermally, according to the following schedule: two weeks, one month, two, there, six, eight and twelve months after B.C.G. vaccination. O.T. 1/2,000 was inoculated on the central part of the right forearm on the flexor surface, and O.T. 1/10,000 on the left. The results were read according to the specifications designated by the Ministry of Health and Social Affairs (1939) 48 hours after the O.T. inoculations.

For those students who showed natural conversion in the first and second O.T. test, another tuberculin test with 1/2,000 and 1/10,000 O.T. was given about one year after the first tuberculin test for comparison.

RESULTS

1. The results of tuberculin tests before B.C.G. vaccination:

As shown in Table 1, tuberculin testing with 1/2000 O.T. among 993 pupils produced 455 negative reactions and 538 positive reactions. As shown in Table 2, of 439 students tuberculin tested with 1/500 O.T. who were negative with 1/2000 O.T. in the first test, 422 students were negative and 17 students positive, to whom B.C.G. vaccination had not been given.

Table 1. Tuberculin test with 1/2,000 old tuberculin before B.C.G. vaccination

<table>
<thead>
<tr>
<th>Concentration of O.T.</th>
<th>Number of students tested</th>
<th>Number of negative reactions</th>
<th>% of negative reactions</th>
<th>Number of positive reactions</th>
<th>% of positive reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2000</td>
<td>993</td>
<td>455</td>
<td>46</td>
<td>538</td>
<td>54</td>
</tr>
</tbody>
</table>

2. The results of a series of tuberculin tests after B.C.G. vaccination:

As shown in Table 3, the relationship between the conversion rate of those tested with 1/2,000 O.T. and 1/10,000 O.T. and the interval after B.C.G. vaccination and the probability on each column is interesting to note. The maximum conversion rate to both concentrated old tuberculin reached 74% and 41% respectively when one month had passed after B.C.G. vaccination had been done; then the conversion rate gradually dropped to 17% with 1/2,000 O.T. and 5% with 1/10,000 O.T. respectively.

Table 2. Tuberculin test with 1/500 old tuberculin before B.C.G. vaccination

<table>
<thead>
<tr>
<th>Concentration of O.T.</th>
<th>Number of students tested</th>
<th>Number of negative reactions</th>
<th>% of negative reactions</th>
<th>Number of positive reactions</th>
<th>% of positive reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/500</td>
<td>439</td>
<td>422</td>
<td>96</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. Tuberculin tests with 1/2,000 O.T. and 1/10,000 O.T. after B.C.G. vaccination at various intervals

<table>
<thead>
<tr>
<th>Duration after B.C.G. vaccination</th>
<th>Number of students tested</th>
<th>1/2,000 O.T.</th>
<th>Number of positive reactions</th>
<th>% of positive reactions</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>358</td>
<td>233</td>
<td>65</td>
<td>128</td>
<td>36</td>
</tr>
<tr>
<td>1 month</td>
<td>361</td>
<td>266</td>
<td>74</td>
<td>166</td>
<td>41</td>
</tr>
<tr>
<td>2 months</td>
<td>344</td>
<td>154</td>
<td>48</td>
<td>105</td>
<td>31</td>
</tr>
<tr>
<td>3 months</td>
<td>320</td>
<td>81</td>
<td>25</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>6 months</td>
<td>310</td>
<td>74</td>
<td>24</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>8 months</td>
<td>255</td>
<td>46</td>
<td>18</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>12 months</td>
<td>254</td>
<td>43</td>
<td>17</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>

3. The results of re-tuberculin testing of the naturally-converted children one year after the first tuberculin test are shown in Table 4: 414 pupils who

Table 4. Tuberculin tests with 1/2,000 O.T. and 1/10,000 O.T. to naturally-converted children

<table>
<thead>
<tr>
<th>Number of students tested</th>
<th>1/2,000 O.T.</th>
<th>1/10,000 O.T.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>414</td>
<td>410</td>
<td>99</td>
<td>402</td>
</tr>
</tbody>
</table>

{...}
showed positive reactions to both 1/2,000 O.T. and 1/500 O.T. were tested again and revealed 4 (1%) negative reactions and 410 (99%) positive reactions to 1/2,000 O.T..

4. Local reactions to B.C.G. vaccination:

On the next day after B.C.G. vaccination, local reaction was not seen; however, localized redness and swelling were noticed at the site of the vaccination on the third day of B.C.G. administration. One case of vesicle and four cases of pustules were seen on the seventh day of B.C.G. vaccination. Healing associated with swollen induration was seen in 328 cases (94%) of 346 children observed; 15 cases (5%) of purulent discharge and 5 cases (1%) of ulceration were also seen, but these healed completely without treatment or complications three months after the B.C.G. vaccination.

5. Differences in local reaction, at the site of tuberculin test, between children converted naturally and children converted with B.C.G.:

In the naturally converted reaction, almost all children showed a positive reaction to both 1/2,000 O.T. and 1/10,000 O.T., brownish dark red in color, more oval shaped than round and showing relatively strong local reactions such as localized fever, tenderness, induration, vesicle formation and necrotic reaction, etc., whereas in the B.C.G.-converted reaction, erythema was rather a thin pink, more round than oval, and showing weak local induration never with fever, tenderness, vesicle formation or necrotic reaction. B.C.G. conversion was demonstrated with the tuberculin test within five months after vaccination; after five months, the number of negative conversions increased.

DISCUSSION

Although the degree of reaction to tuberculin testing after B.C.G. vaccinations does not coincide with the defense mechanisms to tubercle bacilli infectivity in presuming B.C.G. immunity, it is generally agreed that tuberculin testing is being performed to find out the duration of continuing B.C.G. immunity after vaccination as an index of its inducing immunity in the human body. According to Kim (1960), Ohkura (1968), and Baumann (1955), the degree of reaction to old tuberculin varies, just as the concentration of old tuberculin varies. Kim (1960) described the conversion rate from positive to negative as being more marked with 1/2,000 O.T., but a high positive rate of more than 85% was maintained with 1/100 O.T. or 1/500 O.T. for a long time. He, therefore, stated that the B.C.G. immunity has become weak or null after B.C.G. vaccination when a tuberculin test has converted from positive to negative. Chassain (1947) also stated that further observation was needed to decide whether or not B.C.G. immunity continues after conversion from positive to negative when tuberculin testing after vaccination. On the other hand, Brandberg (1955) described the immunity as continuing as long as six years, as demonstrated by positive reactions to tuberculin tests. In our study, the maximum positive conversion rate after B.C.G. vaccination, 74% to 1/2,000 O.T. and 41% to 1/10,000 O.T., was obtained around one month after B.C.G. vaccination. According to Ohkura et al (1958), a maximum positive conversion rate was obtained two to five months after vaccination, and it gradually decreased after six months. They also observed that maximum positive conversion to 1/10,000 O.T. was reached two months after vaccination, and no further positive conversion was noted after three months. A negative conversion from a natural positive reaction rarely occurs. Shigematsu (1951), however, observed about 50% conversion from positive to negative within one year when the tuberculin reaction showed only redness without induration, but it is generally agreed that the duration of continuing positive reactions in natural conversion to tuberculin tests is much longer than that in B.C.G. conversion. It is difficult to differentiate natural conversion from B.C.G. conversion by using 1/2,000 O.T. alone, although we have been customarily using this for tuberculin test in our clinics; and Ohkura et al (1958) have already recommended utilizing both 1/2000 O.T. and 1/10, 000 O.T. to differentiate them. Yanazawa (1955) used to differentiate the natural conversion from B.C.G. conversion when the tuberculin test showed positive with induration six months after B.C.G. vaccination. Sakawa (1953) emphasized also a different point of view.
when he stated that the tuberculin test is specific for natural conversion when it shows induration as well as redness. As Ohkura et al (1958) have already pointed out, when a tuberculin test with both 1/2,000 O.T. and 1/10,000 O.T. show a positive reaction three months after B.C.G. vaccination or thereafter, it is hard to determine whether it is due to natural conversion or to B.C.G. conversion. But as is shown in Table 3 and 4, in a B.C.G. converted group, the difference between the conversion rates with 1/2,000 O.T. and with 1/10,000 O.T. two weeks, one month, two, three, six, eight and twelve months after B.C.G. vaccination, shows a "P" of much less than 0.01 respectively, which indicates that the difference between the two distributions is statistically significant, whereas in the naturally-converted group, the difference between conversion rates with 1/2,000 O.T. and 1/10,000 O.T. shows a "P" of 0.1, which indicates that the difference between the two groups can be by chance. Therefore the following schedule may be recommended from the results of our study and from a review of some of the previous articles on this matter.

In order to differentiate natural conversion from B.C.G. conversion, tuberculin testing should be done using both 1/2,000 O.T. and 1/10,000 O.T. at the same time, rather than using 1/2,000 O.T. alone, as has been practised until now in this country. When one test with 1/2,000 O.T. shows a positive, and another with 1/10,000 O.T. shows a negative reaction after B.C.G. vaccination, the result can be read as a B.C.G. conversion. When both show a strong positive reaction with induration, vesicles or necrotic reaction without much difference in their severity, the result can be read as a natural conversion, regardless of whether B.C.G. vaccination has recently been done not. When both skin tests show a weak positive reaction without induration, vesicles or necrotic reaction within three months after B.C.G. vaccination, this result may be read as a B.C.G. conversion; however, in this case, repeated tuberculin tests in the same manner should be done every three months for a few more times and then, if both reactions remain positive to the same degree six to nine months after the B.C.G. vaccination, these results can be read as indicating a natural conversion. When a 1/2,000 O.T. test shows positive and a 1/10,000 O.T. test converts to a negative this reaction, this result can be read to indicate a B.C.G. conversion.

REFERENCES
Ministry of Health and Social Affairs in Korea: Direction for B.C.G. Pilot Test 1959.