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—Original Article—

IMMUNOPROPHYLAXIS OF HEPATITIS A OF THE CHILDREN BY IMMUNE SERUM GLOBULIN

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Summary

An outbreak of hepatitis A occurred in Kyoto. Immune serum globulin was administered prophylactically to children who had not yet developed the disease. However 52 children in succession contracted hepatitis A. Late injections of immune serum globulin had no effect on the clinical course. Middle injections suppressed only jaundice. Early or preexposure injection suppressed the disease remarkably. All who had overt hepatitis A seroconverted to positive antibody to hepatitis A virus. In inapparent infection, those who had slight elevation of transaminase developed passive active immunization irrespective of pre or postexposure administration of immune serum globulin. Three children who might block hepatitis A virus completely had no change of transaminase and failed to establish passive active immunization.

Key Words: *Hepatitis A, Immune serum globulin.*

Introduction

An outbreak of hepatitis A (HA) occurred at an institution for mentally retarded children in Kyoto in 1978. For prevention, immune serum globulin (ISG) was administered to children who had no abnormal liver function tests. However, almost all children developed hepatitis. Thus, hepatitis A virus (HAV) infection occurred during a short period in almost all children, and the epidemic then subsided rapidly.

The efficacy of ISG in preventing and attenuating infectious hepatitis has been established[1,2]. However, until recently a precise diagnosis of HA was difficult. Therefore, confirmed diagnoses of HA, antibody response to HAV, and detailed descriptions of the clinical course of HA are relatively scarce. Accurate analyses of the immunoprophylaxis of HA have not been sufficient.

In this study HA was diagnosed by radioimmunoassay (RIA) of antibody to HAV (anti-

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HA), and pre and postexposure immunoprophylaxis of HA by ISG was analyzed.

Materials and Methods

Patients. A total of 55 youths, aged 5 to 24 years old (mean 13), resided and ate together in the institution. They were mainly mentally handicapped and had no overt liver anomaly or metabolic liver diseases. The first ill child was admitted temporarily because his mother had acute hepatitis. He had a high fever on April 5 and developed acute hepatitis. On April 8, he was hospitalized. Subsequent cases of acute hepatitis began to appear on April 20. We examined all the children on May 3 and collected blood samples on May 4. Thereafter blood was drawn every week until June 14. One year later examinations and blood samplings were repeated. The general condition of the children was recorded daily by the personnel of the institution.

Immune serum globulin. Commercially available ISG (Green Cross Corp.) was used. Anti-HA titers were determined as follows: ISG was serially diluted twofold, and the dilution of 50% inhibition was considered the anti-HA titer. The titers of three lots of ISG were 2^{11}, 2^{12} and 2^{12}. One ml was injected intramuscularly in children under 15 years of age, and 2 ml in those over 16.

Laboratory studies. Serum glutamic pyruvic transaminase (SGPT) and total bilirubin (T.B.) were measured by autoanalyzer. SGPT was expressed in Karmen units/ml; the normal range being 1-35 unit/ml. The normal range of T.B. is 0.1-1.0 mg/ml. Anti-HA and IgM class anti-HA were assayed by RIA (ANTI-HA and HAM RIA KIT, Dainabot, Japan). Hepatitis B surface antigen was assayed by RIA or reverse passive hemagglutination.

Statistical analysis. The mean values were compared by Student's t-test.

Results

HA epidemic. The diagnosis of HA was made by assaying paired sera for anti-HA or one point assays of IgM class anti-HA. In 52 children HA was confirmed serologically. Only three children were seronegative and showed no evidence of HA infection. There was no hepatitis B infection.

The onset of HA. Descriptions by the personnel revealed that the first symptom was fever and/or vomiting in 38 children (78%) (**Table 1**). In 14 children symptoms were absent or non-specific, and the onset was determined by SGPT elevation and/or IgM class anti-HA. Clinical and/or biochemical onset was confirmed by changes in the titer of IgM class anti-HA, which was low or negative at the onset of symptoms and positive when SGPT reached its peak (**Fig. 1**).

Table 1. First symptom of children who developed hepatitis A

Fever with or without other symptoms	37
Vomiting	1
Anorexia or malaise	3
None	11
Total	52

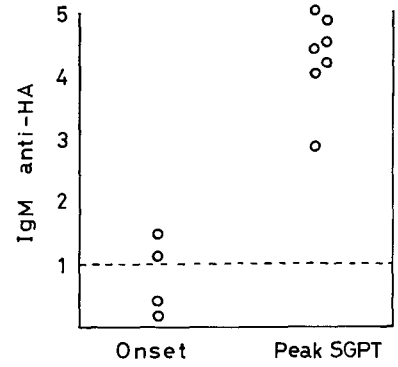

Fig. 1. Titer of IgM class antibody to hepatitis A virus (IgM anti-HA) at the onset and peak serum glutamic pyruvic transaminase (SGPT). Above the dotted line indicates positive anti-HA.

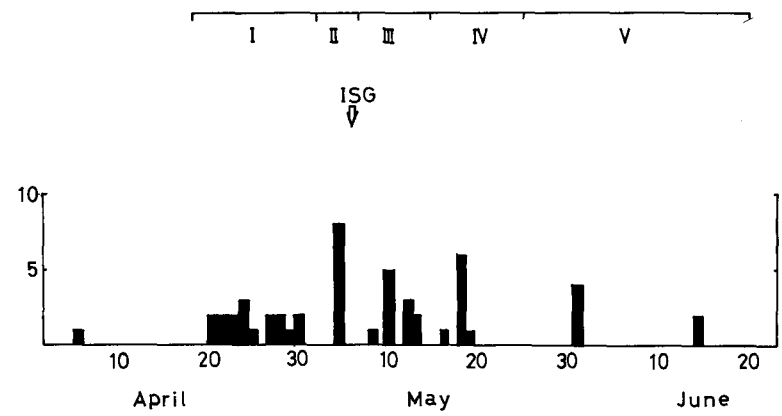

Fig. 2. The number of patients developing hepatitis A each day. Five groups were divided on the basis of the onset. ISG=immune serum globulin

Table 2. Comparison of clinical data in each group

	No. of patients (male)	Age mean ± S.D.	Peak SGPT* (unit/ml) mean ± S.D.		Peak T.B.† (mg/ml) mean ± S.D.	
Group 2	8 (3)	13.4±6.2	930±263	NS	2.6±1.6	NS
Group 3	13 (9)	12.2±3.6	827±251	p<.025	2.7±1.4	p<.01
Group 4	8 (5)	15.5±4.9	502±278	p<.005	1.2±0.7	
Group 5	6 (3)	15.8±3.4	69± 43		0.6±0.2	

*SGPT=serum glutamic pyruvic transaminase
†T.B.=total bilirubin
NS=not significant

Grouping of patients. Dates of onset of HA are shown in **Fig. 2**. The children were divided into five groups according to the date of onset. The mean age of each group was not significantly different (**Table 2**). One of them had his first contact on May 3 and developed HA on June 6, so the incubation period was about 30 days. Therefore, group 1 and 2 probably had secondary infection, group 3 and 4 tertiary, and group 5 partly tertiary and partly quaternary.

Effect of ISG. Groups 1 and 2 had already developed HA, so ISG was not injected with a few exceptions (**Table 3**). Group 2 was followed from the onset of the disease without administration of ISG. Group 3 was injected with ISG late in the incubation period, and showed no significant difference from group 2 in the mean titer of T.B. and SGPT. Group 4 had much lower T.B. and SGPT levels from group 3, but the mean peak SGPT was about 500 unit/ml. Group 5 had only slight elevation of SGPT and was considered to have inapparent infection (**Table 2**).

Table 3. Summary of administration of immune serum globulin in each group

	No. of the patients	
	with ISG	without ISG
Group 1	2	15
Group 2	2	6
Group 3	13	0
Group 4	8	0
Group 5	6	0

Immune response. In groups 1 to 4 all children had abnormal SGPT and developed posi-

tive anti-HA titers. In group 5 five children had slight elevation of SGPT, four above and one within the normal range. All developed anti-HA. One child who had abnormal SGPT from the first also seroconverted. Three children were seronegative even after a year. They had no significant elevation of SGPT including one child who had abnormal SGPT from the beginning.

Discussion

HA is usually sporadic and self-limiting. However under some conditions, epidemics occur. In Japan some epidemics in institutions or elementary schools have been reported[3]. This observation was also made in an institution for mentally retarded children. The first patient developed HA about a month after admission. Secondary, tertiary, and quaternary infections followed and involved 52 of 55 children. Since exposure to HA was extensive during a short period, the outbreak of HA developed and subsided rapidly. Therefore, this epidemic was easy to analyze.

Previous reports on the immunoprophylaxis of HA have not been satisfactory because the diagnosis of HA was presumptive, and detailed data of liver function tests were relatively sparse. Recently assays of anti-HA have become available, so a few detailed reports have been published[4,5].

In this study all but three children developed clinical, biochemical, and/or serological evidence of HA. On the basis of the day of onset the children were divided into five groups. Groups 1 and 2 received no ISG, with a few exceptions. Group 3 was injected late in the incubation period, group 4 during the middle of the incubation period, and group 5 early in the incubation period or during preexposure. There were no significant differences in peaks of T.B. and SGPT between group 2 and group 3. Group 4 had a significantly lower T.B. and SGPT, but SGPT was still high; therefore only jaundice was suppressed. Group 5 had inapparent infection. These facts confirm that preexposure and early postexposure injection of ISG suppresses HA remarkably, while late injection had no effect on the clinical course.

The dose of ISG used in our study was that recommended for prophylaxis of HA[6] and showed no variation in anti-HA titer between lots. Since it has been reported that higher doses reduce HA more[7], it is possible that higher doses might have improved the laboratory data of group 4.

All who had overt HA seroconverted to positive anti-HA. In group 5 four children who seroconverted before June 6 may have been injected after exposure, and two who seroconverted after June 6 may have been injected before exposure. Five of the six had slight elevations of SGPT. One of them had abnormal SGPT from the beginning. Three were seronegative even after a year. They were not isolated and all ate together. They were probably exposed to HAV, but ISG seems to have prevented infection completely, and failed to establish passive active immunization. All but one, who had abnormal SGPT from the first, had no SGPT elevation. These facts indicate that those who had slight elevation of SGPT, even within the normal range, developed passive active immunization whether the administration of ISG was pre or postexposure, and those in whom HAV was blocked by ISG may have failed to establish passive active immunization. After a year none of the children had any significant elevation of T.B. or SGPT or any evidence of chronic HA.

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