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APPLICATION OF LIVE ATTENUATED MEASLES AND MUMPS VACCINES IN CHILDREN WITH ACUTE LEUKEMIA

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SUMMARY Eight children with acute leukemia in remission were immunized with live attenuated measles vaccine and 4 with mumps vaccine. Immunological examinations before vaccination showed that the numbers of white blood cells, percentages of lymphocytes, levels of immunoglobulins and responses to skin tests with DNCB, PPD, PHA and varicella antigen were within normal ranges in most of these children. Chemotherapy against leukemia was stopped for 2 weeks, from one week before to one week after vaccination. One child had a transient fever 10 days after measles vaccination, but no side reactions were observed in the others. Seroconversion was observed in all but one child who received measles vaccine, and neutralizing antibodies have persisted for at least 4 weeks and at most 3 years, when this study was terminated.

INTRODUCTION

Measles and mumps are highly contagious diseases in children and measles infection is often severe or even fatal in children with acute leukemia (Mitus et al., 1962; Pullan et al., 1976; Young et al., 1980). Mumps is usualy mild in healthy children but may be complicated by meningitis or pancreatitis. In our experience, unlike measles or varicella, mumps infection usually causes similar clinical reactions in leukemic children and healthy children. But, there are some reports that mumps is severe in immunocompromised children (Henson et al., 1971; Rashid et al., 1977). As children with acute leukemia now tend to survive for longer, prevention of their infection with viruses has become very important. So, we administered live attenuated measles and mumps vaccines to children with acute leukemia under careful immunological survey. The results obtained in this study suggest that these vaccines are useful for immunizing children with acute leukemia.

MATERIALS AND METHODS

1. *Vaccines*

The measles vaccine used was live further attenuated " CAM 70 ", each dose of the vaccine contained approximately 5×10^4 $TCID_{50}$ of attenuated measles virus. The mumps vaccine used was live attenuated " BIKEN mumps vaccine ", each dose of the vaccine contained approximately 1×10^5 $TCID_{50}$ of attenuated mumps virus. Volumes of 0.5 ml of vaccine were injected subcutaneously into each child.

2. *Vaccinees and vaccination*

Measles vaccine was administered to 7 children with acute lymphocytic leukemia and one with acute myelocytic leukemia. Mumps vaccine was administered to 4 children with acute lymphocytic leukemia. All the children were attending our outpatient clinic. They had been in a state of remission for more than 4 months and had received anticancer medication with 6-mercaptopurine (6MP) (2.0 to 3.0 mg/kg/day orally) and methotrexate (30 mg/m^2 once a week intravenously) as maintenance therapy and intermittent intrathecal injection of methotrexate, vincristine and steroid hormone as enforcement therapy. Administration of anticancer medication was suspended from one week before to one week after vaccination in 5 children (case 1–5, Table 1) with measles vaccine, but oral administration of 6MP was not suspended in the other children.

3. *Immunological examinations before vaccination*

Before vaccination, hematological examination, serum immunoglobulin estimation, and skin tests with dinitrochlorobenzene (DNCB), purified protein derivative (PPD), phytohemagglutinin (PHA) and varicella virus antigen were done to determine the immunological potential of the children.

4. *Clinical observation and follow up study*

After vaccination, children were observed at weekly intervals by physicians. Hematological examinations were also performed at weekly intervals. Parents of the children were asked to record and report the daily body temperature and any clinical manifestations that might develope. When these were seen, physicians examined the children carefully. In follow-up studies, all vaccinees received clinical examinations in the outpatient clinic weekly, and the

TABLE 1. *Immunological examinations of children with acute leukemia before vaccination*

Case[a] No.	Age/ Sex	Disease[b]	WBCs/ mm^3	Lympho-cytes (%)	Serum immunoglobulins (mg/dl)			Skin tests[c]			
					IgA	IgM	IgG	DNCB	PPD	PHA	Vari-cella antigen
1	3/F	AML	4900	49	42	195	730	+	−	n.t.[d]	n.t.
2	5/M	ALL	4300	57	96	88	660	+	+	n.t.	n.t.
3	4/F	ALL	1650	42	77	108	800	+	+	n.t.	n.t.
4	3/F	ALL	4200	43	25	100	750	+	−	+	−
5	2/F	ALL	5100	57	35	98	1010	+	−	+	−
6	12/M	ALL	5600	53	40	24	445	+	−	+	+
7	4/M	ALL	4900	45	35	25	690	−	−	+	+
8	1/M	ALL	3350	42	105	191	690	+	−	+	−
9	2/F	ALL	5500	53	132	125	1020	+	+	−	n.t.
10	2/M	ALL	9700	35	118	134	1040	+	+	−	+
11	5/F	ALL	11100	23	58	100	1200	+	−	+	+
12	6/F	ALL	4600	61	145	191	1450	−	+	+	+

[a] 1-8=measles vaccinees, 9-12=mumps vaccinees.
[b] ALL: acute lymphocytic leukemia, AML: acute myelocytic leukemia.
[c] DNCB: dinitrochlorobenzene, PPD: purified protein derivative, PHA: phytohemagglutinin.
[d] n.t.: not tested.

parents were asked to report any contact with cases of measles or mumps at home or school. Sera were collected every few months and tested mainly for neutralizing antibody titers against measles and mumps viruses.

5. *NT and HI tests*

Measles neutralizing antibody titration (NT) and hemagglutination inhibition (HI) tests were done as reported by Ueda (1971). The NT tests was done by the micro-method and the HI tests by the macro-method. Mumps neutralizing antibody titers were measured by the Biken method, a micro-method (Yamanishi et al., 1970).

RESULTS

1. *Immunological states of vaccinees*

The results of immunological examinations before vaccination are shown in Table 1. Leukopenia (less than 3,000/mm^3) was observed in one child (case 3; 1,650) and a low IgG level was detected in another child (case 6; 445 mg/dl). All the children showed two or more positive reactions in skin tests with DNCB, PPD, PHA and varicella antigen, except one (case 1) who was tested only with DNCB and PPD. The children who did not respond to PPD or varicella antigen gave negative reactions at the time of admission.

2. *Measles vaccination*

Table 2 shows the clinical reactions and antibody responses after measles vaccination. Only one child (case 8) had a fever of 38 C, lasting 1 day, 10 days after vaccination. There were no other adverse effects related to vaccination or to suspension of anticancer medication. No hematological changes were detected in these vaccinees (data not shown). Rise in measles antibody was detected in 7 of 8 vaccinees, the range of the titers being 1:2 to 1:128. One child (case 7) had a second bone marrow relapse 2 months after vaccination and contracted natural measles 6 months after vaccination. Although he had no measles NT antibody 1 month after vaccination, the clinical course of measles was moderate. NT antibodies were persistently detected for up to 3 months after vaccination in one child and for up to 36 months in 2 children, and these children were free from measles symptoms.

We observed 3 cases of leukemic relapse among the measles vaccinees. Case 1 (AML) relapsed 6 months after vaccination and died 6 months later. Case 2 relapsed 10 months

TABLE 2. *Clinical reactions and antibody responses of children with acute leukemia to live attenuated measles vaccine*

Case No.	Vaccination		Clinical reaction	Antibody response[a]								
	Date	Time after remission (mo)		Before	4 wk	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
1	Oct. '73	4	—	< 2	64	32	16	64				
2	Jun. '75	6	—	< 2	8	n.t.[c]	64	32				
3	Aug. '75	7	—	< 2	128	128	16	64	n.t.	n.t.	64	n.t.
4	Nov. '77	4	—	< 2	2	16	64	n.t.	n.t.	8	n.t.	128
5	Feb. '78	4	—	< 2	16	n.t.	n.t.	(16)	n.t.	16	n.t.	8
6	Mar. '80	5	—	<(8)	64	n.t.	8					
7	Mar. '80	12	—	<(8)	<2	n.t.	2[b]					
8	Jul. '80	6	fever	<(8)	n.t.	8						

[a] ( )=HI, others=NT.
[b] When measles was diagnosed.
[c] n.t.: not tested.

TABLE 3. *Clinical reactions and antibody responses of children with acute leukemia to live mumps vaccine*

Case. No.	Vaccination		Clinical reaction	Antibody response (NT)		
	Date	Time after remission (mo)		Before	4 wk	3 mo
9	Nov. '76	5	—	<2	n.t.[a]	32
10	Dec. '76	18	—	<2	32	n.t.
11	Aug. '79	6	—	<2	4	16
12	Jul. '80	13	—	<2	8	n.t.

[a] n.t.: not tested.

after vaccination and died 10 months later. Case 7 had a second bone marrow relapse 2 months after vaccination and developed natural measles infection 4 months later, although his clinical course was moderate. In this case, no measles NT antibody was detected 1 month after vaccination. This may be due to his depressed immunological condition at the time of vaccination.

3. *Mumps vaccination*

The results of sequential NT antibody examinations are shown in Table 3. An antibody response was detected in all vaccinees. The geometric mean titer was $2^{3.5}$ (1: 11.3) 4 weeks after vaccination. No clinical reaction was observed.

DISCUSSION

Measles is severe in children with leukemia (Mitus et al., 1962; Pullan et al., 1976; Yong et al., 1980). But in our experience, unlike measles or varicella, mumps infection usually develops similarly in leukemic children and healthy children. In a nation wide survey of infectious diseases in children with acute leukemia (Kamiya, 1976), it was found that varicella was the most severe and highly fatal viral infection followed by measles, and that mumps was not so severe. Among 46 children with acute leukemia infected with measles, 8 had a severe course and 5 died, whereas mumps was severe in 3 of 16 children. Henson et al. (1971) and Rashid et al. (1977) suggested that mumps virus infection may have a serious outcome in immunocompromised children. The recent increase in longevity of children with acute leukemia and the more frequent use of immunosuppressive agents for treatment of the disease have increased the number of children with risk of developing severe illness, though fortunately few leukemic children are susceptible to measles.

Mitus et al. (1962) reported that application of live measles vaccine to children with acute leukemia was contraindicative. But, Izawa et al. (1977) reported that live varicella vaccine was useful for prevention of varicella in high-risk children with leukemia or other malignancies, when applied under careful hematological and immunological survey. Nowadays, live measles vaccine has been further attenuated and can be used more widely than in the early 1960s in normal children, and live mumps vaccine that does not cause side effects is now commercially available. Therefore, we applied live measles and mumps vaccines to 8 and 4 children with acute leukemia, respectively. Recently, one of us proposed criteria for use of several live virus vaccines in children with malignant diseases (Ihara, 1981) (Table 4). We applied live varicella vaccine in 22 children with acute leukemia, live attenuated measles vaccine in 2 and live mumps vaccine in 1 according to these criteria. Good responses were ob-

TABLE 4. *Criteria for vaccinating children with acute leukemia and other malignancies with live vaccine*

1	Status of disease
	1) Complete remission of leukemia
	2) Disease-free state of children with solid malignant tumors
2	Immunological status Positive skin reaction to DNCB and PHA or PPD
3	High risk of natural infection
4	Anticancer agents other than oral 6MP can be suspended safely from one week before to one week after vaccination

tained in most cases and there were no severe side effects (data not shown).

As mentioned above, 3 cases of leukemia vaccinated with measles vaccine showed relapse. However, we do not consider that measles vaccination was responsible for these relapses because there was a long time between vaccination and relapse and this was different in each children. We obtained good results with mumps vaccine in these patients, and there were no serious problems. But unfortunately, the number of vaccinated cases was small and the observation period was only 3 months.

In conclusion, although the number of vaccinated children was small, our results suggest that live attenuated measles vaccination is not contraindicative in children with leukemia. However, the vaccine must be administered to children with acute leukemia with great care, giving special consideration to immunological conditions. Live mumps vaccine is safer and more effective than measles vaccine.

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