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PERSISTENCE OF PROTECTIVE IMMUNITY AFTER INOCULATION WITH LIVE VARICELLA VACCINE (STRAIN OKA)

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INTRODUCTION

In 1974, we have first reported the successful application of the Oka strain of live varicella vaccine to prevent the spread of varicella in a children's ward. (Takahashi et al., 1974; Asano et al., 1975) Since then, so many reports were published, which supported the efficacy and the safety of the vaccine. The properties of the vaccine are summarized in the Table 1. The purpose of this report is to review our data concerning the protective efficacy and the persistence of immunity after vaccination briefly.

INCIDENCE OF VARICELLA AFTER VACCINATION

In order to know the incidence of varicella after vaccination, inquiries were mailed to the parents of the vaccinated children. They were asked to report any instance of varicella or herpes-zoster in their family, school, or neighborhood, and whether their children had had varicella or herpes-zoster infection since being immunized. First, the incidence of varicella was evaluated in 179 vaccinated children in Nagoya 2 years after vaccination. (Asano and Takahashi, 1977) Well documented contact with varicella patients was reported for 80 of the 179 vaccinees. Only 1 of the household contacts manifested symptoms of varicella 16 months after vaccination. The attack rate of the vaccinees in each setting is shown in the first row in the Table 2. In total, 1.3% of the 80 vaccinees developed varicella during this observation period. Secondly, another group of 26 vaccinated children in Osaka was followed for the incidence of varicella 5 years after vaccination. (Asano et al., 1983b) None of the vaccinees contracted varicella in spite of 23 documented contact exposure, shown in the second row in the Table 2.

Recently, we studied longer term protective immunity of the varicella vaccine. Subjects

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TABLE 1. *Properties of live attenuated varicella vaccine (strain Oka)*

1)	Causes little or no clinical reactions[a]
2)	Induces antibody (measurable by CF[b], Nt[c], FAMA[d], IAHA[e] tests)
3)	Induces cell-mediated immunity (delayed type skin reaction, lymphocyte transformation)
4)	Lack of contact infection in most cases
5)	Long term protective immunity
6)	Prevents natural infection when administered up to 3 days after exposure

[a] Mild clinical reactions in 15% to 75% of leukemic children.
[b] Complement fixation.
[c] Neutralization.
[d] Fluorescent antibody to membrane antigen.
[e] Immune adherence hemaggutination.

TABLE 2. *Actual protective efficacy of the live varicella vaccine (strain Oka) in various settings*

No. of subjects (references)	Known exposure to varicella			
	Place	No. of children	No. of children developed varicella	Attack rate (%)
179, 2 years after vac. (Asano and Takahashi, 1977)	Household	13	1[a]	7.7
	School	38	0	0
	Neighborhood	29	0	0
	Total	80	1	1.3
26, 5 years after vac. (Asano et al., 1983)	Household	2	0	0
	School	14	0	0
	Neighborhood	7	0	0
	Total	23	0	0
106, 10 years after vac. (Asano et al., unpublished data)	Household	26	1[b]	3.9
	School	66	4[c]	6.1
	Neighborhood	55	0	0
	Total	147	5	3.4

[a] Developed mild varicella with no fever, about 10 vesicles, and no crust formation, 16 months after vaccination.
[b] Developed moderate varicella with fever and vesicles 3 years after vaccination.
[c] Very mild varicella, developed within 1 year after vaccination.

were 282 healthy and sick children who received vaccination of the Oka strain of varicella vaccine 7 to 10 years earlier. We received 106 replies. The age and sex distributions of children at the time of immunization are shown in Fig. 1. The mean age was 4.4 years ranging from 10 months to 13 years old. There were 59 males and 47 females. The name of underlying diseases and the number of vaccinees at the time of immunization are shown in Table 3. Among the children with various underlying diseases, 14 (35%) had been receiving steroid hormone treatment at the time of vaccination. Well-documented contacts with varicella patients were reported, in total, from 147 children. They were 26 children in family, 66

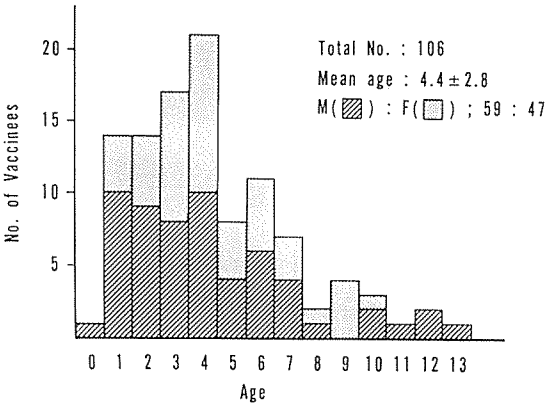

FIGURE 1

TABLE 3. *Number of vaccinated children in relation to underlying diseases*

Underlying diseases	No. of vaccinees	No. of receiving steroid therapy
Nephrotic syndrome	13	11
Nephritis	20	1
Asthma	1	0
Purulent meningitis	2	1
Hepatitis	1	1
Epilepsy	1	0
Kawasaki disease	1	0
Enterocolitis	1	0
Healthy children	66	0
Total	106	14

in school epidemic, and 55 in the neighborhood. In spite of these exposures, only 5 children developed varicella in each setting as shown in the third row in Table 2. The attack rate of varicella was calculated as 3.4% in this study.

The excellent protective efficacy of the vaccine against natural disease was shown in the 3 studies, which could be easily understood if we look the attack rate after contacts with varicella patients in natural setting shown in Table 4. If susceptible children are exposed to varicella virus in their family, 80% to 100% of them contract natural disease. (Ross, 1962; Yorke and London, 1973; Asano et al., 1977b) The attack rate are reported as 100% in the epidemic of varicella in institution (Baba et al., 1978), 68% in hospital (Gordon, 1962), and 46% in society (Yorke and London, 1973), respectively.

TABLE 4. *Attack rate of natural varicella in various settings reported previously*

Type of setting	Attack rate of varicella	References
Household	80%	Yorke & London, 1973
	87%	Ross, 1962
	100%	Asano, et al., 1977
Institution	100%	Baba, et al., 1978
Hospital	68%	Gordon, 1962
Society	46%	Yorke & London, 1973

On the other hand, none of the children contracted herpes-zoster in the 3 studies.

PROPERTIES OF CASES WITH VACCINE FAILURE

Table 5 shows the informations of 5 cases who developed natural varicella during 10-year observation (5 cases in the third row in Table 1). Most of the vaccinees except case 1 developed varicella within 1 year of vaccination and showed very mild signs and symptoms of the disease. They received vaccination on August and September, so hot season in Japan. So, we suppose the vaccine failure may partly be related to the decrease of infections virus particles in the inoculum at the time of immunization. Because of an unstable nature of this virus, this preparation seems to be the killed-like vaccine, but may be still immunogenic in human. If so, short-lasting antibody after inoculation of this preparation may show incomplete protection against natural exposure. Recently, it has been shown that heat-inactivated virus preparations are immunogenic in human (Russa et al., 1983), pygmy marmosets (Asano et al., 1983a), and rhesus monkeys

TABLE 5. *Clinical and serologic informations of 5 cases who developed natural varicella after vaccination*

Case No.	Age	Sex	Dose of vaccine (PFU)	Vaccinated	Initial antibody response		Interval between vaccination and onset of varicella	Place of exposure	Signs and symptoms of varicella	Confirmed by doctor
					Pre	Post				
1	1	F	4,000	May '76	ND[a]	ND	3 yr	Family	Moderate	Yes
2	6	F	1,500	Sept. '75	<2	2	10 mo	School	Very mild	No
3	4	F	1,500	Sept. '75	<2	2	4 mo	School	Very mild	Yes
4	4	M	1,500	Aug. '75	<2	4	7 mo	School	Very mild	Yes
5	2	F	1,500	Aug. '75	<2	16	7 mo	School	Very mild	?

[a] Not done.

(Asano et al., unpublished data).

PERSISTENCE OF IMMUNITY AFTER VACCINATION

The evaluation of humoral immunity has been done 2 and 5 years after vaccination (same subjects in Table 2). The seroconversion rates have been reported to be 96% to 100% measured by a number of different techniques (Asano and Takahashi, 1977; Asano et al., 1983c). The seropositive rate 2 years after vaccination was 98.0% by neutralization (Nt) test, with a geometric mean titer (GMT) of 9.2 (Asano and Takahashi, 1977). Five years later, the seropositive rate was 96% with a GMT of 12 by fluorescent antibody to membrane antigen (FAMA) assay, which was one third of the titer in children with natural infection (Asano et al., 1983b; Asano et al., 1983c). When the same samples were tested by an enhanced Nt test, the seropositive rate was 100% with a GMT of 310, which was almost equal to that following natural infection (Asano et al., 1983b). Recently, it was possible to obtain serum samples and to do skin testing in 38 children from 106 vaccinees 10 years after vaccination (in the third row in Table 2). In order to compare the vaccine-induced immunity with that following natural infection, 29 naturally infected children who had shown typical clinical manifestations of varicella 7 to 10 years earlier, were bled and received the skin testing against varicella-zoster virus (VZV) antigen (Kamiya et al., 1977; Asano et al., 1981). The seropositive rates were 97.4% in the vaccinated children and 100% in naturally infected group. The GMTs were 9.7 and 10.5, indicating no significant difference in both groups (Table 6). Both groups were also evaluated for cell-mediated immunities by skin testing to VZV antigen. Positive rate of vaccinated group was 97.3% and 96.6% in naturally infected group. Mean diameter was 13.4 mm in the vaccinees and 12.9 mm in the naturally infected group (Table 6). The possible explanations for long lasting immunity induced by the inoculation of the Oka strain of live varicella vaccine are as follows. Probably, the most important point is the attenuated Oka strain has an excellent immunogenic nature. So many studies for human immunization with this strain, so far reported, seem to strongly support this explanation. Furthermore, this excellent immunogenic nature of the Oka strain has been shown in the animal experiment (Asano et al., unpublished data). Seroconversion rate and the persistence of antibody after primary inoculation of animals with cell-free virus preparation, and secondary antibody responses after challenge were compared between rhesus monkeys which received the attenuated Oka strain and the animals inoculated with the KMcC strain. The latter strain was developed as candidate strain for human immunization by Neff et al. at MSD in the United States

TABLE 6. *Evaluation of humoral and cell-mediated inmmunities to varicella-zoster virus 10 years after vaccination or natural infection*

Number	Vaccinated 38	Naturally infected 29
Age (mean±SD)	12.1±3.0	13.3±3.3
Age when immunized or infected (mean±SD)	4.2±2.9	4.3±2.1
FAMA antibody		
% Positive (≥4)	97.4	100
GMT±SD (log 10)	0.97±0.37	1.02±0.31
Skin reaction to VZV antigen		
% Positive (≥5 mm)	97.3	96.6
Mean diameter±SD	13.4±4.9	12.9±5.7

(Neff et al., 1981). In this experiment, better immunogenic nature of the attenuated Oka strain was shown when compared to that by the KMcC strain (Asano et al., 1983a). Another explanation is that antibody level in the vaccinated children was, in part, maintained by subclinical infections due to contact exposures. This explanation has been already proved in the studies reported previously, in which naturally immune person (Caunt and Shaw, 1969) or vaccinated children (Asano and Takahashi, 1977; Asano et al., 1977a) showed secondary antibody responses without symptoms of the disease after contact exposure.

CONCLUSION

The Oka strain of live varicella vaccine has an excellent immunogenic nature. The vaccine-induced protective immunity persists at least for 10 years, and the degree of which is almost equal to that following natural infection. The life-long immunity can be expected by administration of the vaccine.

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