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Retrospective Cohort Study

Hepatitis B virus infection in patients with Wilson disease: A large retrospective study

Hua-Ying Zhou, Xu Yang, Kai-Zhong Luo, Yong-Fang Jiang, Wen-Long Wang, Jun Liang, Ming-Ming Li, Hong-Yu Luo

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Abstract

BACKGROUND

Wilson disease (WD) is the most common genetic metabolic liver disease. Some studies have shown that comorbidities may have important effects on WD. Data on hepatitis B virus (HBV) infection in patients with WD are limited.

AIM

To investigate the prevalence and clinical impact of HBV infection in patients with WD.

METHODS

The clinical data of patients with WD were analyzed retrospectively, and the data of patients with concurrent WD and HBV infection were compared with those of patients with isolated WD.

RESULTS

Among a total of 915 WD patients recruited, the total prevalence of current and previous HBV infection was 2.1% [95% confidence interval (CI): 1.2%-3.0%] and 9.2% (95%CI: 7.3%-11.1%), respectively. The main finding of this study was the identification of 19 patients with concurrent WD and chronic hepatitis B (CHB) infection. The diagnosis of WD was missed in all but two patients with CHB infection. The mean delay in the diagnosis of WD in patients with concurrent WD and CHB infection was 32.5 mo, which was significantly longer than that in patients with isolated WD (10.5 mo). The rates of severe liver disease and mortality in patients with concurrent WD and CHB infection were significantly higher than those in patients with isolated WD (63.1% vs 19.3%, $P = 0.000$ and 36.8% vs 4.1%, $P < 0.001$, respectively). Binary logistic regression analysis revealed a significantly higher risk of severe liver disease at the diagnosis of WD in patients

with current HBV infection [odds ratio (OR) = 7.748; 95%CI: 2.890-20.774; $P = 0.000$] or previous HBV infection (OR = 5.525; 95%CI: 3.159-8.739; $P = 0.000$) than in patients with isolated WD.

CONCLUSION

The total prevalence of current HBV infection in patients with WD was 2.1%. The diagnosis of WD in CHB patients is usually missed. HBV infection is an independent risk factor for severe liver disease in WD patients. The diagnosis of WD should be ruled out in some patients with CHB infection.

Key Words: Wilson disease; Hepatitis B virus; Chronic hepatitis B; Kayser-Fleischer ring; Ceruloplasmin; Concurrent Wilson disease and hepatitis B virus infection

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Core Tip: Data on hepatitis B virus (HBV) infection in patients with Wilson disease (WD) are limited. This is the largest investigation of HBV infection in WD patients. The most important finding of this study was the identification of 19 patients with concurrent WD and chronic hepatitis B (CHB) infection. The total prevalence of current HBV infection in patients with WD was 2.1%. The diagnosis of WD in CHB patients is usually missed. HBV infection is an independent risk factor for severe liver disease in WD patients. The diagnosis of WD should be ruled out in some patients with CHB infection.

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INTRODUCTION

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism caused by a mutation of the gene coding for copper-transporting P-type ATPase (ATP7B). It is characterized by an excessive accumulation of copper in the liver and brain, and occurs in all ethnic groups with an average prevalence of 1:30000[1,2]. The WD gene was cloned in 1993[3-5], and more than 600 gene mutations have been identified[6]. Disease progression in WD may vary, ranging from fulminant WD to an insidious progression to cirrhosis over 20-30 years. Overall, available data in literature strongly suggest that genotypic variability alone does not explain the surprisingly heterogeneous presentation of WD[7]. Some studies have shown that comorbidities may have important effects on WD[8,9].

Currently, hepatitis B virus (HBV) infection is the common cause of liver disease worldwide, affecting 290 million individuals[10,11]. However, data on the prevalence of HBV infection in WD patients are limited and inconsistent. A study from Italy reported that after monitoring 60 WD patients for 20 years, no active HBV infection was found. Accordingly, they hypothesized that the excessive copper levels caused by WD could prevent HBV infection[12]. Contrarily, a study conducted in Taiwan in 1998 reported that the prevalence of HBV infection in 61 patients with WD was 16%, which was similar to that in the general population[13]. However, this finding is different from the previously published observations of Lau *et al*[14] in Hong Kong. Moreover, these studies were conducted many years ago and in small sample size populations; therefore, more studies involving larger sample size populations are needed. Furthermore, the influence of HBV infection on the diagnosis and clinical aspect of WD remains unclear. Given the paucity of studies in this field, this study was undertaken to investigate the prevalence of HBV infection in patients with WD and to explore the impact of HBV infection on the diagnosis, clinical aspect, treatment and prognosis of WD.

MATERIALS AND METHODS

Design overview, setting, and patients

We retrospectively analyzed the data of WD patients diagnosed between May 2003 and December 2020 at the Department of Infectious Diseases/Institute of Hepatology, the Second Xiangya Hospital, Central South University, China, which is the oldest and largest tertiary referral hospital in the Hunan Province. The Institute of Hepatology of this hospital is one of the first centers to carry out research on WD in China, and it offers services to WD patients in the whole province, neighboring provinces, and all over the country.

Patients with suspected WD underwent slit-lamp examination [to identify Kayser-Fleischer (KF) rings], neurological examination, measurement of serum ceruloplasmin levels, and determination of 24 h urinary copper excretion (before and after a penicillamine challenge). In cases where there were no contraindications, a liver biopsy was performed to confirm the presence of copper deposits, and in some other cases, gene analysis was performed. The diagnosis of WD was made based on a combination of clinical symptoms and laboratory tests, and on the WD scoring system published in 2003

[15,16]. WD was confirmed if the WD score was ≥ 4 . The WD phenotypes were classified based on previously published criteria[16]. All WD patients were tested for HBV markers, including hepatitis B surface antigen (HBsAg), anti-HBs, hepatitis B e antigen (HBeAg), anti-HBe, and anti-HBc, at the time of diagnosis. Patients positive for HBsAg underwent further analysis to quantify HBV DNA levels. For each patient, all the data obtained at the time of diagnosis and at each follow-up time point were recorded in a medical record specifically designed for the WD study.

All the patients diagnosed with WD during the study period were eligible for inclusion. We excluded WD patients with other types of viral hepatitis (A, C, or E), autoimmune hepatitis, drug-induced liver disease, a history of alcohol intake > 30 g ethanol/day, and patients whose HBV markers were not tested.

Laboratory methods

Routine laboratory data were obtained using standard methods. HBV markers were tested using commercial diagnostic kits (ELISA; Shanghai Kehua Bioengineering Co. Ltd., Shanghai, China). HBV DNA levels were quantified using a commercial hepatitis B DNA quantitative fluorescence diagnostic kit (Sansure Biotech Inc, Changsha, Hunan Province, China). The lower limits of the HBV DNA quantification were 100 and 10 IU/mL before 2011 and after 2012, respectively. The KF rings were examined under a slit-lamp by an experienced ophthalmologist. Serum ceruloplasmin levels were measured using the nephelometric method (normal range, 210-500 mg/L; Beckman Coulter, Image® Immunochemistry System, Brea, CA, United States). Copper levels in serum, urine, and liver were determined as previously described[17]. Moreover, the ATP7B coding region and exon/intron boundaries were amplified and sequenced, as previously described [18].

Study outcomes

The study outcomes included the following: The proportion of patients with WD who had current HBV infection (positive for HBsAg); the proportion of those with previous HBV infection (negative for HBsAg but positive for anti-HBc, with or without anti-HBs); the rate of severe liver disease [defined as the proportion of WD patients who experienced severe decompensated cirrhosis [Child-Turcotte-Pugh (CTP) score ≥ 10] or acute-on-chronic liver failure (ACLF) in WD patients with HBV infection and those without HBV infection]. The CTP score was determined based on a previously described criterion[19,20]. ACLF was diagnosed according to a combination of consensus recommendations published by the Asian Pacific Association for the Study of the Liver (in 2009) and the guidelines for the diagnosis and treatment liver failure published by the Chinese Society of Hepatology in 2006[21,22]. The criteria were as follows: (1) Acute severe exacerbation of liver disease complicated within 4 wk by clinical ascites and/or encephalopathy, with previously diagnosed or undiagnosed chronic liver disease/cirrhosis; (2) Serum bilirubin ≥ 10 mg/d; and (3) Coagulopathy (international normalized ratio ≥ 1.5 or prothrombin activity $< 40\%$).

Statistical analysis

Continuous data were expressed as mean \pm SD and compared using the unpaired *t*-test or Mann-Whitney *U* test. Categorical variables were expressed as proportions and compared using the chi-squared test or Fishers exact test. We used a binary logistic regression model to evaluate the association between HBV infection and the risk of severe liver disease at the time of diagnosis of WD, the results were summarized as odds ratio (OR) with 95% confidence intervals (CI). All statistical analyses were performed using the software Statistical Packages for the Social sciences, SPSS version 20.0 Windows (IBM Corp., Armonk, NY, United States). Statistical significance was set at a two-tailed *P* value < 0.05 .

RESULTS

During the study period, 973 patients were diagnosed with WD. Among them, 58 patients were excluded because of concurrent hepatitis E infection ($n = 3$), hepatitis C infection ($n = 3$), thalassemia ($n = 3$), and schistosomiasis japonica ($n = 2$), as well as insufficient length of hospital stay to perform the tests ($n = 47$). The remaining 915 patients with WD (532 men, 383 women; mean age, 20.2 ± 13.1 years; age range, 1-68 years) were included in our analysis. The patients resided in 25 provinces and belonged to 825 families. Moreover, 644 (70.4%), 218 (23.8%), 35 (3.8%), and 18 (2.0%) patients presented with only hepatic disease, neuropsychiatric and hepatic disease, only neuropsychiatric disease, and neither hepatic nor neurological disease, respectively. WD diagnosis was confirmed by a liver copper level ≥ 250 $\mu\text{g/g}$ dry weight, the identification of two disease-causing mutations or homozygosity for a single disease-causing mutation, or both criteria in 320, 378, and 102 patients, respectively. All patients met the criteria of the WD scoring system, with 735 (80.3%), 87, and 93 patients having WD scores ≥ 6 , 5, and 4, respectively.

Prevalence of HBV infection among patients with WD

Among the 915 patients with WD, 393 tested negative for all HBV markers (43.0%, 95%CI: 39.8%-46.15%) and 419 (45.8%) tested positive for immunization-related anti-HBs alone (45.8%, 95%CI: 42.5%-49.0%). The total prevalence of current and previous HBV infections were 2.1% (95%CI: 1.2%-3.0%) and 9.2% (95%CI: 7.3%-11.1%), respectively. Table 1 summarizes the prevalence of HBV infection stratified by sex and age. The prevalence of both current and previous HBV infections were significantly lower in women than in men and in patients aged ≤ 10 years than in those aged ≥ 11 years. The prevalence of previous HBV infection increased with age; however, the prevalence of current HBV infection remained low irrespective of age (Table 1).

Table 1 Prevalence of hepatitis B infection in patients with Wilson disease stratified by gender and age

	Number of patients	Negative for HBVM (%)	Anti-HBs(+) alone (%)	Prior HBV infection (%)	Current HBV infection (%)
Total group	915	393 (43.0)	419 (45.8)	84 (9.2)	19 (2.1)
Sex					
Male	532	228 (42.9)	239 (44.9)	52 (9.8)	13 (2.4)
Female	383	165 (43.1)	180 (47.0)	32 (8.4)	6 (1.6)
Age group (yr)					
2-10	231	105 (45.5)	119 (51.5)	7 (3.0)	0 (0.0)
11-20	340	156 (45.9)	159 (46.8)	15 (4.4)	10 (2.9)
21-30	153	63 (41.2)	73 (47.7)	13 (8.5)	4 (2.6)
31-40	106	40 (37.7)	42 (39.6)	21 (19.8)	3 (2.8)
41-65	85	29 (34.1)	26 (30.6)	28 (32.9)	2 (2.3)

HBVM: Hepatitis B virus markers; HBV: Hepatitis B virus.

Characteristics of WD patients with current HBV infection

During the study period, 19 WD patients with current HBV infection were consecutively diagnosed (men, 13; women, 6; mean age, 25.1 ± 13.3 years; age range, 11-64 years). Among them, six and ten patients were positive for HBeAg and HBV DNA, respectively. Moreover, 16 patients had a 1- to 30-year history of HBV-related liver disease, among whom there were three patients who had undergone splenectomy 3 years earlier and five patients who had been receiving a treatment based on lamivudine or entecavir for 2-24 mo. All patients met the WD criteria. More specifically, WD diagnosis was based on elevated liver copper levels, identification of two disease-causing mutations or homozygosity for a single disease-causing mutation, or both in 10, 6, and 5 patients, respectively. Furthermore, 16 patients had a WD score ≥ 6 (84.2%). However, among the patients, only two were suspected of having WD; 17 were referred to our hospital because of chronic hepatitis B (CHB) and had never been diagnosed of WD before.

There was a high variability in the clinical manifestations in patients with WD and current HBV infection. Five patients (cases 2, 6, 7, 11, and 19) presented with ACLF, characterized by severe jaundice, markedly decreased albumin levels, and prolonged prothrombin time (except for case 6, the remaining four patients among these patients died within 15-30 d following diagnosis). Two and eight patients presented with evidence of compensated and decompensated cirrhosis, respectively. Two patients presented with symptoms and signs of chronic liver disease, including hepatic enlargement or abnormal serum aminotransferases levels. Two patients were entirely asymptomatic, with normal serum aminotransferase and mild hepatomegaly or splenomegaly (Tables 2-4).

Characteristics of WD patients with previous HBV infection

During the study period, 84 patients with WD and previous HBV infection were consecutively diagnosed (men, 52; women, 32; mean age, 33.3 ± 15.9 years; age range, 3-68 years). Among them, 74 patients were positive for anti-HBs and anti-HBc, 10 patients were positive for anti-HBc only, and none of the patients had detectable levels of HBV DNA. The diagnosis of WD was based on elevated liver copper levels, identification of two disease-causing mutations, or both in 16, 47, and 8 patients, respectively. All patients met the criteria of the WD scoring system, with 70 patients having WD scores ≥ 6 (83.3%).

Comparison between patients with isolated WD and those with concurrent WD and HBV infection

There were no differences in sex, WD phenotype, copper metabolism parameters (such as the positivity rates of KF rings, urinary copper excretion, and hepatic copper content), and mean WD score distribution between patients with isolated WD and those with concurrent WD and current or previous HBV infection. Compared with patients with isolated WD, WD patients having HBV infection were significantly older and had significantly more severe liver function damage (including lower serum albumin levels, higher serum total bilirubin levels, and longer prothrombin time). The ACLF rates in WD patients with current and previous HBV infection were 26.3% and 13.1%, respectively, which were significantly higher than the rate in patients with isolated WD (4.5%, $P = 0.000$). The rates of severe decompensated liver cirrhosis in WD patients with current and previous HBV infection were 40.5% and 36.8%, respectively, and these were significantly higher than the rate in patients with isolated WD (14.8%; $P = 0.000$). The mortality rates during the first 60 d of follow-up following diagnosis were 36.8% and 15.5% in WD patients with current and previous HBV infection, respectively; these values were significantly higher than the rate in patients with isolated WD (4.1%, $P = 0.000$) (Table 5). Based on the binary logistic regression analysis model, after accounting for age, sex, and HBV infection and taking as reference the groups of patients with isolated WD, there was a significantly higher risk of severe liver disease at WD diagnosis in WD patients with current (OR = 7.748; 95%CI: 2.890-20.774; $P = 0.000$) or previous HBV infection (OR = 5.525; 95%CI: 3.159-8.739; $P = 0.000$).

Table 2 Characteristics of patients with Wilson disease and chronic hepatitis B: The demographic characteristics and parameters of hepatitis B virus infection

Case	Sex	Age (yr)	History of HBV (yr)	HBsAg	HBeAg	Anti-HBe	HBV DNA
1	Female	16	2	+	-	+	< 100
2	Male	19	2	+	-	+	9.3e8
3	Female	19	2	+	-	-	< 100
4	Male	26	3	+	+	-	1.9e6
5	Male	43	3	+	-	+	5.6e5
6	Female	37	2	+		+	7.3e3
7	Male	19	3	+	-	+	< 100
8	Male	11	5	+	+	-	3.2e7
9	Male	26	20	+	-	+	1.9e4
10	Female	17	3	+	-	+	< 10
11	Male	20	10	+	+	-	2.3e4
12	Male	11	?	+	-	+	< 10
13	Female	32	?	+	-	+	81
14	Male	27	?	+	+	-	1.3e6
15	Male	24	16	+	+	-	2.1e8
16	Male	15	16	+	-	+	< 10
17	Male	65	30	+	-	+	22.3
18	Female	35	16	+	-	+	< 10
19	Male	15	10	+	+	-	1.8e6

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

Treatment and outcomes of WD patients with current HBV infection

Five patients with concurrent WD and current HBV infection diagnosed before 2007 were treated with a chelator alone. The patients refused liver transplantation for financial reasons, rapidly deteriorated, and died from liver failure 2-4 wk after admission. Eight patients with detectable HBV DNA levels, diagnosed after 2008, were treated with a combination of penicillamine and nucleoside. Among them, two patients (cases 11 and 19) with ACLF rapidly deteriorated and died 1 mo after admission. Two patients (cases 6 and 8) were lost to follow-up. The condition of the remaining four patients gradually improved with treatment; however, one patient (case 5) developed hepatocellular carcinoma and died 7 mo after admission. Six patients with undetectable HBV DNA levels, diagnosed after 2008, were initially treated with a chelator only. Their condition gradually improved. However, three among them experienced HBV replication at 7-12 mo after therapy. Among the latter, there was one patient (case 10) with severe hepatitis reactivation and increased serum alanine aminotransferase (ALT; 930 IU/L), aspartate aminotransferase (AST; 790 IU/L), and HBV DNA (9.2×10^4 IU/mL) levels. This patient was treated with entecavir and penicillamine. However, within 2-3 mo after treatment initiation, HBV DNA levels were undetectable, and the AST and ALT levels normalized. The remaining three patients continued treatment with a chelator only. Currently, nine of the 14 patients diagnosed after 2008 have achieved a stable disease status after therapy and have resume their routine living activities (full-time work or study). WD patients with a previous HBV infection were treated using a chelator only. None of the patients experienced HBV reactivation during the study period.

DISCUSSION

To the best of our knowledge, the prevalence of HBV infection in patients with WD has been reported in only two small studies, and only two case studies involving single cases of concurrent WD and CHB infection have been reported in the English literature[23,24]. This is the largest investigation of HBV infection in WD patients, and it is helpful in understanding the true prevalence of HBV infection in WD patients and the impact of HBV infection on WD.

A national survey conducted in 1992 reported that the overall HBsAg prevalence in the Chinese population was 9.8%, declining to 7.2% in 2006[25,26]. In the present study, the total HBsAg prevalence was 2.1% in WD patients, a figure which is far lower than previously reported national HBsAg rates. However, this does not imply that the prevalence of

Table 3 Characteristics of patients with Wilson disease and chronic hepatitis B: Diagnostic parameters of Wilson disease

Case	Neurologic signs	KF rings	Cerulo plasmin (mg/L)	Urinary copper/after PC (μg/24 h)	Hepatic copper (μg/g/dw)	Mutation analysis	WD score
1	No	P	65.0	177/1600	ND	ND	5
2	No	P	50.0	1222/4250	ND	ND	6
3	No	P	95.0	1818/2266	ND	ND	6
4	Yes	P	187.0	434/ND	ND	ND	7
5	No	P	172.0	107/1295	347	ND	6
6	No	P	216.0	431/1436	1165	ND	6
7	No	P	50.0	5171/15398	ND	ND	6
8	No	P	250.0	305/1933	1173	ND	6
9	No	N	74.0	474/1500	926	3532G>T/3532G>T	10
10	No	P	84.0	595/1725	ND	2755C>G/2975C>T	10
11	No	N	135.0	1297/2984	ND	588C>A/2333G>T	7
12	No	P	78.4	160/1773	741	2975C>T/2975C>T	11
13	No	P	129	855/2505	ND	ND	5
14	No	P	31.0	310/1984	1067	3809 >G/	9
15	No	N	104.0	187/1836	896	0	4
16	Yes	P	86.5	237/2374	404	ND	10
17	No	P	83.1	64/714	265	2975C>T/	7
18	No	P	43.0	155/171	906	2804C>T/2810delT	11
19	No	P	63.0	584/2473	ND	2666G>T/2333G>T	10

WD: Wilson disease; KF rings: Kayser-Fleischer rings; ND: Not done; PC: Penicillamine challenge; N: Negative; P: Positive.

HBV infection in patients with WD is lower than that in the general population. First, since the 1990s, the rate of HBV infection in China has been decreasing annually. The data of WD patients today should not be compared with those of the general population many years ago. Second, the age composition of WD patients is different from that of the general population. Among our patients, 41% were aged below 14 years; however, the HBV infection rate is known to be very low in this age group. Therefore, the average HBsAg positivity rate in WD patients should not be directly compared with that in the general population. To find studies with more comparable data, we conducted a literature search and found a large survey on HBV infection conducted in the Henan Province in 2015. This has been the largest survey on HBV infection in China during the recent years, and it involved a total of 13207 children and 16685 adults[27,28]. The Henan Province is located in the middle of China and is adjacent to Hunan. Its economic development level and HBV infection rate are similar to those in Hunan, making the data from Henan comparable with those from our study. We calculate the HBsAg positivity rates among different age groups of the WD patients, according to the age group divisions used in the Henan study (Table 6). The positivity rates of HBsAg in WD patients aged 1-4, 5-9 and 10-14 years were 0.0%, 0.0%, and 1.6%, respectively, which were similar to those in Henan children of the same age groups (0.5%, 0.7%, and 1.2%, respectively). The positivity rates of HBsAg in the 18-34, 35-54, and 55-74 years age groups of WD patients were 3.0%, 2.5%, and 5.3%, respectively, which were similar to those in the general population of the same age group (3.1%, 4.7%, and 5.1%, respectively). Our study indicates that the prevalence of HBV infection in WD patients is similar to that in the general population, and that WD patients are equally susceptible to HBV infection.

The most important finding of this study was the identification of 19 patients with concurrent WD and CHB infection. It is worth noting regarding the 19 patients that 17 were referred for CHB infection and not WD; thus, the WD was diagnosed at our hospital. There was a significant delay in the diagnosis of WD in these patients (mean delay = 32.5 and 10.5 mo in WD patients with concurrent CHB infection and in patients with isolated WD, respectively). Our results suggest that the diagnosis of WD may be missed in patients with CHB infection. Although a missed diagnosis of WD is not uncommon given the rarity of the disease[29-31], it is worth noting that many patients with CHB infection suffer from undiagnosed WD. The clinical manifestations of patients with concurrent CHB infection and WD are nonspecific and difficult to distinguish from those of patients with isolated CHB infection, unless the clinicians deliberately and diligently examine the patients to rule out WD. Therefore, more attention should be paid regarding the coexistence of WD in patients with CHB infection. WD should be considered and ruled out in some patients with CHB infection, especially in those with cirrhosis, hepatic failure, or poor response to antiviral therapies.

Table 4 Characteristics of patients with Wilson disease and chronic hepatitis B: Parameters of liver disease

Case	ALT	AST	ALB	TBIL	GGT	ALP	INR	Severity of liver disease	Outcome
1	29	50	20.3	46.7	46	74	2.61	CTP: 13	Died
2	70	185	26.8	264	84	61	2.8	ACLF	Died
3	86	50	25.1	123	58	85	2.7	CTP: 13	Died
4	41	60	30.4	44.4	90	70	4.5	CTP: 13	Died
5	102	170	35.7	48.0	110	95	1.5	CTP: 10	Died
6	119	291	27.6	417	186	390	2.1	ACLF	Alive
7	79	123	31	456	45	57	4.1	ACLF	Died
8	231	237	37.5	16.5	353	105	1.2	CTP:6	Alive.
9	74	101	29.8	39.0	42	116	1.5	CTP:10	Alive
10	79	105	24.5	42.0	110	130	2.4	CTP:12	Alive
11	223	268	30.0	368	147	252	2.8	ACLF	Died
12	71	83	31.0	23.0	62	357	1.6	CTP:10	Alive
13	70	76	28.0	25.6	35	375	1.63	CTP:10	Alive
14	82	151	37.8	28.7	152	149	1.36	CTP:5	Alive
15	276	102	39.9	25.3	113	93	0.95	Hepatitis	Alive
16	22	47	36.5	16	32	219	1.25	Hepatitis	Alive
17	31	28	47.3	26.3	23	76	1.01	Hepatitis	Alive
18	56	34	42.0	22.0	90	60	1.01	Hepatitis	Alive
19	57	74	28.0	373	268	293	3.01	ACLF	Died

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TBIL: Total bilirubin; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; INR: International normalized ratio; ACLF: Acute-on-chronic liver failure; CTP: Child-Turcotte-Pugh.

Compared to patients with isolated WD, patients with concurrent WD and CHB infection had significantly lower serum albumin levels, higher serum total bilirubin levels, and longer prothrombin time. The mortality rates of WD patients with current and previous HBV infection during the first 60 d of follow-up (following diagnosis) were 36.8% and 15.5%, respectively; these rates were significantly higher than those of patients with isolated WD (4.1%, $P = 0.000$). The ACLF rates in WD patients with current and previous HBV infection were 26.3% and 13.1%, respectively, which were significantly higher than those in patients with isolated WD (4.5%, $P = 0.000$). Binary logistic regression analysis revealed that the risk of severe liver disease in WD patients with current and previous HBV infection was 7.7 and 5.3 times (respectively) higher than that in patients with isolated WD. Our findings indicate that HBV infection substantially affects the severity liver disease in patients with WD (Tables 5 and 7). The mechanism through which CHB causes severe liver injury could involve the induction, by viral hepatitis, of hepatic injury and copper accumulation, which could additively or synergistically aggravate WD-induced liver damage. Many studies have shown that HBsAg clearance usually results in good long-term prognosis[32]. However, an unexpected finding was that previous HBV infection also had a significant impact on the severity of liver disease in patients with WD. The reason for this may be that WD patients with a previous HBV infection usually have severe liver injury and cirrhosis (due to the joint action of HBV and WD) that occurred before the HBsAg clearance. After the HBsAg clearance, the severe liver injury and cirrhosis that had been formed usually persist[33,34]. Considering the serious impact of HBV infection on the clinical aspect of WD patients, current and previous HBV infections must be screened when evaluating the clinical aspect and prognosis of WD patients.

The strengths of this study are: (1) Considering the rarity of the disease, the sample size of the WD patient cohort was very large; (2) All patients were diagnosed in our department and met the diagnostic criteria; among them, 80% were confirmed by genetic examination and/or liver copper level determination; and (3) All data were prospectively collected by the authors and therefore were complete and reliable. The limitation of this study is the relatively small number of WD patients with concurrent CHB infection, as this might impede the detection of more significant differences between patients with isolated WD and those with co-existing CHB infection and WD.

In conclusion, our study indicates that the prevalence of HBV infection stratified by sex and age in patients with WD is similar to that in the general population. There was a significant delay in the diagnosis of WD in CHB patients. Furthermore, our findings suggest that HBV infection significantly affects the severity of liver disease in patients with WD. Therefore, more attention should be paid to patients suffering from concurrent WD and CHB infection. Although we found that previous HBV infection is an independent factor in the exacerbation of WD, its mechanism remains unknown.

Table 5 Factors associated with severe liver disease at the Wilson disease diagnosis

Factors (at diagnosis)	OR	95%CI	P value
Gender			
Male	1		
Female	1.945	1.402-2.698	0.000
Age at diagnosis (yr)			
Group 1 (0-10)	1		
Group 2 (11-20)	1.766	1.145-2.723	0.010
Group 3 (21-30)	0.757	0.423-1.352	0.346
Group 4 (31-40)	1.178	0.646-2.148	0.594
Group 5 (41-65)	1.455	0.777-2.724	0.241
HBV infection			
WD alone	1		
WD with previous HBV	5.255	3.159-8.739	0.000
WD with current HBV	7.748	2.890-20.774	0.000

Severe liver disease is defined as patients with acute-on-chronic liver failure or a Child-Turcotte-Pugh score ≥ 10 at the Wilson disease diagnosis, HBV: Hepatitis B virus; WD: Wilson disease; OR: Odds ratio; CI: Confidence interval.

Table 6 Comparison of hepatitis B surface antigen positivity rates among different age groups between patients with Wilson disease and the general population

Age groups (yr)	Wilson disease		General population (Henan)		P value
	Number tested	HBsAg(+) (n, %)	Number tested	HBsAg(+) (n, %)	
1-4	40	0, 0.0	5474	26, 0.5	0.827
5-9	148	0, 0.0	4407	32, 0.7	0.625
10-14	191	3, 1.6	3376	40, 1.2	0.505
15-17	97	3, 3.1	Not done		
18-34	298	9, 3.0	6764	220, 3.1	0.825
35-54	122	3, 2.5	6777	275, 4.7	0.490
55-74	19	1, 5.3	3144	147, 5.1	0.599
Total	915	19, 2.1	29892	740, 2.5	0.510

HBsAg: Hepatitis B surface antigen.

Further research is needed to confirm this finding and to elucidate the mechanisms underlying the associations between WD progression and previous HBV infection or cryptogenic HBV infection.

CONCLUSION

This is the largest investigation of HBV infection in WD patients, and it is helpful in understanding the true prevalence of HBV infection in WD patients and the impact of HBV infection on WD.

Table 7 Comparison between Wilson disease patients alone and Wilson disease patients with hepatitis B virus infection

	WD alone (n = 812)	With previous HBV (n = 84)	With current HBV (n = 19)	P1	P2
Sex					
Male (n, %)	467 (57.5)	46 (61.9)	12 (63.2)	0.509	0.797
Female (n, %)	345 (42.5)	32 (38.1)	7 (36.8)	0.509	0.797
Mean age (yr)	18.8 ± 12.0	33. ± 15.9	25.0 ± 13.	0.000	0.031
Diagnosis delay	12.1 ± 21.3	13.7 ± 26.1	34.6 ± 53.5	0.542	0.000
Phenotype					
Pure H (n, %)	564 (69.5)	63 (75.0)	17 (89.5)	0.352	0.104
H and N (n, %)	195 (24.40)	21 (25.60)	2 (10.5)	0.352	0.104
Pure N (n, %)	35 (4.3)	0 (0.0)	0		
Others (n, %)	18 (2.2)	0	0		
Copper metabolic					
KF positive	67.6%	84.1%	78.9%	0.102	0.456
Ceruloplasmin	64.1 ± 46.0	97.1 ± 60.3	105.0 ± 61.6	0.000	0.000
Urinary copper	502.4 ± 1030.5	916.3 ± 245.8	767.7 ± 1165.0	0.005	0.323
Urinary Cu after PC	2236.4 ± 1582.1	2283.7 ± 1287.8	2793.8 ± 3157.5	0.842	0.144
Hepatic Cu	832.2 ± 457.7	680.1 ± 407.7	789.0 ± 338.2	0.191	0.767
Mean WD score	7.4 ± 2.3	8.0 ± 2.2	7.8 ± 2.3	0.124	0.412
Biochemical					
ALT (IU/L)	86.2 ± 105.7	63.3 ± 51.0	94.6 ± 71.1	0.0051	0.722
AST (IU/L)	84.25 ± 90.3	90.47 ± 70.4	125.3 ± 80.5	0.0532	0.058
Albumin (g/L)	38.5 ± 8.3	32.5 ± 7.6	32.1 ± 6.8	0.000	0.001
TBIL (μmol/L)	52.1 ± 131.0	104.7 ± 166.7	126.6 ± 158.3	0.001	0.002
GGT (IU/L)	90.9 ± 85.6	138.6 ± 112.3	109 ± 93.3	0.000	0.399
ALP (IU/L)	186.7 ± 133.6	137.7 ± 87.7	171.9 ± 123.0	0.001	0.650
INR	1.42 ± 0.81	1.88 ± 0.86	2.09 ± 1.04	0.000	0.000
Liver disease severity					
Hepatitis (n, %)	372 (45.8)	7 (8.3)	3 (15.8)	0.000	0.009
CTP5-6 (n, %)	189 (23.3)	18 (21.4)	3 (15.8)	0.702	0.444
CTP7-9 (n, %)	94 (11.6)	14 (16.7)	1 (5.3)	0.173	0.713
CTP10-14 (n, %)	120 (14.8)	34 (40.5)	7 (36.8)	0.000	0.008
ACLF (n, %)	37 (4.5)	11 (13.1)	5 (26.3)	0.001	0.000
Mortality (n, %),	33 (4.1)	13 (15.5)	7 (36.8)	0.000	0.000

HBV: Hepatitis B virus; WD: Wilson disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; INR: International normalized ratio; ACLF: Acute-on-chronic liver failure; CTP: Child-Turcotte-Pugh; PC: Penicillamine challenge.

ARTICLE HIGHLIGHTS

Research background

Although hepatitis B virus (HBV) infection is the most common cause of liver disease in China, the occurrence of HBV infection in Wilson disease (WD) patients and the clinical manifestations of concurrent WD and HBV infections have rarely been reported.

Research motivation

Our study suggests that both WD and HBV infections may coexist. The clinical symptoms of concurrent WD and HBV infections are difficult to distinguish from those of simple viral hepatitis. Therefore, the existence of WD may be hidden. The study of concurrent WD and HBV infection deserves careful consideration.

Research objectives

To investigate the incidence of HBV infection in patients with WD and to analyse how HBV infection affects WD.

Research methods

The clinical data of patients with WD were analyzed retrospectively, and the data of patients with concurrent WD and HBV infection were compared with those of patients with isolated WD. Considering the rarity of the disease, the sample size of the WD patient cohort was very large.

Research results

Among a total of 915 WD patients recruited, the total prevalence of current and previous HBV infection was 2.1% and 9.2% respectively. The main finding of this study was the identification of 19 patients with concurrent WD and chronic hepatitis B (CHB) infection. The mean delay in the diagnosis of WD in patients with concurrent WD and CHB infection was 32.5 mo, which was significantly longer than that in patients with isolated WD (10.5 mo). The rates of severe liver disease and mortality in patients with concurrent WD and CHB infection were significantly higher than those in patients with isolated WD (63.1% *vs* 19.3%), respectively. Binary logistic regression analysis revealed a significantly higher risk of severe liver disease at the diagnosis of WD in patients with current HBV infection or previous HBV infection than in patients with isolated WD.

Research conclusions

Our study indicates that the prevalence of HBV infection stratified by sex and age in patients with WD is similar to that in the general population. There was a significant delay in the diagnosis of WD in CHB patients. HBV infection is an independent risk factor for severe liver disease in WD patients. WD should be considered and excluded in some patients with CHB infection.

Research perspectives

As we found that previous HBV infection was an independent factor in the exacerbation of WD, the mechanism of which is speculative, future studies could further explore the mechanism by which WD is exacerbated by previous HBV infection and whether it is related to occult HBV infection.

FOOTNOTES

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