BIKEN JOURNAL Vol. 24 119–122, 1981

SHORT COMMUNICATION

AN EXTREMELY ATTENUATED, LIVE MEASLES VIRUS VACCINE (CAM-EX). PERSISTENCE OF LOW TITER-ANTIBODY IN INSTITUTIONALIZED CHILDREN WITH PSYCHOMOTOR RETARDATION AFTER VACCINATION

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(Received March 13, 1981)

SUMMARY Fifty children with psychomotor retardation, who had no detectable measles hemagglutination-inhibition (HI) antibody, were vaccinated with an extremely attenuated, live measles virus vaccine (CAM-EX). Only 10% of the children had fever after vaccination. No other symptoms were observed. Forty of 44 vaccinated children showed increase in HI antibody titers of 2^3 or more, with a geometric mean titer of $2^{4.2}$. A five-year follow-up study revealed that the initially low-titer antibodies persisted well under conditions without a booster response due to natural measles.

An extremely attenuated, live measles virus vaccine (CAM-EX) was developed in 1972 in Japan (Ueda et al., 1972). The vaccine caused less clinical reactions than other commercially available further attenuated, live measles virus vaccines (FAL). A febrile reaction occurred in only 10% of the children who received the CAM-EX. However, this vaccine has not been widely used because of its rather poor immunogenicity. Although seroconversion rates were over 97%, the geometric mean neutralizing antibody titers of children one month after vaccination with the CAM-EX varied between $2^{3.1}$ and $2^{5.0}$ (mean, $2^{3.6}$).

Children with psychomotor retardation have a tendency to react severely to infectious

agents. To protect such children from natural measles without inducing serious side effects, we vaccinated these children with the CAM-EX. We report here the clinical reactions and antibody responses of these children to the CAM-EX, and also the persistence of low titer-antibody observed in a 5-year follow-up study.

A total of 110 children with psychomotor retardation who were in 3 wards in the Minami-Fukuoka National Chest Hospital were examined. Among them, 50 children (24 boys and 26 girls) of 4 to 14 years old had no detectable measles hemagglutination-inhibition (HI) antibody. After vaccination with the CAM-EX (Lot No. 003B, $5\times10^{3.5}$ $TCID_{50}$/dose) on June 21, 1973, these 50 children were examined for fever, a rash and other symptoms, every day for 4 weeks by nurses. Then they were followed-up for 5 years under conditions without natural measles. The first blood specimens were collected from 44 of the 50 children 6 to 12 weeks after vaccination to examine the measles HI antibody response. Thereafter, blood specimens were collected 4 to 5 times at yearly intervals from 20 of the 44 children. All sera were kept at −20 C until measurement of measles neutralizing antibody tirers.

Measles neutralizing antibody was measured by the micro-method (Ueda et al., 1971) with some modification by one of us (S.U.). By using CV-1 cells instead of FL cells and the Nagahata strain (Ueda et al., 1972) instead of the Toyoshima strain of measles virus, in the hemadsorption method, the cytopathic effect (CPE) of the challenge virus could be detected by naked eye. Briefly, after serial dilution of sera with 0.025 ml of diluent in wells of rigid plastic 96-hole U-bottom microplates, 0.025 ml of the challenge virus suspension containing 100–300 $TCID_{50}$/0.1 ml was added to all wells. After incubation for 1 h at 37 C in a 5% CO_2 incubator, 0.1 ml of CV-1 cell suspension ($1.5–2.0\times10^5$ cells/ml) in growth medium (a mixture of equal volumes of Medium 199 and Eagle's minimum essential medium (199/MEM) supplemented with 10% fetal bovine serum) was added to the wells. After 4-days culture at 37 C in a 5% CO_2 incubator without changing the culture medium, 0.05 ml of 0.5% suspension of African green monkey red blood cells in 0.01 *M* Dulbecco's phosphate buffered saline (PBS, pH 7.2) was added to the wells and the plates were incubated further for 1 h at 37 C. Then the plates were washed in 3 series of beakers containing PBS to remove unattached red cells. Sites of CPE, mainly consisting of syncytial giant cells, were seen as brown spots by naked eye.

Five of the 50 vaccinees had a temperature of over 37.5 C between 9 and 11 days after vaccination; two of them had a temperature of 38.0 C or over lasting one day and the other three children had a temperature of less than 38.0 C lasting one or 2 days. No other symptoms were observed. These 5 children all remained in good spirits even when they were febrile. Measles HI antibody titers of 2^3 or more were found in 40 (91%) of the 44 vaccinees 6 to 12 weeks after vaccination. The antibody titers ranged between 2^3 and 2^7 (Table 1), the geometric mean antibody titer being $2^{4.2}$.

Twenty of the 44 vaccinees were followed-up for 5 years. Three of the 20 children did

TABLE 1. *Measles HI antibody titers of institutionalized children with psychomotor retardation 6 to 12 weeks after vaccination with the CAM-EX vaccine*

	HI antibody titers (2^n)						
	<3	3	4	5	6	7	Total
No. of children	4	17	9	8	3	3	44
(%)	9.1	38.6	20.5	18.2	6.8	6.8	100

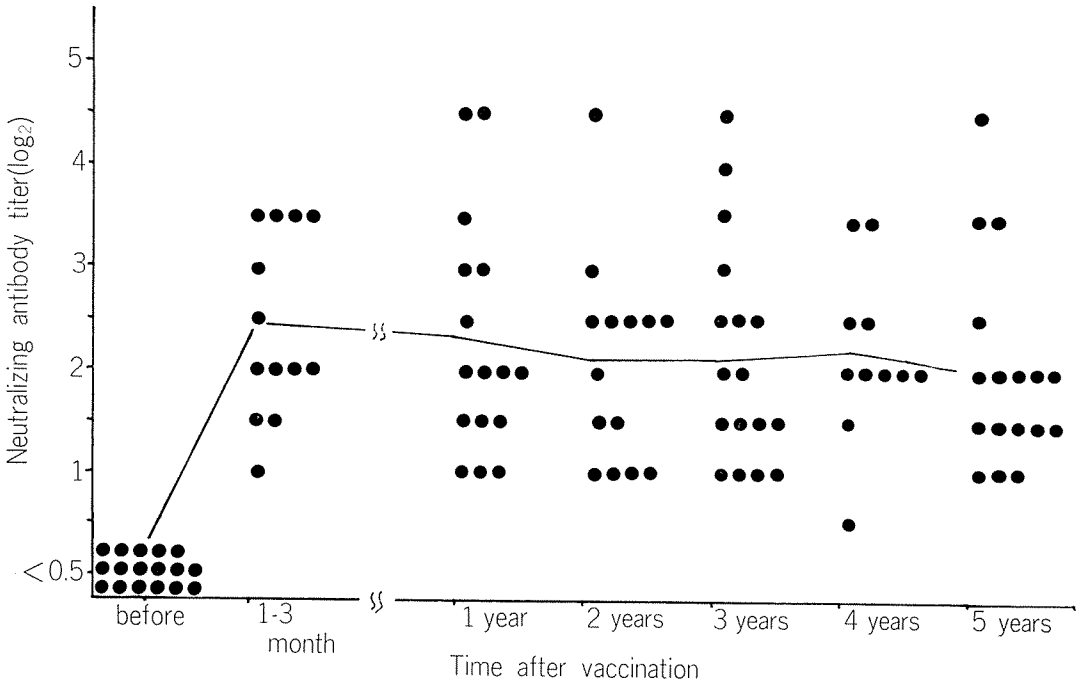

FIGURE 1. Pattern of neutralizing antibody persistence in institutionalized children with psychomotor retardation after vaccination with the CAM-EX vaccine without booster by natural measles.

not show any rise in neutralizing and HI antibody after vaccination and they remained seronegative during the follow-up study. Figure 1 shows the neutralizing antibody titers of 17 children who showed an antibody rise after vaccination. There was no marked decrease in antibody titers during the 5-year period, and the geometric mean antibody titers 6 to 12 weeks and 1, 2, 3, 4, and 5 years after vaccination were $2^{2.5}$, $2^{2.3}$, $2^{2.1}$, $2^{2.1}$, $2^{2.2}$ and $2^{1.5}$, respectively.

There has been no outbreak of exanthematous disease among the 110 handicapped children including the 50 vaccinees in the 3 wards of the hospital except for one outbreak of varicella between January and March 1975 (Ueda et al., 1977).

The efficacy of FAL is well established (Krugman, 1977). Three different FAL, namely CAM vaccine (Okuno et al., 1971), Schwarz vaccine (Schwarz, 1964) and AIK-C vaccine (Makino et al., 1974), are commercially available in Japan. However, these vaccines cause febrile reactions in 30 to 50% of the children vaccinated (Shishido et al., 1978). Ueda et al. (1970) reported that mentally retarded handicapped children respond to FAL similarly to healthy children. However, less reactive vaccine, if any, is desirable for immunizing handicapped children. The CAM-EX vaccine seemed suitable for this purpose, although there was some uncertainty about antibody persistence. As reported above, we found that even when the initial titer was low, measles neutralizing antibody persisted well for at least 5 years without a booster by natural measles. It has been reported that antibody of quite low titer can prevent the onset of measles (Ueda et al., 1969). So, the children vaccinated with the CAM-EX vaccine should be immune to infection from measles.

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