Importance of markers of hepatitis B virus in alcoholic liver disease

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Abstract

To determine the importance of the presence of serological markers of hepatitis B virus infection in patients with alcohol related liver disease we compared cumulative alcohol intake and clinical and histological features in patients with markers of hepatitis B virus infection and in those without. Hepatitis B surface antigen (HBsAg) was detected in five (2%) out of 285 patients studied and antibody to HBsAg (anti-HBs) in 41 (14%); one patient had antibody to hepatitis B core antigen alone. The combined prevalence of markers of hepatitis B virus infection was similar in patients with alcoholic cirrhosis (18%) and precirrhotic liver disease (13%). Two patients positive for HBsAg had histological features of both alcoholic liver disease and chronic active hepatitis, with stainable HBsAg. Patients with anti-HBs were, however, histologically indistinguishable from patients without markers, and the mean cumulative alcohol intake of patients with anti-HBs was similar to or even higher than that of patients with liver disease of comparable severity who had no evidence of previous infection. The presence of markers of hepatitis B virus infection was related to former residence in countries with a high prevalence of the infection and to previous parenteral treatment and blood transfusions. Infection with hepatitis B virus does not enhance the development of chronic liver disease in heavy drinkers, except in the small number who remain positive for HBsAg.

Introduction

It is well recognised that some patients develop alcohol related cirrhosis after drinking relatively modest amounts of alcohol over five to 10 years whereas others escape liver damage after a lifetime of heavy drinking. The basis for this variation in susceptibility is only partly understood. Genetic factors play a part: women develop liver disease more rapidly and at a lower alcohol intake than men,¹ and the histocompatibility antigens HLA-B8 and B40 have been associated with a higher incidence and more rapid development of cirrhosis.²⁻⁵ Even so, much of the variation in susceptibility remains unexplained.

One hypothesis that has gained popularity recently is that chronic exposure to alcohol renders the liver more liable to injury from hepatotropic viruses or environmental toxins. The

possibility that infection with hepatitis B virus might favour the development of chronic liver disease in heavy drinkers was suggested by reports that serological markers of past or current infection with hepatitis B virus were found more often in patients with alcoholic cirrhosis than in alcoholics who had no liver disease or in healthy non-alcoholic subjects.⁶⁻⁸

If infection with hepatitis B favoured the development of cirrhosis in heavy drinkers patients who had evidence of past or continuing infection with hepatitis B virus would be expected to present with cirrhosis earlier and after a lower cumulative alcohol intake than patients who had no evidence of infection. As part of a research programme into genetic and environmental factors predisposing to alcohol related liver disease we analysed serum samples from 285 patients with various types of alcoholic liver disease for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc). We compared cumulative alcohol intake, established by a standardised interview schedule,⁹ and clinical and histological features in patients with and without hepatitis B virus infection. We also examined the importance of known risk factors for infection with the virus in determining the presence, or absence of serological markers and by discriminant analysis assessed their relative contribution. Levels of antibodies to other viruses were determined to assess susceptibility to infection and antibody response in relation to the severity of liver damage and the presence or absence of markers of hepatitis B virus infection.

Patients and methods

Over a three year period we studied 189 men aged 23-74 and 96 women aged 22-71. All had been drinking at least 40 g alcohol a day for four years or more, and in 263 (92%) habitual daily consumption had exceeded 80 g. They represented a consecutive series of British white subjects who had been admitted to the liver unit for the first time and in whom biopsy appearances were compatible with alcohol related liver disease. During the period of study we also interviewed 36 patients who drank similar quantities of alcohol but had no features of alcoholic liver disease on biopsy. These included four patients with chronic active hepatitis positive for HBsAg.

Liver biopsy appearances were classified by a specialist histopathologist (BP) into one of the following categories⁹: fatty liver with or without fibrosis (41 patients), alcoholic hepatitis (46), cirrhosis (90), cirrhosis with alcoholic hepatitis (97), and cirrhosis with superimposed hepatocellular carcinoma (11). Individual histological features including fatty change, fibrosis, spotty necrosis, piecemeal necrosis, and parenchymal inflammatory cell infiltration were scored on a five point scale (0, 1+, 2+, 3+, 4+) in ascending order of severity.

HEPATITIS B AND OTHER VIRAL SEROLOGY

Serum samples taken at admission were tested initially for HBsAg and anti-HBs by standard radioimmunoassay methods (HBsAg test kit, Travenol Laboratories Ltd, and Ausab, Abbott Laboratories Ltd). Sera positive for HBsAg were also tested for the presence of hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) (HBe and anti-HBe test kit, Abbott Laboratories Ltd). If sera were negative for both HBsAg and anti-HBs they were tested additionally for anti-HBc (Corab, Abbott Laboratories Ltd). Twenty-six of the 41 samples positive for anti-HBs were also tested for anti-HBc. Results were accepted as positive if counts per minute exceeded 2.1 times the netagive control mean.

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Sufficient serum was available from 170 patients for determination of measles antibodies (by complement fixation and haemagglutination inhibition) and rubella antibodies (by haemagglutination inhibition and radial haemolysis). In 110 patients antibody levels to strains of influenza A virus (Hong Kong, Port Chalmers, Victoria) were determined by radial haemolysis.

ASSESSMENT OF ALCOHOL INTAKE AND RISK FACTORS FOR HEPATITIS B VIRUS INFECTION

One hundred and ninety-eight patients (70%) were interviewed to obtain information about their lifetime alcohol intake and potential risk factors for infection with hepatitis B virus. The remaining 87 patients were not interviewed because they were too ill (47), had evidence of intellectual impairment (19), or were not available for interview (21). Alcohol intake was ascertained with a standardised and well validated interview schedule.⁵ Key events in the patients' lives were determined and used as anchor points to define the evolution of their drinking habits. The patients were questioned about the type of alcoholic drink consumed and the quantity of each drink habitually taken per week during successive periods of their lives up to the time of presentation with liver disease. Cumulative lifetime consumption, the duration of drinking over 40 g alcohol a day, and mean daily intake and cumulative intake during this time were then calculated.¹⁰

Patients were also questioned about previous episodes of jaundice and potential risk factors for infection with hepatitis B virus. These included previous admissions to hospital, blood transfusions, treatment with multiple injections, parenteral drug abuse, homosexuality, and residence in countries with a high (>2%) prevalence of HBsAg.

STATISTICAL PROCEDURES

Data were stored and analysed in a CDC 6600 computer. Statistical procedures (χ^2 test, Student's *t* test, and the Mann-Whitney U test) were carried out by using subprogrammes of the Statistical Package for the Social Sciences.¹¹ Viral antibody titres were expressed as the geometric mean $\pm$ SE. Factors influencing the presence of markers of hepatitis B virus were examined by discriminant analysis. Variables were entered in a stepwise fashion so that the Mahalanobis distance between groups was maximised. Statistical significance was assessed on the resulting change in Rao's V.

Results

Sera from five patients (1.8%) were positive for HBsAg (table I), and two of these were positive for HBeAg. Anti-HBs was found in samples from 41 patients (14%), and one patient had anti-HBc alone. Anti-HBc was also found in 16 (62%) of 26 sera positive for anti-HBs.

TABLE I—Prevalence of markers of hepatitis B virus in alcoholic liver disease

	Men					Women				
	No of patients	HBsAg	Anti-HBs with or without anti-HBc	Anti-HBc only	Total No (%) with markers	No of patients	HBsAg	Anti-HBs with or without anti-HBc	Anti-HBc only	Total No (%) with markers
Fat + fibrosis	30	1	5	0	6 (20)	11	0	2	0	2 (18)
Alcoholic hepatitis	29	1	1	0	2 (7)	17	0	1	0	1 (6)
Cirrhosis	76	2	12	0	14 (18)	14	0	2	1	3 (21)
Cirrhosis + alcoholic hepatitis	43	0	10	0	10 (23)	54	1	5	0	6 (11)
Hepatoma	11	0	3	0	3 (27)	0				
Total	189	4	31	0	35 (19)	96	1	10	1	12 (12)

TABLE II—Comparison of age and alcohol intake in patients with cirrhosis with anti-HBs and those without markers of hepatitis B virus. (Results expressed as means (SE))

	Men			Women		
	Anti-HBs present (n = 16)	No markers (n = 70)	p	Anti-HBs present (n = 6)	No markers (n = 42)	p
Age at diagnosis (years)	56.1 (1.8)	49.1 (1.3)	< 0.005	50.4 (4.7)	47.2 (1.6)	> 0.40
Duration of drinking > 40 g/day (years)	25.6 (3.7)	22.2 (1.2)	> 0.20	17.0 (3.9)	12.5 (1.4)	> 0.30
Mean daily alcohol intake when > 40 g/day (g)	133 (14)	134 (8)	> 0.90	94 (12)	84 (7)	> 0.50
Cumulative alcohol intake when > 40 g/day (kg)	1208 (209)	1063 (80)	> 0.30	547 (114)	349 (36)	0.05
Cumulative lifetime alcohol intake (kg)	1257 (208)	1103 (79)	> 0.30	672 (122)	400 (35)	< 0.02

There was no significant difference in the prevalence of markers of hepatitis B virus between patients with cirrhosis with or without alcoholic hepatitis superimposed (19% and 16% respectively) and those with fatty liver (20%) or alcoholic hepatitis without cirrhosis (7%). The combined prevalence of markers of hepatitis B virus was somewhat higher in men than women (19% and 12% respectively), but this difference did not reach significance ($\chi^2 = 1.8$, $p > 0.10$). The proportions of patients with cirrhosis with ascites, encephalopathy, or variceal bleeding who had markers of hepatitis B virus (18%, 18%, and 23% respectively) were similar to that of patients with "compensated" disease (19%).

All the patients positive for HBsAg had fatty change. Piecemeal necrosis was present in four biopsy specimens but was prominent (+2+) in only two, one of which had the characteristic "ground glass" appearance of the hepatocytes. Orcein staining of HBsAg was found in two patients.

Patients with anti-HBs were histologically indistinguishable from those without any markers of hepatitis B virus. Of those with cirrhosis, 22 (76%) with anti-HBs had fatty change compared with 111 (72%) of those without markers, and the numbers who had alcoholic hyaline were 14 (48%) and 89 (58%) respectively. The degree of fibrosis was similar in patients with anti-HBs (mean score 3.45) and those without markers (3.28; $p > 0.5$, Mann-Whitney U test). Scores for spotty necrosis (0.95 v 1.18, $p > 0.5$), piecemeal necrosis (0.86 v 0.90, $p > 0.8$), and inflammatory infiltration (1.8 v 1.8) were similar in the two groups.

COMPARISON OF ALCOHOL INTAKE

Alcohol intake was elicited in 198 patients (70%); the prevalence of markers of hepatitis B virus was similar in this group and in those who were not interviewed. The number of patients positive for HBsAg was too small to permit appropriate statistical comparisons with those without evidence of hepatitis B virus infection. Among those with anti-HBs there was no evidence that any type of alcoholic liver disease had developed after a lower alcohol intake compared with in patients without markers of infection (table II). Women with cirrhosis with anti-HBs had a higher mean cumulative alcohol intake than those without markers; among the men there was no significant difference between those with and without anti-HBs in any of the measures of alcohol consumption analysed. Patients with anti-HBs tended to be older (in men by 7.0 years, $p < 0.005$) than those without markers of infection.

RISK FACTORS FOR INFECTION WITH HEPATITIS B VIRUS

The two factors that were significantly associated with the presence of markers of hepatitis B virus were residence in a country with a high prevalence of infection with the virus (such as southern Europe, tropical Africa, or Asia) and previous blood transfusions or courses of

TABLE III—Potential risk factors for infection with hepatitis B virus and prevalence of history of jaundice in patients with cirrhosis with and without markers of hepatitis B virus (figures are numbers (%) of patients)

	Patients with markers (n = 24)	Patients without markers (n = 112)	p
Hospital admission for major illness or surgery	15 (63)	53 (47)	> 0.10
Blood transfusions or injections	8 (33)	12 (11)	< 0.005
Residence for over 1 year in country with high prevalence of hepatitis B virus	14 (58)	21 (19)	< 0.001
Service in armed forces	7 (29)	26 (23)	> 0.20
Jaundice in childhood	2 (8)	4 (4)	> 0.50
Jaundice in adult life	7 (29)	11 (10)	< 0.02

TABLE IV—Results of discriminant analysis to distinguish patients with markers of hepatitis B virus from those without

	Whole group (n = 198)		Patients with cirrhosis (n = 136)	
	Change in Rao's V	p	Change in Rao's V	p
Resident in country with high prevalence of hepatitis B virus	32.4	< 0.001	14.2	< 0.001
Previous injections or blood transfusions	7.4	< 0.01	4.7	< 0.05
Social class IV or V	3.0	0.05 < p < 0.10	1.5	> 0.20
Male sex	2.2	> 0.10	2.0	> 0.10

injections. Fourteen out of 24 (58%) patients with cirrhosis with markers of infection had been resident in an area of high prevalence for at least a year, compared with 21 out of 112 (19%) without markers (table III). Three times as many patients with markers had received blood transfusions or injections, though the proportion who had been admitted to hospital was not significantly different. Of the other recognised risk factors, parenteral drug abuse was admitted by only three patients (one with anti-HBs) and homosexuality by 12 (three with markers of the virus).

TABLE V—Comparison of exposure to other viruses in patients with cirrhosis with anti-HBs and those without markers of hepatitis B virus

	Anti-HBs present			No markers		
	No positive (%)	Mean (SE) geometric mean titre	Mean (SE) zone diameter (mm)	No positive (%)	Mean (SE) geometric mean titre	Mean (SE) zone diameter (mm)
Measles:						
Complement fixation	15/16 (94)	30 (1.4)		99/102 (97)	27 (1.1)	
Haemagglutination inhibition	16/16 (100)	28 (1.4)		101/102 (99)	27 (1.1)	
Rubella:						
Haemagglutination inhibition	15/16 (94)	95 (1.5)		98/102 (96)	122 (1.2)	
Radial haemolysis	15/16 (94)		10.9 (0.6)	99/102 (97)		11.4 (0.2)
Influenza A (all strains)	12/13 (92)		6.9 (0.3)	53/61 (87)		6.5 (0.1)
Influenza A (Hong Kong)	7/13 (54)		5.8 (0.4)	30/61 (49)		5.8 (0.1)
Influenza A (Port Chalmers)	4/13 (31)		5.9 (0.7)	14/61 (23)		5.7 (0.2)
Influenza A (Victoria)	3/13 (23)		4.8 (0.7)	7/61 (12)		4.5 (0.4)

These risk factors were entered in a discriminate analysis together with age, sex, social class, marital state, duration of drinking, mean daily intake, histological features, and the presence or absence of ascites, encephalopathy, and variceal haemorrhage. Former residence in an area with a high prevalence of infection was confirmed as the variable that most clearly distinguished patients with markers of the virus from those without (table IV). Neither of the measures of alcohol intake discriminated these two groups from each other.

LEVELS OF ANTIBODIES TO OTHER VIRUSES

There were no significant differences in the proportions of patients in each histological category who had detectable levels of antibody to measles, rubella, or any of the influenza strains, or in the levels of antibody to these viruses. Similarly, there were no differences between patients with anti-HBs and those without markers of the virus in the proportions showing seropositivity or in antibody levels (table V).

Discussion

The suggestion that exposure to hepatitis B infection might influence the development of alcoholic liver disease was first made in 1972 by Pettigrew *et al.*¹² who found evidence of lymphocyte transformation in response to HBsAg in 11 patients with alcoholic liver disease who were serologically negative for HBsAg. These findings, however, have not been confirmed. Recently, several surveys have shown that patients with alcoholic cirrhosis show evidence of past or current infection with hepatitis B virus more commonly than do healthy non-alcoholic subjects.^{6-8 13-16} Our experience was similar. The combined prevalence of markers of hepatitis B virus was significantly higher in patients with alcoholic cirrhosis (18%) than in a group of patients in hospital matched for age and sex and without liver disease, in whom it was 6% ($p < 0.01$; Y S White, unpublished observations).

There is disagreement about whether markers of hepatitis B virus are found more commonly in patients with alcoholic cirrhosis than in those with fatty liver or alcoholic hepatitis. Two surveys from Scotland⁷ and one from France⁸ showed that they were, but other groups have found no difference in prevalence between patients with cirrhosis and those with precirrhotic disease,¹⁴⁻¹⁷ and in the present study the prevalence of markers in patients with cirrhosis (18%) was not significantly higher than that (13%) in patients with less severe disease.

Only six patients (2%) in the present series had HBsAg or anti-HBc alone (which may reflect persistent viral replication), and the e antigen was present in only two of these. The more usual finding was the presence of anti-HBs and usually anti-HBc in addition, a pattern of antibody response that indicates recovery from infection with hepatitis B virus with elimination of virus particles from serum.¹⁸ The preponderance of this serological pattern agrees with findings of other studies in northern Europe,^{7 14-16} but elsewhere a relatively higher proportion of patients have evidence of active infection.^{8 17} Neither the proportion of patients who had antibodies to other viruses nor the levels of antibodies were related to the degree of alcoholic liver

damage or to the presence or absence of antibodies to hepatitis B virus, indicating that no particular group was characterised by greater susceptibility to viral illnesses or abnormal antibody production.

Hepatitis B infection might influence the development of liver disease in heavy drinkers in several ways. Persistent infection with hepatitis B virus might potentiate alcohol induced liver damage, and there is evidence that this may occur at fairly low alcohol intakes (60-80 g/day).¹⁹ Secondly, chronic active hepatitis associated with HBsAg may coexist with alcoholic liver disease, and the two disease processes would probably result in more rapid progression to cirrhosis. In our experience the co-existence of alcoholic liver disease and chronic active hepatitis associated with HBsAg is uncommon: only two patients in the present series had prominent piecemeal necrosis, the hallmark of chronic active hepatitis. Four other patients positive for HBsAg were encountered who were heavy drinkers; all had features

of chronic active hepatitis but none of alcoholic liver disease, and they were not included in the analysis. In a Danish study,¹⁴ no patients with typical alcoholic cirrhosis were serologically positive for HBsAg, although among a small group of alcoholics with cirrhosis who had no features of alcoholic liver damage 26% had HBsAg present in serum.

The presence of anti-HBs indicates recovery from infection with cessation of viral replication.¹⁸ Usually it represents recovery from acute hepatitis, but some patients may have undergone seroconversion after being positive for HBsAg for many years, during which chronic liver damage may have occurred. Hepatitis B viral DNA is found integrated into the host genome in some patients with anti-HBs,²⁰ indicating that permanent changes at the molecular level take place that might influence sensitivity to alcohol. The results of the present study suggest, however, that heavy drinkers who have had infection with hepatitis B virus in the past do not develop cirrhosis more rapidly, as judged by how long our patients had been drinking hepatotoxic quantities of alcohol, and do not develop it at a lower daily alcohol intake. Indeed, they tend to be older and to have higher alcohol intakes. Anti-HBs was not associated with any particular histological features of chronic liver disease, although it was more common in the small group of patients with hepatoma.

The most important determinant of the presence of markers of virus in the present series was whether the patient had lived in a country with a high prevalence of infection with the virus; previous blood transfusion or injections was the only other factor definitely identified. The way in which infection with hepatitis B virus had been contracted by patients who had lived abroad was not established, although transmission via insect vectors and sexual contacts are possibilities. The development of hepatitis B in patients with alcoholic liver disease receiving blood transfusions or blood products is well recognised²¹ and occurs despite screening of donors for HBsAg. Variation in the risk of exposure to hepatitis B virus probably explains the difference in prevalence of markers reported in previous studies among groups of alcoholic patients. In a study from France⁸ those with alcoholic cirrhosis were on average 14 years older than alcoholics without liver damage and would potentially have been at risk of infection for a correspondingly longer time. The higher prevalence of markers in alcoholic compared with non-alcoholic subjects is probably explained simply by a higher prevalence of exposure to the virus, although chronic alcohol consumption may possibly favour the development of hepatitis in subjects exposed to the virus by depressing immune response.

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ONE HUNDRED YEARS AGO At the present season, a mistaken and mischievous practice is much in vogue. Daily torture is inflicted on thousands of tender and helpless infants by forcibly plunging their bodies, in spite of shrieks and struggles, into the open sea. This cruel and time-honoured process may now be seen in full operation at any sea-side resort. Affectionate mothers hand over their infants to stalwart and impassive bathing-women, to be plunged head foremost into the sea, under the absurd notion that the procedure vastly benefits the little ones. Day after day, with relentless regularity, very young children and babies are borne out amidst the waves and subjected to their dreaded ducking, in the firm belief that their trembling bodies, often writhing to the verge of convulsions, are thus made healthy and hardy. All experience on the subject, and the teachings of all medical authorities on sea-bathing, agree in support of the two following rules; namely, that a child under two years of age ought never, under any circumstances, to be bathed in the open sea, and that no one, child or adult, can enter the sea without danger while under the influence of emotional excitement. Under two years of age, a child's body is too weak to gain any benefit from the shock of immersion in the open sea. Its nervous and circulating forces are too feeble for the development of that vigorous reaction, without which sea-bathing is either useless or hurtful. In the absence of strength for such reaction, a sea-bath tends to chill an infant's body, and predispose to internal congestions. At any age, the shock of immersion in the sea brings risk of danger, and even of death, when the emotions are powerfully excited, and especially when the mind and body are dominated by that most depressing of human emotions, fear. Infants are not always bathed in the sea merely with the intention of making them strong. There is an old sea-side tradition that babies diligently bathed become fearless in the water when they grow up. This notion is also false. Than that infants gain courage by being plunged in the sea, it is more probable that many a nervous child has acquired a dread of bathing which no after-experience could remove, because it was compelled in fear and trembling to plunge under water. If a child be sufficiently robust to develop a good reaction, if it be over two years of age, and, above all, if it be not afraid, it may be bathed in the sea with advantage. If any of these conditions be wanting, sea-bathing for children is likely to be positively injurious. (*British Medical Journal*, 1883;ii:344.)