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USE OF A LIVE VARICELLA VACCINE TO PREVENT THE SPREAD OF VARICELLA IN HANDICAPPED OR IMMUNOSUPPRESSED CHILDREN INCLUDING MCLS (MUCO-CUTANEOUS LYMPHNODE SYNDROME) PATIENTS IN HOSPITALS

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SUMMARY A live varicella vaccine of Oka strain was used in a ward of an institution for handicapped children after the consecutive occurrence of 7 cases of varicella in about 40 days. There were 22 susceptible children in the ward and 13 of these were vaccinated. There were 4 further cases of varicella in vaccinated children and 1 case in unvaccinated children within 10 days after vaccination, but there were no further cases.

In 2 other wards of the same institution, 16 susceptible children were vaccinated while 25 susceptible children were not, to see whether contact infection occurred from the recipients of vaccine. All but one of the vaccinated children responded serologically without a clinical reaction, but none of the unvaccinated children showed a clinical or serological reaction. Thus no contact infection occurred from the recipients of vaccine to susceptible children in contact with them.

In a children's ward of a hospital, a patient with MCLS (Muco-Cutaneous Lymphnode Syndrome) who had been receiving steroid treatment developed severe varicella symptoms and died 3 days after the onset of symptoms. Two days later, varicella vaccine was given to 4 cases of MCLS and 2 cases of nephrosis who were receiving steroid therapy. Eleven days after the vaccination, only 1 of the cases of MCLS vaccinated developed varicella in a mild form while 1 unvaccinated cases of MCLS who had not been receiving steroid therapy developed severe varicella symptoms. Immediately, 4 other patients with various diseases were vaccinated, but none of the vaccinated patients except the one described above, exhibited varicella sym-

ptoms, and seroconversion was observed in all of them. These results suggest that live varicella vaccine may safely be used for handicapped children and immunosuppressed children including MCLS patients, and that immediate vaccination is effective for preventing spread of varicella among children in wards.

INTRODUCTION

Varicella is usually mild in healthy children but severe and occasionally fatal to children with malignancies, immunodeficiencies, or receiving immunosuppressive therapy (Finkel, 1961; Haggerty and Eley, 1956; Grunberg, 1968; Johnston and Janeway, 1969; Sheinman, 1969; Gershon et al., 1972). A live varicella vaccine was developed and used for preventing spread of varicella in hospital or family contacts (Takahashi et al., 1974; Asano et al., 1975; Asano et al., 1977a, b) and for children with acute leukemia or other malignancies (Hattori et al., 1976; Izawa et al., 1977). For clinical purposes, it seems important to define to which patients should be given this vaccine and when it should be given.

Recently we had two occasions for using this vaccine in a ward of an institution for handicapped children and in a pediatric ward of a hospital where there were immunosuppressed patients including cases of MCLS (Kawasaki et al., 1974) at the time when varicella developed in these wards. On both occasions, vaccination was effective for preventing spread of varicella among susceptible children. Furthermore contact infection from the vaccinees to susceptible children was examined in 2 wards of an institution for handicapped children. The detailed results are given in this paper.

MATERIALS AND METHODS

1. *Vaccine and Vaccination*

Live varicella vaccine of Oka strain (Takahashi et al., 1974, 1975) passaged 11 times in human embryonic lung (HEL) cell, 12 times in guinea pig embryonic cells and then 4 to 7 times in human diploid cells (W1–38) was used in this study. The virus concentration was about $10^{2.0}$TCID$_{50}$/0.1 ml and a dose of 0.5 ml/person was injected subcutaneously. Vaccinated children were examined every day by physicians and nurses.

2. *Serological examination*

Complement fixation (CF) test and neutralization (NT) test were done essentially as described previously (Takahashi et al., 1975). Kawaguchi strain (Takahashi et al., 1975) was used for CF and NT tests. CF test was done by microtiter method using 4 units of antigen and 2 units of complement with fixation at 4 C overnight. For NT test, phosphate buffered saline (PBS) containing 5% sucrose and 10% inactivated fetal calf serum was used as a diluent for serum and virus. The virus preparation diluted to contain 100–200 plaque forming units/0.1 ml was mixed with equal volume of serial two fold dilutions of serum inactivated at 56 C for 30 min, and the mixtures were incubated at 37 C for 30 min. Samples of 0.2 ml of the serum-virus mixture were then inoculated onto HEL cells in plastic dishes and the inoculated cultures were incubated at 37 C for 60 min, with occasional shaking. Then fresh medium was added and the cultures were incubated at 37 C for 6 to 7 days until viral lesions were large enough to be counted. No secondary foci appeared within this period. The antibody titer was expressed as the highest dilution of serum producing a 50% or greater reduction in the number of foci. Serum samples were divided into 2 parts, and serological tests on the two parts were done independently at the laboratories of Kyushu University, School of Health Sciences and Osaka University, Research Institute for Microbial Diseases.

RESULTS

1. *Vaccination of handicapped children in an institution on the outbreak of varicella*

The institution for handicapped children in

Minami-Fukuoka National Chest Hospital has 3 separate wards (I, II, III), each accomodating 40 children of 2 to 19 years old. On Jan. 20, 1975, a case of varicella occurred in Ward II and 6 children successively developed varicella between that date and Feb. 27 (Table 1).

On March 7, when there were 22 susceptible children in Ward II, we vaccinated 13 of them and left 9 unvaccinated as controls. In Wards I and III, there were 19 and 22 susceptible children and 7 and 9 of them, respectively, were vaccinated. The other children were not vaccinated to see whether contact infection occurred from the vaccinees. Serum samples were obtained before and 8 weeks after vaccination.

Varicella symptoms developed in 4 vaccinated children and 1 unvaccinated child in Ward II within 10 days after vaccination (Table 1), but then there were no further cases of

TABLE 1. *Occurrence of cases of varicella in a ward for handicapped children and the effect of vaccination on spread of varicella infection (Minami-Fukuoka National Chest Hospital, 1975)*

Case No.	Age & Sex (years)		Date of onset of varicella	Vaccination (Mar 7)	Varicella antibody titer (CF/NT)	
					Mar 6,	May 1.
1.	7	F	Jan 20,	−	16/2	4/2
2.	15	F	Feb 6,	−	16/8	4/8
3.	17	M	Feb 8,	−	16/16	4/4
4.	14	F	Feb 9,	−	32/4	16/4
5.	7	F	Feb 20,	−	64/4	32/8
6.	4	M	Feb 22,	−	64/4	16/4
7.	5	M	Feb 27,	−	32/8	16/8
8.	16	F	Mar 9,	+	8/<2	8/4
9.	17	F	Mar 14,	+	<4/<2	64/64
10.	6	M	Mar 17,	+	<4/<2	8/4
11.	6	F	Mar 17,	+	<4/<2	64/4
12.	14	M	—	+	<2/<2	<2/8
13.	18	F	—	+	<2/<2	<2/2
14.	18	F	—	+	<2/<2	<2/8
15.	7	F	—	+	<2/<2	<2/8
16.	11	F	—	+	<2/<2	<2/2
17.	7	F	—	+	<2/<2	<2/2
18.	18	F	—	+	<2/<2	<2/2
19.	5	M	—	+	<2/<2	4/4
20.	4	M	—	+	<2/<2	32/64
21.	6	F	Mar 14,	−	<2/<2	64/8
22.	18	F	—	−	<2/<2	<2/<2
23.	12	F	—	−	<2/<2	<2/<2
24.	8	M	—	−	<2/<2	<2/<2
25.	13	M	—	−	<2/<2	<2/<2
26.	12	F	—	−	<2/<2	<2/<2
27.	13	F	—	−	<2/<2	<2/<2
28.	8	M	—	−	<2/<2	<2/<2
29.	11	M	—	−	<2/<2	<2/<2

varicella. Judging from the incubation period of natural varicella, the 5 later cases had probably been exposed to varicella before vaccination. Serological examination showed that seroconversion occurred in all the vaccinated children and that unvaccinated children remained seronegative except for the one case who developed varicella.

There were no cases of varicella in Wards I and III and all the vaccinated children responded serologically except for one. In contrast, unvaccinated children were still seronegative 8 weeks after vaccination indicating that no contact infection occurred from the

TABLE 2. *Serological and clinical findings in handicapped children with or without vaccination of a live varicella vaccine (Minami-Fukuoka National Chest Hospital, 1975)*

	Vaccinated	Clinical reaction	Seroconversion[a]	Not vaccinated	Clinical reaction	Seroconversion[a]
Ward I	7	0	6	12	0	0
Ward III	9	0	9	13	0	0

[a] Serum samples were obtained before and 8 weeks after vaccination and examined by neutralization test.

TABLE 3. *Occurrence of varicella patients in a children's ward and effect of vaccination on*

Patient No.	Age & Sex (year)		Underlying disease (Date of onset)	Steroid therapy period (Total doses of predonisolon until vaccination)	Date of onset of varicella
1.[a]	3	F	MCLS[c] (May 17, 76)	May 22, 76- (1.900 mg)	Jul 19, 76 (severe and fatal)
2.	4	F	MCLS (Jun 4, 76)	Jun 8, 76- (1.975 mg)	—
3.	2	M	MCLS (Jun 26, 76)	Jul 6-Jul 31, 76 (545 mg)	—
4.	8	M	MCLS (Jun 13, 76)	Jun 22, 76- (700 mg)	Aug 4, 76 (mild)
5.	1	M	MCLS (Mar 18, 76)	Mar 24-Jun 25, 76 (1.900 mg)	—
6.	2	M	MCLS (Jul 10, 76)	—	Aug 4, 76 (severe)
7.[b]	11	F	Nephrosis (May 8, 76)	May 10, 76- (4.400 mg)	—
8.	4	F	Nephrosis (Mar 10, 76)	Mar 25, 76- (3.350 mg)	—
9.	3	M	Acute colitis (Aug 1, 76)	—	—
10.	7	F	JRA[d] (Jan 13, 76)	Jan 20, 75- (8.660 mg)	—
11.	4	F	CHD[e] PAP (Jul 19, 76)	—	—
12.	8	M	Acute colitis (Jun 31, 76)	—	—

[a] A area in children's ward
[b] B area in children's ward
[c] MCLS: Muco-Cutaneous Lymphnode Syndrome

recipients of vaccine (Table 2).

2. *Immediate vaccination of immunosuppressed children including MCLS patients in a hospital*

The children's ward of Hamanomachi Hospital covers 2 areas (A, B) with the nurse station in between them. There are 2 rooms (10 beds) in area A and 3 rooms (16 beds) in area B. A MCLS patient in area A who had been receiving steroid therapy developed severe varicella symptoms on July 19, 1976 and died on July 22. Seven children in area A had direct contact with the varicella patient, and 5 of these and 6 of the 13 children in area B had no history of varicella. Four patients with MCLS (in area A) and 2 patients with nephrosis (in area B) who had been receiving steroid treatment were immediately vaccinated on July 24 (Table 3).

On Aug. 4 (11 days after vaccination), one vaccinated MCLS patient developed varicella, but the symptoms were mild (i.e., no fever and about 40 vesicles). Judging from the incubation period of varicella, this case had probably been exposed to the index case before being vaccinated and the symptoms were modified by vaccination. In contrast, a MCLS patient in area A who had not been receiving steroid treatment and had not been vaccinated, developed severe varicella at the same time, Aug. 4, with a temperature of 38 C–39 C for 3 days and numerous vesicles. Immediately, 4 other patients with no history of varicella in area B were vaccinated. There were no

spread of varicella infection (Hamanomachi Hospital, Fukuoka, 1976)

Date of varicella vaccine inoculation	Antibody for varicella after vaccination (CF/NT)				
	Pre	2W	4W	8W	12W
Died on Jul 21, 76					
Jul 24, 76	32/64	32/64			32/64
Jul 24, 76	<2/<2	4/4			8/128
Jul 24, 76	<2/<2	4/128			16/32
Jul 24, 76	<2/<2	<2/<2	4/4		
—					32/—
Jul 24, 76	<2/<2	8/8			
Jul 24, 76	<2/<2	2/8	16/32		
Aug 4, 76	<2/<2				
Aug 4, 76	<2/<2			4/2	
Aug 4, 76	<2/<2			<2/2	
Aug 4, 76	<2/<2			8/2	

[d] JRA: Juvenile rheumatoid arthritis

[e] CHD, PAP: Congenital heart disease, Primary atypical pneumonia

further cases of varicella in area A or B, and no disturbance was detected by weekly hematological and urinary examinations of the vaccinated children. Seroconversion was observed in all the vaccinated children in area A except one who was already seropositive before vaccination (Table 3).

DISCUSSION

Varicella is a highly contagious disease. We have frequently observed that when a case of varicella occurred in a ward, the disease spread to susceptible children one after another for several months causing much trouble for the staff even when the patient was immediately placed in isolation. At such times, isolation of the wards (prohibiting visitors to the children, prohibiting children from going home for the night and prohibiting exchange of staff between the wards) for long periods was unavoidable.

During the outbreak of varicella described here there were 7 successive cases within about 40 days in a ward for handicapped children. To prevent further spread, we inoculated the live varicella vaccine into 13 of the 22 susceptible children in the ward, leaving the other 9 children unvaccinated as controls. There were 4 more cases of varicella among vaccinated children and 1 case among the unvaccinated children within 10 days after vaccination, but then there was no more varicella. Judging from the incubation period of varicella, these 5 later cases were probably infected before vaccination. It was fortunate, but rather unexpected, that only one of the 9 unvaccinated children developed varicella. Possibly only immunized children came into contact with the last varicella patient and thus there was no further spread of the disease, because on other occasions when the patients were not vaccinated, cases of varicella continued to develop for several months. Thus vaccination seemed effective in preventing the spread of varicella among handicapped children in the ward.

It was previously reported that no contact infection occurred from vaccine recipients to susceptible children in a closed institution (Asano et al., 1976). We confirmed this in the 2 wards (Wards I and III) for handicapped children.

It is well known that varicella is serious and even fatal to the immunosuppressed children. In the present study, one MCLS patient who had been receiving steroid therapy developed severe symptoms of varicella and died in three days. There were 5 other MCLS patients without history of varicella in the same area of the ward, and 4 of them had been receiving steroid therapy. Since these patients had been exposed to the index case, they seemed likely to develop varicella. Thus they were immediately vaccinated. As a consequence, only one of the vaccinated children developed varicella symptom 11 days after vaccination and the symptoms were so mild that the varicella seemed to have been modified by vaccination, judging from the incubation period of natural varicella. In contrast, a MCLS patient, who had not received steroid treatment and had not been vaccinated, developed severe varicella symptoms. There was a 5-day interval between the day of onset of varicella in the index case and the day of vaccination of susceptible patients. Yet only one of the 4 vaccinated patients developed mild varicella symptoms. This observation suggests that vaccination is effective for preventing the disease even when the vaccination is done after exposure to natural varicella.

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