Occasional Survey

NON-A, NON-B HEPATITIS IN WEST LONDON

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Summary Acute and convalescent sera from 368 patients drawn from a 3-year survey of viral hepatitis in West London were tested by radioimmunoassay for evidence of recent infection with hepatitis A or B and, if neither was found, antibody to Epstein-Barr (EB) virus and cytomegalovirus. In 215 patients (58%) there was evidence of hepatitis A, in 98 (27%) hepatitis B, and in 5 both A and B. 2 patients with evidence of recent EB virus infection were excluded, leaving 48 (13%) attributed to non-A, non-B hepatitis. This illness was milder than hepatitis B as judged by duration of jaundice and peak serum bilirubin alanine-aminotransferase levels. The ratio of men to women was 1·4 to 1, but there was an excess of women in their twenties, most of whom were single. Only one had received blood, and none was a drug addict.

INTRODUCTION

THE possibility that acute viral hepatitis might be due to more than two viruses was suggested by reports of multiple episodes of hepatitis in drug addicts.[1,2] A significant proportion of transfusion-associated hepatitis cannot be serologically attributed to hepatitis B,[3,4] hepatitis A, cytomegalovirus, or Epstein-Barr (EB) virus infection.[4-6] These observations had led to the term non-A, non-B hepatitis. This form of hepatitis also occurs sporadically.[7]

At present, there are no reliable serological markers for non-A, non-B hepatitis. The diagnosis is made on clinical and biochemical evidence of viral hepatitis and the serological exclusion of recent hepatitis A, B, cytomegalovirus, and EB virus infection.

A preliminary report of the relative importance of this form of hepatitis in a total population survey in West London suggested that 4·3% of the patients surveyed had sporadic non-A, non-B hepatitis.[8] We now report the results of further investigations of patients in that survey.

PATIENTS AND METHODS

Acute and convalescent sera, stored at −20°C, from 368 patients were available for study. This group of patients was drawn from a total population survey of acute viral hepatitis carried out in three London boroughs between March, 1972, and February, 1975.[9,10] Patients with presumed viral hepatitis were referred to the field team consisting of a physician and a health visitor and assessed epidemiologically and clinically. The patients were seen initially about once a week for clinical examination and for collection of blood samples. Patients were accepted as having viral hepatitis if the clinical picture was associated with a serum level of alanine aminotransferase (ALT) at least twice normal, on epidemiological evidence, and on the absence of other causes of infective jaundice.[9,10]

Sera from each patient were tested under code by radioimmunoassay for HBsAg and for total and IgM-specific antibody to hepatitis-B core antigen (anti-HBc). Total and IgM-specific antibodies to hepatitis-A virus were measured by radioimmunoassay or enzyme-linked immunosorbent assay (ELISA). Comparison of the two methods revealed identical and reproducible results.

The presence of HBsAg or IgM-specific anti-HBc was accepted as evidence of recent infection with hepatitis B. Hepatitis-A IgM in the acute serum or the appearance of total hepatitis-A antibody in the convalescent serum indicated recent exposure to hepatitis A.

Patients without serological markers of recent infection to either hepatitis A or B in both acute and convalescent sera were tested for IgM and IgG antibody to EB virus and cytomegalovirus by indirect immunofluorescence and for total antibody to cytomegalovirus by complement fixation.

Biochemical tests of liver function were done at intervals throughout the illness as previously described.[10]

The significance of the different factors was tested with the chi-square test. Percentages were rounded up to the nearest whole number.

RESULTS

99 of the 368 patients tested had evidence of infection with hepatitis B, 88 were positive for HBsAg, and 11 had IgM-specific anti-HBc in the acute serum. However, 1 of the HBsAg-positive patients also had hepatitis-A IgM during the acute phase of the illness. Thus hepatitis-B infection alone was thought to be the cause of the illness in 98 patients (table I).

215 patients had hepatitis-A IgM in their acute or in both acute and convalescent sera, suggesting that they had hepatitis A.

In addition to the HBsAg-positive patients with hepatitis-A IgM, there were 4 HBsAg-negative patients with both IgM-specific anti-HBc and hepatitis-A IgM in the acute phase of the illness. Thus 5 patients showed evidence of recent exposure to both hepatitis A and B.

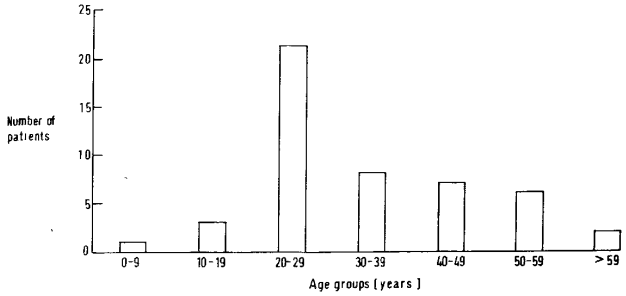
In 17 patients neither acute nor convalescent sera contained hepatitis-A antibody or anti-HBc. The remaining 33 patients had IgG but no hepatitis-A IgM, indicating previous but not recent infection with hepatitis-A virus. These 50 patients were tested for antibody to EB virus and cytomegalovirus.

1 of the 17 patients without serological markers of hepatitis A or B and 1 of the 33 patients with evidence of previous infection to hepatitis-A virus showed a four-fold or greater increase in the titre of the IgG antibody to EB virus between the acute and convalescent samples. Even though the IgM antibody to EB virus was not found in these 2 patients, their

TABLE I—CLASSIFICATION OF 368 PATIENTS TESTED FOR SEROLOGICAL EVIDENCE OF HEPATITIS A AND B

—	No. of patients	
Hepatitis A:		
IgM or seroconversion		215
Hepatitis B:		
HBsAg alone	87	
IgM anti-HBc or seroconversion	11	98
Hepatitis A and B:		
IgM anti-HBc and hepatitis A IgM	4	
HBsAg and hepatitis A IgM	1	5
Non-A, non-B hepatitis:		
Negative serology	16	
Hepatitis-A IgG only	32	48
EB virus		2*
Total no. of patients		368

*2 patients with evidence of EB virus infection were excluded from the 50 patients who showed no evidence of recent infection with hepatitis A or B.



Age distribution among 48 patients with non-A, non-B hepatitis (median 28 years).

illness may have been due to EB virus and they were therefore excluded. Thus, 48 (13%) of the remaining 368 patients were accepted as having non-A, non-B hepatitis (table I).

Age and Sex Distribution

Nearly a half (21/48) of the non-A, non-B patients were young adults aged 20 to 29 (see figure). The majority of the remainder were aged 30 or more. There were only 2 children under 15—a boy and a girl. Overall there were slightly more males (28) than females (20), a ratio of 1·4 to 1. Over the age of 30 years, males predominated in a ratio of 2·8 to 1. Approximately two-thirds of the women were aged between 15 and 29 (table II).

Clinical Features

The illness was clinically more similar to hepatitis A than hepatitis B, being generally milder and of shorter duration than hepatitis B. Just over a third (17/46) of the patients were either not jaundiced or jaundiced for 2 weeks or less. 2 patients remained jaundiced for more than 8 weeks, but 3 adults and 1 child were anicteric. The duration of jaundice was significantly shorter in the icteric adults with non-A, non-B hepatitis than in the adults with hepatitis B ($p<0·025$), table III). The median duration of jaundice was 24 days (range 2–90) in the non-A, non-B adults and 30 days (range 7–98) in those with hepatitis B.

Both arthralgia, which occurred in 26% (12/46), and skin rashes, which were noted early in the illness in 15% (7/47), were less common than in hepatitis B; these differences did not reach significance.

Biochemical Features

Of the 34 adults with non-A, non-B hepatitis who had blood taken within a week of the onset of jaundice, 19 (56%) had a peak serum-bilirubin of less than 86 μmol/l (5 mg/dl), compared with 12 (19%) of 62 patients with hepatitis B. Only 1 (3%) of the non-A, non-B patients and 17 (27%) of the hepatitis-B adults had a peak bilirubin of greater than 259 μmol/l (15 mg/dl). These differences were significant at the 0·1% level (table IV). The median peak serum-bilirubin level of the non-A, non-B patients was 76·6 μmol/l (range 27·5 to 392), whereas in the hepatitis-B patients it was 187·5 μmol/l (range 18·9 to 576).

Blood was obtained with 2 weeks of the onset of illness for measurement of serum ALT levels in 31 adult patients with non-A, non-B hepatitis and 46 with hepatitis B (table V). In 17 (55%) of the non-A, non-B and 4 (9%) of the hepatitis-B patients the peak ALT level was 400 IU/l or less. Only 5 (16%) of the non-A, non-B adult patients compared with 17 (37%) of the hepatitis-B patients had peak levels greater than 12000 IU/l. Again, these differences were significant at the 0·1% level. The median peak ALT in the non-A, non-B patients was 337 IU/l (range 74–2675), whereas that in the hepatitis-B patients was 981 IU/l (range 92–2458).

Epidemiological Factors

27 patients, including the 2 children, gave a history of skin puncture within 6 months of the onset of the illness. There were no addicts, and the only person who had had a non-therapeutic skin puncture was a child who had had her ears pierced. 1 adult had received blood, and the remainder had had a skin puncture for medical reasons (e.g., vaccination, inoculation, dental treatment).

6 adults and 1 child (15%) had been in close contact with another jaundiced person before they became ill. 4 were in the same household, 2 were at work, and 1 was a close friend. Of the 4 household contacts, 2 were married, and the other 2

TABLE II—AGE AND SEX DISTRIBUTION IN 48 NON-A, NON-B PATIENTS

Sex	Age (yr)	No. of patients
Male	0–14	1
	15–29	10
	30+	17
	Total	28
Female	0–14	1
	15–29	13
	30+	6
	Total	20

Ratio of male:female 1·4:1 all ages, 2·8:1 >30 yr.

TABLE III—DURATION OF JAUNDICE IN ICTERIC ADULTS WITH NON-A, NON-B HEPATITIS AND HEPATITIS B

Duration of jaundice (wk)	Non-A, non-B hepatitis	Hepatitis B	Total
≤2	12	14	26
>2 ≤4	15	21	36
>4 ≤6	9	27	36
>6	5	29	34
Total	41	91	132

$\chi^2_3 = 9·5$, $p<0·025$.

TABLE IV—PEAK SERUM-BILIRUBIN IN ADULTS WITH NON-A, NON-B HEPATITIS AND HEPATITIS B (BLOOD TAKEN 1 WK OR LESS FROM ONSET OF JAUNDICE)

Peak serum-bilirubin (μmol/l)	Non-A, non-B hepatitis	Hepatitis B	Total
≤86	19	12	31
87–171	8	16	24
172–259	6	17	23
>259	1	17	18
Total	34	62	96

$\chi^2_3 = 17·0$, $p<0·001$.

TABLE V—PEAK SERUM-ALANINE-AMINOTRANSFERASE (ALT) IN ADULTS WITH NON-A, NON-B HEPATITIS AND HEPATITIS B (BLOOD TAKEN WITHIN 2 WK OF ONSET OF ILLNESS)

Peak ALT (IU/l)	Non-A, non-B hepatitis	Hepatitis B	Total
≤400	17	4	21
401–800	5	13	18
801–1200	4	12	16
>1200	5	17	22
Total	31	46	77

$\chi^2_3 = 20·0$, $p<0·001$.

were a mother and daughter. 2 patients lived in institutions but had no known contacts.

Significantly more of the women patients in their twenties were single compared with a similar age group in the community. Thus 11 (92%) of the 12 patients, compared with 36% of similarly aged women in the community were unmarried ($p<0.0005$). The proportion of single male patients (7/9) aged 20 to 29 years was also higher than in the community, but the difference was not significant.

DISCUSSION

In this survey of viral hepatitis in an urban community 13% (48/368) appeared to have non-A, non-B hepatitis. This is surprisingly similar to the figure of 14% (10/73) patients reported in a consecutive series of patients admitted to hospital in Denmark.[11] Our 368 patients were selected from 489 patients detected during the 3 years of the survey.[10] The selection was on the basis of availability of serum for further detailed testing. This selection may have introduced bias and so no conclusion could be drawn about the prevalence of this type of hepatitis. The ratio of non-A, non-B hepatitis to hepatitis B and hepatitis A in the 368 patients studied was 1:2:4 (table I).

There are few reports on sporadic non-A, non-B hepatitis. In a study of 103 patients with endemic viral hepatitis in Costa Rica, Villarejos et al.[7] found 11 who, by exclusion, were thought to have this form of hepatitis. None had received a blood transfusion. 4 of these cases occurred in one family, which strongly suggested person-to-person transmission. In the United States an estimated 25% of sporadic cases may be due to virus(es) of non-A, non-B hepatitis.[12] Investigation of 69 stored serum specimens from patients involved in two water-borne outbreaks and sera of endemic cases in three areas of India indicated that many cases of hepatitis in that country were due to viruses other than hepatitis A and B.[13] It has been suggested that non-A, non-B hepatitis is a milder illness than hepatitis B as judged by the proportion of icteric cases and the maximum bilirubin and transaminase levels.[11,14,15] Our findings are in keeping with these reports.

A significantly higher proportion of the women patients were single than in the local population of women of the same age. This may simply have reflected a greater chance of exposure to the infective agent as a consequence of more frequent and varied close social contacts than experienced by married women. It is of interest that non-A, non-B disease predominated in women of 35 years or more in Los Angeles.[12]

In contrast to the reports from the United States[12,16,17] and one British study,[18] neither drug addiction nor the administration of blood or its products appeared to be important factors in the transmission of non-A, non-B hepatitis in the present study. This may be because the patients investigated were drawn from a community survey. Although household contacts were significantly less common than in hepatitis A, the finding of 4 patients with such a history indicated that close personal contact may be important.[7]

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Public Health

MALIGNANT MESOTHELIOMA AND RADIOLOGICAL CHEST ABNORMALITIES IN TWO VILLAGES IN CENTRAL TURKEY

An Epidemiological and Environmental Investigation

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Summary A comparative epidemiological and environmental study in two neighbouring villages, Karain and Karlik, in Central Turkey showed an excess adult mortality, shortening of life expectancy, and an excess of pleural radiological abnormalities in Karain. This supports an earlier report of an endemic of pleural mesothelioma in the village. Concentrations of airborne respirable fibres were uniformly very low in Karlik and higher in some of the air samples from Karain, the fibres being similar in composition to those of erionite—a mineral of the zeolite family and the major contributor to the Karain clouds. This is compatible with the hypothesis of a causal association between endemic mesothelioma and inhalation of erionite fibres, but the fibre concentrations in all samples are so low as to leave in question

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