Epidemiological Report

A COMPARISON OF YOUNG AND AGED POPULATIONS FOR THE DIPHTHERIA AND TETANUS ANTITOXIN TITERS IN JAPAN

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(Received March 7, 1997. Accepted July 23, 1997)

SUMMARY: The antitoxin levels for diphtheria and tetanus were measured with samples of a young group immunized with diphtheria-tetanus-acellular pertussis combined vaccine and those of an aged group, members of which had not received vaccination in their youth. In the young group members of which had already received basic immunization with diphtheria-tetanus-acellular pertussis combined vaccine, the levels of both antitoxins rose well after injection at 11 to 12 years old with diphtheria-tetanus combined toxoids and remained high until 20 years of age. In the aged group, more than 80% showed antitoxin levels above 0.01 u/ml for diphtheria, while all had levels below that for tetanus, except three persons with confirmed tetanus immunization history. Maintenance of the protective antitoxin levels in the population by vaccination is necessary to prevent outbreaks of infection among unvaccinated or only partially immunized persons.
Owing to the extensive toxoid vaccination, both tetanus and diphtheria cases have become very rare in Japan. Annual incidence of diphtheria is limited to a few patients, and only few suffer from severe illness. Epidemic diphtheria, however, has been re-emerging in the former Soviet Union since 1990, and spread to all the New Independent States (NIS) by 1995. In NIS, a total of 125,000 cases and about 4,000 deaths were reported, accounting for 90% of all the cases reported in the world between 1990 and 1995 (1). A decreased vaccination rate due to economic depression seems to be the main cause of the epidemic (2,3).

In Japan, the annual incidence of tetanus decreased steadily from 1950 to 1980, but after 1981, the incidence has remained nearly constant, counting 50 cases per year with a fatality rate of over 30% (4). The risk of both diseases depends upon individual immunity, i.e., the toxin-neutralizing antibody level conferred by vaccination.

Diphtheria and tetanus toxoids were introduced for routine childhood vaccination at the end of the 1940s. Both the Centers for Disease Control and the World Health Organization recommend that not only children but adults receive diphtheria-tetanus-acellular pertussis combined vaccine (DTaP) and/or diphtheria-tetanus combined toxoid (DT) vaccination. It is necessary to investigate the antitoxin levels for both diphtheria and tetanus for implementation of an immunization program in the aged population born before the start of vaccination.

Although cases of illness have decreased in number, the side effects of vaccination have emerged as a new problem. In particular, such local responses as swelling and hardening observed after additional booster vaccination with DT given at ages of 11 to 12 years have become severer and more frequent with currently used DTaP than with formerly used diphtheria-tetanus-whole-cell pertussis combined vaccine (DTwP). One possible explanation for this may be that the DTaP vaccine used after 1981 confers a longer-lasting immunity and accordingly a higher level of antitoxin when the additional booster is given at the age of 11 to 12 years, resulting in over-immunity.

The outline of the problems involved in preventive vaccination for both diseases is as follows: concerning diphtheria, there is a need to pinpoint cases of vaccination omission, and provide the unvaccinated with immunity. Concerning tetanus, several tens of cases have continued to crop up each year for the past 10 years, with no sign of decrease but are increasingly limited to the aged group.

Blood samples were obtained from 85 healthy persons from the toxoid immunization at ages up to 20 years old between July 1994 and March 1995 and aged group samples from 122 healthy persons over 50 years between October
1995 and December 1995. All samples were selected from the Kanto area by the St. Marianna University Hospital. Sera were separated by centrifugation and stored at $-20\,\text{C}$ for antitoxin assay.

All members of the young population had received one to three doses of DTaP between 0 to 4 years, four doses of DTaP by 12 years, and an additional DT booster at age 12. The vaccination history of the aged population was unclear with the exception of three persons immunized with tetanus toxoid one month prior to blood sampling. The diphtheria antitoxin titer was measured by the cell culture method (5) and the tetanus antitoxin titer by the particle agglutination method (6). For both assay methods, the minimal detectable antitoxin level was 0.003 u/ml. To calculate the geometrical means, the samples with undetectable levels were given a figure of 0.0005 u/ml. Both young and aged populations were divided into five groups for assay of diphtheria and tetanus antitoxin titers (Table I).

In the young population, the diphtheria antitoxin level rose after primary immunization with DTaP and an additional booster vaccination with DT given at 12 years old was also effective (Fig. 1, Table I). Basic immunization given at 0 to
<table>
<thead>
<tr>
<th>Age of subjects</th>
<th>Number of subjects</th>
<th>Diphtheria titer</th>
<th>Number of persons showing &lt; 0.01 u/ml (%)</th>
<th>Tetanus titer</th>
<th>Number of persons showing &lt; 0.01 u/ml (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>G. M.</td>
<td>C. I.</td>
<td></td>
<td>G. M.</td>
</tr>
<tr>
<td>0 ~ 4</td>
<td>9</td>
<td>2.17</td>
<td>2.07 ~ 2.28</td>
<td>0 (0)</td>
<td>4.45</td>
</tr>
<tr>
<td>5 ~ 8</td>
<td>18</td>
<td>1.07</td>
<td>0.63 ~ 1.81</td>
<td>0 (0)</td>
<td>3.08</td>
</tr>
<tr>
<td>9 ~ 12</td>
<td>11</td>
<td>0.45</td>
<td>0.42 ~ 0.49</td>
<td>0 (0)</td>
<td>1.47</td>
</tr>
<tr>
<td>13 ~ 16</td>
<td>39</td>
<td>0.71</td>
<td>0.57 ~ 0.88</td>
<td>2 (5.1)</td>
<td>1.16</td>
</tr>
<tr>
<td>17 ~ 20</td>
<td>8</td>
<td>0.37</td>
<td>0.26 ~ 0.52</td>
<td>0 (0)</td>
<td>1.5</td>
</tr>
<tr>
<td>50 ~ 59</td>
<td>6</td>
<td>0.38</td>
<td>0.32 ~ 0.46</td>
<td>0 (0)</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>60 ~ 69</td>
<td>9</td>
<td>0.03</td>
<td>0.02 ~ 0.05</td>
<td>2 (22.2)</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>70 ~ 79</td>
<td>31</td>
<td>0.04</td>
<td>0.02 ~ 0.07</td>
<td>8 (25.8)</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>80 ~ 89</td>
<td>59</td>
<td>0.10</td>
<td>0.08 ~ 0.13</td>
<td>6 (10.2)</td>
<td>&lt; 0.003</td>
</tr>
<tr>
<td>90 ~ 99</td>
<td>17</td>
<td>0.09</td>
<td>0.09 ~ 0.10</td>
<td>2 (11.8)</td>
<td>&lt; 0.003</td>
</tr>
</tbody>
</table>

G.M. : Geometric mean antitoxin titer.
Geometric mean includes undetectable titers.
C.I. : 95% confidence interval.
< 0.01 u/ml : Number of subjects with antitoxin levels below the protective one (0.01 u/ml).
Fig. 2. Diphtheria antitoxin titers of the aged group. CCu and the symbols are the same as in Fig. 1.

4 years old attained an average titer of 2.17 u/ml, which is far in excess of the protective level of 0.01 u/ml. At 9 to 12 years old, before receiving an additional booster, the antitoxin level decreased to about 0.45 u/ml. At 13 to 16 years old, after receiving an additional booster, the level was 0.71 u/ml, which again decreased to 0.37 u/ml at 17 to 20 years old. Only two of 39 individuals between 13 to 16 years showed an antitoxin levels below the lowest detectable level, <0.003 u/ml, the remainders all showing levels above the protective level. In the aged population, the average diphtheria antitoxin level for 50 to 59 years old (six persons) showed a average of 0.38 u/ml (Table I). The averages of those aged 60 to 69 years (nine persons), 70 to 79 (31), 80 to 89 (59), and over 90 (17) were 0.03, 0.04, 0.10, and 0.09 u/ml, respectively, the majority showing levels above the protective level (Fig. 2).

In the young population, the average tetanus antitoxin level at one to 4 years old was 4.45 u/ml, which was, as was the diphtheria antitoxin level, far above the protective level (Table I, Fig. 3). It then dropped gradually to an average of 3.08 u/ml at 5 to 8 years old, and 1.47 u/ml at 9 to 12 years old. The average for 13 to 16 years old, after receiving a DT additional booster, was 1.16 u/ml, and at 17 to 20 years old an average level of 1.50 u/ml was maintained. On the other
hand, the antitoxin levels of the aged population were below the protective level (0.01 u/ml) for all members of the group with an exception of three individuals who had received tetanus toxoid (Fig. 4). With regard to the tetanus antitoxin level, like the diphtheria antitoxin level, the additional booster given at the age of 12 years old appears to have some effect, and the antitoxin level at 20 years old was maintained for a long period.

According to the 1988 survey for antitoxin levels conducted in Japan by Takayama et al. (7), the diphtheria antitoxin levels reached a peak at 18 to 20 years old, after which they decreased at 36 to 40 years old. Since the lowest age of the subjects in Takayama's survey was 6 years, it is difficult to make any comparison with the 0 to 4 years old, but the average of 0.45 u/ml for the 9 to 12 years old, and 1.1 u/ml for the 13 to 16 years old in our survey agreed with the results of the previous survey 0.2 u/ml for 9 to 14 years old and 0.3 u/ml for 12 to 17 years old. Such a high average level of diphtheria antitoxin for the aged group (0.1 u/ml) was on a level similar to that of Takayama's study.

These results suggest that the three doses administered for primary immunization are sufficient. Future vaccination programs should take account of more detailed examinations of the response of the young group to the current program.
Fig. 4. Tetanus antitoxin titers of the aged group. PAu and the symbols are the same as in Fig. 2.

and to the antitoxin levels of the aged group. Although it is uncertain whether the difference observed in the antitoxin level of the post additional booster group between the present survey and the previous one was due to the switch from DTwP to DTaP vaccine, the additional booster appears to have some effect on both diphtheria and tetanus antitoxin levels. The present study has revealed that most people in the aged group showed diphtheria antitoxin levels above the protective level but about 10% were below this level.

In August 1992, a small diphtheria outbreak occurred in Akita Prefecture in Japan, with three cases of illness and five individuals from which gravis-type bacteria were detected. Two additional patients were reported in Oita Prefecture in 1993. As these outbreaks show, diphtheria has not been eradicated, but is merely being kept at bay by toxoid vaccination. Maintenance of protective antitoxin levels in the population through vaccination is necessary to prevent outbreaks of infection among unvaccinated or only partially immunized persons. It is clear that preventive vaccination programs and the improved vaccines have influenced the immunity levels (8).

Tetanus is also a disease which can clearly be prevented by vaccination, and the vaccine is highly effective. However, our survey showed that except the indi-
viduals with vaccination records, the antitoxin levels of all of the aged group were below the protective level. Moreover, the records of the Ministry of Health and Welfare show a steady rise in the mean age of tetanus patients in recent years. This rise is clearly due to universal vaccination of children which brought about a continual decrease in number of patients up to 1980. The fact that patient numbers have shown no clear decrease since then is due to the lack of programed vaccination for the aged group.

Though tetanus cases have decreased in recent years, several deaths are still recorded every year (9). Diphtheria cases occur also sporadically, with no decrease in recent years. Toxoid vaccination showed guarantee immunity to both diseases, and a vaccination program covering not only the aged population but all persons with antitoxin levels below the protective level is urgently called for.

ACKNOWLEDGMENTS

We express our appreciation to Dr. Kunio Ohkuma, the Chemo-Sero-Therapeutic Research Institute, Kumamoto, for supplying us with the tetanus toxoid-conjugated particle antigen used in these experiments.

REFERENCES

