Isolated Hepatitis B Core Antibody is Associated with Advanced Hepatic Fibrosis in HIV/HCV Infection but not in HIV infection alone

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Summary

HIV+/HCV+ persons with isolated HBcAb have a higher prevalence of advanced fibrosis than persons who are non-immune to HBV, who have resolved HBV, or who are HbsAb+ only.

Keywords

Hepatitis B Core Antibody; HIV; hepatitis C

Introduction

Isolated hepatitis B virus (HBV) core antibody (HBcAb+), defined as the presence of HBcAb in the absence of HBV surface antigen (HBsAg) and surface antibody (HBsAb), occurs in up to 34%, 50%, and 59% of HIV-HCV-coinfected, HCV monoinfected, and HIV monoinfected persons, respectively[1-6]. Isolated HBcAb can indicate occult HBV viremia (the presence of HBV viremia in the absence of HBsAg, resolved infection with low titers of HBsAb, a window period during acute infection, or a false positive result. However, the relationship between isolated HBcAb pattern and liver disease remains unclear with some, but not all, studies describing an association with liver disease[3,7-10]. Our objective was to characterize the prevalence of isolated HBcAb pattern among HIV and HIV/HCV-infected veterans in the Veterans' Aging Cohort Study (VACS) and to determine whether the isolated HBcAb pattern was associated with advanced fibrosis in HIV and HIV/HCV-coinfected Veterans.

Methods

Study Design and Setting

We conducted a cross-sectional study among HIV-infected individuals in the Veterans Aging Cohort Study Virtual Cohort (VACS-VC)[11]. Comprised of electronic medical record data from all HIV-infected veterans at Veterans Affairs (VA) medical facilities in the US, data include hospital and outpatient diagnoses, laboratory results, and pharmacy data[12].

Study Patients

The study sample included all HIV-infected individuals who enrolled in the VACSVC between October 1996 and September 2010, had at least 180 days of follow-up, and who had all three HBcAb, HBsAg, and HBsAb serologies tested. We then searched for the first

positive or negative HBcAb test and included only those who had subsequent HBsAb and HBsAg testing +/− 12 months from the first positive or negative HBcAb result. We further evaluated those for whom data variables to calculate FIB-4 and APRI scores were available within +/− 12 months of the earliest complete serologic data. The following five serologic patterns were assessed:

1) Isolated HBcAb: HBsAg negative, HBcAb positive, HBsAb negative

2) Resolved HBV infection: HBsAg negative, HBcAb positive, HBsAb positive

3) Non-immune HBV: HBsAg negative, HBcAb negative, HBsAb negative

4) Immunized HBV: HBsAg negative, HBcAb negative, HBsAb positive

5) Active HBV infection: HBsAg positive, HBcAb negative or positive, HBsAb negative

The main outcome was advanced hepatic fibrosis, defined by a FIB-4 >3.25 at the time of serologic evaluation (within one year of markers obtained). Secondary outcomes defining advanced hepatic fibrosis were assessed individually and included: 1) aspartate aminotransferase (AST)-to-platelet ratio index (APRI) >2.0, and 2) platelet count <140,000/μL. Both FIB-4 (based upon age, AST, alanine aminotransferase (ALT)[13] and APRI have been shown to validly identify patients with advanced hepatic fibrosis/cirrhosis[14]. Similarly, platelet counts of <140,000/μl have been associated with advanced fibrosis/cirrhosis[15].

HCV infection was defined as HCV Ab positive, HCV RNA positive, or an ICD-9 diagnosis of HCV. Age, race/ethnicity, CD4 count, log HIV viral load, diabetes, body mass index, alcohol-related disorders, drug use, smoking were collected from all patients at inclusion. Diabetes was defined by a random glucose level 200 mg/dL or anti-diabetic medication use. Alcohol-related disorders and injection/non-injection drug use were defined by ICD-9 codes.

Logistic regression was used to evaluate associations between serological patterns of HBV and advanced hepatic fibrosis for patients with and without chronic HCV infection, adjusting for age, race/ethnicity, CD4 count, log HIV RNA, diabetes, body mass index, alcohol-related disorders, injection/non-injection drug use, and smoking. As substance use can be associated with immune dysfunction[16], which in turn can be associated with the isolated HBcAb pattern, interactions between serological patterns and alcohol-related disorders, injection/non-injection drug use, and smoking were also evaluated. All analyses were carried out using SAS version 9.2 (Cary, NC).

Results

Among 44,180 HIV infected veterans (14,568 with and 29,612 without HCV infection), 41,088 had at least 180 days of follow-up, 26,924 had all three serologies tested, and 23,970 veterans had all three serologies within one year of the first positive or negative HBcAb result. Among 23,970 HIV infected veterans, 9,327 with and 14,643 without HCV infection, 7,290 and 12,196, respectively, had complete data allowing for calculation of FIB-4 and APRI). Complete information on persons with missing hepatitis data included race, smoking

status, and age. Those that were included were more likely to be white (37% vs 30%), older (mean age 47 vs 46), and less likely to be current smokers (59% vs. 64%), all p<0.01.

In this cohort, 12.3% (1504/12196) and 37% (2707/7290) of HIV and HIV/HCV individuals, respectively, had the isolated HBcAb pattern (Table 1). Persons with isolated HBcAb were the same age or older and more likely to be nonwhite, or to have an alcohol related disorder, than were persons with resolved HBV, non-immune HBV, or HBsAb only. HIV-monoinfected persons with isolated HBcAb were more likely to have <200 CD4 cells/μL and a higher median level of HIV-1 RNA copies/mL. In addition, coinfected persons who were non-immune to HBV and persons who were HBsAb+ only had a higher median HIV-1 RNA copies/mL than did persons with isolated HBcAb. In both groups there was not a statistically significant interaction noted between substance use and the isolated HBcAb pattern.

In both HIV monoinfected and HIV/HCV coinfected groups, AST, FIB-4, and APRI scores were higher while platelets were lower in isolated HBcAb patients, when compared to those with resolved HBV, non-immune HBV, or HBsAb only serologic profiles. However, in multivariable analysis, when compared to HBsAg-negative groups, only HIV/HCV coinfected patients with isolated HBcAb exhibited an association with advanced hepatic fibrosis. HIV+/HCV+ patients with isolated HBcAb had higher OR for advanced hepatic fibrosis by FIB-4 compared with those who had resolved HBV (OR, 1.34; 95% CI, 1.15-1.58), were non-immune (OR, 1.32; 95% CI, 1.09-1.60), or were HBsAb+ (OR, 1.65; 95% CI, 1.20-2.28), Similar results were observed when APRI and platelet counts <140,000/μL were evaluated. Not unexpectedly, advanced fibrosis was less in patients with isolated HBcAb than in those who were HBsAg positive. We performed a sensitivity analysis (not shown) that included HCV viremic patients which showed a similar association with HCV viremia, the isolated HBcAb profile, and advanced fibrosis, but this was not statistically significant, likely a reflection of the smaller sample size.

Discussion

In this large cross-sectional study of isolated HBcAb patterns of both HIV-infected and HIV/HCV-coinfected Veterans, we found that the isolated HBcAb pattern was associated with advanced hepatic fibrosis in HIV/HCV-coinfected patients, but not in HIV infection without concomitant HCV infection. While most clearly seen using a FIB-4 threshold of >3.25, similar results were seen with an APRI threshold of >2.0 or a platelet count of <140,000/μL.

The fact that the isolated HBcAb pattern was associated with advanced liver disease in HIV/HCV coinfected, but not HIV monoinfected patients, suggests that there might be a multiplicative effect of HCV, HIV, and previous or ongoing low-grade HBV infection on the liver (as demonstrated by the isolated HBcAb pattern). Alternatively, both chronic HCV and the isolated HBcAb pattern may reflect a suboptimal immune response that facilitates HCV persistence, isolated HBcAb persistence, and ongoing liver damage, as manifested by an association with lower CD4 counts in a cohort of HIV infected women and in this study[17]. However, CD4 was incorporated into the logistic regression model for this study, suggesting that other components of the immune response may be involved. Although there were no

interaction effects, an increased prevalence of substance use in those with the isolated HBcAb pattern, may be indicative of other defects in immune response, as has been seen with opiates, marijuana, and alcohol[16]. As this is a cross-sectional study, it was not possible to distinguish whether the advanced fibrosis reflected previous versus ongoing liver damage.

Strengths of the current analysis included a large sample size of patients with a full panel of HBV serologies and direct comparison of HCV infected and uninfected veterans with HIV infection. Limitations of the study include the cross-sectional nature of the analysis and missing data in those who had complete serologies, which represented 19% of the cohort. This may have led to selection bias, especially in the HCV uninfected group where hepatitis B serologies were disproportionately not evaluated. However, as patients who did not have serologies were likely to be healthier than those who did, it is unlikely that this would have affected our results. Additionally, we did not assess HBV DNA in the serum, as only a fraction of the study population had serum HBV DNA measured. Moreover, FIB-4 and APRI might not be accurate in assessing intermediate degrees of fibrosis. Finally, our study was conducted in HIV-infected veterans who may have differing risk factors, including socioeconomic factors, for liver disease than other HIV infected cohorts potentially limiting generalizability to other cohorts.

In summary, we found that the isolated HBcAb pattern was associated with advanced hepatic fibrosis in HIV/HCV-coinfected, but not HIV-monoinfected, Veterans. These findings suggest that HIV- and HCV-infected persons with isolated HBcAb may be at increased risk of clinical liver complications and support the need for further studies in the longitudinal assessment of liver disease.

Acknowledgments

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Table 1

Patient Characteristics and Comparative Prevalence of Advanced Fibrosis for Isolated HBcAb Compared to Other HBV Serologic Patterns

	Isolated HBcAb		Resolved HBV		Non-Immune HBV		HBsAb+ only		HBsAg+		Total	
	HIV	HIV/HCV	HIV	HIV/HCV	HIV	HIV/HCV	HIV	HIV/HCV	HIV	HIV/HCV	HIV	HIV/HCV
N	1504	2707	4283	2345	4089	1294	1471	452	849	492	12196	7290
Age (Median, IQ)	47 (44-54)	48 (44-53)	47 (40-55)	48 (43-53)	46 (39-54)	46 (42-52)	41* (32-50)	47* (42-52)	44* (38-52)	46* (40-50)	46 (39-54)	48 (43-53)
Sex (%)												
Male	98.7	99.0	98.6	98.5	95.1	96.8	96.0	96.2	98.8	99.4	97.1	98.3
Ethnicity (%)												
White	33.2*	19.8	47.0*	31.7*	37.4*	32.8*	43.0*	32.3*	37.7*	35.4	41.0	27.8
Habits (%)												
Tobacco (current/past)	59.8/14.6	74.2/14.1	48.4/17.9*	68.2/15.5*	53.4/16.6*	69.4/13.2*	45.4/13.8*	63.1/15.4*	57.2/11.6*	66.0/13.8*	51.6/16.1	70.2/14.5
ETOH Abuse	19.6	40.9	14.4*	36.3*	17.7*	34.1*	14.1*	33.2*	16.6	31.5*	16.3	37.1
Drug-Related Condition	23.0	49.1	15.3*	44.2*	17.1*	36.1*	13.8*	35.6*	17.3*	34.6*	16.8	43.4
ALT	28	47	29	42*	27	43*	27	40*	41*	50	29	44
AST	29	50	28	42*	28*	41*	26*	41*	42*	50	28	45
Log HIV-1 VL Undetectable (%)	3.70 35.2%	3.40 38.2%	3.08* 44.9%	3.28 40.0%	3.48* 39.3%	3.74* 35.0%	3.15* 44.6%	3.68 37.4%	3.67 38.0%	3.57 36.4%	3.35 41.3%	3.45 38.0%
CD4 (cells/µL) (%)												
CD4 <200	37.3	33.1	28.4*	32.4	33.4*	31.1	23.2*	25.0*	38.3	42.1*	31.2	32.6
Platelet (*1000/µL)	214	191	218	196*	221*	205*	227*	202*	180*	180*	218	195

Comparative Prevalence of Advanced Fibrosis for Isolated HBcAb Compared to Other HBV Serologic Patterns, from Multivariable Logistic Regression Model

	Isolated HBcAb	Resolved HBV		Non-Immune HBV		HBsAb+ only		HBsAg+	
		HIV	HIV/HCV	HIV	HIV/HCV	HIV	HIV/HCV	HIV	HIV/HCV
FIB-4 >3.25	Ref	1.14 (0.85-1.53)	1.34 (1.15-1.58)	1.04 (0.78-1.39)	1.32 (1.09-1.60)	1.26 (0.84-1.89)	1.65 (1.20-2.28)	0.32 (0.23-0.44)	0.75 (0.58-0.98)
APRI >2.0	Ref	1.16 (0.79-1.70)	1.40 (1.15-1.71)	1.42 (0.78-1.40)	1.15 (0.92-1.44)	1.67 (0.99-2.82)	1.88 (1.25-2.84)	0.22 (0.15-0.32)	0.68 (0.51-0.91)
Platelets <140,000/µL	Ref	0.97 (0.78-1.22)	1.19 (1.02-1.40)	1.16 (0.93-1.46)	1.27 (1.05-1.54)	1.15 (0.86-1.54)	1.09 (0.82-1.44)	0.49 (0.37-0.65)	0.76 (0.60-0.99)

ETOH=Alcohol, IVDU=Intravenous Drug Use, FIB-4=FIB-4 fibrosis score, APRI=AST-to-platelet ratio index; All data from multivariable logistic regression model presented as Odds Ratio (95% confidence interval). Analyses were adjusted for age, race/ethnicity, CD4 count, log HIV VL, diabetes, body mass index, alcohol, drug use, smoking.

*p<0.0001, indicated group compared with isolated HBcAb patients