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Antibody to hepatitis B core antigen in chronic active hepatitis

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Summary and conclusions

Antibody to hepatitis B core antigen (anti-HBc), which has been assumed to be a more sensitive indicator of hepatitis B virus replication than hepatitis B surface antigen (HBsAg), was detected in the sera of 26 of our 65 patients with HBsAg-negative chronic active hepatitis. Thus despite the absence of HBsAg the liver disease could be the consequence of chronic infection with hepatitis B virus in these patients. They differed, however, from a group of 35 patients with HBsAg-positive hepatitis in being older on average and having less active liver lesions. The two groups could represent either two stages of chronic infection with hepatitis B virus or two types of response to it.

Introduction

The presence in serum of hepatitis B surface antigen (HBsAg) is a recognised indicator of hepatitis B virus replication. HBsAg in the serum of patients with chronic active hepatitis is regarded as evidence that the liver disease results from infection with hepatitis B virus.¹ Serum antibody to hepatitis B core antigen (anti-HBc) is another indicator of virus replication, possibly more sensitive than HBsAg.² We carried out our investigation to see whether some patients with HBsAg-negative chronic active hepatitis have anti-HBc in their serum and thus have liver disease that could also be the consequence of infection with hepatitis B virus.

Patients and methods

We investigated 100 patients, 50 men and 50 women (aged 16-80, mean 48 years), with histologically proved chronic active hepatitis, 36 of whom had spent 10 years or more in Africa or Asia. The hepatic lesions were classified as moderately (grade A) or extremely (grade B) active in 75 and 25 patients according to the histological criteria of De Groote *et al*.³ Chronic active hepatitis was associated with cirrhosis in 64 and with hepatocellular carcinoma in three patients. The liver lesions were judged to be chronic on the basis of (a) histologically proved cirrhosis associated with chronic active hepatitis or (b) clinical signs, abnormal results of liver function tests, or histological lesions (or all three) persisting for a year or more after the histological recognition of the liver disease. We excluded patients who during the year before this study had resided in Africa or Asia, had received blood transfusions or intramuscular injections, or had had clinical manifestations or biochemical disorders compatible with acute viral hepatitis (that is, transient jaundice, episodes of fever, or appreciably increased serum transaminase activity).

Serum glutamic pyruvic transaminase (SGPT) activities ranged from 2 to 506 and averaged 94 international units (IU) (normal < 25 IU) at the time of the liver biopsy. HBsAg and antibody to it (anti-HBs), detected by radioimmunoassay (AusRIA II and AusAB, Abbott Laboratories, North Chicago, Illinois, USA), were present in the sera of 35 and 24 patients.

Anti-HBc was detected by counterelectrophoresis.⁴ In all the patients in whom HBsAg was absent and anti-HBc was shown by counterelectrophoresis the anti-HBc titres were determined by complement fixation⁵; the results were expressed as values for the rate constant K_{37} .⁶ In 10 of these patients anti-HBc titres were determined in paired samples taken 12-18 months apart.

The means were compared by the Student *t* test and the percentages by the χ^2 test.⁷

Results

The patients were divided into three groups (table I) according to the presence or absence of HBsAg and anti-HBc in their serum. Group 1 included 35 HBsAg-positive patients, all having anti-HBc detected in their serum; in none of them was anti-HBs detected in the serum. Group 2 included 26 HBsAg-negative patients who had anti-HBc in their serum (see tables II and III for anti-HBc titres); in 16 anti-HBs was present. Group 3 included 39 HBsAg-negative, anti-HBc-negative patients, in 8 of whom anti-HBs was detected.

Statistically significant differences between the three groups are shown in table I. In group 2 the mean age was 15 years greater than in group 1, and there was a higher percentage of patients with moderately active liver lesions, a greater prevalence of cirrhosis associated with chronic active hepatitis, and a lower mean value for SGPT. The percentage of patients who had lived in Africa or Asia was higher in groups 1 and 2 than in group 3; the difference is statistically significant, however, only between groups 2 and 3. The three patients with hepato-

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TABLE I—Some features of the three groups of patients

	1 HBsAg-positive, anti-HBc positive	2 HBsAg-negative, anti-HBc positive	3 HBsAg-negative, anti-HBc negative	1-2	P 2-3	1-3
No patients	35	26	39			
Mean ($\pm$ SD) age(y)	41 $\pm$ 15	56 $\pm$ 14	50 $\pm$ 16	<0.001	NS	<0.01
No (%) of men	24 (69)	12 (46)	14 (36)	NS	NS	<0.02
No (%) of patients having resided in Africa or Asia	13 (37)	14 (54)	9 (23)	NS	<0.02	NS
No (%) of patients with moderately active hepatitis lesions	22 (63)	25 (96)	28 (72)	<0.01	<0.05	NS
No (%) of patients with cirrhosis	15 (43)	19 (73)	30 (77)	<0.05	NS	<0.01
No (%) of patients with hepatocellular carcinoma	0	3 (12)	0	NS	NS	NS
Mean ($\pm$ SD) SGPT (IU)	120 $\pm$ 103	42 $\pm$ 34	106 $\pm$ 107	<0.001	<0.01	NS

NS = Not significant.

cellular carcinoma belonged to group 2, but the small number does not permit meaningful statistical analysis.

TABLE II—Anti-HBc titres in the patients of group 2

K ₃₇ * No of patients	0.5-0.9 4	1.0-1.4 8	1.5-1.9 10	2.0-2.4 4
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*The anti-HBc titres were measured by complement fixation⁵ and were expressed as values of the rate constant K₃₇.⁶

TABLE III—Anti-HBc titres in paired samples taken 12-18 months apart in 10 patients of group 2

Case No:	1	2	3	4	5	6	7	8	9	10	Mean ($\pm$ SD)
K ₃₇ * { 1st determination	1.0	1.0	1.1	1.1	1.3	1.5	1.5	1.6	1.8	2.1	1.4 $\pm$ 0.4†
2nd determination	1.1	1.1	1.1	2.0	1.2	1.5	1.6	1.5	1.8	2.1	1.5 $\pm$ 0.4†

*See footnote to table II.

†The means are not significantly different (P>0.20).

Discussion

Our main finding is that anti-HBc is present in the sera of a certain number of patients with HBsAg-negative chronic active hepatitis. This confirms our preliminary report,⁸ based on a small number of patients (who have been included in the present series), and several others⁹⁻¹³ that anti-HBc is detected in some HBsAg-negative patients suffering from chronic active hepatitis or cryptogenic cirrhosis; only one investigation,¹⁴ of 26 patients, found anti-HBc in no HBsAg-negative patients.

Hoofnagle *et al*¹² have suggested that the presence in serum of anti-HBc in the absence of HBsAg could reflect hepatitis B virus replication. We therefore put forward the hypothesis that in our HBsAg-negative, anti-HBc-positive patients chronic active hepatitis would be the consequence of chronic infection with hepatitis B virus. In most of our patients it is unlikely that anti-HBc resulted from recent infection with hepatitis B virus for the following reasons: (a) we excluded patients with possible clinical manifestations of acute viral hepatitis; (b) we excluded patients who could have been exposed in the previous year to hepatitis B virus through blood transfusions or intramuscular injections or during visits to Africa or Asia; (c) the anti-HBc titres were similar in the paired samples taken 12-18 months apart, whereas they would have decreased in patients with recent acute infection. It is likewise improbable that the association of anti-HBc and liver disease was fortuitous: as many as 40% of the HBsAg-negative patients were anti-HBc-positive (and 28.6% even if those who had lived in Africa or Asia are excluded), compared with 4% in the general population in France.⁵ Moreover, their anti-HBc titres were higher than those of healthy HBsAg-negative, anti-HBc-positive blood donors.¹⁵ Direct evidence that the presence of anti-HBc reflected hepatitis B virus replication would be the detection of hepatitis-

B core antigen in the hepatocytes of HBsAg-negative, anti-HBc-positive patients with chronic active hepatitis; this we have not attempted in our patients. The hypothesis that the disease resulted from chronic infection with hepatitis B virus could account for, and is reinforced by, the large number of our HBsAg-negative, anti-HBc-positive patients who had lived in Africa or Asia, areas with a high incidence of infection.¹⁶

The mean age was greater and the activity of the liver lesions, as attested by the histological examination and the SGPT concentration, was lower in our HBsAg-negative, anti-HBc-positive patients than in our HBsAg-positive patients. There are two possible explanations. These two groups of patients could represent two stages of chronic infection with hepatitis B virus: in the first stage, on this theory, HBsAg would be present in serum and the liver lesions would be active; in the second stage HBsAg would disappear, anti-HBc would persist, and the liver lesions would be less active. Alternatively, the two groups could represent two types of response to chronic infection with the virus: the liver lesions would be less active from the onset of the infection, the course of the disease more protracted, and the average age therefore greater in HBsAg-negative, anti-HBc-positive than in HBsAg-positive patients.

Cirrhosis was more prevalent in our HBsAg-negative, anti-HBc-positive patients (that is, the older group) than in our HBsAg-positive group. This may simply indicate that cirrhosis is a relatively late complication of chronic active hepatitis.¹⁷ All the patients with hepatocellular carcinoma were HBsAg-negative and anti-HBc-positive, possibly because hepatocellular carcinoma is also a late complication of chronic infection with hepatitis B virus¹⁸; but as there were only three cases the finding must be treated with caution.

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