

SHORT PAPERS

Parenterally Transmitted Non-A, Non-B Hepatitis

An Epidemic Reassessed

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In 1972 a nosocomial outbreak of parenterally transmitted hepatitis affected both marrow transplant patients and normal platelet donors in an oncology unit. Because of the characteristics of the clinical illness, the incubation period of 27 days, and the effect of immune serum globulin on the clinical illness, the outbreak was attributed to hepatitis A; there was no serologic evidence of either hepatitis B virus or cytomegalovirus infection. Stored serums from this outbreak were re-examined by more recently developed serologic techniques for evidence of hepatitis A (HA) virus infection. Ten patients and donors had undetectable anti-HA titers before illness and none seroconverted; five persons had pre-existent anti-HA titers and showed no further rise in convalescent serums. The serum of one patient was invaluable. With the availability of serologic techniques for the diagnosis of both hepatitis A and hepatitis B virus infections, it is clear that most cases of post-transfusion hepatitis are not due to either of these agents, and short-incubation-period hepatitis can not be assumed to be hepatitis A without further investigation.

IN 1972 A NOSOCOMIAL OUTBREAK of parenterally transmitted hepatitis involving nine bone-marrow transplant patients, 26 normal platelet donors, and one nondonor family member occurred in a marrow transplant unit (1). Eight patients and six donors had symptomatic hepatitis, whereas the remaining patient and donors had elevated serum glutamic oxalacetic transaminase (SGOT) levels without symptoms. Because of the characteristics of the clinical illness, the mean incubation period of 27 days in normal donors, the apparent effect of immune serum globulin on clinical illness in donors, and the absence of serologic

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evidence of cytomegalovirus, Q-fever, or hepatitis B virus infections, the epidemic was attributed to hepatitis A (HA) virus. More recently, techniques for the serologic diagnosis of hepatitis A virus infection have been developed (2-6), but few serologically proven cases of parenterally transmitted type A viral hepatitis have been described (7-10). Other outbreaks of plasmapheresis-associated hepatitis not due to hepatitis B virus have been reported (11), as has an outbreak of short-incubation-period hepatitis caused by parenterally transmitted Epstein Barr virus (12). In order to further study the possible etiologic role of hepatitis A and Epstein Barr virus in this outbreak of parenterally transmitted short-incubation-period hepatitis, stored serums were re-examined for serologic evidence of HA or EB virus infection.

Methods

Serums were available for retesting from eight transplant patients (all with clinical hepatitis), eight normal donors (two with clinical hepatitis and six with subclinical illness), and one donor with no clinical or biochemical evidence of infection (1). In the original investigation, all nine transplant patients and 11 of the 26 donors had been negative for hepatitis B surface antigen (HBsAg) by both counterelectrophoresis (Hyland Laboratories; Costa Mesa, California) and solid-phase radioimmunoassay (Ausria 1, Abbott Laboratories; North Chicago, Illinois), whereas 11 additional donors had been tested and found to be negative by counterelectrophoresis alone. These tests were not repeated.

Serums were tested for the presence of antibody to hepatitis A antigen (anti-HA) by immune adherence hemagglutination (IAHA), as modified by Moritsugu and associates (6). Each serum was tested at a dilution of 1:10, 1:100, and 1:1000; when indicated, end-point titrations were done. Antibody to Epstein Barr virus was detected by immunofluorescence, with HR1-K cells (13) as source of antigen, as described by Henle and Henle (14).

Results

Clinical data and the results of hepatitis A antibody (anti-HA) tests are summarized in Table 1. Five of eight transplant patients had no serologic evidence of previous

Table 1. Antibody Titers Against Hepatitis A and Epstein-Barr Viruses

Patient	Clinical Status	Type of Illness	Onset Date*	Serum Dates		Anti-HA Titer †		Anti-EBV Titer †		Interval Between Onset of Illness* and Convalescent Serum
				First	Convalescent	First	Convalescent	First	Convalescent	
262	Patient ‡	Clinical	10/29	9/22	12/20	<10	<10	≥10§	10	52 days
267	Patient	Clinical	11/23	11/5	11/28	<10	<10	<10	<10	5 days
269	Patient	Clinical	11/29	11/29	1/9	<10	<10	<10	<10	42 days
263	Patient	Clinical	12/6	10/2	1/10	<10	<10	<10	<10	35 days
270	Patient	Clinical	12/20	12/14	1/9	<10	<10	40	20	20 days
266	Patient	Clinical	11/23	11/29	12/31	<80**	NS††	<10	<10	33 days
264	Patient	Clinical	11/29	10/12	1/9	400	200	40	80	41 days
265	Patient	Clinical	12/6	10/24	12/19	≥1000	≥1000	40	20	13 days
A	Donor	Clinical	11/21	10/10	...	≥100	...	10
B	Donor	Clinical	12/4	10/10	1/2	200	200	<10	10	29 days
C	Donor	Subclinical	12/14	12/14	2/16	<10	<10	≥10§	10	64 days
D	Donor	Subclinical	12/15	12/15	2/20	<10	<10	10	10	67 days
E	Donor	Subclinical	12/15	12/15	1/13	<10	<10	20	40	29 days
F	Donor	Subclinical	12/18	12/18	2/15	<10	<10	10	10	59 days
G	Donor	Subclinical	12/19	12/19	1/2	<10	<10	20	20	16 days
H	Donor	Subclinical	12/15	11/14	1/12	500	500	≥10§	10	27 days
I	Donor	None	...	12/26	...	<10	...	>10

* Onset date recorded as date of first unusual SGOT rise for transplant patients (1), of first symptoms for normal donors with clinical hepatitis, and of first known SGOT elevation for normal donors without symptoms.

† Expressed as reciprocal of serum dilution; see text for methods.

‡ Marrow transplant patient.

§ Not titered to end-point because seroconversion or four-fold titer rise not possible.

|| Day of death.

** Nonspecific reaction at 1:40 dilution; negative at 1:80 dilution.

†† Nonspecific reaction to 1:4000 dilution; end-point not reached.

hepatitis A virus infection before the onset of illness. Four of these showed no anti-HA rise in convalescent serums drawn 20 to 52 days later, whereas the fifth patient died 5 days after onset of illness. Two patients had detectable anti-HA in serums drawn before the onset of illness and did not show a rise in anti-HA titer. Both serum samples from the eighth patient (Patient 266) had nonspecific activity in the IAHA test; though the titer of this nonspecific reaction rose from 1:40 in the first sample to 1:4000 in the convalescent sample, no specific anti-HA activity could be seen.

Both normal donors with icteric hepatitis had significant anti-HA titers in serums taken 42 and 55 days, respectively, before the onset of clinical illness. There was no further titer rise in the one individual with convalescent serum drawn 29 days after clinical illness.

Five of six normal donors with subclinical hepatitis had no detectable anti-HA titer at the time their SGOT was first found to be elevated, and there was no titer rise in serums taken 16 to 67 (mean, 47) days later. One donor had an anti-HA titer of 1:500 1 month before his SGOT was found to be elevated. A repeat titer 27 days after subclinical illness was unchanged.

One normal donor (Donor I) who donated during the period of risk without developing clinical or biochemical evidence of hepatitis (1) had no detectable anti-HA by IAHA in the first serum examined. A later specimen was not available.

Results of testing for antibody to Epstein Barr virus were similar. Half of the patients and one of eight donors had no detectable Epstein Barr virus antibody in first serums; in no case was a significant rise in antibody titer demonstrable, regardless of initial titer. Although one do-

nor showed a rise from <1:10 to 1:10, this was not considered significant.

Discussion

There was no serologic evidence that this epidemic was due to parenterally transmitted hepatitis A virus. Ten susceptible individuals who developed clinical or biochemical evidence of hepatitis, or both, manifested no antibody response to hepatitis A antigen by immune adherence hemagglutination, whereas five other cases had pre-existent anti-HA titers, and, therefore, can be presumed to have been immune. Convalescent serum was drawn long enough after the onset of clinical symptoms or biochemical abnormalities to have shown antibody rise in all but two or three of the cases (4-6). Epstein-Barr virus and cytomegalovirus (previously reported) also did not appear to play a role.

The humoral response of immunosuppressed patients to hepatitis A virus infection has not been studied. However, immunosuppressed patients do develop antibody to hepatitis B surface antigen, and marrow transplant patients have been shown to seroconvert or show an anamnestic response to cytomegalovirus and varicella-zoster infection. Furthermore, the five susceptible donors who did not seroconvert to anti-HA-positive in this study are presumed to have been normal immunologically.

Now that serologic tests for hepatitis A virus infection as well as hepatitis B virus infection are available, most cases of parenterally transmitted hepatitis have been clearly shown not to be caused by either hepatitis B virus (15-18), or apparently by hepatitis A virus (7-9), and their cause remains uncertain. The incubation period of the cases described here, 22 to 37 days with a mean of 27 days (1), is consistent with that characteristically at-

tributed to hepatitis A virus infection. This study emphasizes that a short incubation period does not necessarily implicate hepatitis A virus, nor does the apparent prevention of secondary spread by immune serum globulin, as described in our original report (1). The existence of an as yet unidentified hepatitis agent is suggested by the data presented here. Whether the agent responsible for this outbreak is the same as that responsible for the more common occurrence of non-B post-transfusion hepatitis, or for the non-parenterally spread non-A, non-B "viral" hepatitis more recently described (19) is, of course, not known. Finally, the brevity of hepatitis A viremia and the absence of chronic hepatitis A virus carriage suggest that parenteral transmission of type A viral hepatitis is not a significant public health problem.

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