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ORIGINAL ARTICLE

Prevalence and co-infection of schistosomiasis/hepatitis B among rural populations in endemic areas in Hubei, China

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Background: Both hepatitis B virus (HBV) infection and schistosomiasis are important public health problems in China. Concurrent infection between HBV and schistosomiasis is often observed in areas where schistosomiasis is endemic. The aim of this study was to determine the prevalence of schistosomiasis and HBV in schistosomiasis-affected areas, to explore whether schistosomiasis patients are more susceptible to HBV and to determine if the prevalence of HBV in high-endemic areas of schistosomiasis is higher than in low-endemic areas.

Methods: A total of 6526 participants from 13 villages in Hubei province were included in a cross-sectional study and blood samples were collected and examined. Qualitative variables were compared between groups using Pearson's chi-squared test or Fisher's exact test as appropriate.

Results: Of the 6526 participants, the overall prevalence was 8.27% for schistosomiasis and 2.67% for HBV. The prevalence of hepatitis B among participants who were *Schistosoma* antibody positive (25.37%) was higher than the prevalence in participants who were *Schistosoma* antibody negative (0.62%; χ^2=1169.358, p<0.001, odds ratio 54.659). We also observed that there was no difference in the prevalence of hepatitis B between males and females in areas where schistosomiasis was endemic (χ^2=1.827, p=0.177), but the prevalence of hepatitis B in middle-aged people was higher than in other age groups (χ^2=47.877, p<0.001).

Conclusions: There was an association between schistosomiasis and HBV infection. However, more work is needed to find the causal relationship between schistosomiasis and HBV infection.

Keywords: co-infection, hepatitis B, hepatitis B virus, schistosomiasis

Introduction

Hepatitis B virus (HBV) infection remains a major public health problem worldwide, with high levels of morbidity and mortality, and often leads to chronic liver disease, liver cirrhosis and liver cancer.[1] It was estimated that about 248 million individuals worldwide were positive for hepatitis B surface antigen (HBsAg) in 2010.[2] The economic burden of HBV infection is substantial due to the high morbidity and mortality associated with end-stage liver disease, cirrhosis and hepatocellular carcinoma.[3] Recent global disease burden studies have shown that HBV infection is the 10th leading cause of death worldwide, with approximately 786 000 cases of HBV-related deaths each year.[4] Positive strategies and effective actions have significantly reduced the prevalence of HBV in China, with HBsAg prevalence declining from 9.75% in 1992 to 7.18% in 2006,[5,6] and prevalence among children <15 y of age is <3%.[5,7] However, older age groups, especially adults, have not received sufficient attention. Coupled with a large population base, HBV remains an important public health issue in China.

Schistosomiasis remains one of the most important parasitic diseases in tropical and subtropical regions and a major public health problem.[8] It is a complex parasitic disease caused by trematode flukes of the genus *Schistosoma*. The spread of schistosomiasis occurs only in places where the freshwater snail vector is present and where there is contact between the population and infested water.[9] Despite the marked reduction in transmission observed over the last decade, this infection affects at least 230 million people in 76 countries.[10] The main species of schistosomiasis infecting humans are *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum*. In China, the main species is *S. japonicum*. Documented evidence indicates that *S. japonicum* has been endemic in China for a long time.[11] In China, schistosomiasis is mainly endemic in lake

and marshland areas (Hubei, Hunan, Jiangxi, Anhui and Jiangsu provinces) and in hilly and mountainous regions (Sichuan and Yunnan provinces).[12] Hubei province is a highly endemic area of schistosomiasis in China, located in the middle reaches of the Yangtze River. In addition to being an endemic area, it is one of the regions with the highest transmission rate of schistosomiasis in China.[13] Gongan county is located in the Jianghan Plain, with a dense river network and numerous lakes. It is an important schistosomiasis endemic area in Hubei province.

The two diseases, schistosomiasis and HBV infection, both lead to chronic liver inflammation.[14] Co-infection with HBV and schistosomiasis is often observed in areas where schistosomiasis is endemic and can cause chronic liver inflammation.[15] We also observed this situation in Gongan county. A review by Abruzzi et al.,[16] describing studies conducted on general, largely asymptomatic populations, tends to support the view that having schistosomiasis does not necessarily predispose one to becoming co-infected with HBV or hepatitis C virus (HCV). Rather, the probability of becoming co-infected seems most closely associated with modes of transmission for either HBV or HCV in schistosome-endemic areas, such as the past use of parenteral antischistosomal therapy or frequent blood transfusions. Gasim et al.[17] believe that concurrent infections of HBV and schistosomiasis are often associated with countries where schistosomiasis is endemic and may lead to chronic liver inflammation. Therefore we hypothesized that schistosomiasis infection is a risk factor for HBV infection, which may increase the incidence of hepatitis B, and the prevalence of HBV in the high-endemic area of schistosomiasis is higher than in low-endemic areas. In 2018 we conducted a survey about schistosomiasis and HBV in Gongan county, Hubei province. The aim of this study was to determine the prevalence of schistosomiasis and HBV in schistosomiasis-affected areas of Hubei province and explore the association between schistosomiasis and HBV.

Materials and methods

Study area and population

Gongan county is a typical schistosomiasis endemic area in Hubei province. A cross-sectional study was conducted from January to May 2018 in 13 villages randomly selected in Gongan county. These are agricultural areas, based on crop cultivation and fish, shrimp and poultry farming, that depend on river water, lake water and groundwater for irrigation and domestic water use. We collected information on the status of schistosomiasis and HBV infection at the time. Approximately 400 villagers were selected from each village to participate in the study using a simple random sampling method. A total of 6526 participants between the ages of 4 and 91 y were included to assess the prevalence of schistosomiasis and HBV in the area.

Collection and examination of samples

A total of 6526 participants were included and blood samples were collected and examined. Personal and behavioural information from participants was collected in a questionnaire, including age, sex, address and attitude towards water contact patterns. All the participants attending during the study period that had been tested for HVB and screened for schistosomiasis were included in the analysis. To investigate *Schistosoma* parasitization, specific *Schistosoma* antibody testing was carried out via an indirect haemagglutination assay [IHA] for detection of *Schistosoma japonica* (Anji Pharma, Hefei, China). To study HBV infection status, the determination of HBsAg in serum was carried out with an HBsAg diagnostic kit (enzyme-linked immunosorbent assay; Shanghai Kehua Bioengineering, Shanghai, China).

Statistical analysis

The data were statistically analysed using SPSS version 21.0 (IBM, Armonk, NY, USA). Proportions were used to describe the sociodemographic characteristics of the participants. Qualitative variables were compared between groups using Pearson's chi-squared or Fisher's exact test as appropriate. The positive rates of *Schistosoma* antibodies were compared between participants of different ages and genders, as well as the positive rates of HBsAg. To explore the association between schistosomiasis and HBV we compared the difference in HBsAg-positive rates between schistosomiasis-positive and negative participants. In addition, according to the *Schistosoma* antibody–positive rate, we divided the 13 villages into high-endemic areas and low-endemic areas of schistosomiasis and compared the differences in seroprevalence of HBsAg between the high- and low-endemic areas. The differences were considered to be significant when the p-value was <0.05.

Ethical considerations

Before the study we informed all participants about the study design and obtained a signed informed consent form from each. The informed consent form of minors was signed by the guardian. The protocol was approved by the Ethics Committee of the Wuhan University School of Medicine. We recommended that villagers with positive *Schistosoma* antibodies go to the schistosomiasis specialist hospital of Gongan county for further examination. Drugs for treating schistosomiasis were free. We also recommended that HBsAg-positive patients go to the local township hospital for further examination and treatment. However, this part of the cost was borne by the patients.

Results

A total of 6526 participants were selected for this study and blood samples were collected and examined. There were 3121 males (47.82%) and 3405 females (52.18%). Nearly half of the participants were $\geq$60 y of age. There are 2656 (40.70%) in the 40–59 y age group, 341 (5.23%) in the 20–39 y age group and 297 (4.55%) were $<$20 y of age. Of the 6526 blood samples examined, 540 were positive for *Schistosoma* antibody, with an overall seroprevalence of 8.27%, and 174 were positive for HBsAg, with the overall seroprevalence of 2.67%. *Schistosoma* antibody was found in all the studied villages, with a seroprevalence of *Schistosoma* antibody ranging from 1.80% (Guanai) to 14.46% (Hexiang). The seroprevalence of HBsAg ranged from 1.44% (Gaofeng and Guanai) to 5.03% (Shuangfu) (Table 1).

As shown in Table 2, the seroprevalence of *Schistosoma* antibody in males (10.19%) was higher than in females (6.52%), and

Table 1. Results of *Schistosoma* antibodies and HBsAg in different populations

Group		Number (%)	*Schistosoma* antibody	HBsAg
			positive, n (%)	positive, n (%)
Sex	Male	3121 (47.82)	318 (10.19)	92 (2.95)
	Female	3405 (52.18)	222 (6.52)	82 (2.41)
Age (years)	<20	297 (4.55)	0 (0)	0 (0)
	20–39	341 (5.23)	22 (6.45)	9 (2.64)
	40–59	2656 (40.70)	295 (11.11)	113 (4.25)
	≥60	3232 (49.52)	223 (6.90)	52 (1.61)
Village	Hexiang	581 (8.90)	84 (14.46)	15 (2.58)
	Shengtiancha	509 (7.80)	73 (14.34)	12 (2.36)
	Hexing	526 (8.06)	63 (11.98)	12 (2.28)
	Baohengyuan	510 (7.81)	50 (9.80)	17 (3.33)
	Hongansi	511 (7.83)	50 (9.78)	22 (4.31)
	Shuangfu	398 (6.10)	33 (8.29)	20 (5.03)
	Tongqiang	544 (8.34)	41 (7.54)	19 (3.49)
	Zhalingxin	534 (8.48)	38 (7.12)	12 (2.25)
	Yangjiaju	478 (7.32)	30 (6.28)	8 (1.67)
	Zhonghe	473 (7.25)	29 (6.13)	11 (2.33)
	Gaofeng	487 (7.46)	23 (4.72)	7 (1.44)
	Shuangtan	418 (6.41)	16 (3.83)	11 (2.63)
	Guanai	557 (8.54)	10 (1.80)	8 (1.44)
Total		6526 (100.00)	540 (8.27)	174 (2.67)

the difference was statistically significant (χ^2=28.885, p<0.001). With the exception of the <20 y age group, the seroprevalence of *Schistosoma* antibody was higher in males than females among all age groups. The seroprevalence of *Schistosoma* antibody in the 40–59 y age group was the highest, whether for males or females (seroprevalence in males 12.44%, seroprevalence in females 10.03%). The difference in the seroprevalence of *Schistosoma* antibody among different age groups was statistically significant (χ^2=64.407, p<0.001). Whether for males or females, the difference in the seroprevalence of HBsAg among different age groups was statistically significant (males: χ^2=25.544, p<0.001; females: χ^2=23.516, p<0.001). Overall there were no HBsAg-positive individuals in the <20 y age group, while the seroprevalence of HBsAg in the 40–59 y age group was highest (4.25%) (Table 2).

As shown in Figure 1, the trend of the distribution curve of the seroprevalence of *Schistosoma* antibody and the seroprevalence of HBsAg according to age is basically the same. Whether for males or females, the seroprevalence of *Schistosoma* antibody and the seroprevalence of HBsAg was highest in the 40–59 y age group. No one was infected with schistosomiasis or HBV among men and women <20 y of age.

In an attempt to determine the relationship between schistosomiasis and HBV, 6526 blood samples were examined. As shown in Table 3, the distribution of hepatitis B among participants who were *Schistosoma* antibody positive (25.37%) was higher than in the participants who were *Schistosoma* antibody negative (0.62%), and the difference was statistically significant (χ^2=1169.358, p<0.001, odds ratio [OR] 54.659). Using the difference in the *Schistosoma* antibody–positive rate, the 13 villages were divided into schistosomiasis high-endemic areas and schistosomiasis low-endemic areas, with 8.00% as the boundary. We compared whether there was a difference in the HBsAg seroprevalence between the high-endemic area and the low-endemic area of schistosomiasis. Table 4 shows that the seroprevalence of HBsAg in high-endemic areas of schistosomiasis (3.23%) was higher compared with that in the low-endemic areas (2.18%), with a significant difference (χ^2=6.923, p=0.009, OR 1.499).

Discussion

Schistosomiasis is a water-borne disease of global concern that infects humans when they come into contact with larval stage (cercariae) a snail transmitted via contaminated water.[16] Infection intensity is influenced by exposure and susceptibility.[18] Host exposure varies with the duration and type of water contact.[9] In general, both males and females are susceptible to schistosomiasis when exposed to water contaminated with cercariae. However, in this study we found that males had a higher prevalence of schistosomiasis compared with females. Gongan county is located in the Jianghan Plain, with a dense river network and numerous lakes. It is a large agricultural county. Because of the different division of labour between males and females in agricultural work, males are exposed more than females. Accordingly, the higher seroprevalence of *Schistosoma* antibody in this study in males may be due to this greater exposure. In addition, as with

Table 2. Seroprevalence of *Schistosoma japonicum* antibody and HBsAg among people examined, according to age and sex, in Gongan county

Age group (years)	*Schistosoma* antibody					HBsAg				
	Male, % (n)	Female, % (n)	Total, % (n)	χ^2	p-Value	Male, % (n)	Female, % (n)	Total, % (n)	χ^2	p-Value
<20	0 (0/153)	0 (0/144)	0 (0/297)			0 (0/153)	0 (0/144)	0 (0/297)		
20–39	11.25 (18/160)	2.21 (4/181)	6.45 (22/341)	11.500	0.001	3.13 (5/160)	2.21 (4/181)	2.64 (9/341)	0.277	0.599
40–59	12.44 (148/1190)	10.03 (147/1466)	11.11 (295/2656)	3.863	0.049	4.79 (57/1190)	3.82 (56/1466)	4.25 (113/2656)	1.517	0.218
≥60	9.39 (152/1618)	4.40 (71/1614)	6.90 (223/3232)	31.387	<0.001	1.85 (30/1618)	1.36 (22/1614)	1.61 (52/3232)	1.231	0.267
Total	10.19 (318/3121)	6.52 (222/3405)	8.27 (540/6526)	28.885	<0.001	2.95 (92/3121)	2.41 (82/3405)	2.67 (174/6526)	1.827	0.177
χ^2	25.243	57.062	64.407			25.544	23.516	47.877		
p-Value	<0.001	<0.001	<0.001			<0.001	<0.001	<0.001		

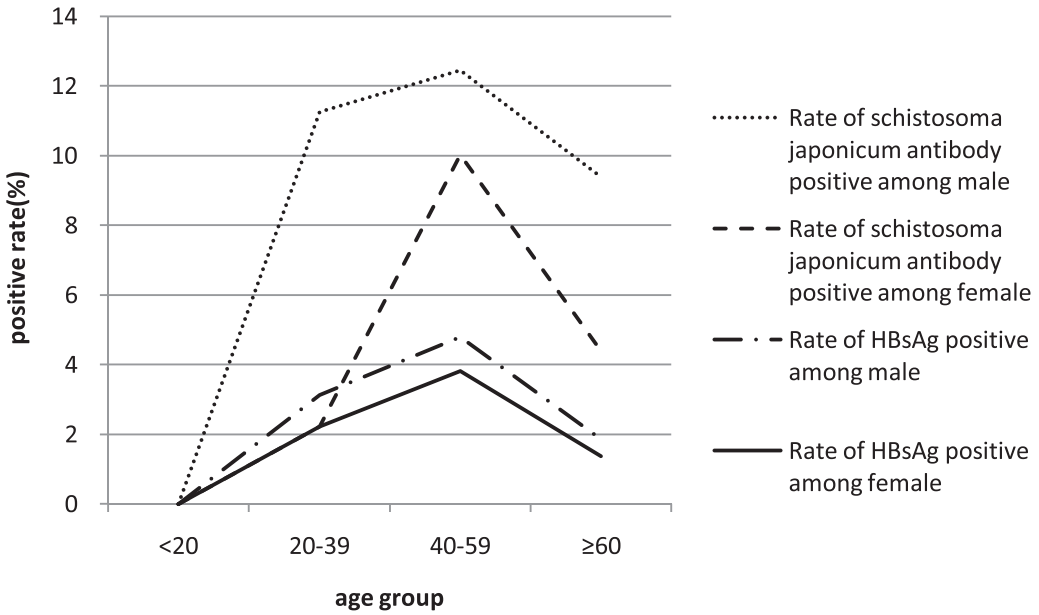

Figure 1. Distribution curve of seroprevalence of *Schistosoma japonicum* antibody and HBsAg among people examined, according to age and sex.

Table 3. Distribution of HBsAg in high-endemic areas and low-endemic areas of schistosomiasis

Infection	HBsAg		χ^2	p-Value
	Positive, % (n)	Negative, % (n)		
High-endemic areas (n=3035)	3.23 (98/3035)	96.77 (2937/3035)	6.923	0.009
Low-endemic areas (n=3491)	2.18 (76/3491)	97.82 (3415/3491)		

Table 4. Distribution of HBsAg in *Schistosoma* antibody–positive and –negative populations

Infection	HBsAg		χ^2	p-Value
	Positive, % (n)	Negative, % (n)		
Schistosoma antibody–positive (n=540)	25.37 (137/540)	74.63 (403/540)	1169.358	0.001
Schistosoma antibody–negative (n=5986)	0.62 (37/5986)	99.38 (5949/5986)		

other related studies,[19] we also observed a higher seroprevalence of *Schistosoma* antibody in middle-aged people compared with adolescents and the elderly. Family farming is usually undertaken by middle-aged people, so they are exposed more than adolescents and the elderly.

The local governments have invested in schistosomiasis prevention and control, killing snails in the spring and autumn, and good results have been achieved. A study conducted in Gongan county showed that from 2004 to 2013, the human *Schistosoma* infection rate decreased from 10.66% to 0.58% and the cattle *Schistosoma* infection rate decreased from 12.75% to 0. Also, the snail areas and densities were reduced and the *Schistosoma*-infected snails were eliminated.[20] Another study showed that the infection rate of snails and the area with infected snails has decreased yearly: the infection rate of snails decreased from 0.0007% in 2000 to 0.0002% in 2011 and the area with infected snails decreased from 267.8 hm^2 in 2000 to 6.37 hm^2 in 2011.[21] The low seroprevalence of *Schistosoma* antibody in young people in this study may be attributed to the schistosomiasis control campaigns in previous years in the area.

Some previous studies have shown the seroprevalence of HBsAg to be higher in males than in females.[22–24] The reason for the higher seroprevalence of HBsAg in males remains unclear.[22] Some researchers thought the reason may be related to differences in lifestyle or behaviour between males and females in China.[25] In our study, we found that the seroprevalence of HBsAg in males was higher than that in females. However, there was no significant difference in the seroprevalence of HBsAg between males and females. It is well known that HBV infection is transmitted by mucosal exposure to infected blood and various body fluids, sexually or from mother to child. Our research was carried out in rural areas of Gongan county. Differences in male and female behaviours, such as social range, eating out and sexual activity, were not as great as the above studies suggest. We do not think that males are more exposed or that males are more susceptible to HBV infection than females.

Variations in HBsAg prevalence in the populations in different provinces may be caused by the varied terrain and climate, imbalance of economic development, diverse ethnic population structure and different comprehension of HBV transmission and treatment.[26,27] Our study showed that the seroprevalence of HBsAg was 2.67% in Gongan county, which is markedly lower than that recorded in the national HBV sero-epidemiological surveys conducted in 2006.[5] It was also lower than reports from other provinces of China. In 2007, one survey in Jilin province showed that the HBsAg seroprevalence of the population 18–70 y of age was 4.38%.[28] In addition, this may be due to the difference in the survey population. The national HBV sero-epidemiological survey population in 2006 was <60 y of age. However, we investigated the seroprevalence of HBsAg in the entire population. And since Gongan county is located in a schistosomiasis-affected area, in order to control the prevalence of schistosomiasis, liver tests are performed on a large number of people every year and health education about liver-related diseases is also carried out. This may control the spread of HBV to a certain extent. We also found a statistically significant difference in the seroprevalence of HBsAg between different age groups in our study. Despite the large number of tested individuals in the <20 y age group (n=297), none was positive for HBsAg. These results indicate that the strong efforts made among children have had some success since the HBV vaccination was integrated into the planned immunization management in 1992 and the national childhood immunization program in 2002. In addition, hepatitis B immunoglobulin and HBV vaccine treatment at delivery for newborns of HBV-infected mothers could also contribute to the significant reduction of vertical or perinatal transmission of HBV.[29]

The seroprevalence of HBsAg in the 40–59 y age group was 4.25%, but the seroprevalence of HBsAg in the ≥60 y age group was only 1.61%. A similar trend was reported in a Korean study.[30] The reason for the decrease in the seroprevalence of HBsAg in the elderly may be due to the spontaneous clearance of HBsAg over time (a 40% cumulative rate of HBsAg seroclearance has been observed among HBV carriers after 25 y).[31] Another reason could be an increased risk of occult hepatitis B (negative HBsAg and positive HBV DNA) in the elderly with a high prevalence of schistosomiasis.[32] In addition, mortality from HBV-related sequelae may lead to a lower seroprevalence in the elderly.[33] HBsAg-positive compensated cirrhosis patients have a 5-y survival rate of 84% and a 10-y survival rate of 68%.[34]

Through statistical analysis, we found that the seroprevalence of HBsAg in the high-endemic areas of schistosomiasis was significantly higher than that in the low-endemic areas and the seroprevalence of HBsAg in participants with positive *Schistosoma* antibody was also significantly higher than that in the negative participants. This suggested that there may be some association between schistosomiasis and HBV infection. As described in the review by Abruzzi et al.,[16] the probability of becoming co-infected seems most closely associated with modes of transmission for either HBV or HCV in schistosome-endemic areas, such as the past use of parenteral antischistosomal therapy or frequent blood transfusions. However, parenteral antischistosomal therapy is rarely used in China. Oral praziquantel is the main means of treating schistosomiasis.[35] The results of Omar et al.[32] showed that the prevalence of occult hepatitis B is higher in chronic

hepatitis C patients with schistosomiasis compared with those without schistosomiasis. And according to Hammad et al.,[36] a high prevalence of chronic hepatitis B antigenaemia (58%) has been demonstrated in children with schistosomal hepatic fibrosis (SHF), but only in 2% of normal children. This suggests that schistosomiasis infection may cause an increase in HBV susceptibility. One study showed that mice infected with chronic *S. japonicum* did not generate high levels of antibodies after vaccination with HBV vaccine. The results indicate that chronic *S. japonicum* infection inhibits the immune response of mice to HBV vaccine.[37] In contrast, other studies rejected the thesis. Studies by Ye et al.[38] in China and Larouzé et al.[39] in Egypt do not support the hypothesis that schistosomiasis interacts with HBV infection. One study concluded that *Schistosoma* infection did not alter the course of hepatitis B in the studied area.[40] Therefore more work is needed to find the relationship between schistosomiasis and HBV infection.

The main limitation of the study is that we could not confirm the relationships between *Schistosoma* infection and HBV infection to be causal, because of the nature of the cross-sectional design. Moreover, serologic testing for schistosomiasis cannot accurately distinguish between active and past and resolved infections, so studies based on serological diagnostics may include patients infected in the past but currently cured.[41] Because of insufficient baseline information, it is difficult to make comparisons with the health demographic survey. This is also one of the limitations of this study.

Conclusions

The seroprevalence of HBV in schistosomiasis patients is higher than in non-schistosomiasis patients and the prevalence of HBV in high-endemic areas of schistosomiasis is higher than in low-endemic areas. However, further research is needed to determine the causal relationship between schistosomiasis and HBV infection.

Authors' contributions: YZ and XT conceived the study. YZ and YX designed the study protocol. YZ, ZD and QC collected the data and performed the analysis and interpretation of data. YZ and YX drafted the manuscript. ZD, XC and QC critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. XT and YZ are guarantors of the paper.

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