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The hepatitis B core antibody positive/hepatitis B surface antigen negative pattern is associated with the increased risk of intracranial atherosclerotic stenosis

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Abstract

The high prevalence of hepatitis B virus (HBV) infection and intracranial atherosclerotic stenosis (ICAS) in Asia raises the question as to whether HBV infection is associated with ICAS. To answer this question, we tested the association between HBV infection and ICAS. Totally, 3072 in-hospital subjects were retrospectively enrolled. All subjects underwent computed tomography angiography (CTA) and serological testing for HBV infection. Based on the results of CTA, all subjects were categorized into 4 groups including ICAS, extracranial atherosclerotic stenosis (ECAS), ICAS/ECAS (both ICAS and ECAS), and normal. HBV infection was divided into 4 patterns including hepatitis B core antibody (anti-HBc) positive/hepatitis B surface antigen (HBsAg) positive, anti-HBc-positive/HBsAg-negative, anti-HBc-negative/HBsAg-positive, and anti-HBc-negative/HBsAg-negative. Risk factors for atherosclerosis were collected based on medical records. Multiple logistic regression models were used to determine the association between infection patterns and ICAS. We found that the anti-HBc-positive / HBsAg-negative pattern was associated with the increased risk of ICAS (OR = 1.462) and not associated with ECAS or ICAS / ECAS. The HBc-positive/HBsAg-positive pattern was not associated with ICAS, ECAS or ICAS/ECAS. In conclusions, the anti-HBc-positive/HBsAg-negative pattern was associated with the increased risk of ICAS. Anti-HBc should be employed to investigate the association between HBV infection and cerebrovascular diseases.

Abbreviations: Anti-HBc = hepatitis B core antibody, Anti-HBe = anti-hepatitis B e antigen, Anti-HBs = anti-hepatitis B surface antigen, CTA = computed tomography angiography, ECAS = extracranial artery stenosis, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, ICAS = intracranial artery stenosis, OR = odds ratio, WASID = warfarin-aspirin symptomatic intracranial disease.

Keywords: hepatitis B core antibody, hepatitis B surface antigen, hepatitis B virus, intracranial arterial diseases, intracranial atherosclerosis

1. Introduction

Hepatitis B virus (HBV) infection is highly endemic in China. The prevalence of hepatitis B surface antigen (HBsAg) positivity for people aged 1 to 59 years was 7% in 2006.[1,2] Among Chinese adults, HBsAg-positive prevalence is 8.5% to 10.5%.[2–5] The prevalence of hepatitis B core antibody (anti-HBc) positivity is much higher. A recent study analyzed serum samples of 2 million men aged 21 to 49 years in rural China and reported that 6% were HBsAg-positive and 9% were anti-HBc-positive.[6] Another study reported a higher HBsAg-positive and anti-HBc-positive prevalence in the population over 20 years old (7.9% and 39%, respectively).[4]

Similar to HBV infection, the prevalence of intracranial atherosclerotic stenosis (ICAS) is also higher in Asia than in other regions. The epidemiology is similar in Africa,[7] which also has a high HBV infection prevalence and ICAS. ICAS is the underlying cause of up to 30% to 50% of strokes in the Asian population, much higher than the 5% to 10% rate reported in the population of European descent and the 15% to 29% reported among the populations of African descent.[8–13] Asian individuals are more susceptible to ICAS while individuals of European descent are more susceptible to extracranial carotid stenosis.[12,14,15] Potential explanations include genetic susceptibility, lifestyle differences, and variations in risk factor profiles among individuals of different ethnicities.[8,9,16–20] However, the cause of this difference remains unclear.

The high HBV and ICAS prevalence in Asia raise the question as to whether HBV infection is associated with ICAS. Theoretically, a chronic inflammatory response evoked by virus can contribute to the initiation and progression of atherosclerotic

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plaques, based on experimental and epidemiologic evidence.[21–23] Polyarteritis nodosa (PAN) is the case. The HBV infection is strongly linked with PAN, which is a vasculitis characterized by necrotizing inflammatory lesions affecting medium and small-sized muscular arteries, preferentially at vessel bifurcations.[24] However, there is no evidence to support the view that HBV can affect intracranial arteries. Therefore, our study aimed to investigate the potential association between HBV infection and ICAS.

2. Methods

Totally, 3438 in-hospital subjects were consecutively enrolled in this study from January 2014 to September 2016 in Xinqiao hospital. Inclusion criteria were as follow:

1. subjects underwent computed tomography angiography (CTA) due to suspected cerebral vascular diseases;
2. subjects underwent routine serological testing for HBV infection.

Exclusion criteria were:

1. subjects with intracerebral hemorrhage confirmed by cranial computed tomography;
2. subjects with the diagnosis of brain tumors, cerebral vascular malformations, vasculitis, trauma, coagulopathy, and cerebral venous sinus thrombosis;
3. a history of sympathomimetic drug abuse;
4. subjects with missed medical data.

Based on the result of CTA, all subjects were categorized into 4 groups including ICAS, ECAS, ICAS/ECAS (both ICAS and ECAS), and normal. ICAS was defined as atherosclerotic stenosis occurring in 6 major intracranial arteries including middle cerebral artery, siphon carotid artery, anterior cerebral artery, posterior cerebral artery, intracranial segment of vertebral artery, and basilar artery. ECAS was defined as atherosclerotic stenosis occurring in 4 major extracranial arteries including the common carotid artery, cervical segment of internal carotid artery, the first segment of vertebral artery, and subclavian artery. The arterial stenosis was measured using the WASID (in warfarin-aspirin symptomatic intracranial disease trial) method. The arterial stenosis ≥50% was defined as stenosis.

Finally, 3072 subjects were included in final analysis, including 519 subjects with ICAS, 414 subjects with ECAS, 1292 subjects with ICAS / ECAS (both ICAS and ECAS), and 847 normal subjects (without ICAS or ECAS).

Five serological markers of HBV infection were measured, namely, HBsAg, anti-HBc, anti-hepatitis B surface antigen (anti-HBs), hepatitis B e antigen (HBeAg), and anti-hepatitis B e antigen (anti-HBe). Based on the result of serological testing of HBsAg and anti-HBc, we divided all subjects into 4 patterns: anti-HBc-positive/HBsAg-positive, anti-HBc-positive/HBsAg-negative, anti-HBc-negative/HBsAg-positive, and anti-HBc-negative/HBsAg-negative.

The study protocol was approved by the ethics committee of Xinqiao Hospital, Army Medical University. Information regarding the risk factors for atherosclerosis, including age, gender, history of hypertension, history of diabetes mellitus, creatinine, alanine aminotransferase, triglyceride, total cholesterol, low density lipoprotein cholesterol, thyroid-stimulating hormone, free triiodothyronine, free thyroxine, and hemoglobin were collected from subjects' medical records. The difference of the factors between groups were tested with Chi-Squared test and analysis of variance. Multiple logistic regression models were used to analyze the potential association between HBV infection and ICAS. Analyses were performed by using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). A two-sided P value < .01 was considered statistically significant.

3. Results

Baseline characteristics of factors in 4 groups were in Table 1. The ICAS prevalence was about 59% (519 + 1292/3072) and ICAS/ECAS about 42% (1292/3072). The prevalence of age, gender,

Table 1

The prevalence of cerebral artery stenosis and factors.

	ICAS n=519	ECAS n=414	ICAS / ECAS n=1292	Normal n=847	*P* value
Age (yrs, mean±SD)	61.66±11.66	64.13±10.78	68.45±10.14	57.35±12.06	
<60%	37.6	33.3	18.0	54.0	<.001
6%0–70%	34.5	33.3	32.9	28.1	
>70%	27.9	33.3	49.1	17.9	
Sex, male %	16.3	14.0	46.0	23.7	<.001
HP %	18.3	7.7	57.0	17.0	<.001
DM %	17.5	9.0	57.5	16.1	<.001
Cre (μmol/l)	69.62±19.68	69.44±15.60	75.73±28.23	68.85±22.14	.137
TCH (mmol/l)	4.39±1.10	4.40±1.00	4.35±1.14	4.40±0.95	.150
TG (mmol/l)	1.62±1.18	1.53±1.15	1.57±1.50	1.63±1.53	.236
LDLC (mmol/l)	2.83±0.78	2.81±0.75	2.81±0.87	2.80±0.72	.132
FT3 (pmol/l)	4.42±0.85	4.51±0.70	4.32±1.03	4.50±0.83	.331
FT4 (pmol/l)	15.56±2.53	15.34±2.63	15.63±2.56	15.47±2.42	.795
TSH (mmol/l)	2.82±3.87	2.88±3.86	2.83±3.97	2.91±3.04	.111
HGB (g/l)	129.22±17.47	130.34±16.70	126.67±18.17	128.63±17.74	.897
ALT (IU/L)	23.44±18.30	22.15±15.89	23.59±20.60	25.12±29.71	.886

The prevalence of cerebral artery stenosis and factors. The prevalence of age, gender, hypertension, and diabetes mellitus were significantly different between the 4 groups. The factors, including Cre, TCH, TG, LDLC, FT3, FT4, TSH, HGB, and ALT had no significant difference between groups. *P* values from the comparison between groups.

ICAS = intracranial atherosclerotic stenosis; ECAS = extracranial atherosclerotic stenosis; ICAS/ECAS = both ICAS and ECAS; HP = hypertension; DM = diabetes mellitus; Cre = creatinine; TCH = total cholesterol; TG = triglyceride; LDLC = low density lipoprotein cholesterol; FT3 = free triiodothyronine; FT4 = free thyroxine; TSH = thyroid-stimulating hormone; HGB = hemoglobin; ALT = alanine aminotransferase.

Table 2

The hepatitis B virus infection patterns in 4 groups.

	ICAS n = 519	ECAS n = 414	ICAS / ECAS n = 1292	Normal n = 847	*P* value
HBV infection patterns %					
Anti-HBc (+) / HBsAg (+)	5.2	8.5	5.7	9.7	.001
Anti-HBc (+) / HBsAg (-)	70.9	67.1	69.0	57.6	<.001
Anti-HBc (-) / HBsAg (+)	0.0	0.2	0.3	0.2	.666
Anti-HBc (-) / HBsAg (-)	23.9	24.2	25.0	32.5	<.001

The anti-HBc-positive/HBsAg-negative pattern was the most common and the anti-HBc-negative/HBsAg-positive pattern was the rarest. The anti-HBc-positive/HBsAg-negative pattern was significantly different between groups. *P* values from the comparison between groups.
anti-HBc = anti-hepatitis B core antigen, ECAS = extracranial atherosclerotic stenosis, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, ICAS / ECAS = both ICAS and ECAS, ICAS = intracranial atherosclerotic stenosis.

hypertension, and diabetes mellitus were significantly different between groups. In ICAS group, the prevalence of aged less than 70 years was about 72.1% (37.6% + 34.5%) and about 50.9% (18% + 32.9%) in ICAS / ECAS group. The prevalence of male, hypertension, and diabetes mellitus in ICAS group were lower than that in ICAS/ECAS group. The prevalence of factors, including creatinine, total cholesterol, triglyceride, low density lipoprotein cholesterol, free triiodothyronine, free thyroxine, thyroid-stimulating hormone, hemoglobin, and alanine aminotransferase, had no significant difference between groups. Infection patterns are illustrated in Table 2. The most common pattern was anti-HBc-positive/HBsAg-negative (n = 2026) which had the highest prevalence in ICAS group. Variables included in multiple logistic regression model were age, gender, hypertension, diabetes mellitus, hyperlipidemia (merged by triglyceride, total cholesterol and low-density lipoprotein), and infection patterns (anti-HBc-positive/HBsAg-positive, anti-HBc-positive/HBsAg-negative, and anti-HBc-negative/HBsAg-negative). The anti-HBc-negative / HBsAg-positive pattern was not included in multiple logistic regression model due to the small sample size.

Multiple logistic regression analyses (Tables 3 and 4) found that individuals less than 60 years of age had a decreased risk of ICAS and/or ECAS than those above 70 years of age. The male had the higher risk of ICAS and/or ECAS than female. Hypertension and diabetes mellitus increased the risk of ICAS and both ICAS and ECAS. Hyperlipidemia had no association with ICAS and/or ECAS. The anti-HBc-positive / HBsAg-negative pattern was associated with the increased risk of ICAS (OR = 1.462, 95% CI = 1.129–1.893, *P* = .004) and not associated with ECAS or ICAS/ECAS. The anti-HBc-positive/HBsAg-positive pattern was not associated with ICAS, ECAS or ICAS/ECAS. The factors, such as gender, hypertension, and diabetes

Table 3

Association between cerebral artery stenosis and factors.

	ICAS n = 519	ECAS n = 413	ICAS / ECAS n = 1288
Age OR (95%CI), *P*			
<60 yrs	0.484 (0.361–0.647) <0.001	0.333 (0.246–0.453) <0.001	0.125 (0.097–0.161) <0.001
60–70 yrs	0.824 (0.608–1.117) 0.212	0.652 (0.476–0.894) 0.008	0.443 (0.345–0.569) <0.001
>70 yrs	Ref.	Ref.	Ref.
Sex, OR (95%CI), *P*			
male	1.341 (1.069–1.683) 0.011	1.567 (1.228–2.000) <0.001	1.970 (1.616–2.402) <0.001
female	Ref.	Ref.	Ref.
HP, OR (95%CI), *P*			
Yes	2.127 (1.677–2.698) <0.001	0.869 (0.657–1.150) 0.326	3.179 (2.588–3.905) <0.001
No	Ref.	Ref.	Ref.
DM, OR (95%CI), *P*			
Yes	1.728 (1.316–2.270) <0.001	1.132 (0.826–1.553) 0.441	2.370 (1.875–2.996) <0.001
No	Ref.	Ref.	Ref.
HL, OR (95%CI), *P*			
Yes	1.066 (0.847–1.341) 0.589	1.123 (0.878–1.437) 0.355	1.205 (0.987–1.471) 0.068
No	Ref.	Ref.	Ref.

The results showed that aged less than 60 years had decreased risk of ICAS and/or ECAS than aged above 70 years. The male had the higher risk of ICAS and/or ECAS than female. Hypertension and diabetes mellitus increased the risk of ICAS and both ICAS and ECAS. Hyperlipidemia had no association with ICAS and/or ECAS. Hyperlipidemia was defined as abnormal plasma level of triglyceride, total cholesterol or low-density lipoprotein. Data are presented as odds ratio (OR) and 95% confidence interval (CI). P values from the comparison between category and reference category in the multiple logistic regression. DM = diabetes mellitus, ECAS = extracranial atherosclerotic stenosis, HL = hyperlipidemia, HP = hypertension, ICAS = intracranial atherosclerotic stenosis, Ref. = reference category.

Table 4

Association between HBV infection and cerebral artery stenosis.

HBV infection patterns OR (95%CI), *P*	ICAS n=519	ECAS n=413	ICAS / ECAS n=1288
Anti-HBc (+)/HBsAg (+)	0.746 (0.456–1.222) 0.245	1.125 (0.706–1.790) 0.621	0.77 (0.517–1.147) 0.198
Anti-HBc (+)/HBsAg (-)	1.462 (1.129–1.893) 0.004	1.339 (1.014–1.768) 0.04	1.149 (0.922–1.431) 0.216
Anti-HBc (-)/HBsAg (-)	Ref.	Ref.	Ref.

The results showed that the anti-HBc (+)/HBsAg (-) pattern was associated with the increased risk of ICAS and not associated with ECAS or ICAS / ECAS. The anti-HBc (+)/HBsAg (+) pattern was not associated with ICAS, ECAS or ICAS / ECAS. Data are presented as odds ratio (OR) and 95% confidence interval (CI). P values from the comparison between category and reference category in the multiple logistic regression. anti-HBc=anti-hepatitis B core antigen, ECAS=extracranial atherosclerotic stenosis, HBsAg=hepatitis B surface antigen, ICAS=intracranial atherosclerotic stenosis, Ref.=reference category, -, seronegativity; +, seropositivity.

mellitus were associated with an increased risk of ICAS and ICAS/ECAS.

4. Discussion

In this study, we found that the anti-HBc-positive/HBsAg-negative pattern was associated with an increased risk of ICAS. Previous studies had not showed the association. The cause might be the employed indicator of HBV infection. The most of previous studies only employed HBsAg as the indicator of HBV infection and showed that HBV infection was associated with a decreased risk of ischemic stroke and not with cardiovascular disease.[25–29] Only 1 case report found that HBV infection might be associated with multiple cerebral arterial stenosis.[30] Due to the detectable window period, the HBsAg would underestimate the prevalence of HBV infection. HBsAg became detectable in several weeks after HBV infection and lasted for several months (as shown in Fig. 1). Meanwhile, anti-HBc gradually reached the detectable level and lasted for 10 to 20 years or more.[31] Therefore, when HBsAg was employed as the only indicator of HBV infection, the anti-HBc-positive/HBsAg-negative pattern would be considered as normal control. Consequently, the results were biased. Anti-HBc has been considered the most sensitive indicator of HBV infection in recent years.[32] In this study, the anti-HBc-positive prevalence was higher than HBsAg-positive in all groups. Therefore, we suggested employing both anti-HBc and HBsAg as indicators of HBV infection.

Furthermore, we found that the anti-HBc-positive/HBsAg-negative pattern was not associated with ECAS or ICAS / ECAS. The cause might be the structural difference between intracranial and extracranial arteries. Intracranial arteries are muscular arteries with few elastic fibers,[33] thinner media and adventitia,[33,34] thicker internal elastic lamina,[33] and no external elastic lamina.[34] Intracranial atherosclerotic plaques were primarily composed of fibrous plaques and fatty streaks.[34,35] Extracranial atherosclerotic plaques were complicated lesions including calcification, hemosiderin deposition, and luminal surface disruption.[36,37] On the other hand, ICAS usually developed with more fibrosis in the early stage contrary to the eroded and ruptured plaques more commonly identified in ECAS.[38] Relative paucity of vasa vasorum in intracranial artery would further facilitate the formation of ICAS.[39] Vasa vasorum constitutes a network of microvessels that supply the vessel wall oxygen and nourishment, and eliminate the wastes. These observations suggested that the development of intracranial and extracranial atherosclerotic plaques may involve different mechanisms. In addition, the Chinese population had obviously different features of intracranial atherosclerotic plaques compared to individuals of European ancestry.[39] Chinese individuals tended to have early onset of intracranial atherosclerotic plaques that developed at a younger age[40–43] and were more likely to develop ICAS,[44–47] whereas individuals of European ancestry were more likely to develop ECAS. Chinese individuals had more universal and more critical patterns of ICAS.[44–47] The

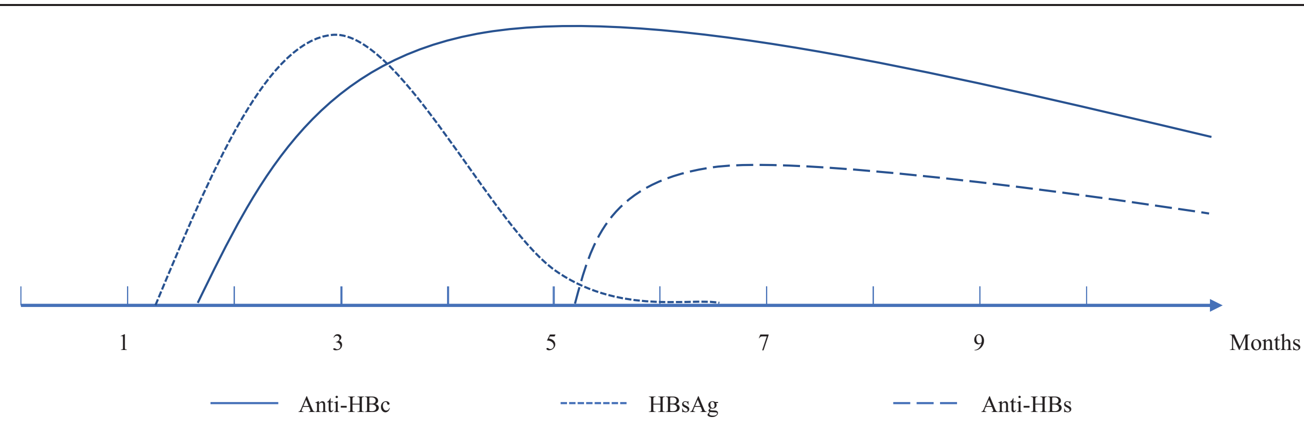

Figure 1. Natural history of HBV infection with anti-HBc, HBsAg and anti-HBs. After HBV infection, HBsAg became detectable in several weeks and lasted for several months. Meanwhile, anti-HBc gradually reached the detectable level and lasted for 10 to 20 years or more. Anti-HBc = anti-hepatitis B core antigen, Anti-HBs = anti-hepatitis B surface antigen, HBsAg = hepatitis B surface antigen.

incidence of advanced stage atherosclerosis, including calcification and intraplaque hemorrhage, were much higher in Chinese than in individuals of European ancestry.[48] Inflammation within atherosclerotic plaques was also different between the Chinese and individuals of European ancestry. Individuals of European ancestry showed a lower macrophage load and, in contrast, more involvement of both macrophages and lymphocytes within atherosclerotic plaques.[48] The difference of atherosclerotic plaques between Chinese and European ancestry also suggested that the cause involved different mechanisms. The duration of HBV infection might affect the location of arterial stenosis. However, the duration of HBV infection was difficult to determine. The subjects with anti-HBc-positive/HBsAg-negative may be infected for several months or several years. We cannot know the duration of HBV infection of subjects but we speculated that ICAS might occur prior to ECAS after HBV infection. The structural difference between intracranial and extracranial artery might be the cause. Moreover, the intracranial artery with small luminal diameter was also more likely to develop arterial stenosis (in this study, arterial stenosis $\geq$50% was defined as stenosis). In this study, the anti-HBc-positive prevalence was far higher than 2 previous studies reported. The 2 studies enrolled the general population and we enrolled in-hospital subjects with suspected cerebral vascular diseases in this study. The previous studies enrolled men aged 21 to 49 years and adults over 20 years old. In this study, we enrolled elderly subjects with mean age of 62. The in-hospital and elderly population had higher anti-HBc-positive prevalence than general and young population. Therefore, our results showed a higher anti-HBc-positive prevalence.

This study was a retrospective design, which limited the power of the findings. All the data were collected through the medical records and selection bias possibly existed. The lack of clinical data may bias these results including the history of HBV vaccine, HBV infection, anti-HBV drug, smoking, alcoholism, antihypertension drug, etc. and results of our study should be further proved by prospective observational data.

Author contributions

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