Isolation of rubella virus in milk after postpartum immunization

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Several studies have shown that successful rubella vaccination of rubella-susceptible mothers in the immediate postpartum period does not lead to the appearance of detectable levels of rubella HAI antibodies in the children. The absence of antibodies is not related to the type of feeding (breast or formula) and no attempts have been made to detect rubella virus in the mother's milk.

Recently, we studied a postpartum vaccinee and her breast-fed infant for a period of 15 months. Rubella virus was isolated from breast milk and from a pharyngeal swab from the infant. Specific humoral and cell-mediated immune responses measured serially reflected an unusual exposure to rubella vaccine. We report this experience: (1) to document the presence of rubella vaccine virus in breast milk, (2) to describe the infant's provocative immune responses, and (3) to add reassurance concerning the safety of breast-feeding after postpartum rubella immunization.

CASE REPORT

Patient K.F., a 32-year-old woman, was vaccinated with rubella vaccine (HPV-77 DE, strain)* one day after delivering her first child, a boy, on September 5, 1975, and was advised to use contraceptives for the next three months. She breast-fed her child from the first day of birth till 12 months of age. Twelve days after vaccination, she developed painless, nontender cervical adenopathy and a maculopapular rash over the face and on the arms and legs that lasted for two days. She had no fever or other complaint. Breast milk, blood, and a throat swab from the mother and a throat swab from her infant were obtained on the first day of maternal rash. Additional selected specimens were collected during the subsequent 15 months.

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MATERIALS AND METHODS

Rubella virus isolation was attempted in African green monkey kidney cells using the interference technique with Echovirus, type 11. Confirmation of isolates as rubella virus was accomplished using rubella specific rabbit antiserum. The HAI antibody titers were determined according to Center of Disease Control protocol.1 Immunoglobulin fractionation of sera and milk was done by ultracentrifugation in a continuous sucrose gradient. The 12 fractions collected by puncture of the centrifuge tube were tested for rubella antibody by HAI titration. With this method, no pretreatment for removal of beta lipoprotein inhibitors is required. Rubella specific cell-mediated immunity was measured by uptake of 14C-thymidine in Ficoll-Hypaque purified lymphocyte cultures obtained from heparinized blood. Cultures stimulated with a purified rubella virus antigen, with a purified noninfected cell antigen and with non-stimulated cultures were tested.

*The rubella vaccine HPV-77 DE, strain used in this study is marketed as Meruvax by Merck, Sharp & Dohme.
Table I. Laboratory results after maternal postpartum rubella vaccination (HPV-77 DE~)

<table>
<thead>
<tr>
<th>Interval after vaccination</th>
<th>Rubella virus</th>
<th>Rubella IgG</th>
<th>Rubella IgM</th>
<th>HAI IgG</th>
<th>HAI IgM</th>
<th>Throat rubella virus</th>
<th>Throat rubella IgG</th>
<th>Throat rubella IgM</th>
<th>SR</th>
<th>Blood</th>
<th>Blood IgG</th>
<th>Blood IgM</th>
<th>SR</th>
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<tbody>
<tr>
<td>12 days</td>
<td>+</td>
<td>&lt;1:8</td>
<td>Trace</td>
<td>1:2</td>
<td>3.0</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>35 days</td>
<td>-</td>
<td>Trace</td>
<td>1:8</td>
<td>+</td>
<td>Trace</td>
<td>2.7</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>70 days</td>
<td>-</td>
<td>Trace</td>
<td>NT</td>
<td>NT</td>
<td>-</td>
<td>2.2</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
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<td>NT</td>
</tr>
<tr>
<td>7 mo</td>
<td>NT</td>
<td>NT</td>
<td>1:32</td>
<td>+</td>
<td>-</td>
<td>2.0</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>13 mo*</td>
<td>NT</td>
<td>NT</td>
<td>1:32</td>
<td>+</td>
<td>-</td>
<td>1.9</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
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<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>2 wk†</td>
<td>NT</td>
<td>NT</td>
<td>1:32</td>
<td>+</td>
<td>-</td>
<td>3.7</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>8 wk†</td>
<td>NT</td>
<td>NT</td>
<td>1:32</td>
<td>+</td>
<td>-</td>
<td>3.7</td>
<td>NT</td>
<td>NT</td>
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<td>NT</td>
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</tbody>
</table>

Abbreviations used: NT: Not tested; HAI: rubella hemagglutination inhibition antibody titer; SR: stimulation ratio—ratio between 14C-thymidine uptake in rubella virus antigen stimulated and nonstimulated lymphocyte cultures.

*Infant was vaccinated at 13 months with rubella vaccine (HPV-77 DE~).
†Interval after infant's vaccination.

RESULTS AND COMMENTS

On the twelfth day after vaccination, when the mother noted rash and adenopathy, rubella virus was isolated from her breast milk and from her infant's throat swab specimen (Table I). Virus was not isolated from the mother's throat swab. Virus isolated from the infant's throat swab was probably ingested.

Although the ingested rubella vaccine did not provoke a detectable serologic response in the infant as measured by HAI with treated serum or sucrose gradient separated IgG fractions, it did stimulate a significant level of rubella specific CMI. The infant's stimulation ratio with rubella virus was 6 on Day 35 (Table I) and close to unity with control antigen prepared from uninfected cells. This observation is consistent with previous work which has demonstrated sensitization of T lymphocytes prior to that of B lymphocytes. Primary serologic response, as measured by HAI antibody is not detected until at least 14 days after rubella vaccination, whereas CMI measured by leukocyte migration inhibitory factor and by LT has been detected seven to ten days after vaccination.

Absence of IgM two weeks after the child received rubella vaccine (HPV-77 DE~ strain) at age one year is consistent with a secondary rather than a primary type vaccine response. Multiple testing for IgM at more frequent intervals was not possible. Vaccination, however, stimulated a renewed increase in the CMI response of the child from a stimulation ratio of 3.7 to 7. This increase, according to our experience, is consistent with a booster type response.

We have failed to isolate rubella virus in breast milk from two women who received RA27/3 strain of rubella vaccine in the immediate postpartum period. In previous trials of rubella vaccines during which throat swabs specimens were collected on a daily basis, it was well documented that pharyngeal shedding occurred for only a few days and at relatively low titer. In the cases reported here, study of breast milk collected at such frequent intervals was not practical.

This report documents, for the first time, that breast-feeding after postpartum rubella vaccine immunization can provide exposure to vaccine virus for the young infant. This exposure was not accompanied by any untoward effect; maternal postpartum immunization should be continued whenever necessary. Additional studies of the immune responses of infants exposed by this procedure to vaccine virus during the neonatal period may yield rewarding information concerning developmental immunology.

REFERENCES

3. Center for Disease Control: A procedural guide to the performance of the standardized rubella hemagglutination-inhibition test, United States Department of Health, Education, and Welfare, Mental Services and Mental Health
Clinical experience in dietary management of phenylketonuria with a new phenylalanine-free product

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PHENYLKETONURIA has been treated effectively with diets low in phenylalanine. Early diagnosis and careful dietary management are essential in preventing intellectual deterioration during the newborn period and in improving intellectual achievement and have contributed to a decrease in the number of PKU patients admitted to institutions for the mentally retarded. Mental deterioration in older PKU children following discontinuation of the diet has been noted recently; however, long-term studies will be required to validate this observation. Additional clinical findings such as eczema, hyperkinesis, and abnormal electroencephalogram have been noted occasionally in parallel with a rising serum level of phenylalanine.

The only commercial low-phenylalanine product readily available in the United States has been Lofenalac; most PKU patients have responded favorably to this diet, but some have difficulty accepting or continuing it, especially after starting in school. Other older PKU patients on a normal diet may have problems in returning to Lofenalac when indicated by specific clinical situations, e.g., pregnancy.

A new product for older infants and children with PKU is now available. The material, currently designated 3229, is a mixture of synthetic amino acids fortified appropriately with fats (corn oil), carbohydrate (corn syrup solids, tapioca starch), vitamins, and minerals. The purpose of this paper is to report our experience with product 3229 over a period of one year.

MATERIALS AND METHODS

The clinical trial of 3229 was designed to answer the following questions: (1) Will control of serum phenylalanine level be as satisfactory as previously achieved with Lofenalac? (2) Will there be any change in biochemical measures of phenylalanine metabolism consequent to use of 3229? (3) Will physical growth be impaired by administration of 3229? (4) Will continuity of mental development be maintained with no detrimental effects on learning or behavior?

Ten children with classical PKU were studied (four girls and six boys); they ranged in age from 2 to 13 years. In clinic visits at 0, 3, 6 and 12 months after inception of the trial period, the following assessments were made: (1)

*Commercial name of a low-phenylalanine dietary formula manufactured by Mead Johnson and Company.
†A phenylalanine-free dietary product manufactured by Mead Johnson Laboratories. Its composition has been published.