PAPERS AND ORIGINALS

Non-B hepatitis in Melbourne: a serological study of hepatitis A virus infection

IAN D GUST, JULES L DIENSTAG, ROBERT H PURCELL, C RONALD LUCAS

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Summary

A study was performed to establish the value of immune adherence haemagglutination tests for antibody to hepatitis A virus in the diagnosis of non-B hepatitis. Infection with hepatitis A virus was confirmed in 14 out of 16 patients from six families and seven out of nine patients in whom the source of infection was unknown. One additional patient, who had had two episodes of jaundice, was shown to have had an attack of hepatitis A followed by an attack of hepatitis B. In patients with acute hepatitis A antibody detectable by immune adherence haemagglutination becomes detectable three or four weeks after the onset of symptoms and reaches peak levels about five weeks later.

Introduction

For many years two forms of acute viral hepatitis have been recognised. They have different epidemiological features but both produce similar clinical illnesses. During the past six years several techniques have been developed for detecting infection with hepatitis B virus, so that it is now relatively simple to recognise patients suffering from hepatitis B. Because of the lack of specific tests for the hepatitis A virus, hepatitis A is usually diagnosed on the basis of clinical and epidemiological findings

together with negative tests for hepatitis B surface antigen (HBsAg) and antibody (HBsAb). The recent development of techniques for detecting the hepatitis A virus and antibody, directed against it (HAAb)¹⁻³ offers the prospect of positive confirmation of diagnosis and has provided an impetus to studies of the epidemiology of the disease. Serological evidence of infection with hepatitis A virus has been established in experimentally and naturally acquired disease^{1,4} and in outbreaks of hepatitis associated with the ingestion of contaminated water,¹ food,^{5,7} and shellfish.⁷ Recently, hepatitis A virus has been serologically associated with some attacks of non-B hepatitis, in which no source of infection could be shown—a condition referred to as sporadic non-B hepatitis (J L Dienstag *et al*, personal communication).

In Melbourne viral hepatitis is a major public health problem, resulting in the admission of up to 800 patients a year to Fairfield Hospital for Communicable Diseases. Recently about a third of these patients have been diagnosed as having hepatitis B; of the remainder with non-B hepatitis, less than half have a history of recent contact with the disease. Our study was undertaken to establish the value of HAAb serology in the diagnosis of non-B hepatitis.

Patients and methods

Twenty-six patients were admitted to Fairfield Hospital for Communicable Diseases Melbourne between 1971 and 1974 with illnesses consistent with viral hepatitis. The diagnosis was made on the basis of a typical illness, compatible liver function tests, and, in some cases, exclusion of other possible causes of jaundice. An attack was regarded as non-B if HBsAg was not detected in sera collected during the acute phase of the illness and if HBsAb was not detected during convalescence. The patients were divided into three groups.

Group 1 consisted of patients selected because of epidemiological features suggesting hepatitis A. The group comprised 16 patients from six families in which two or more cases of hepatitis had occurred within three months.

Group 2 comprised eight patients with hepatitis selected because they had no known source of infection. No patient in this group had a history of jaundice, transfusion, tattooing, parenteral drug abuse, or exposure to hepatotoxic drugs and chemicals.

Repeated tests for HBsAg and HBsAb gave negative results in all members of groups 1 and 2.

Fairfield Hospital for Communicable Diseases, Melbourne 3078, Australia

I D GUST, DIP BACT, FRCPA, medical virologist
C R LUCAS, MB, FRACP, specialist physician

Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

J L DIENSTAG, AB, MD, research associate, hepatitis virus section (now research fellow in medicine, Massachusetts General Hospital, gastrointestinal unit, Massachusetts 02114, USA)

R H PURCELL, MD, head of hepatitis virus section

Group 3 comprised two parenteral drug abusers, both of whom had had two attacks of acute hepatitis.

Serum specimens were obtained from all patients at weekly intervals or more often if indicated and stored at -20°C . Tests of liver function included measurement of serum bilirubin and aminotransferase levels. In each patient the illness was measured from the onset of symptoms. At least two serum specimens from each patient were examined under code for HBsAg and HBsAb by solid phase radioimmunoassay⁸ and radioimmunoprecipitation (RIP)⁹ respectively, and at least two specimens were examined for HAAb by immune adherence haemagglutination.¹⁰

Serological tests to detect infection with cytomegalovirus, herpes simplex virus, Epstein-Barr virus, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Toxoplasma gondii*, *Leptospira interrogans*, *Treponema pallidum*, and *Brucella abortus* were performed by standard methods.

Results

The results of liver function tests and tests for HAAb are shown in tables I-III. Table III also includes the results of tests for HBsAg and HBsAb in the two patients who had two attacks of hepatitis.

The diagnosis of hepatitis A was confirmed by seroconversions or significant rises in HAAb titres in 14 of the 16 patients in group 1, seven of the eight patients in group 2, and one of the two attacks of non-B hepatitis in patients in group 3. Overall, only four out of 28 attacks of hepatitis lacked serological confirmation of diagnosis. Further details about these four attacks are given below.

Case 6—Group 1. This girl became ill a few days after her twin brother. She was initially treated at home but was admitted to hospital eight weeks later when a relapse of symptoms occurred. As a result no acute-phase serum was available. The first test, performed on the 58th day of illness, contained HAAb to a titre exceeding 1/16 000 and a similar titre was present in a further serum sample obtained 145 days after the onset of illness.

Case 8—Group 1. This boy received human normal immunoglobulin on the day his brother's illness was diagnosed as hepatitis. The dose given and its titre of HAAb are unknown. Ten days later he developed symptoms, which were followed in a few days by transient jaundice. The first serum

TABLE I—Family outbreaks of hepatitis (group 1)

Case No	Age (years)	HAAb†	Day of illness
Family A			
1	38	<10, >1000	14, 109
2	33	<10, >1000	11, 92
3	17	<10, >16 000	8, 41
4	7	<10, 4000	1, 34
Family B			
5*	17	200, >16 000	12, 101
6	17	>16 000, >16 000	58, 145
Family C			
7	11	<10, 1000	23, 37
8†	10	SE, 1600	4, 13
Family D			
9	50	<10, 8000	10, 60
10	15	10, 4000	12, 27
Family E			
11	31	<10, 2000	5, 40
12	7	<10, >1000	5, 52
13	3	100, 2000	11, 26
Family F			
14	31	<10, 8000	8, 19
15	26	<10, 1000	7, 36
16	7	<10, 400	3, 31

*Received normal immunoglobulin 2 days before onset of symptoms.

†Received human normal immunoglobulin 10 days before onset of symptoms.

‡Titres expressed as reciprocal of dilution.

SE = Serum exhausted.

TABLE II—Sporadic attacks of hepatitis

Case No	Age (years)	HAAb	Day of illness
17	23	<10, 160	14, 33
18	35	<10, <10	17, 39
19	6	<10, 4000	13, 41
20	24	<10, 400	15, 36
21	18	400, 4000	23, 45
22	23	<10, 800	10, 43
23	31	<10, 2000	21, 60
24	32	<10, 400	9, 40

TABLE III—Details of patients who had two attacks of hepatitis

Age (years)	Date of onset of illness	Day of illness	HAAb	HBsAg	HBsAb
Case 25					
21	11 June 1971	17		+	-
		20	<10	-	+
		47		-	+
	1 June 1973	15	<10	-	+
		31		-	+
		145	<10	-	+
Case 26					
23	19 February 1972	6	<10	-	-
	26 March 1974	37	4000	-	-
		7	8000	+	-
		20		+	-

available for testing was obtained on the 13th day after the onset of illness—that is, 23 days after the administration of immunoglobulin. It contained HAAb to a titre of 1/1600; the titre had not risen significantly by day 29, when a further test was performed.

Case 18—Group 2. This woman had an illness that was clinically typical of acute viral hepatitis, with recovery in five weeks. Sera collected on the 17th and 39th days of the illness contained no detectable HAAb. Additional tests showed no evidence of current infection with Epstein-Barr virus, herpes simplex virus, *Mycoplasma pneumoniae*, *Treponema pallidum*, *Toxoplasma gondii*, *Leptospira interrogans*, *Coxiella burnetii*, or *Brucella abortus*. The complement fixation antibody titre to cytomegalovirus rose from 16 to 64. A late convalescent serum specimen to test for HBsAb was not obtained.

Case 25—Group 3. This young woman, a parenteral drug abuser, was first admitted in 1971 with acute hepatitis B, from which she recovered in five weeks. She was readmitted two years later with similar symptoms. Biochemical tests showed evidence of acute hepatocellular damage, which resolved in four weeks. Sera obtained during her first illness and on days 15 and 145 of her second illness contained no detectable HAAb. Additional tests gave no evidence that her second illness was due to the other agents listed above.

Antibody response—The figure shows the HAAb titre related to time from the onset of dark urine in the 22 patients in whom a diagnosis of hepatitis A was confirmed by seroconversion or a rise in antibody titre. HAAb was rarely detected within three weeks of the onset of symptoms. Of the 21 sera obtained during this period only four contained antibody and none of these were taken in the first week. Four out of five sera collected during the fourth week of illness contained HAAb, and all sera obtained after this was positive. The general pattern of response indicated that peak titres may not be reached for eight or nine weeks after the onset of symptoms.

HAAb titres related to time from onset of dark urine in 22 patients with confirmed diagnosis of hepatitis A.

Discussion

In this study hepatitis A virus was implicated as the aetiological agent in six family outbreaks of non-B hepatitis. Of the 16 patients affected, 14 developed rising titres of HAAb. In the other two hepatitis A could be confidently diagnosed on epidemiological grounds as their contacts showed serological evidence of infection. Failure to confirm the diagnosis in these two patients was probably due to the absence of adequate specimens. One (case 6) was not seen until 58 days after the onset of

illness, at which time she had a titre of HAAb consistent with recent infection. Another patient (case 8), in whom the level of HAAb did not rise significantly between days 13 and 29 of illness, had received an injection of human normal immunoglobulin 10 days before the onset of symptoms, which may have caused a modified antibody response.

Two studies of sporadic non-B hepatitis have been reported recently. In the first a highly selected group of patients was tested, and infection with hepatitis A virus was confirmed in only two out of 73 patients.⁴ The second study, which was carried out prospectively in Los Angeles, found only 48% of sporadic non-B hepatitis to be type A (J L Dienstag *et al*, personal communication) and suggested that the remaining cases may have been due to other, as yet unidentified, viruses. In Melbourne infection with hepatitis A virus was confirmed in seven of the eight patients with sporadic disease, but the small number of patients studied makes it impossible to draw firm conclusions about the prevalence of non-A non-B hepatitis. The patient in whom hepatitis A was not diagnosed had a rising titre of complement fixation antibody to cytomegalovirus.

Until 1971 hepatitis B was uncommon in Melbourne,¹¹ and second attacks of hepatitis were almost unknown.¹² In the last two years, however, several patients (usually intravenous drug users) have been admitted with second and even third attacks. Each of the two such patients studied was found to have had one attack of hepatitis B, and one had had an attack of hepatitis A. The remaining episode of hepatitis was not diagnosed. HAAb was not detected in acute and convalescent serum samples and no evidence was obtained of infection with other viral, bacterial, or rickettsial agents known to produce acute liver damage. Possibly this illness may have been due to a hepatitis virus other than A or B.

The antibody response to hepatitis A virus, detected by immune adherence haemagglutination, was similar to that described in a group of patients who developed hepatitis after eating contaminated shellfish.⁷ HAAb was not detected in sera collected during the first week after the onset of symptoms and

was detected in only three of the 12 sera collected during the second week. In most patients antibody was first detected in the third or fourth week after the onset of symptoms, then rose in titre, peaking in the eighth or ninth week. No substantial data on the duration of antibody were obtained, but in two patients from whom sera were obtained at 210 days and 217 days no fall in titre had occurred.

Our results confirm that the detection of rising titres of HAAb by immune adherence haemagglutination is a reliable index of infection with the hepatitis A virus and that the presence of antibody in high titre during the first two weeks of illness or its absence in sera collected six weeks or more after the onset of symptoms makes a diagnosis of hepatitis A unlikely.

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Requests for reprints should be addressed to Dr I D Gust, Department of Virology, Fairfield Hospital for Communicable Diseases, Fairfield, Victoria 3078, Australia.

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Rheumatoid arthritis: relation of serum C-reactive protein and erythrocyte sedimentation rates to radiographic changes

R S AMOS, T J CONSTABLE, R A CROCKSON, A P CROCKSON, B McCONKEY

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Summary

Serum C reactive protein (CRP) levels and erythrocyte sedimentation rates (ESR) were measured in 56 patients with rheumatoid arthritis. Radiographical damage,

based on a count of erosions, was significantly more likely to occur when serum CRP and ESR were persistently raised, irrespective of the presence or absence of rheumatoid factor. Measurements of both CRP and ESR were more helpful than either alone, but CRP was probably the more informative. Serial measurements of CRP and ESR provide a reliable means of discriminating between drugs that provide symptomatic relief only and those with a more profound effect in rheumatoid arthritis.

Introduction

The acute-phase reactants are a class of serum proteins, mainly glycoproteins, whose concentration in the blood increases after various stimuli such as trauma or inflammation.¹ The magnitude of the acute-phase protein response is roughly proportional to the severity of the stimulus.^{2,3} Serial measurements of these proteins can therefore be used, like the erythrocyte sedimenta-

Dudley Road Hospital, Birmingham B18 7QH

R S AMOS, BSC, MRCP, Sheldon clinical research fellow

T J CONSTABLE, MB, MRCP, Sheldon clinical research fellow (now senior registrar, Northern General Hospital, Edinburgh)

Department of Experimental Pathology, University of Birmingham, Birmingham B15 2TJ

R A CROCKSON, FIMLS, technical superintendent

A P CROCKSON, FIMLS, senior chief technician

B McCONKEY, DM, FRCP, consultant physician and honorary research fellow