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Clinical significance of "anti-HBc alone" in human immunodeficiency virus-positive patients

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Abstract

AIM: To determine the prevalence and clinical relevance of isolated antibodies to hepatitis B core antigen as the only marker of infection ("anti-HBc alone") among human immunodeficiency virus (HIV) type-1 infected patients. Occult hepatitis B infection frequency was also evaluated.

METHODS: Three hundred and forty eight histories from 2388 HIV-positive patients were randomly reviewed. Patients with serological markers of hepatitis B virus (HBV) infection were classified into three groups: past hepatitis, "anti-HBc alone" and chronic hepatitis. Determination of DNA from HBV, and RNA and genotype from hepatitis C virus (HCV) were performed on "anti-HBc alone" patients.

RESULTS: One hundred and eighty seven (53.7%) HIV-positive patients had markers of HBV infection: 118 past infection (63.1%), 14 chronic hepatitis (7.5%) and 55 "anti-HBc alone" (29.4%). Younger age [2.3-fold higher per every 10 years younger; 95% confidence intervals (CI) 1.33-4.00] and antibodies to HCV infection [odds ratio (OR) 2.87; 95% CI 1.10-7.48] were factors independently associated with the "anti-HBc alone" pattern. No differences in liver disease frequency were detected between both groups. Serum levels of anti-HBs were not associated with HCV infection (nor viral replication or HCV genotype), or with HIV replication or CD4 level. No "anti-HBc alone" patient tested positive for HBV DNA.

CONCLUSION: "Anti-HBc alone" prevalence in HIV-positive patients was similar to previously reported data and was associated with a younger age and with antibodies to HCV infection. In clinical practice, HBV DNA determination should be performed only in those patients with clinical or analytical signs of liver injury.

Key words: Human immunodeficiency virus; "Anti-HBc alone"; Occult hepatitis; Hepatitis B virus DNA; Liver disease

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INTRODUCTION

Infections by hepatitis B (HBV) and C (HCV) viruses are common in human immunodeficiency virus (HIV) infected patients, since nearly all these viruses share the same routes of transmission. HBV infection is present in between 49.2%-68% of HIV-positive patients[1-3] and there is evidence that co-infection can modify the natural history of HBV[4], involves potential consequences on morbidity and mortality and has implications in management of both infections[5]. In fact, nowadays

HBV status is systematically and regularly assessed and systematic HBV vaccination is proposed in those patients without HBV markers.

Over recent years, numerous studies have been published about HBV-HIV co-infection, though some issues still remain unclear, such as clinical relevance and management of those patients with an isolated positive test for antibodies against hepatitis B core antigen ("anti-HBc alone" or defective immunological response)[6,7]. This serological pattern is the second most frequent serological profile of HBV infection, occurring in about 30% of HBV infected patients[1-3].

One of the most controversial questions is about the frequency of occult hepatitis, i.e. HBV DNA positive markers without HBV surface antigen (HBsAg), among patient with a defective immunological response. Some authors consider the "anti-HBc alone" pattern to be a marker of occult HBV infection[1,3,8,9], whereas others have not been able to demonstrate HBV DNA in the sera of these patients[10-13].

This work was carried out to establish the prevalence and clinical significance of the "anti-HBc alone" pattern among HIV-positive patients. The frequency of HBV occult infection, determined by standard assays commonly used in routine clinical practice, was also determined.

MATERIALS AND METHODS

Xeral-Cíes University Hospital is a 700 bed Vigo University-affiliated Hospital which serves an urban population of about 400 000 inhabitants. From 2388 HIV-positive patients, who were followed-up in a specialised clinic of the hospital, 348 clinical histories were consecutively reviewed. Patients with some HBV markers were classified into three groups: chronic hepatitis [positive HBsAg and IgG anti-HBc, negative anti-HBs and IgM anti-HBc and positive or negative "e" antigen (HBeAg)]; past hepatitis (positive anti-HBs and IgG anti-HBc, negative HBsAg and IgM anti-HBc); and "anti-HBc alone" (positive IgG anti-HBc and negative HBsAg, anti-HBs, IgM anti-HBc and anti-HBe).

"Anti-HBc alone" patients were included only when a confirmatory test, performed two weeks later, showed a concurrent result. Patients that had been vaccinated against HBV were excluded.

In every "anti-HBc alone" patient and in those with past hepatitis epidemiologic characteristics (age, sex, risks conduct), co-morbidities (active infections, renal failure, diabetes, cancer, *etc*), antibodies against HCV, immunoglobulin levels and liver function tests were gathered. HCV RNA, HCV genotype and HIV viral load were tested and CD4 level was determined by flow cytometry. Also, abdominal imaging (ultrasound, CT, magnetic resonance) was performed to evaluate the presence of chronic liver disease (inhomogeneous hepatic texture or surface, rarefied hepatic central vein, an enlarged caudate lobe, splenomegaly or collateral veins)[14]. In every case, intake of antiretroviral therapy active against HBV, such as lamivudine or tenofovir, was recorded. Changes in the serological response after introduction of antiretroviral therapy or after an immunological improvement were evaluated. When it was possible, serum was extracted to determine HBV DNA.

Laboratory tests

HBs Ag, anti-HBe and anti-HBc were determined with 3rd generation microparticle enzyme immunoassays (MEIA) for qualitative detection of surface antigen, antibodies against "e antigen" and antibodies against "core antigen" of HBV [AxSYM HBsAg (V2) System, anti-HBe System y Core System. Abbott Laboratories, Chicago, IL, USA]. Anti-HBs was determined by 3rd generation MEIA for quantitative assessment of HBV surface antibodies (Abbott Laboratories, Chicago, IL, USA). Detection limits of the assay were 10-1000 IU/L. Serum HBV DNA levels were determined by an automated quantitative technique of molecular hybridation with genomic amplification; owned primers against the core region of the genome contained in a National "Reference Laboratory" were used. The lower detection limit of this assay was 10^4 copies/mL.

Antibodies against HCV were measured with 3rd generation MEIA to qualitatively determine this antibody (AxSYM HCV version 3.0 System. Abbott Laboratories, Chicago, IL, USA). Serum HCV RNA was quantified by molecular hybridation using a branched DNA technique [Versant HCV-RNA 3.0 (bDNA) - Bayer Diagnostics]. This assay has a lower detection limit of 3200 copies/mL. HCV genotype was determined by automatic sequencing with a fluorescent marker.

Antibodies against HIV-type 1, HIV-type 2 and p24 antigen were determined at the same time by 3rd generation MEIA (AxSYM HIV Ag/Ab Combo System. Abbott Laboratories, Chicago, IL, USA). Positive test results were confirmed by Western-Blot (NEW LAV-BLOT I Bio-Rad. France). HIV viral load was quantified by the Amplicor HIV-1 Monitor (Roche Diagnostics). The lower detection limit of this assay was 40 copies/mL.

The study was reviewed and approved by the Research Ethical Committee of Vigo Hospitality University Complex. All patients gave informed consent to participate in the study.

Statistical analyses

Results were expressed as absolute values (percentage) and median (interquantile range, IQR) as appropriate. Baseline characteristics were compared by using χ^2 or Fisher exact test for categorical data and Mann-Whitney *U* test for continuous data.

When variables were significantly associated ($P < 0.05$) with a defective pattern in the univariate analysis, a backward logistic regression analysis was conducted to identify those factors independently associated with "anti-HBc alone".

Table 1 Differences between HIV-positive patients with "anti-HBc alone" and past hepatitis B

	"anti-HBc alone" pattern (*n* = 55)	Past hepatitis B (*n* = 55)	*P*
Age, yr	38 (33-43)	45 (37-49)	0.001
Male, *n* (%)	38 (69.1)	38 (69.1)	1.000
Transmission mode *n* (%)			0.021
IDU	44 (80)	34 (61.8)	
Homosexual	4 (7.3)	15 (27.3)	
Heterosexual	7 (7.7)	6 (10.9)	
AST (IU/mL)	43 (23-65)	31 (22-47)	0.092
ALT (IU/mL)	39 (19-73)	29 (20-45)	0.301
Albumin (g/L)	42 (38.8-45.6)	43 (40.8-45.9)	0.261
Anti-HCV positive, *n* (%)	45 (81.8)	34 (61.8)	0.020
CDC C stage, *n* (%)	15 (27.3)	19 (34.5)	0.409
CD4 (cells/mm^3)	434 (325-714)	459 (303-636)	0.740
HIV DNA < 50 copies/mL	25 (47.2)	32 (59.3)	0.210

IDU: Intravenous drug user; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

RESULTS

From 348 clinical histories, 187 (53.7%) patients had positive tests against HBV; 118 past hepatitis (33.9%), 14 chronic hepatitis (4%), and 55 "anti-HBc alone" (15.8%). Among patients who had been infected by HBV, 29.4% developed an "anti-HBc alone" pattern and 63% showed a cured past infection. Fifty five patients with past hepatitis were randomly selected to be compared with "anti-HBc alone" patients. Epidemiologic characteristics of both groups are shown in Table 1.

The factors independently associated with a defective pattern were younger age [2.3-fold higher per every 10 years younger; 95% confidence intervals (CI) 1.33-4.00] and antibodies to HCV infection [odds ratio (OR) 2.87; 95% CI 1.10-7.48]. Intravenous drug users (IDU) were significantly more frequent in the "anti-HBc alone" group (80% *vs* 61.8%, $P = 0.021$).

Liver function tests, CD4 levels, HIV viral load or AIDS stages were not significantly different between the two groups. Ultrasound signs of chronic liver disease were only present in HCV co-infected patients ($P < 0.05$). Serum levels of anti-HBs were not associated with HCV infection (nor with viral replication or HCV genotype), and were not associated with HIV replication or CD4 level.

Serum HBV DNA was tested in 30 "anti-HBc alone" patients and no-one was positive. However, 10 patients were taking lamivudine or tenofovir when the tests were performed.

DISCUSSION

In the present study, as in other studies[1-3], a high prevalence of HBV infection (53.7%) among HIV infected patients was found. Although diverse frequencies in the "anti-HBc alone" pattern have been reported according to different geographic areas or selected populations[15,16], the frequency data among HIV patients (24.5-37.8%[1-3]) are fairly similar to data reported in this study (29.4%).

One of the independent factors related to the defective serological pattern was a younger age. This event has been previously reported in only one study[17], in which a higher frequency of "anti-HBc alone" status was also found among women. Nevertheless, in our study the proportion of women in the "anti-HBc alone" group was the same as that in the past hepatitis group (30.9%).

The presence of HCV infection is another independent factor identified in our work which has been reported before[1,3,9,16,18]. A study showed that "anti-HBc alone" phenotype was significantly more frequent in HCV-viraemic than in HCV-recovered patients[18]. HCV replication could produce a down regulation in HBV replication, and this could be expressed as a defective serological pattern[7,18].

IDU has also been reported previously as significantly more frequent in the "anti-HBc alone" group[19] and it has been related to a higher frequency of HCV, as IDU is one of the strongest risk factors for HCV infection.

This is the first study that evaluates liver disease by abdominal imaging scan and no statistically significant differences were found between "anti-HBc alone" patients and past hepatitis patients. In both groups, signs of liver disease were only demonstrated in patients co-infected with HCV.

Occult hepatitis prevalence data reported in "anti-HBs alone" HIV-positive patients varies greatly from 0% to 89.5%[1-3,9,12,17,20,21]. However, in those studies that have found viral replication, detected viral load was usually very low (< 10^3 copies/mL)[3,20]. Ultrasensitive PCR techniques (50-10^2 copies/mL) were broadly used in those experimental studies, but are not available in daily clinical practice. In our study, no case of occult hepatitis was proved by standard assays commonly employed in routine clinical practice that can detect 10^4 copies/mL. Clinical relevance and management of this low viral replication is unclear because a higher incidence of hepatic damage was not found in these patients[16]. On the other hand, current therapeutic guidelines do not recommend starting treatment if the viral load is lower than 10^4-10^5 copies/mL[6,21-24]. More than 90% of doctors that attend HIV patients follow this practice[22]. However, the latest recommendations in HIV-positive patients with the "anti-HBc alone" pattern advise to test for HBV DNA in every patient[6,10,12,13,20]. We believe that HBV DNA testing should be performed only in those patients with an unexplained high level of alanine aminotransferase (ALT) or signs of liver disease.

The present study has some limitations. HBV DNA was not tested in every "anti-HBc alone" patient but non medical reasons prevented us from getting some serum specimens. Moreover, some tested patients were taking lamivudine or tenofovir. However, a study showed that the mean HBV load was similar among patients whether

or not they were treated with lamivudine, and that this was probably associated with an increasing number of resistance mutations[2]. Furthermore, in another study in which one case of occult hepatitis was demonstrated the patient was on lamivudine[11]. The present study displays a complete evaluation of HIV-positive patients with the "anti-HBc alone" pattern, since clinical, virological and radiological parameters have been considered in these patients.

In conclusion, in our population "anti-HBc alone" prevalence in HIV-positive subjects is similar to previously reported data and is associated with a younger age and with antibodies to HCV infection. After evaluating the results of the present study and others with similar results, HBV DNA determination should not be performed in every patient with the "anti-HBc alone" pattern, but only in those patients with unexplained clinical or analytical signs of liver injury.

COMMENTS

Background

Over recent years, numerous studies have been published about hepatitis B virus (HBV)-human immunodeficiency virus (HIV) co-infection, though some issues remain still unclear, such as clinical relevance and management of those patients with "anti-HBc alone" pattern or the frequency of occult hepatitis among patients with a defective immunological response. Some authors consider the "anti-HBc alone" pattern to be a marker of occult HBV infection, whereas others have not been able to demonstrate HBV DNA in the sera of these patients.

Research frontiers

The authors studied the prevalence and clinical significance of the "anti-HBc alone" pattern among HIV-positive patients and the frequency of HBV occult infection, determined by standard assays commonly used in routine clinical practice.

Innovations and breakthroughs

This is the first study that evaluates liver disease by abdominal imaging scan and no statistically significant differences were found between "anti-HBc alone" patients and past hepatitis patients. In both groups, signs of liver disease were only demonstrated in patients co-infected with hepatitis C virus (HCV). No single case of occult hepatitis was proved by standard assay commonly employed in routine clinical practice that can detect 10^4 copies/mL.

Applications

Although the latest recommendations in HIV-positive patients with the "anti-HBc alone" pattern advise to test for HBV DNA in every patient, this and other studies show that viral load reported in these patients is usually low. Current therapeutic guidelines do not recommend starting treatment when viral load is lower than 10^4-10^5 copies/mL. The authors believe that HBV DNA testing should be performed only in those patients with an unexplained high level of alanine aminotransferase (ALT) or signs of liver disease.

Terminology

"Anti-HBc alone" pattern or defective immunological response: positive hepatitis B core antigen as the only marker of hepatitis B infection. Occult hepatitis B: HBV DNA positive without HBV surface antigen.

Peer review

The "anti-HBc alone" pattern is very common among HIV-positive patients and it is not associated with liver injury. However this serological pattern can be associated with occult hepatitis B, usually with a very low viral load of HBV. The authors recommend testing DNA HBV only in those patients with the "anti-HBc alone" pattern and unexplained high levels of ALT or signs of liver disease.

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