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RAPID COMMUNICATION

Isolated antibody to hepatitis B core antigen in patients with chronic hepatitis C virus infection

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Abstract

AIM: To evaluate the prevalence of isolated anti-HBc in patients with chronic hepatitis C virus (HCV) infection, and its relation to disease severity.

METHODS: We screened all patients with chronic HCV infection referred to King Faisal Specialist Hospital and Research Center for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and anti-HBc. One hundred and sixty nine patients who tested negative for both HBsAg and anti-HBs were included in this study.

RESULTS: Pathologically, 59 had biopsy-proven cirrhosis and 110 had chronic active hepatitis (CAH). Of these 169 patients, 85 (50.3%) tested positive for anti-HBc. Patients with CAH had significantly higher prevalence of isolated anti-HBc than patients with cirrhosis, 71 (64.5%) and 14 (23.7%) respectively ($P < 0.001$). Twenty-five patients were tested for HBV DNA by qualitative PCR. The test was positive in 3 of them (12%; occult HBV infection).

CONCLUSION: Isolated anti-HBc alone is common in Saudi patients with chronic HCV infection, and is significantly more common in those with CAH than those with cirrhosis. Therefore, a screening strategy that only tests for HBsAg and anti-HBs in these patients will miss a large number of individuals with isolated anti-HBc, who may be potentially infectious.

Key words: Cirrhosis; Chronic hepatitis; Dual infection; Co-infection; Hepatitis B screening; Super-infection

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INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections account for a substantial proportion of acute and chronic liver diseases world-wide[1-4], including Saudi Arabia[5-7]. Both viruses share similar risk factors and modes of transmission and as a consequence, combined HBV and HCV infection is frequent especially in areas endemic for HBV, and among people at high risk of parenteral infection[1-5]. Indeed, patients with HCV-related chronic liver disease (CLD) frequently show markers of previous HBV infection. Moreover, they may carry occult HBV infection. These features might influence clinical and biochemical features as well as stage of disease.

Screening patients with chronic HCV for the coexistence of HBV infection is usually based on serum testing for the presence hepatitis B surface antigen (HBsAg). This screening is critical, because HBV infection needs treatment if present, can be prevented by vaccination if absent, and may adversely affect liver pathology and the response to therapy.

Isolated hepatitis B core antibody (anti-HBc) represents either resolved HBV infection with loss of hepatitis B surface antibody (anti-HBs); occult chronic HBV infection with levels of the HBsAg below the limits of detection; or a false-positive test result. Many western publications have reported that 2%-5% of healthy blood donors have isolated anti-HBc[8-10]. Similarly, isolated anti-HBc was reported in 125 (2%) of 6035 consecutive Saudi blood donors[11]. In addition, we have previously shown that the prevalence of isolated anti-HBc in HBsAg negative potential liver donors is 32%, and is significantly higher in non-Saudi nationals (41.3%) compared with Saudi citizens (16.7%)[12]. However, the prevalence of isolated anti-HBc in patients with chronic HCV infection has not been studied. Therefore, the aims of the present study were to

evaluate the prevalence of "isolated anti-HBc" in patients with chronic HCV infection, and to assess its relation to disease severity.

MATERIALS AND METHODS

The subjects included in this study are referrals to King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia, between January and December 2004.

Subjects included in this study (n = 169) are patients with confirmed chronic HCV infection genotype 4, and negative HBsAg and anti-HBs. HCV antibody testing was performed with an enzyme immunoassay (Abbott HCV EIA 2.0; Abbott Laboratories) and positive polymerase chain reaction (PCR) for HCV RNA for more than 6 mo. Routine liver function tests and diagnostic liver biopsy were done to all patients. Histological diagnosis was evaluated, using the modified Knodell's histological activity index,[13] by a pathologist who was unaware of the patient's serological data.

Tests for HBsAg, anti-HBs, and anti-HBc were done using (Auszyme; Abbott Laboratories), (Ausab EIA; Abbott Laboratories) and (Hepatitis B Virus Core Antigen Corzyme; Abbott Laboratories) respectively**.** In addition, sera from a subgroup of patients (n = 25) who tested positive (n = 19) and negative (n = 6) for anti-HBc only were further tested for the presence of HBV DNA using nested-PCR with primers deduced from the core region. In the cases tested positive (n = 3), viral load was performed using HBV-Amplicor Monitor (Roche Molecular System). The lower limit of detection for this assay is 2000 copies/mL. As this study concentrates on isolated anti-HBc in patients with chronic HCV infection, subjects with overt HBV infection alone or in combination with HCV were excluded.

This study was approved by the Institutional Research Committee and the Review Board of the KFSH&RC.

Statistical analysis

Results were collected in a Microsoft *Exel* spread sheet, and expressed as mean ± SD unless otherwise stated. Data were examined by the Pearson's correlation coefficient and two-tailed paired, un-paired Student's t-tests, Chi-Square, as appropriate Using SPSS Statistical Package version 10 (SPSS Chicago, IL, USA). Statistical significance was taken at the 5% level.

RESULTS

A summary of the demographic patient' characteristics is shown in Table 1. A total of 169 patients with chronic HCV infection were included. Based on liver function testing, positive serum anti-HCV, positive HCV RNA, and liver histopathology, 59 patients had biopsy-proven cirrhosis and 110 had CAH. Of these 169 patients, 85 (50.3%) tested positive for anti-HBc. The potential mode of transmission was identified in 123 patients (72.8%), and includes blood transfusion, surgical and dental interventions before the availability of HCV testing. The remaining cases may fall under intra-familial spead. We did not test the partners for HCV or HBV infection in this study. Therefore, the sexual transmission can not be excluded.

Table 1 Subjects characteristics (n = 169)

Variable	Mean	SD
Age (yr)	44.0	18.0
Sex		
Female	57 (33.7%)	
Male	112 (66.3%)	
INR	1.1	0.26
AST (U/L)	81.1	97.3
ALT (U/L)	74.4	88.3
GGT (U/L)	117.8	194.9
Bilirubin (μmol/L)	29.9	53.1
ALP (U/L)	149.9	111.3
Albumin (g/L)	35.7	6.2
Urea (mmol/L))	6.9	6.4
Creatinine (μmol/L)	144.5	196.6
Liver histopathology		
Cirrhosis	59 (34.9%)	
CAH	110 (65.1%)	
Anti-HBc		
+ve	85 (50.3%)	
-ve	84 (49.7%)	

Data are expressed as mean ± SD or number (%). NS = not significant. ALP; alkaline phosphatase. ALT; alanine aminotransferase. AST; aspartate aminotransferase. CAH; chronic active hepatitis. GGT; Gamma-glutamyl transferase. HBcAb; hepatitis B core antibody. INR; international normalization ratio.

Comparison between patients with positive anti-HBc and negative anti-HBc

Compared with patients with negative anti-HBc, patients with chronic HCV infection and positive isolated anti-HBc antibody had significantly higher mean age, and significantly lower mean ALT levels ($P < 0.001$ and $P < 0.5$ respectively; Table 2). The mean AST levels were also less in patients with negative HBc antibody, though it did not reach statistical significance. In addition, and despite their higher mean age, patients with isolated anti-HBc antibody pathologically showed a significantly less cirrhotic and significantly more chronic hepatitis picture ($P < 0.001$, Table 2).

HBV DNA Polymerase Chain Reaction

Qualitative PCR testing for HBV DNA was performed in 25 cases (14.8%); 6 were negative for anti-HBc, and 19 were positive for isolated anti-HBc antibody. Positive serum HBV DNA was detected in 3 patients, all had positive isolated anti-HBc (15.8% of the 19 cases with positive anti-HBc, and 12% of the 25 cases tested by PCR), two were cirrhotic and the third was in the chronic inflammatory stage. The viral load in these 3 patients was 4820, 3800, and 4300 copies/mL respectively. Therefore, they represent an "occult HBV Infection", and are potentially infectious.

Independent predictors of cirrhosis

Multivariate regression analysis of variables of interest (age, sex, ALP, AST, ALT, urea, creatinine, International

Table 2 Comparison between patients with positive anti-HBc and those with negative anti-HBc

Variable	Patients with HCV & positive anti-HBc (n = 85)	Patients with HCV & negative anti-HBc (n = 84)	P value
Age (yr)	39.1 ± 18.3	48.9 ± 16.3	< 0.001
Sex			
Female	33 (38.8)	24 (28.6)	NS
Male	52 (61.2)	60 (71.4)	
INR	1.1 ± 0.3	1.1 ± 0.2	NS
AST (U/L)	68.1 ± 44.5	94.4 ± 130.1	NS
ALT (U/L)	61.0 ± 39.9	88.8 ± 119.0	< 0.05
GGT (U/L)	100.2 ± 134.0	137.2 ± 245.8	NS
Bilirubin (μmol/L)	30.0 ± 50.1	29.7 ± 56.6	NS
ALP (U/L)	133.2 ± 89.5	168.0 ± 129.1	NS
Albumin (g/L)	35.9 ± 6.1	35.4 ± 6.3	NS
Urea (mmol/L)	6.2 ± 4.3	7.8 ± 8.0	NS
Creatinine (μmol/L)	117.5 ± 138.9	1792.9 ± 240.6	NS
Liver pathology			
Cirrhosis	14 (16.5)	45 (83.5)	< 0.001
CAH	71 (53.6)	39 (46.4)	

Data are expressed as mean ± SD or number (%). NS = not significant; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAH: chronic active hepatitis; GGT: Gamma-glutamyl transferase; HBcAb: hepatitis B core antibody; INR: international normalization ratio.

Table 3 Multivariate regression analysis for the predictors of liver cirrhosis

Variable	B	P value	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Age	-0.01	NS	1.0	0.95	1.02
Sex	0.64	NS	1.9	0.55	6.45
INR	7.69	0.002	2182	18.01	264549
AST	-0.01	NS	1.00	0.99	1.00
Bilirubin	0.00	NS	1.00	0.98	1.01
ALP	-0.01	0.006	1.00	0.99	1.00
Albumin	-0.02	NS	0.98	0.98	1.11
Urea	0.05	NS	1.10	0.87	1.27
Creatinine	0.00	NS	1.00	1.00	1.00
+anti-HBc	-2.63	0.0001	0.07	0.02	0.28
Constant	-3.36	NS			

NS: not significant; CI: confidence interval; PCR: polymerase chain reaction; INR: international normalization ratio; ALP: alkaline phosphatase.

Normalization Ratio, bilirubin, albumin, +ve anti-HBc) revealed the presence of raised INR (P = 0.002), increased ALP (P = 0.006), and -ve serum anti-HBc antibody (P = 0.0001) to independently predict liver cirrhosis in the studied cohort (Table 3).

DISCUSSION

The findings of this study suggest that > 50% of patients with chronic HCV infection for whom there is no serological evidence for HBV, when screened with HBsAg and anti-HBs, will be positive for anti-HBc antibody especially those in the chronic inflammatory stage of the disease.

HCV-infected patients should be tested for HBV markers to determine those who should receive HBV vaccination and those who need anti-HBV treatment. For patients with chronic HCV infection, prevention of HBV infection is critical, because this viral infection can be particularly severe and may adversely affect disease outcome.

Isolated Anti-HBc was previously reported to exist in 2% of 6035 Saudi blood donors[11]. A figure that is similar to what has been reported else where[8-10]. The high prevalence of isolated anti-HBc antibody in patients with chronic HCV infection detected in this study (50.3%) has previously been reported in a similar study in patients with HCV with or without HIV-1 coinfection[14]. This reflects the similar mode of transmission, high endemicity of both infections. Indeed, the detection of HBV DNA by PCR in these patients rules out the possibility of false positive results and confirms the diagnosis of occult coinfection.

Occult HBV infection may be manifested by having negative test results for HBsAg, but positive results for HBV DNA. The frequency of occult HBV infection in patients with anti-HBc is controversial. In one study, occult HBV infection was reported in 33% of subjects with chronic liver disease due to HCV infection and was more frequent in subjects with isolated anti-HBc[15]. Diagnosing occult HBV infection requires sensitive HBV-DNA PCR assay. The postulated mechanisms underlying occult HBV infection include mutations of HBV-DNA sequence, formation of immune complexes-containing HBV, an integration of HBV-DNA into host's chromosomes, HBV infection of leucocytes, altered host immune responses, and interference by other viruses. The clinical implications of occult HBV infection involve different clinical aspects including first; harboring potential risk of HBV transmission through blood transfusion, hemodialysis, and organ transplantation; second, causing cryptogenic liver disease; third, contributing to the development of acute exacerbation or even hepatocellular carcinoma; and fourth, affecting disease progression and response to treatment of patients with chronic HCV infection[16].

The precise prevalence of occult HBV infection is variable. In the present study, we found occult HBV infection in 15.8% in patients with chronic HCV infection with positive anti-HBc antibody. Higher figures were detected in other studies. For example, using PCR with primer pairs from three different regions of the HBV genome, Jilg *et al* demonstrated that 32.9% of patients with anti-HBc alone are positive for HBV DNA, the majority of them showing very low HBV concentrations[17]. Also, Feraro *et al* 2003 found occult HBV infection in 7 out of 22 patients with HCV. However, this was unrelated to anti-HBc status[18]. Similarly, occult HBV infection was detected in 42% of HIV-infected patients, and was significantly common in subjects with concomitant HCV infection (80%) than those with HIV-1 infection alone[14]. This supports the suggested policy of donor exclusion based on the anti-HBc and anti-HBs serology as a means to eliminate low grade carriers of HBV in endemic areas without jeopardizing the blood supply. This variation in the prevalence of occult HBV may be related to differences in prevalence of each viral infection in

different communities, differences in the PCR technique, or population selection bias. Highly sensitive, quantitative, and functional molecular analyses of HBV, combined with a well-designed prospective clinical assessment will provide the best approach for the future study of occult HBV infection.

The higher prevalence of anti-HBc antibody in patients with chronic HCV hepatitis than in patients with cirrhosis observed in this study may be explained by a possible inhibitory effect exerted by HBV on HCV replication[19]. In agreement with this, a study by Kao *et al* showed that occult HBV infection does not have clinical significance in patients with chronic hepatitis C residing in areas where HBV infection is endemic[15]. Furthermore, occult HBV infection had no effect on early response to PEG-INF alpha[20]. Further follow up into the maintenance and post-treatment phases will clarify if and when occult HBV affects the sustained viral response. However, Giannini *et al* have reported a different observation[21]. In their study, the positivity for markers of HBV infection was more frequent in the cirrhotic group as compared to patients with CAH. They also reported higher histological grading and scoring in patients with CAH with anti-HBc[21]. Reasons of this disagreement are not clear, but a difference in the HCV genotype and duration of infection may be implicated, as most of our patients are genotype 4, while those included in Giannini study were Genotype 1b[21]. Other factors that may aggravate the histological scoring and grading in the study of Giannini *et al* such as alcohol intake, may have contributed to this difference.

Finally, subjects with isolated anti-HBc who test negative for HBV DNA may have cleared HBV infection and lost undetectable anti-HBs or have a false-positive test result for anti-HBc due to cross-reacting antibodies present in individuals with HCV infection. For patients with isolated anti-HBc who have cleared HBV infection and have undetectable levels of anti-HBs, immunization with HBV vaccine may result in an anamnestic response, which is the presence of detectable anti-HBs within a few weeks after the first vaccination[22,23].

The possible limitations of the present study include; First, KFSH&RC is a tertiary center, which raises a question regarding the generalizability of the findings. However, studies conducted in Europe show similar results[10,24,25], which suggest that our conclusions are not specific to a particular geographic region. Second, we tested subjects for total anti-HBc level, rather than IgG and IgM isotypes. Therefore, acute HBV infection, in which only IgM antibody is present, can not be differentiated from the chronic one. Finally, not all subjects who tested negative for HBsAg and anti-HBs and positive anti-HBc underwent testing for HBV DNA. However, the subgroup tested for HBV DNA revealed positive cases (3 in 19, 15.8%), confirming the conclusions of this study. Missing isolated anti-HBc positivity, which represents occult HBV infection in > 10% of cases may have serious implication if these cases were used in organ donation, blood transfusion. They may also be misdiagnosed as cryptogenic liver disease, in patients who test negative for anti-HBsAg and HCV antibody.

In conclusion, isolated anti-HBV sero-pattern is a common finding in patients with chronic HCV infection, and may represent an occult infection in a smaller percent. A screening strategy that tests only for HBsAg and anti-HBs in HCV-infected patients will miss a large number of individuals with isolated anti-HBc, and a smaller number of patients with occult HBV infection. Addition of anti-HBc antibody screening is recommended, to avoid the adverse implications of missed HBV occult co-infection

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