Isolated anti-HBV core phenotype in anti-HCV-positive patients is associated with hepatitis C virus replication

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ABSTRACT

Recovery from hepatitis B virus (HBV) infection is associated with the presence of antibodies against HBV surface (HBs) antigen and HBV core (HBc) antigen. However, anti-HBs antibodies are lost in many cases, and only anti-HBc antibodies persist. A higher frequency of the anti-HBc-alone pattern has been demonstrated for anti-hepatitis C virus (HCV)-positive patients. In this report, 1126 anti-HCV-positive/anti-HBc-positive patients were studied, and the role of HCV replication in influencing the presence or absence of anti-HBs antibodies was investigated. The anti-HBc-alone phenotype was significantly more frequent in HCV-viraemic than in HCV-recovered patients. This finding represents new information regarding the immunopathogenesis of chronic HCV infection and supports previous data indicating impaired humoral immune responses in HCV infection.

Keywords Antibodies, hepatitis B, hepatitis C

Original Submission: 26 November 2002; Revised Submission: 17 February 2002; Accepted: 11 March 2003

Clin Microbiol Infect 2004; 10; 70–72

The presence of antibodies against both hepatitis B virus (HBV) surface antigen (HBsAg) and HBV core antigen (HBcAg) are serological markers of recovery from HBV infection. However, in many cases, anti-HBc, but no anti-HBs, antibodies can be detected. The clinical relevance of this phenomenon is controversial, and the mechanisms responsible for the loss of anti-HBs antibodies are not known. Previously, it has been shown that subjects with antibodies only to HBV core (anti-HBc alone) were more often co-infected with hepatitis C virus (HCV) than subjects who also had antibodies to HBsAg in addition to HBcAg [1]. Recently, Greub and Frei reported a 30% frequency of the anti-HBc-alone pattern among anti-HBc/anti-HCV-positive patients [2]. However, about 20% of the anti-HCV-positive patients tested in routine diagnostic laboratories are negative for HCV RNA in serum, indicating recovery from HCV infection. The earlier studies investigating patients with antibodies against HBV core alone did not distinguish between HCV-viraemic and HCV RNA-negative patients [1,2]. Since it is not known whether active HCV replication is associated with the anti-HBc-alone phenotype in anti-HCV-positive subjects, the present study addressed this issue in 1126 anti-HCV-positive and anti-HBc-positive individuals.

In total, 3153 consecutive anti-HCV-positive sera collected from patients between 1992 and 2001 at the Hannover Medical School, Germany were investigated for serological markers of ongoing or previous HBV infection. All patients tested positive for anti-HCV in the Laboratory of Gastroenterology and Hepatology. Patients comprised inpatients admitted to Hannover Medical School and outpatients seen in the clinic of our department. Patients with HIV co-infection were excluded from the analysis. None of the patients was tested while receiving antiviral treatment.

Routine serological markers for hepatitis viruses consisted of anti-hepatitis A virus IgG, anti-HBs, anti-HBc, HBsAg, anti-HCV and anti-hepatitis D virus. Serological testing was done as described previously with commercial immunoenzymatic assays (Abbott Laboratories, Chicago, IL, USA) [3,4]. Anti-HCV was tested from 1992 on by the second-generation assay, and then after 1995 by the third-generation assay. Detection and quantification of HCV RNA, as well as HCV genotyping, was also performed exactly as described previously [5,6].

Sixty-eight patients underwent liver biopsy. The liver biopsy material was fixed in formalin and embedded in paraffin for routine staining with haematoxylin and eosin. The biopsy material was examined by a single experienced pathologist, who...
was unaware of the clinical and virological data. Biopsy specimens were assessed for fibrosis (staging, score 0–6) and activity (grading, score 0–18) according to the hepatitis activity index of Knodell and co-workers, as modified by Ishak et al. [7].

In total, 1126 anti-HCV-positive individuals were identified who also tested positive for anti-HBc antibodies in the absence of HBsAg. HCV RNA was detectable by PCR (detection limit 600 copies/mL) in 887 (79%) of these patients. As expected for German patients, the dominant HCV genotype was genotype 1 (303 of 426 sera tested; 71%). Antibodies against both HBsAg and HBeAg were found in 881 (79%) patients, while the anti-HBc-alone phenotype was present in 245 (21%) individuals. This frequency is about one-third lower than that found by Greub and Frei [2]. It can be speculated that a different proportion of patients with additional risk factors, e.g., intravenous drug abuse or haemodialysis, might have contributed to the higher number of patients lacking anti-HBs in that study. In addition, genetic factors could potentially contribute to the ability of patients to produce anti-HBs antibodies.

Importantly, the anti-HBc-alone pattern was found significantly more often in HCV-viraemic patients (214 of 887; 22%) than in HCV RNA-negative individuals (31 of 249; 13%; p < 0.0001). In addition, among anti-HBs-positive/HCV RNA-viraemic patients, HCV RNA levels, as investigated by Cobas Amplicor, tended to be higher in patients with anti-HBs titres <50 IU/mL than in patients with anti-HBs titres >50 IU/mL (p = 0.12, data not shown). In contrast, no significant association was evident between the anti-HBc-alone antibody phenotype and HCV genotypes, age, sex, previous exposure to hepatitis A virus, liver function tests or histological grading and staging (Table 1).

Thus, active HCV replication was associated with decreased anti-HBs antibody production in HBcAg-positive/HBsAg-negative patients. The present data are in line with previous reports of impaired humoral immune responses after vaccination against HBV or hepatitis A virus in patients with chronic HCV infection [8,9].

What could be the explanation for these observations? First, humoral and cellular immune responses are induced by activation of dendritic cells. This cell type has been shown to be functionally impaired in chronic HCV infection, but not after recovery from HCV infection [10,11]. Second, HCV replication is associated with decreased HBV replication [12]. Thus, some of the patients might not have recovered totally from HBV infection, but HBV could instead have been suppressed by HCV co-infection. In this scenario, latent ongoing chronic HBV infection could be the reason for undetectable anti-HBs antibodies that are captured by low levels of HBsAg. Finally, cellular immune responses against HCV might interfere with HBV-specific B-cell and T-cell responses. Specific cross-reactivity or non-specific bystander mechanisms could be involved in

<table>
<thead>
<tr>
<th>Table 1. Relationship between antibody production and other patient characteristics</th>
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<tr>
<td>HCV RNA positive</td>
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<tr>
<td>HCV genotyped (n)</td>
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<tr>
<td>Genotype 1</td>
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<tr>
<td>Genotype 2/3</td>
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<tr>
<td>Other genotypes</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Female/male</td>
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<tr>
<td>ALT (U/L)*</td>
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<tr>
<td>AST (U/L)*</td>
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<tr>
<td>Bilirubin (mmol/L)*</td>
</tr>
<tr>
<td>Inflammationb</td>
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<tr>
<td>Fibrosisb</td>
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<td>aLiver functions tests were available for 192 patients.</td>
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<tr>
<td>bHistological grading (inflammatory score 0–18) and staging (fibrosis score 0–6) was performed according to the Ishak score (11) in 68 patients (56 anti-HBs positive and 12 anti-HBc alone).</td>
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ALT, alanine aminotransferase; AST, aspartate aminotransferase.
suppressing anti-HBs-producing B-lymphocytes. Alternatively, a stronger anti-HBV humoral immune response, as indicated by the presence of anti-HBs antibodies, might in part suppress HCV replication [13]. Heterologous immunity and viral interactions are much more frequent than previously thought, and cross-reactivity between influenza A virus and HCV determinant-specific cytotoxic T-cells has been described [14]. The potential clinical relevance of viral co-infections has been emphasised by reports on the improved survival of HIV-positive patients who are co-infected with GB virus C [15].

Future studies will be needed to clarify the detailed mechanisms by which HCV replication suppresses anti-HBs production in anti-HBC-positive patients. Understanding the pathogenesis of HBV–HCV co-infection is important not only for hepatologists, but also for virologists in general, since infection with multiple hepatitis viruses represents a unique and clinically well defined model to study viral interactions and heterologous immunity in humans.

REFERENCES


RESEARCH NOTE

Relationship between ciprofloxacin resistance and extended-spectrum \( \beta \)-lactamase production in Escherichia coli and Klebsiella pneumoniae strains

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ABSTRACT

Resistance to fluoroquinolones has increased markedly since their introduction. Mechanisms of resistance to any antibiotic class might play a role in resistance to an unrelated antibiotic class.