MEDICAL SCIENCE MONITOR

PUBLIC HEALTH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 1955-1959
DOI: 10.12659/MSM.893691

Received: 2015.01.26
Accepted: 2015.02.16
Published: 2015.07.06

Hepatitis B Virus Infection Rate and Distribution in Chinese Systemic Lupus Erythematosus Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BC 1 Xumin Chen
CD 2 Lingyao Hong
DE 1 Wang Zhang
EF 1 Meng Yuan
FG 1 Qiongqiong Yang
DF 1 Haiping Mao
ABCD 1 Wei Chen
CG 1 Xueqing Yu

1 Department of Nephrology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P.R. China
2 Epidemiology Research Unit and Clinical Trails Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P.R. China

Corresponding Author: Wei Chen, e-mail: guangzhouweichen@163.com

Source of support: This work was supported by grants from the National Key Technology Research and Development Program of the Ministry of Science and Technology of China (No. 2011BAI10B05) the 5010 Clinical Research Program of Sun Yat-sen University (No. 2007007) to Dr Xueqing Yu, National Natural Science Foundation of China (No. 81470952), Outstanding Young Scholars Foundation of The First Affiliated Hospital, Sun Yat-sen University to Dr Wei Chen

Background: The aim of this study was to investigate the hepatitis B virus (HBV) infection rate in systemic lupus erythematosus (SLE) patients in China, and to determine the age and sex distribution.

Material/Methods: A total of 3981 SLE patients diagnosed in The First Affiliated Hospital of Sun Yat-sen University from January 1996 to December 2011 were retrospectively investigated for evaluation of the HBV infection rate. The HBV infection rate and the positive rate of hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) were standardized to national census data in 2000 and compared with the prevalence found in the 2006 national survey.

Results: The age and sex standardized HBV infection rate in Chinese SLE patients was 3.3%. The age and sex standardized positive rate of HBsAb and HBcAb were 58.1% and 26.1%, respectively. As compared with the prevalence from the 2006 national survey, the HBV infection rate and the positive rate of HBcAb were lower and the positive rate of HBsAb was higher in SLE patients aged 15–49 years old compared to peers in the general population. There was no difference in HBV infection rate between males and females (4.2% *vs.* 2.8%, p=0.088) in SLE patients.

Conclusions: The HBV infection rate was relatively lower in SLE patients compared with the general population, but there was no difference in pediatric patients or patients aged above 50 years old. Unlike in the general population, the HBV infection rate had no statistical differences between males and females in SLE patients.

MeSH Keywords: Age • Hepatitis B Antibodies • Systemic Lupus Erythematosus

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893691

1705 3 — 24

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

The hepatitis B virus (HBV) infection rate in systemic lupus erythematosus (SLE) patients has been investigated in various studies. Some earlier studies found a higher prevalence of hepatitis B surface antigen (HBsAg) in SLE patients [1–3], while others found a lower HBV infection rate in SLE patients [4–7]. Thus, it is deduced that HBV infection plays a protective role in the development of SLE.

HBV infection and SLE are age- and sex-specific. According to the Chinese national survey, the prevalence of HBV infection was higher in males than in females, and the highest prevalence before 1992 was in children [8]. To control HBV infection, the national government implemented infant vaccination with a hepatitis B vaccine program since then. HBV infection was most prevalent in people aged 20–30 years old, as reported by the 2006 national survey [9]. SLE is commonly seen in women of reproductive age. The female-to-male ratio was 10.1, the mean age at disease onset was 29.2 years old with confirmed diagnosis 1 year later at the age of 30.3 years old, according to multicenter research carried out by the Chinese SLE Treatment and Research Group [10].

We therefore conducted this cross-sectional study to investigate the infection rate of HBV in SLE patients in China, and to determine the age and sex distribution of HBV infection in Chinese SLE patients.

Material and Methods

Patients

This is a cross-sectional study carried out in The First Affiliated Hospital of Sun Yat-sen University. We enrolled the patients who met these inclusion criteria: hospitalized patients diagnosed as SLE according to the American College of Rheumatology classification criteria for SLE revised in 1982 [11] or 1997 [12] from January 1, 1996 to December 31, 2011. The exclusion criteria were: (1) patients who had malignant diseases or drug-induced SLE; and (2) patients who did not demonstrate HBsAg.

Definitions of HBV infection

HBV infection was defined as positive for serological HBsAg according to the Guidelines of the National Medical Association Conference on Management of Chronic Hepatitis B [13]. HBsAg, hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) were detected by counter-immunoelectrophoresis on agarose gel from 1996 to 1997, and by enzyme-linked immunosorbent assay (ELISA) or chemiluminescence after 1997.

Ethics

This study was independently designed by the authors, conducted in compliance with the 1975 Declaration of Helsinki, and was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University.

Statistical analysis

The categorical data were presented as numbers (in percent). The chi-square test or Fisher's exact test was used to analyze the categorical variables. The HBV infection rate in SLE patients was compared with the prevalence in 2006 national survey [9], standardized to national census data in 2000. We compared 95% confidence intervals (95% CI) for the HBV infection rate of each variable; 95% CI which did not overlap were considered as statistically significant. Statistical analysis was performed using SPSS version 16.0 (SPSS for Windows; SPSS, Chicago, IL, USA). Statistical significance was considered as $p<0.05$.

Results

The infection rate of HBV

There were 4808 patients diagnosed as SLE in The First Affiliated Hospital of Sun Yat-sen University from January 1, 1996 to December 31, 2011, we excluded 803 patients who were not checked for serological HBsAg, 23 patients who were diagnosed with malignancy, and 1 patient who was diagnosed with drug-induced lupus. A total of 3981 patients were finally included in the analysis of HBV infection rate. The female-to-male ratio was 6.0 (3410/571) and the mean age was 31.1±14.5 years old in the investigated period. In the study population, 10.6% of patients were aged 0–14 years old, 77.6% were aged 15–49 years old, and 11.8% were aged 50 or older.

A total of 122 patients were positive for HBsAg at the first investigation. Thus, the HBV infection rate in this SLE cohort was 3.1%. Among them, the 118 patients who were tested for hepatitis B e antigen (HBeAg), the positive rate of HBeAg was 38.5% (45/118). There were 3809 patients with detected HBsAb and HBcAb in our SLE cohort. The positive rate of HBsAb was 60.1% (2289/3809), and for HBcAb was 25.8% (981/3809).

The age and sex distribution of HBV serological markers

Because most of the SLE patients were women of reproductive age, the HBV infection rate was standardized by sex and age. As compared to the prevalence of HBV infection reported by the national survey in 2006, the sex-standardized HBV infection rate in adults aged 15–49 years old with SLE was lower, but there was no difference in children or adults older than 50

This work is licensed under a Creative Commons
Attribution-NonCommercial-NoDerivs 3.0 Unported License

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Age distribution of HBsAg in SLE patients.

Age group, yrs	No. of SLE (total)	No. of SLE (male/female)	HBV infection rate in SLE, %			Sex-standardized HBV infection rate in SLE, % (95% CI)		Sex-standardized prevalence of HBsAg found in 2006 national survey, % (95% CI)[9]	
			Male	Female	p				
0–14	421	80/341	5.0	1.8	0.192	3.5	(0.9–6.1)	1.9	(1.8–2.0)
15–19	499	85/414	0.0	2.7	0.265	1.3	(0.5–2.0)*	5.4	(4.4–6.4)
20–29	1165	125/1040	4.8	2.2	0.147	3.5	(1.6–5.4)*	10.5	(8.2–12.7)
30–39	900	92/808	4.3	2.8	0.633	3.6	(1.4–5.8)*	8.6	(7.5–9.6)
40–49	527	70/457	2.9	3.9	0.916	3.4	(1.2–5.6)*	8.5	(7.4–9.6)
50–59	285	59/226	10.2	4.9	0.126	8.2	(3.8–12.6)	8.9	(7.1–10.7)
60–100	184	60/124	3.3	4.8	0.933	4.1	(1.2–7.0)	–	
Total	**3981**	**571/3410**	**4.2**	**2.8**	**0.088**	**3.7**	**(2.8–4.7)***	**7.2**	**(6.7–7.7)**

* HBV infection rate was significantly lower than that in the general population.

Table 2. Age distribution of HBcAb in SLE patients.

Age group, yrs	No. of SLE (total)	No. of SLE (male/female)	HBcAb positive rate in SLE, %			Sex-standardized HBcAb positive rate in SLE, % (95% CI)		Sex-standardized prevalence of HBcAb found in 2006 national survey, % (95% CI)[9]	
			Male	Female	p				
0–14	401	73/328	11.0	10.7	0.943	10.8	(6.7–14.9)	10.7	(9.7–11.7)**
15–19	472	79/393	10.1	18.7	0.085	14.0	(10.1–17.9)*	25.0	(22.3–27.7)
20–29	1115	123/992	22.8	25.9	0.451	24.3	(20.3–28.3)*	38.9	(36.6–41.3)
30–39	859	90/769	28.9	26.9	0.691	27.9	(22.3–33.0)*	41.8	(39.3–44.3)
40–49	513	69/444	33.3	32.4	0.882	32.9	(26.8–39.0)*	45.1	(42.7–47.5)
50–59	272	54/218	46.3	39.4	0.359	43.0	(35.4–50.6)	50.0	(46.6–53.4)
60–100	177	57/120	43.9	31.7	0.113	37.6	(30.0–45.2)	–	
Total	**3809**	**545/3264**	**26.2**	**25.7**	**0.780**	**26.1**	**(24.0–28.1)***	**34.1**	**(32.8–35.5)**

* HBcAb positive rate was significantly lower than that in the general population; ** HBcAb positive rate of the general population aged 10–14 yrs.

years old. Although the prevalence of HBV infection was higher in males than females in the general population (8.6% *vs.* 5.7%, p<0.01), there was no difference between males and females among different age groups in the SLE population. The HBV infection rate in SLE patients standardized by age and sex was 3.3%, lower than that in the general population (Table 1).

Similarly, the sex-standardized HBcAb positive rate was lower in adults aged 15–49 years old with SLE than in general population peers, but there was no difference in children and the elderly. And the positive rate of HBcAb was approximately the same between males and females (26.2% *vs.* 25.7%, p=0.780). The HBcAb positive rate in SLE patients standardized by age and sex was 26.1%, lower than that in the general population (Table 2). Conversely, the HBsAb positive rate in SLE patients standardized by age and sex was 58.1%, higher than that in the general population, especially in patients aged 20–39 years old. The positive rate was higher in females than males (60.8% *vs.* 56.1%, p=0.042) (Table 3).

Discussion

In the present study, the HBV infection rate standardized by age and sex in SLE patients was 3.3%, which was much lower than the HBV infection prevalence of 7.18% to 9.75% obtained in the general population according to the Chinese national

This work is licensed under a Creative Commons
Attribution-NonCommercial-NoDerivs 3.0 Unported License

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 3. Age distribution of HBsAb in SLE patients.

Age group, yrs	No. of SLE (total)	No. of SLE (male/female)	HBsAb positive rate in SLE, %			Sex-standardized HBsAb positive rate in SLE, % (95% CI)		Sex-standardized prevalence of HBsAb found in 2006 national survey, % (95% CI)[9]	
			Male	Female	p				
0–14	401	73/328	65.9	63.1	0.671	64.5	(58.3–70.8)	57.5	(55.4–59.5)**
15–19	472	79/393	51.9	66.4	0.014	59.0	(52.9–65.1)	50.3	(44.4–56.2)
20–29	1115	123/992	57.7	65.1	0.106	61.3	(56.7–66.0)*	45.6	(42.9–48.4)
30–39	859	90/769	56.7	58.6	0.718	57.6	(52.1–63.2)*	46.4	(44.1–48.7)
40–49	513	69/444	53.6	52,7	0.887	53.2	(46.7–50.0)	46.0	(43.5–48.5)
50–59	272	54/218	51,9	56,4	0.545	54.1	(46.5–61.7)	50.3	(47.2–53.5)
60–100	177	57/120	52.6	50.8	0.823	51.7	(43.9–59.5)	–	
Total	**3809**	**545/3264**	**56.1**	**60.8**	**0.042**	**58.1**	**(55.7–60.4)***	**50.1**	**(48.8–51.3)**

* HBsAb positive rate was significantly higher than that in the general population; ** HBsAb positive rate of the general population aged 10–14 yrs.

survey [8,9]. Various studies mentioned the HBV infection rates in patients with SLE. Earlier studies indicated that the positive rates of HBsAg ranged from 25% to 70% in patients with SLE, and were higher than that in normal controls [1–3]. From the 1980s to present, studies reported the positive rates of HBsAg ranged from 1% to 3.5% in patients with SLE, which were lower or equal to that in normal controls [4–7]. Our present HBV infection rate was similar to the rate reported in Taiwan [6]. The discrepancy among the studies might be due to different methods of detecting HBsAg in different races, and the different endemic situations of HBV infection around the world. Patients with HBV infection had higher concentrations of testosterone [14], while SLE patients had lower testosterone levels, which partially explained the lower HBV infection rate in SLE patients. Based on the lower HBV infection rate in SLE patients, it was deduced that HBV infection played a protective role in the development of SLE. HBV induced host immunological tolerance by increasing the proportion of regulatory T cells (Tregs) in CD4 T cells in peripheral blood and maturation arrest of myeloid dendritic cells [15–17], all of which could prevent the occurrence and development of SLE. Another conceivable explanation for the lower HBV infection rate was that SLE protected subjects from HBV infection, probably due to high levels of INF-α [18,19]. The HBcAb positive rate was also lower in SLE patients in our present study, consistent with the results of a study based on a northwestern Colombian population [20]. The presence of HBcAb in serum implies previous or current infection with HBV. The lower HBcAb positive rate further confirms that HBV infection plays a protective role in the development of SLE and vice versa. Conversely, the positive rate of HBsAb was higher in SLE patients. Both HBsAb and HBcAb are immunoglobulin secreted by antigen-specific plasma cells, but are directed against different epitopes. Compared with HBcAb, HBsAb appears later, disappears earlier, and has lower titers in the host immune response to HBV. Unlike HBcAb, HBsAb is a neutralizing antibody that can clear HBV from the host. Thus, despite the 2 reasons mentioned above, the lower HBV infection rate might be attributed to the higher positive rate of HBsAb in SLE patients. HBsAb was detectable after vaccination or during convalescent phase. Hepatitis B vaccination was reported to be associated with increased risk of SLE [21–23]. It is speculated that HBV could induce an overly strong immune response in SLE patients, thus the virus is cleared thoroughly from SLE patients. However, it is still unknown whether the anti-virus immune response is antigen-specific or is just caused by high levels of INF-α.

In the general population, the prevalence of HBV infection is lower in females than males (5.7% *vs.* 8.6%) [9]. However, in our cohort of SLE patients, there was no difference in HBV infection rate between males and females. We might have found a significant difference in a larger sample. The present study showed that although HBV infection was rare in patients with SLE, the infection rate in children was as high as that in general population peers [9]. Compared with adult-onset SLE, pediatric SLE (pSLE) is characterized by more organ involvement and worse prognosis, but the reasons are still unknown. Intricacies of the developing immune system may partly account for the more severe phenotype in pSLE [24]. The difference in HBV infection in adult-onset SLE and pSLE is merely a small part of the difference in immune pathogenesis between the 2 groups.

Conclusions

We found a lower HBV infection rate and HBcAb positive rate in SLE patients aged 15–49 years old compared with the general

This work is licensed under a Creative Commons
Attribution-NonCommercial-NoDerivs 3.0 Unported License

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

population. Thus, we deduced that HBV infection protected subjects from SLE and vice versa. Unlike in the general population, there were no difference in HBV infection rate between males and females. There were several limitations of this study. First, this was a cross-sectional study, and we cannot know whether the discrepancy in HBV infection rate among different age groups was due to different immune status of pSLE and late-onset SLE or if it was just a coincidence. Second, the HBV infection rate was compared with data from the national survey, not an exactly matched sample of the general population, which caused bias.

References:

1. Ziegenfuss JJ, Byrne EB, Stoloff IL, Burka ER: Australia antigen in systemic lupus erythematosus. Lancet, 1972; 1(7754): 800
2. Alarcon-Segovia D, Fishbein E: Australia antigen in systemic lupus. N Engl J Med, 1971; 284(8): 448
3. Alarcon-Segovia D, Fishbein E, Diaz-Jouanen E: Presence of hepatitis-associated antigen in systemic lupus erythematosus. Clin Exp Immunol, 1972; 12: 9–19
4. Abu-Shakra M, El-Sana S, Margalith M et al: Hepatitis B and C viruses serology in patients with SLE. Lupus, 1997; 6: 543–44
5. Lu CL, Tsai ST, Chan CY et al: Hepatitis B infection and changes in interferon-alpha and -gamma production in patients with systemic lupus erythematosus in Taiwan. J Gastroenterol Hepatol, 1997; 12: 272–76
6. Zhao J, Qiu M, Li M et al: Low prevalence of hepatitis B virus infection in patients with systemic lupus erythematosus in southern China. Rheumatol Int, 2010; 30: 1565–70
7. Bonafede RP, van Staden M, Klemp P: Hepatitis B virus infection and liver function in patients with systemic lupus erythematosus. J Rheumatol, 1986; 13: 1050–52
8. Xia GL, Liu CB, Cao HL et al: Prevalence of hepatitis B and C virus infections in the general Chinese population. Results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D, and E virus infections in China. Int Hepatol Comm, 1992; 5: 62–73
9. Liang X, Bi S, Yang W et al: Epidemiological serosurvey of hepatitis B in China – declining HBV prevalence due to hepatitis B vaccination. Vaccine, 2009; 27: 6550–57
10. Li M, Zhang W, Leng X et al: Chinese SLE Treatment and Research group (CSTAR) registry: I. Major clinical characteristics of Chinese patients with systemic lupus erythematosus. Lupus, 2013; 22: 1192–99
11. Tan EM, Cohen AS, Fries JF et al: The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum, 1982; 25: 1271–77
12. Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum, 1997; 40: 1725
13. Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association: [The guideline of prevention and treatment for chronic hepatitis B (2010 version)]. Zhonghua Liu Xing Bing Xue Za Zhi, 2011; 32: 405–15 [in Chinese]
14. James WH: A potential explanation of the reported low prevalence of hepatitis B virus infection in patients with systemic lupus erythematosus. Rheumatol Int, 2012; 32: 835
15. Wang Y, Chen K, Wu Z et al: Immunizations with hepatitis B viral antigens and a TLR7/8 agonist adjuvant induce antigen-specific immune responses in HBV-transgenic mice. Int J Infect Dis, 2014; 29: 31–36
16. Lin C, Zou H, Wang S: Hepatitis B e antigen seroconversion is related with the function of dendritic cells in chronic hepatitis B virus infection. Gastroenterol Res Pract, 2014; 2014: 413952
17. Xu L, Yin W, Sun R et al: Liver type I regulatory T cells suppress germinal center formation in HBV-tolerant mice. Proc Natl Acad Sci USA, 2013; 110: 16993–98
18. Bengtsson AA, Sturfelt G, Truedsson L et al: Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies. Lupus, 2000; 9: 664–71
19. Dall'Era MC, Cardarelli PM, Preston BT et al: Type I interferon correlates with serological and clinical manifestations of SLE. Ann Rheum Dis, 2005; 64: 1692–97
20. Ram M, Anaya JM, Barzilai O et al: The putative protective role of hepatitis B virus (HBV) infection from autoimmune disorders. Autoimmun Rev, 2008; 7: 621–25
21. Finielz P, Lam-Kam-Sang LF, Guiserix J: Systemic lupus erythematosus and thrombocytopenic purpura in two members of the same family following hepatitis B vaccine. Nephrol Dial Transplant, 1998; 13: 2420–21
22. Santoro D, Stella M, Montalto G, Castellino S: Lupus nephritis after hepatitis B vaccination: an uncommon complication. Clin Nephrol, 2007; 67: 61–63
23. Agmon-Levin N, Arango MT, Kivity S et al: Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model. J Autoimmun, 2014; 54: 21–32
24. Ardoin SP, Schanberg LE: Paediatric rheumatic disease: lessons from SLE: children are not little adults. Nat Rev Rheumatol, 2012; 8: 444–45

This work is licensed under a Creative Commons
Attribution-NonCommercial-NoDerivs 3.0 Unported License

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]