Research Article

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Genotype Distributions and Hepatitis B Coinfection in Hepatitis C Patients at a University Hospital

Bir Üniversite Hastanesinde Hepatit C ile Enfekte Hastalarda Genotip Dağılımları ve Hepatit B Koenfeksiyonu

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ABSTRACT

Objectives: Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. Comorbidity with the hepatitis B virus (HBV) leads to progressive fibrosis and severe liver disease. Our study aimed to determine HBV coinfection rates in HCV patients.

Materials and Methods: This single-center study retrospectively examined anti-HCV-positive patients monitored at our center in January 2015-June 2020. The patients' hepatitis B surface antigen, anti-hepatitis B core antigen immünoglobulin (anti-HBc IgG), anti-HBs, anti-delta, anti-human immunodeficiency virus (HIV), HCV-RNA, HBV-DNA and HDV-RNA test results were analyzed.

Results: Among 602 anti-HCV-positive patients, 462 (76.7%) with positive HCV-RNA values were included. The median age was 55.27 (18-88), while 279 (60.4%) were female. The most prevalent genotype was 1b 60.7%. HCV/HBV coinfection was found as 1.8%. HBV exposure was in 27.7%, isolated anti HBc IgG positivity was in 4.4%, and 21% were naturally immune to HBV. HBV-DNA was <2000 IU/mL in all patients.

Conclusion: Due to their similar route of contagion, HCV patients need to be screened for HBV serology. Patients with negative HBV serology should be vaccinated.

Keywords: Genotype, hepatitis B, hepatitis C

ÖZ

Amaç: Hepatit C virüsü (HCV) enfeksiyonu kronik karaciğer hastalığının majör nedenidir. Hepatit B virüsü (HBV) ile birlikteliği ilerleyici fibrozis ve ciddi karaciğer hastalığına yol açmaktadır. Çalışmamızda kronik HCV ile enfekte hastalarda HBV koenfeksiyonu oranlarını saptamayı amaçladık.

Gereç ve Yöntemler: Bu tek merkezli kohort çalışmasında Ocak 2015-Haziran 2020 tarihleri arasında merkezimizde izlenen anti-HCV pozitif hastalar retrospektif olarak tarandı. Hastaların hepatit B yüzey antijen, anti-hepatit B çekirdek antijen immünoglobulin (anti-HBc IgG), anti-HBs, anti-delta, insan bağışıklık yetmezliği virüsü (anti-HIV), HCV-RNA ve HBV-DNA, HDV-RNA test sonuçları istatistiksel olarak analiz edildi.

Bulgular: Anti-HCV pozitif 602 hastanın, HCV-RNA değeri pozitif 462'si (%76,7) çalışmaya dahil edildi. Olguların yaşları medyan 55,27 (18-88), 279'u (%60,4) kadındı. En sık genotip, 1b %60,7 idi. HCV/HBV koenfeksiyonu %1,8 olarak bulundu. HBV maruziyeti olguların %27,7'sinde, izole anti HBc IgG pozitifliği %4,4'ünde tespit edilirken, %21'i HBV'ye doğal bağışıktı. HBV-DNA hastaların tümünde <2000 IU/mL idi.

Sonuç: Benzer bulaş yolları sebebiyle HCV ile enfekte hastalar HBV serolojisi açısından taranmalıdır. HBV serolojisi negatif hastalar aşılanmalıdır.

Anahtar Kelimeler: Genotip, hepatit B, hepatit C

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Introduction

Hepatitis B and hepatitis C infections are among the most prevalent causes of chronic liver (CL) disease in the world (1). It is estimated that more than 250 million people in the world are infected with hepatitis B virus (HBV), and more than 70 million are infected with HCV (1,2,3). According to the current report of World Health Organization, the annual number of deaths related to viral hepatitis is 1.34 million, and this rate is higher in comparison to tuberculosis and the human immunodeficiency virus (HIV). Hepatitis B and hepatitis C infections are responsible for 96% of deaths related to viral hepatitis, and they are a major public health problem. Most deaths take place in relation to end-stage liver disease and hepatocellular carcinoma (HCC) (2,3). It is estimated that HCC develops by 1-3% in HCV-infected patients in 30 years (4).

Dual HCV/HBV infection is not a surprise due to their similar route of contagion. Coinfection is seen in regions that are endemic for HCV or HBV. The risks of viruses to be transmitted through the parenteral route is high in specific groups such as hemodialysis patients, intravenous drug users, those who have organ transplantation, HIV-infected individuals and beta thalassemia patients (5).

It is determined that, in coinfected patients, the HCV prevents HBV replication, and while HCV is involved in viremia, the HBV-DNA levels are suppressed. The interaction between the two viruses is a complex clinical picture, while it is mostly characterized by HBV inhibition applied by HCV. When clinical observational studies are compared to HCV and HBV infections in coinfected cases, they show that CL disease is more progressed (6).

While direct-acting antiviral agents (DAA) that are used during treatment of chronic HCV achieve HCV clearance, the suppressed HBV has a risk of replication. Reactivation may occur without observation of a picture of hepatitis, whereas it may be seen on a broad spectrum to include development of CL failure on a level requiring transplantation. Patients infected with chronic HCV need to be monitored closely and carefully in terms of the serological markers of HBV infection (7,8,9,10).

In this study, we aimed to retrospectively determine the genotype distributions, HBV infection exposure and coinfection prevalence of patients with chronic HCV infection being monitored at our clinic.

Materials and Methods

This single-center retrospective cohort study was carried out at the İstanbul Medeniyet University, Göztepe Training and Research Hospital. The ethical approval for the study was obtained from the İstanbul Medeniyet University, Göztepe Training and Research Hospital on the date of 22.07.2020 and with the decision number of 2020/0461.

In our study, the patients with anti-HCV positivity between January 2015 and June 2020 were retrospectively searched and determined from the hospital database, and those with a positive HCV-RNA value were included in the study. The sex, age and nationality of the patients were recorded, and their anti-HCV, as well as diagnosis hepatitis B surface antigen (HBsAg), anti-hepatitis B core antigen (HBc) immunoglobulin (IgG), anti-HBs, anti-HIV and anti-delta values were studied with the enzyme linked immunosorbent assay (ELISA) method and recorded. The HCV-RNA, HCV genotypes, HBV-DNA and HDV-RNA values were measured by the polymerase chain reaction method.

Statistical Analysis

For the statistical analysis, the Number Cruncher statistical System 2007 (Kaysville Utah, USA) software was used. While analyzing the data of the study, descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were utilized. The compatibility of the quantitative data with normal distribution was tested by Kolmogorov-Smirnov test, Shapiro-Wilk test and graphical assessments. In the comparison of the qualitative data, Pearson's chi-squared test, Fisher-freeman-halton exact test and Fisher's exact test were used. The level of statistical significance was accepted as $p<0.05$.

Results

Among the 602 anti-HCV positive cases, the study included 462 (76.7%) cases with positive HCV-RNA measurements. 279 (60.4%) of the patients were female, and 183 (39.6%) were male. The median age of the patients was 55.27 (18-88) years. The patients were most frequently infected with the genotype 1b (240/399, 60.7%).

In 433 patients with positive HCV-RNA; HBsAg, anti-HBc IgG and anti-HBs were examined. HBsAg was positive in 8 (1.8%) of 433 patients, and HCV/HBV coinfection was determined. One hundred twenty of the patients (27.7%) showed anti HBc-IgG positivity, and there was HBV exposure. Ninety-three patients (21.5%) with anti HBc-IgG and anti-HBs positivity were naturally immune to HBV infection. Isolated anti HBc-IgG positivity was found in 19 (4.4%) patients. One hundred fourty-seven patients with anti-HBs positive values (33.9%) were vaccinated against HBV. In 8 coinfected patients and 8 of the isolated anti HBc IgG positivity patients (42%), HBV-DNA was <2000 IU/mL, and hepatitis B e antigen (HBeAg) was negative. In 2 (25%) patients where dual HCV/HBV infection was determined, HBsAg clearance was determined during follow-ups. One of the patients (50%) developed anti HBs. Anti-delta was positive in 1 patient (1/16, 6.3%), and the HDV-RNA value was negative. One of the patients (1/461, 0.2%) had anti-HIV positivity, whereas this case also showed isolated anti HBc IgG positivity (Table 1, Figure 1).

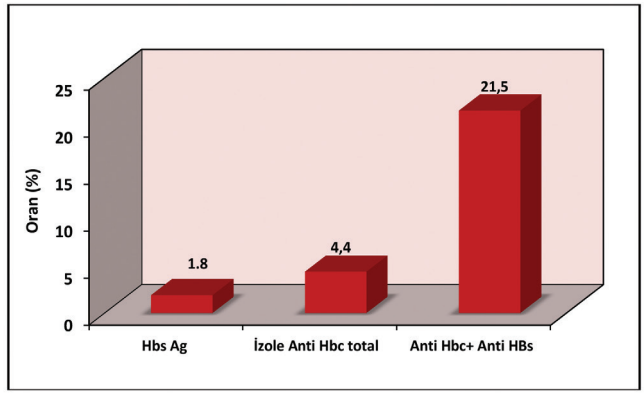

Figure 1. Assessment of HBV exposure rates in HCV-RNA positive cases

HBV: Hepatitis B virus, HCV: Hepatitis C virus, HBsAg: Hepatitis B surface antigen

Table 1. Distribution of descriptive characteristics			
		n	%
Age (years)	Min-max (median)	18-88 (58)	
	X ± SD	55.27±14.58	
	<35 years	49	10.6
	35-44 years	66	14.3
	45-54 years	80	17.3
	55-64 years	133	28.8
	≥65 years	134	29.0
Sex	Female	279	60.4
	Male	183	39.6
Nationality	TC	413	89.4
	Foreign nationality	49	10.6
Genotype (n=399)	1	71	17.8
	1a	40	10.0
	1b	242	60.7
	2	7	1.8
	2a/c	7	1.8
	3	18	4.5
	3a	7	1.8
	4	2	0.5
	4a	2	0.5
	4c/d	3	0.8
HCV-RNA	Min-max (median)	276-98756321 (1698075)	
	X ± SD	5710202.73±11201601.20	
Anti-HIV (n=461)	Negative	460	99.8
	Positive	1	0.2
HBsAg (n=433)	Negative	425	98.2
	Positive	8	1.8
Anti-HBc IgG (n=433)	Negative	313	72.3
	Positive	120	27.7
Anti-HBs (n=433)	Negative	193	44.6
	Positive	240	55.4
Anti-HBc IgG + anti-HBs (n=433)	Negative	340	78.5
	Positive	93	21.5
Isolated anti-HBc IgG (n=433)	Negative	414	95.6
	Positive	19	4.4
HBsAg clearance	Negative	6	75
	Positive	2	25
Isolated anti-HBs (n=433)	Negative	286	66.1
	Positive	147	33.9
HBV-DNA (n=16)	Negative (<2000)	16	100
HBeAg (n=16)	Negative	16	100
Anti-delta (n=16)	Negative	15	93.8
	Positive	1	6.3

Min: Minimum, Max: Maximum, SD: Standard deviation, TC: Republic of Turkey, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, HBc: Hepatitis B core antigen, IgG: Immunoglobulin, HBeAg: Hepatitis B e antigen

In the analysis of the qualitative data, no significant difference was found between the ages of the cases based on their sexes (p>0.05). The HBsAg, anti-HBc IgG, anti-HBs, anti-HIV, anti-delta positivity rates also did not show a significant difference based on sex (p>0.05). The ratio of the female cases being of foreign nationality was significantly higher (p=0.001, p<0.01) (Table 2).

There was a significant difference among the genotypes of the patients based on their nationalities (p=0.048; p<0.05). The genotype 1 rate in the citizens of the Republic of Turkey (TC) nationals and the genotype 3 rate in the foreign nationals were found higher (Table 3).

Discussion

In our study, we determined the HBV coinfection rate in the chronic HCV infected patients being monitored at our clinic to be 1.8%. Studies conducted worldwide have shown the HCV/HBV dual infection rate was determined as 7.2% in Taiwan, 2.4-6% in Turkey, 1.4% in the USA, 8.4% in China, 0.8% in Brazil and 6.6% in Pakistan (10,11,12,13,14,15,16,17,18,19). The prevalence differences in studies may be explained by the differences in the HCV and HBV mono-infection rates in geographical regions. If the mono-infection is endemic in that region, the prevalence of dual infection increases in parallel to this.

Table 2. Assessment of patients based on sex

		Sex		p
		Female	Male	
		n (%)	n (%)	
Age (years)	<35 years	31 (11.1)	18 (9.8)	[a]**0.170**
	35-44 years	37 (13.3)	29 (15.8)	-
	45-54 years	40 (14.3)	40 (21.9)	-
	55-64 years	82 (29.4)	51 (27.9)	-
	≥65 years	89 (31.9)	45 (24.6)	-
Nationality	TC	232 (83.2)	181 (98.9)	[a]**0.001****
	Foreign nationality	47 (16.8)	2 (1.1)	-
Anti-HIV	Negative	278 (100)	182 (99.5)	[b]**0.397**
	Positive	0 (0)	1 (0.5)	-
HBsAg	Negative	259 (98.1)	166 (98.2)	[b]**1.000**
	Positive	5 (1.9)	3 (1.8)	-
Anti-HBc IgG	Negative	190 (72.0)	123 (72.8)	[a]**0.854**
	Positive	74 (28.0)	46 (27.2)	-
Anti-HBs	Negative	115 (43.6)	78 (46.2)	[a]**0.596**
	Positive	149 (56.4)	91 (53.8)	-
Anti-HBc IgG + anti-HBs	Negative	204 (77.3)	136 (80.5)	[a]**0.429**
	Positive	60 (22.7)	33 (19.5)	-
Isolated anti-HBc IgG	Negative	255 (96.6)	159 (94.1)	[a]**0.214**
	Positive	9 (3.4)	10 (5.9)	-
Isolated anti-HBs	Negative	175 (66.3)	111 (65.7)	[a]**0.896**
	Positive	89 (33.7)	58 (34.3)	-
Anti-delta	Negative	6 (85.7)	9 (100)	[b]**0.438**
	Positive	1 (14.3)	0 (0)	-

[a]: Pearson's chi-squared test, [b]: Fisher's exact test, **p<0.01, HIV: Human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, HBc: Hepatitis B core antigen, IgG: Immunoglobulin

Table 3. HCV genotype and nationality relationship

		Genotype						p
		Genotype 1	Genotype 1a	Genotype 1b	Genotype 2	Genotype 3	Genotype 4	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Nationality	**TC**	68 (19.2)	35 (9.9)	214 (60.5)	12 (3.4)	18 (5.1)	7 (2.0)	[c]**0.048***
	Foreign	3 (6.7)	5 (11.1)	28 (62.2)	2 (4.4)	7 (15.6)	0 (0)	

[a]: Pearson's chi-squared test, [c]: Fisher freeman halton exact test, *p<0.05, **p<0.01, TC: Republic of Turkey, HCV: Hepatitis C virus

Approximately two thirds of the HCV-RNA positive patients who were included in the study were 55 years old or older. In various studies, the rate of 50 years old or older patients among those with HCV positivity varied in the range of 72-75% (20,21). This situation may be explained by that patients and physicians do not have a sufficient level of awareness on screening for HCV.

89.4% of our patients were TC nationals, while 10.6% were mostly women of foreign nationality coming from Turkic Republics. The genotype 1b was determined in 60.7% of the cases. The genotype 1 rate in the TC national cases and the genotype 3 rate in the foreign national cases were found to be significantly higher. The finding that the foreign national patients were mostly women may be explained by the migration of women to Turkey to work in childcare and household jobs. Studies have supported the finding that genotype 1 infection is the most frequently seen genotype in Turkey (21,22,23).

The prevalence of HCV and HBV is not exactly known due to the absence of studies covering a large population of patients and occult HBV infection in most patients. This picture that is defined as an occult hepatitis B picture carries a high risk of CL fibrosis and HCC (3). In HCV-positive cases, serological markers of hepatitis B are observed to be positive by 25% (24,25). In our study, there was HBV infection exposure in approximately a third of the patient. Similarly, Tozun et al. (26) determined HBV exposure in one third of patients in Turkey infected with HCV. Different studies have reported this rate as 24-39.1% (10,15,18). Isolated anti HBc IgG positivity was determined in 4.4% of our cases. Previous studies conducted in Turkey reported this rate as 5.4-17% (12,13,15). Determination and monitoring of isolated HBc IgG are important in terms of the risk of HBV reactivation. The HBV vaccination rate in our cases was determined as 33.9%. While Yılmaz-Karadag (15) reported that HBV immunization was not encountered in any of their cases, this rate was determined as 60% in the study by Tahmaz et al. (12). The most effective method of preventing HBV coinfection development is to vaccinate seronegative individuals.

In coinfected patients, while hepatitis C is active, it may lead to suppression of HBV-DNA, HBeAg seroconversion or HBsAg clearance (5). While the HCV infection was dominant in all cases of ours, HBV-DNA was <2000 IU/mL and suppressed. HBsAg clearance developed in 2 of 8 coinfected patients of ours, and anti-HBs formation was observed in 1 of these patients. In their study where they applied HCV treatment on 28 coinfected patients, Uyanikoglu et al. (27) determined HBsAg loss in 2 patients, while they reported anti-HBs development in 1 of these patients. Potthof et al. (28) determined HBsAg clearance and anti-HBs seroconversion during the follow-up of a patient coinfected with HBV for whom they provided HCV treatment.

While HCV clearance is observed during antiviral treatment in dual infection patients, reactivation of hepatitis B which is inactive before treatment may be observed. Today, reactivation is also determined DAA treatments that have replaced interferon-based treatments. Reactivation may result in a broad range of outcomes from alanine aminotransferase (ALT) exacerbation to CL failure or even death. This situation reveals the importance of making sure to investigate HBV serological markers in cases infected with HCV. In HCV patients planned for DAA treatment, HBsAg, anti HBc IgG and anti-HBs should be checked, and if necessary, the ALT and HBV-DNA parameters should be monitored. In suitable cases, it is recommended to use nucleoside analogues for HBV treatment (7,8,9,10). As our data were retrospectively collected, we were not able to determine whether or not there was HBV infection exacerbation in our patients. In their study involving 82 coinfected patients during their chronic HCV treatment, Aygen et al. (29) reported that HBV reactivation developed in 33.3% of the cases while they were receiving pegylated interferon and ribavirin treatment, and HBV-DNA values turned negative by oral antiviral treatment. Likewise, Lee et al. (10) observed HBV reactivation in 28.6% of their cases during DAA treatment, while they did not determine HBsAg clearance in any of the cases.

Among the HCV/HBV coinfected cases, anti-delta positivity was determined in 1 case, anti-HIV positivity was determined in 1 of the isolated anti HBc IgG positive cases, and as HBV, HCV, HIV and HDV have similar parenteral transmission route especially in risky patient populations, this shows the necessity of simultaneous serological screenings. Prevention and/or early diagnosis of coinfections and determination of treatment principles are highly important in preventing progressive CL damage.

Study Limitations

As our study was retrospective, it had limitations due to the missing data on the infection risk factors of our patients, some serological parameters and treatment information.

Conclusion

Consequently, we determined the HCV/HBV dual infection prevalence in chronic HCV infected patients as 1.8%. It should be kept in mind that progressive CL damage in coinfected patients is more frequent in comparison to mono-infections, and hepatitis B serological parameters should be determined in HCV-infected patients. Patients that show positivity in terms of HBV serology should be closely monitored in terms of HBV reactivation during hepatitis C treatment, and they should be assessed in terms of treatment. It should be ensured that patients with negative hepatitis B serological tests are vaccinated in the shortest possible time.

Ethics

Ethics Committee Approval: This study was approved by İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2020/0461, date: 22.07.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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