

## Original Article

**Seroepidemiology of hepatitis B virus infection among Chinese schizophrenia patients**Huijuan Zhu<sup>1\*</sup>, Xingxiang Liu<sup>2\*</sup>, Yong Xue<sup>3\*</sup>, Chong Shen<sup>4</sup>, Yinghui Li<sup>3</sup>, Aili Wang<sup>1</sup>, Yi Ding<sup>5</sup>, Zhi Zheng<sup>3</sup>, Chen Dong<sup>1</sup><sup>1</sup> Department of Epidemiology and Statistics, School of Public Health, Jiangsu Key Laboratory and Translational Medicine for Geriatric Disease, Medical College of Soochow University, Suzhou, Jiangsu, China<sup>2</sup> Huai'an Fourth Hospital, Huai'an, China<sup>3</sup> Huai'an Third Hospital, Huai'an, China<sup>4</sup> Department of Epidemiology and Biostatistics, School of Public Health, Nanjing Medical University, Nanjing, China<sup>5</sup> Suzhou Industrial Park Centers for Disease Control and Prevention, Suzhou, China

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**Abstract**

**Introduction:** This study aimed to analyze the characteristics of HBsAg, HBsAb, coexistence of HBsAg and HBsAb, and the genotypic distribution of HBV in Chinese schizophrenia patients.

**Methodology:** A total of 1,694 schizophrenia patients, 9–85 years of age, were recruited for the present study. HBsAg, HBsAb, and HBV DNA were detected with commercial methods. ALT, AST,  $\gamma$ -GT, TBIL, and IBIL were measured by an automatic biochemistry analyzer. All statistical analyses were performed with SPSS 13.0.

**Results:** The seroprevalence of HBsAg and HBsAb in 1,649 schizophrenia patients was 11.0% and 54.6%, respectively. HBsAb seroprevalence significantly decreased with the duration of the disease ( $p = 0.0009$ ). The lowest seroprevalence of HBsAg was determined in 9.4% of the patients who had had the illness for < 1 year, and then increased to 11.7%, 11.3% and 11.7% in the patients who had had the illness for 1–5 years, 6–10 years and > 10 years. HBsAg and HBsAb coexisted in 69 individuals, which comprised 4.2% of the total subjects, and in 38.1% of the HBsAg-positive patients. Additionally, HBV titers were quantified in 64 HBsAg-positive samples; the highest virus titer was  $6.14 \times 10^8$  copies/mL, while 12 patients had less than 500 copies/mL. Moreover, among 48 HBV strains isolated from 62 HBsAg-positive samples, 33 and 15 strains belonged to genotypes C and B, respectively.

**Conclusion:** Genotypes B and C HBV were the dominant genotypes distributed in schizophrenia patients, and the HBsAb seroprevalence significantly decreased with illness duration. Effective prevention strategies for against HBV transmission are required.

**Key words:** schizophrenia; hepatitis B; HBsAg; genotype.*J Infect Dev Ctries* 2015; 9(5):512–518. doi:10.3855/jidc. 5416

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Copyright © 2015 Zhu *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Introduction**

Hepatitis B virus (HBV) infection is a major public health concern globally. Hepatitis B, caused by HBV, can be complicated by chronic hepatic insufficiency, cirrhosis, hepatocellular carcinoma, and long-term carriage [1]. The World Health Organization estimates that about two billion people worldwide have serologic evidence of past or present HBV infection and that 360 million people are chronically infected and at risk for HBV-related liver disease [2]. Similar to other infectious diseases, the global prevalence of chronic hepatitis B infection varies widely, from < 2% in Western Europe, North

America, and Australia, to 2%–7% in Southern and Eastern Europe, to > 8% in Africa and Asia [3,4].

China is an endemic area of HBV infection, where it is the major cause of chronic liver disease. Since 1992, the national expanded program on immunization with hepatitis B vaccine was instituted in China. After 20 years, more than 200 counties had included the hepatitis B vaccine in their national infant immunization programs. These efforts resulted in a remarkable decrease in hepatitis B virus surface antigen (HBsAg) positivity in the population, especially in children and adolescents [5]. However, an epidemic survey revealed that 7.18% of the Chinese population was HBsAg positive, demonstrating that

HBV infection was still a public health burden in China [5]. According to previous studies, the higher rates of HBV infection could be detected in some specific groups, such as patients undergoing dialysis, parenteral drug users, immunosuppressed patients, and male homosexuals [6-9]. In addition, a higher incidence of hepatitis B has been identified in staff in institutions such as retirement homes and institutions for the intellectually disabled, and in those suffering serious mental illness [10,11].

Previous studies reported that people with severe mental illness are at an increased risk for HBV, hepatitis C virus (HCV), and hepatitis E virus (HEV) infections [12-14]. However, the characteristics of HBV infection among Chinese schizophrenia patients remain unclear. In order to further assist in the prevention and control of such an important public health concern, we conducted the present study to analyze the prevalence of the antibody of HBsAg (HBsAb), HBsAg, and coexistence of HBsAg and HBsAb in 1,649 Chinese schizophrenia patients. The characteristics of genotypic distribution of HBV were also investigated.

## Methodology

### *Study subjects*

Between April 2010 and January 2011, 1,694 schizophrenia patients were recruited by the Department of Psychiatry, Huai'an Third Hospital (Jiangsu, China) for the present study. The median age of the participants was 34 years (range, 9–85 years). The patient's schizophrenia diagnosis was based on the patient's records and was done by two skilled psychiatrists based on International Classification and Diseases 10 (ICD-10; World Health Organization 1992). The present study conformed to the 1975 Declaration of Helsinki. The ethical review committee of Huai'an Third Hospital approved this study. Guidelines set by this committee were strictly followed.

### *Laboratory testing*

The patients or their legal guardians were asked to give their consent to serum sampling and HBsAg and HBsAb testing. Blood samples were obtained by venipuncture and stored at -20°C. All of the samples were tested for HBsAg and HBsAb by enzyme-linked immunosorbent assay (ELISA) with a commercial ELISA kit purchased from Rongsheng Bio, Shanghai, China. Initially reactive samples were tested in duplicate and confirmed as positive only if one of the repeats (two-thirds of the total tests) was positive.

According to the manufacturer's instructions, the sensitivity and specificity is 98% and 97% for the HBsAg detection and 97% and 99% for the HBsAb detection, respectively.

The serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transferase ( $\gamma$ -GT), total bilirubin (TBIL), and indirect bilirubin (IBIL) were measured with commercial reagents. According to the manufacturer's instructions, the reference range of ALT, AST,  $\gamma$ -GT, TBIL, and IBIL was < 40 U/L, < 40 U/L, 8–58 U/L, 5.1–20.1  $\mu$ mol/L, and 1–16  $\mu$ mol/L, respectively.

HBV titer was analyzed by real-time polymerase chain reaction (PCR) with a diagnostic kit for quantification of hepatitis B virus DNA (Kehua Bio-engineering Co, Ltd, Shanghai, China). The range of the quantification of HBV DNA is 500–10<sup>5</sup> copies/mL. In addition, the genotype of HBV was determined using an HBV Genotype Real-Time PCR Kit (Shanghai ZJ Bio-Tech Co, Ltd, Shanghai, China) according to the manufacturer's protocol.

### *Statistical analysis*

Differences in qualitative variables were compared by  $\chi^2$  or trend  $\chi^2$  tests. Unpaired Student's *t*-test was used to test for the differences of continuous variables. All statistical tests were two sided, conducted at a significance level of 0.05. All the statistical analyses were performed with SPSS version 13.0.

## Results

### *Demographic characteristics and laboratory testing*

A total of 1,649 schizophrenia patients were included in the present study. The mean duration of illness was 6 years (range: 3 months–46 years). Among the 1,649 subjects, 760 (46.1%) were male with an average age of 33.19  $\pm$  12.36 years (range, 9–83 years), and 889 (53.9%) were female with an average age of 36.51  $\pm$  13.40 years (range, 15–86 years). Demographic and clinical characteristics are shown in Table 1.

According to the laboratory testing, 227 patients (13.8%) had elevated levels of ALT, ranging from 40.2–315.6 U/L. In addition, increased levels of AST,  $\gamma$ -GT, TBIL, and IBIL were determined in 139, 67, 194, and 96 participants, respectively.

### *Seroprevalence of HBsAb in schizophrenia*

The overall seroprevalence of HBsAb among the schizophrenia patients was 54.6% (901/1,649). It was similar to that observed in the general population in China (50.6%) [5].

**Table 1.** Characteristics of study populations (n = 1,649)

Variables	Schizophrenia patients	
	N	%
Gender		
Male	760	46.1
Female	889	53.9
Age (years)		
9–20	190	11.5
21–30	540	32.8
31–40	377	22.9
41–50	337	20.4
> 50	205	12.4
Duration of illness (years)		
< 1	456	27.7
1–5	566	34.3
6–10	319	19.3
> 10	308	18.7

**Table 2.** Characteristics of HBsAb seroprevalence in Chinese schizophrenia patients

Variables	HBsAb		OR	95% CI	P value
	Positive n (%)	Negative n (%)			
<i>Gender</i>					0.7465
Male	412 (54.2%)	348 (45.8%)	-	-	
Female	489 (55.0%)	400 (45.0%)	1.03	(0.85, 1.25)	
<i>Age (years)</i>					
9–20	128 (67.4%)	62 (32.6%)	-	-	
21–30	304 (56.3%)	236 (43.7%)	0.62	(0.44, 0.88)	
31–40	184 (48.8%)	193 (51.2%)	0.46	(0.32, 0.67)	
41–50	174 (51.6%)	163 (48.4%)	0.52	(0.36, 0.75)	
> 50	111 (54.2%)	94 (45.8%)	0.57	(0.38, 0.86)	
			Trend $\chi^2 = 19.44$ , Z = 2.83, p = 0.0047		
<i>Duration of illness (years)</i>					
< 1	267 (58.6%)	189 (41.4%)	-	-	
1–5	324 (57.2%)	242 (42.8%)	0.95	(0.74, 1.22)	
6–10	163 (51.1%)	156 (48.9%)	0.74	(0.56, 0.99)	
> 10	147 (47.7%)	161 (52.3%)	0.65	(0.48, 0.87)	
			Trend $\chi^2 = 11.92$ , Z = -3.33, p = 0.0009		

As shown in Table 2, HBsAb seroprevalence decreased with the duration of the disease, which was detected in 58.6%, 57.2%, 51.1%, and 47.7% of the patients who had had the illness for < 1 year, 1–5 years, 6–10 years, and > 10 years, respectively ( $\chi^2 = 11.92$ ,  $p = 0.0009$ ). Additionally, the highest HBsAb seropositivity was detected in patients between 9 and 20 years of age, and then decreased with age ( $\chi^2 = 19.44$ ,  $p = 0.0047$ ). However, the prevalence of HBsAb was 54.2% in males and 55.0% in females, which was not statistically different ( $\chi^2 = 1.742$ ,  $p = 0.7465$ ). Among 901 HBsAb-positive patients, elevated levels of ALT, AST,  $\gamma$ -GT, TBIL, and IBIL were detected in 116 (12.9%), 69 (7.7%), 34 (3.8%), 105 (12.0%), and 49 (5.4%) subjects, respectively, similar to levels found in HBsAb-negative patients (14.8%, 9.4%, 4.4%, 11.9%, and 6.3%, respectively).

*Seroprevalence of HBsAg in schizophrenia*

A total of 181/1,649 (11.0%) patients were HBsAg positive, among of which 92 (12.1%) were males and 89 (10.0%) were females ( $p = 0.1751$ ). As shown in Table 3, HBsAg positivity in HBsAb-negative patients was significantly higher than that in HBsAb-positive patients (7.7% vs. 15.0%,  $\chi^2 = 2.12$ ,  $p < 0.0001$ ). The

lowest seroprevalence of HBsAg was determined in 9.4% of the patients who had had the illness for < 1 year, and then increased to 11.7%, 11.3%, and 11.7% of the patients who had had the illness for 1–5 years, 6–10 years, and > 10 years. Additionally, the lowest seroprevalence of HBsAg was detected in patients younger than 20 years of age (8.4%), and the highest HBsAg seropositivity was detected in patients between 31 and 40 years of age (12.2%), which was not statistically different (Table 3,  $p = 0.7950$ ).

Elevated levels of ALT, AST, TBIL, and IBIL were detected in 36 (19.9%), 25 (13.8%), 30 (16.6%), and 17 (9.4%) HBsAg-positive patients, significantly higher than those in the HBsAg-negative patients ( $p = 0.0113$ ,  $p = 0.0057$ ,  $p = 0.0333$ , and  $p = 0.0297$ , respectively). However, no significant difference of  $\gamma$ -GT was observed between the HBsAg-positive patients and HBsAg-negative patients.

*Coexistence of HBsAg and HBsAb*

HBsAg and HBsAb coexisted in 69 individuals, which comprised 4.2% of the total subjects and 38.1% of the HBsAg-positive group. The highest rate of HBsAg and HBsAb coexistence peaked at 21–30 years of age (24/69), while the lowest rate was detected in

**Table 3.** Characteristics of HBsAg seroprevalence in Chinese schizophrenia patients

Variables	HBsAg		OR	95% CI	P value
	Positive n (%)	Negative n (%)			
<i>Gender</i>					
Male	92 (12.1%)	668 (87.9%)	-	-	0.1751
Female	89 (10.0%)	800 (90.0%)	0.81	(0.59, 1.10)	
<i>Age (years)</i>					
9–20	16 (8.4%)	174 (91.6%)	-	-	Trend $\chi^2 = 4.50$ , $Z = -0.26$ , $p = 0.7950$
21–30	63 (11.7%)	477 (88.3%)	1.44	(0.81, 2.55)	
31–40	46 (12.2%)	331 (87.8%)	1.51	(0.83, 2.75)	
41–50	40 (11.9%)	297 (88.1%)	1.47	(0.80, 2.69)	
> 50	16 (7.8%)	189 (92.2%)	0.92	(0.45, 1.90)	
<i>HBsAb</i>					
+	69 (7.7%)	832 (92.3%)	-	-	<.0001
-	112 (15.0%)	636 (85.0%)	2.12	(1.55, 2.92)	
<i>Duration of illness (years)</i>					
< 1	43 (9.4%)	413 (90.6%)	-	-	Trend $\chi^2 = 1.58$ , $Z = 0.92$ , $p = 0.3578$
1–5	66 (11.7%)	500 (88.3%)	1.27	(0.85, 1.90)	
6–10	36 (11.3%)	283 (88.7%)	1.22	(0.77, 1.95)	
> 10	36 (11.7%)	272 (88.3%)	1.27	(0.80, 2.03)	

**Table 4.** Coexistence of HBsAg and HBsAb in Chinese schizophrenia patients

Variable	HBsAg(+)/HBsAb(+)	HBsAg(+)/HBsAb(-)	OR	95% CI	P value
<i>Gender</i>					0.0631
Male	29 (31.5%)	63 (68.5%)	-	-	
Female	40 (44.9%)	49 (55.1%)	1.77	(0.97, 3.25)	
<i>Age (years)</i>					
9–20	6 (37.5%)	10 (62.5%)	-	-	
21–30	24 (38.1%)	39 (61.9%)	1.03	(0.33, 3.18)	
31–40	18 (39.1%)	28 (60.9%)	1.07	(0.33, 3.46)	
41–50	14 (35.0%)	26 (65.0%)	0.90	(0.27, 2.99)	
> 50	7 (43.8%)	9 (56.2%)	1.30	(0.32, 5.33)	
Trend $\chi^2 = 0.40$ , $Z = 0.10$ , $p = 0.9166$					
<i>Duration of illness (years)</i>					
< 1	14 (32.6%)	29 (67.4%)	-	-	
1–5	32 (48.5%)	34 (51.5%)	1.95	(0.88, 4.34)	
6–10	12 (33.3%)	24 (66.7%)	1.04	(0.40, 2.66)	
> 10	11 (30.6%)	25 (69.4%)	0.91	(0.35, 2.37)	
Trend $\chi^2 = 4.79$ , $Z = -0.70$ , $p = 0.4862$					

the patients older than 50 years of age (7/69). Age, gender, and duration of illness were not significantly associated with the coexistence of HBsAg and HBsAb. Moreover, no significant difference was observed in the serum levels of ALT, AST,  $\gamma$ -GT, DBIL, and IBIL between HBsAg(+)/HBsAb(+) patients and HBsAg(+)/HBsAb(-) patients.

#### *HBV titers determination and HBV genotyping*

The virus titers were quantified in 103 of 112 HBsAg(+)/HBsAb(-) patients with sufficient samples by a commercial kit. Among 103 samples, 90 samples had more than 4.0 of the signal cut off value (SCO), and the virus titers were quantified in 62 of 90 samples. The highest virus titer was  $6.14 \times 10^8$  copies/mL, while 12 patients had less than 500 copies/mL of virus titer. Furthermore, 46 samples with the virus titers greater than  $4.42 \times 10^2$  copies/mL were successfully genotyped; 33 samples were determined to belong to genotype C and 13 samples belonged to genotype B.

In addition, 37 HBsAg(+)/HBsAb(+) patients with sufficient samples were also used for virus detection. As the results show, only two genotype B samples were determined with  $2.08 \times 10^3$  copies/mL and  $3.16 \times 10^3$  copies/mL of virus titer, respectively. No virus was isolated in the other samples.

#### **Discussion**

Until now, the knowledge about HBV infection in some special populations such as patients with intellectual disability or serious mental illness was not well defined in China. In the present study, we reported that the overall seroprevalence of HBsAg and

HBsAb in schizophrenia patients was 11.0% and 54.6%, respectively. Moreover, HBsAb seroprevalence significantly decreased with the duration of the disease. Compared to the 9.4% of HBsAg seropositivity in patients who had had the illness for less than one year, about 11.5% patients who had had the illness for more than one year were HBsAg positive. In addition, our results indicate that genotype B and C HBV are the dominant genotypes distributed in Chinese schizophrenia patients. Similar to previous studies of the general population [15], HBsAg positivity in the HBsAb-negative patients was significantly higher than that in the HBsAb-positive patients. However, unlike in the previous studies of the general population [16], no significant relationships were observed between HBsAg prevalence and age, gender, and the duration of the disease.

Previous results showed that the rates of exposure to HBV and HCV infection among psychiatric patients were significantly higher than the estimated general population rates [17-21]. A study by Dinwiddie *et al.* reported that 27.8% patients had HBsAb and 8.5% had HCV RNA of 1,556 psychiatric patients [20]. In Japan, Sawayama *et al.* studied 196 neuropsychiatric patients and found that 10.2% of the patients were HCV antibody positive compared to 1.5% of controls and 44.4% were HBcAb positive compared to 20.5% of controls [21]. In our study, the overall prevalence of HBsAg was 11.0% in schizophrenia patients. It was higher than that observed in the general population in China (7.18%). Despite differences in serologic testing parameters, these results suggested that patients with schizophrenia are at increased risk of HBV exposure. The plausible explanation for the higher

seroprevalence of HBsAg in schizophrenia patients could be these patients' poor judgment and lack of self-care, which may lead to relatively greater probability of infection when exposed to risk factors. Therefore, routine screening for HBV in schizophrenia patients is advocated, and HBV as well as hepatitis A immunization is recommended.

In this study, 38.1% of HBsAg-positive patients showed coexistence of HBsAb, which was significantly higher than previously reported results of 3%–10% [22-26]. The coexistence of HBsAg and anti-HBs was regarded simply as superinfection with a different subtype of HBV [27]. Some studies have suggested that the coexistence of HBsAg and HBsAb is associated with high replicative activity of HBV and mutations in the viral surface gene, which may alter the antigenicity of HBsAg and lead to subsequent failure of HBsAb neutralization [22,23,28]. Additionally, some studies reported that coexistence of HBsAg and HBsAb could be detected in immunosuppressive patients with organ transplantation, HIV infection, and prolonged corticosteroid therapy [29-31]. Considering the significantly higher prevalence of the coexistence of HBsAg and anti-HBs among HBsAg-positive schizophrenia patients, this group may be at high risk of severe disease and should be studied in the future.

In order to further understand the molecular characteristics of HBV infection in schizophrenia patients, the genotypic distribution of HBV was analyzed with a commercial HBV genotyping kit in the present study. As the results show, genotypes B and C HBV were determined, while genotypes A, D, E, F, G, and H were not. HBV genotypes have different biological and epidemiological behavior [32]. Usually, genotype C virus is associated with more severe liver diseases than is genotype B [33]. In addition, patients with HBV genotypes C and D have lower response rates to treatment with IFN- $\alpha$  compared to those with genotypes A and B [34]. Among the 48 HBV strains isolated from the present study, 33 strains belonged to genotype C. Since genotype C HBV is very closely associated with severity, development of severe liver diseases, and antiviral therapy, the larger numbers of the schizophrenia patients and long-time follow-up studies are required.

## Conclusions

The present results revealed that the seroprevalence of HBsAg in Chinese schizophrenia patients was 11.0%, and that 38.1% HBsAg-positive

patients also had HBsAb. In addition, genotypes B and C HBV were determined to be the dominant genotypes distributed in Chinese schizophrenia patients. Considering that HBsAb seroprevalence significantly decreased with the duration of the disease, our findings suggest that regular screening and effective prevention strategies are required for reducing HBV transmission in schizophrenia patients, although the trends of infection seem to have improved in China.

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