Published online 2017 April 30.

The Prevalence of Hepatitis B and C Virus Co-Infection Among a Group of Iranian Population

Sanaz Ahmadi-Ghezeldasht,¹ Mohammad Reza Hedayati-Moghaddam,^{1,*} and Mohammad Mehdi Akbarin¹

¹Blood Borne Infections Research Center, Academic Center for Education, Culture and Research (ACECR), Razavi Khorasan Branch, Mashhad, IR Iran

^{*} *Corresponding author*: Mohammad Reza Hedayati-Moghaddam, Blood Borne Infections Research Center, ACECR-Mashhad, Azadi Square, Ferdowsi University Campus, Mashhad, IR Iran. Tel: +98-5138832361, Fax:+98-5138810177, E-mail: drhedayati@acecr.ac.ir

Received 2017 January 30; Accepted 2017 March 25.

Abstract

Background: The risks of advanced liver disease, cirrhosis, and liver cancer among patients with hepatitis B and C virus co-infection are greater than in patients with either hepatitis B or hepatitis C virus infection.

Objectives: The present study sought to assess the prevalence of hepatitis C virus infection among individuals with hepatitis B surface antigen (HBsAg) seropositivity in Mashhad, the largest city in the northeast of Iran.

Methods: This cross-sectional descriptive-analytical study was conducted in 2017 on 284 individuals with HBsAg seropositivity who referred from April 2016 to March 2017 to the Central Diagnostic Laboratory of the Academic Center for Education, Culture, and Research, Mashhad, Iran. Commercially available enzyme-linked immunosorbent assay kits were used for detection of hepatitis C virus. Moreover, real-time reverse transcriptase-polymerase chain reaction quantification test was performed for individuals with hepatitis C virus antibody.

Results: Participants were aged 4 - 89 years. Among them, 158 (55.6%) were male with a mean age of 43.9 ± 14 and 126 (44.4%) were female with a mean age of 40.5 ± 14.1 . Hepatitis C virus antibody was detected only in four individuals (1.41%) and hepatitis C virus RNA (genotype 3) was detected only in one of these individuals with a viral load of 1000 copies/ml.

Conclusions: Study findings show the low prevalence of hepatitis B and C virus co-infection in Mashhad, Iran.

Keywords: Hepatitis B virus, Hepatitis C virus, Co-infection, Prevalence, Iran

1. Background

Hepatitis B virus (HBV) infection is among the most important health problems in the world, particularly in developing countries. Each year, it causes one million deaths worldwide. About 350 million people in the world and 3% of the Iranian population suffer from HBV infection (1). World Health Organization estimates that about 170 million people in the world have hepatitis C virus (HCV) infection (2). HCV is among the most important causes of chronic liver disease.

HBV and HCV have completely different life cycles. HBV belongs to a family of hepatotropic DNA virus called the Hepadnaviridae family, while HCV is categorized in the hepacivirus genus in the Flaviviridae family (3). Given the similar transmission routes of HBV and HCV, simultaneous infection with both viruses is likely. In other words, people who are at risk for HBV infection are probably at risk for HCV infection and may develop HBV/HCV co-infection (4). HBV and HCV infections can lead to chronic hepatitis (5). Moreover, HBV/HCV co-infection increases the risk for fulminant hepatitis, hepatic cirrhosis, and liver cancer (6).

HBV/HCV co-infection is not uncommon (7). Serologic studies among individuals with hepatitis B surface antigen (HBsAg) seropositivity, chronic hepatitis, cirrhosis, and

hepatocellular carcinoma show that HBV/HCV co-infection in Asia and western countries has a prevalence rate of 10% - 15% (8). The mortality rate of individuals with chronic HBV infection who are also infected with HCV can reach 10% (4). Therefore, assessing individuals with HBV infection respecting affliction by HCV infection is of great importance. Our previous studies showed that the prevalence of HBV and HCV infection among the general population of Mashhad, northeast of Iran, is 1.39% and 0.42%, respectively (9, 10). To our knowledge, however, there is no published data regarding HBV/HCV co-infection in this region.

2. Objectives

The present study sought to assess the prevalence of HCV infection among HBsAg-positive individuals in Mashhad, the largest city in the northeast of Iran.

3. Patients and Methods

This cross-sectional descriptive-analytical study was conducted on individuals who referred from April 2016 to March 2017 to the Central Diagnostic Laboratory of

Copyright © 2017, Modern Care Journal. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited.

Razavi Khorasan Branch of the Academic Center for Education, Culture, and Research (ACECR), Mashhad, Iran. Based on the electronic database of the laboratory, 926 HBsAgseropositive individuals referred to the laboratory during this period, for 284 of whom anti-HCV antibody test had also been performed. HBsAg and anti-HCV antibody tests had been carried out via commercially available enzymelinked immunosorbent assay (ELISA) kits (General Biologicals Corporation, Taiwan). HBV and HCV viral loads had been assessed respectively through DNA and RNA extraction from plasma samples using High Pure Viral Nucleic Acid Kit (Roche Applied Sciences, Mannheim, Germany) based on the instruction manual of the kit. Real-time polymerase chain reaction (PCR) quantification of HBV and real-time reverse transcriptase-PCR quantification of HCV had also been done via a Rotor-Gene 6000 (Q) device, using respectively the artus HBV RG PCR kit (Qiagen GmbH, Germany) and the artus HCV RG RT-PCR kit (Qiagen GmbH, Germany) based on the instruction manual of the kits. HCV genotype had been determined via the HCV Genotype RG kit (Novin Gene, Iran) and the Rotor-Gene 6000 (Q) device based on the instruction manual of the kit. The collected data were analyzed using SPSS software (v. 18.0). This study was approved by the Research Ethics Committee of ACECR, Razavi Khorasan Branch (No.96.48.3786).

4. Results

A total of 284 HBsAg-positive individuals with a mean age of 42.51 \pm 14.03 (range:4-89) were included in the study. Among participants, 158 (55.6%) were male and 126 (44.4%) were female with mean age of 43.9 \pm 14 and 40.5 \pm 14.1, respectively. Anti-HCV antibody was detected only in four individuals (1.41%) and HCV RNA was detected only in one of these individuals with genotype 3 and a viral load of 1000 copies/ml (Table 1).

Table 1. Hepatitis C Virus Viral Load in Individuals With HBV/HCV Co-Infection in Mashhad, Iran

Number	Gender	Age	HCV Viral Load (Copies/mL)
1	Male	83	Undetectable
2	Male	58	1000
3	Female	40	Undetectable
4	Male	44	Undetectable

5. Discussion

Although the exact prevalence of HBV/HCV co-infection is unknown, HBV and HCV infections are highly common

among patients with chronic liver disease (11). HBV/HCV coinfection is not uncommon and it is mostly found in HBV endemic areas such as Asia, the southern parts of the Sahara, and South America (12, 13). On the other hand, in areas with HBV infection prevalence less than 1% (such as Northern Europe), HBV/HCV co-infection is very rare (14, 15); however, this condition mostly common among injection drug users, patients with human immunodeficiency virus, and patients who need hemodialysis or blood transfusion (16).

In this study, the prevalence of HCV infection among HBsAg-positive individuals was 1.41%. This rate is much lower than the rates reported previously in Iran and other countries. For instance, a study in Iran showed that the prevalence of anti-HCV antibody among patients with HBV infection was 12.3% (17). Furthermore, some studies showed that the rate was 11% (18) and 16% (19) in the United States, 8% in Portugal (20), and 25% among patients with cirrhosis and hepatocellular carcinoma in Spain (21). The main concern respecting HBV/HCV co-infection is the synergic effects of HBV and HCV infections can result in more severe liver damage (22, 23). Moreover, some studies reported that HBV/HCV co-infection not only increases the risk of hepatocellular carcinoma but also is associated with a higher rate of mortality caused by liver diseases (12, 24).

The rate of anti-HCV seropositivity in the general population is estimated to be 1% - 2% (25). However, due to undiagnosed occult HBV infection (which is defined as detection of the very low level of HBV DNA in an HBsAg seronegative person), this rate is usually underestimated. Different studies showed that due to the decreased activity of HBV DNA polymerase, the level of HBVDNA is low among patients with HBV/HCV co-infection (12, 18, 26). HCV infection not only suppresses HBV DNA but also can contribute to the seroconversion of hepatitis B envelope antigen or the clearance of HBsAg (4, 27). A longitudinal follow-up study showed that annual HBsAg seroconversion among patients with HBV/HCV co-infection was more than that in in patients with single HBV infection (2.08% vs. 0.43%) (28). On the other hand, some studies suggested a reciprocal influence for HBV and HCV on each other or even the dominant effects of HBV (29-32). A study in Japan revealed the more significant clearance of HCV RNA among patients with HBV/HCV co-infection compared to patients with HCV mono-infection (31). Another study in Italy on 103 patients with HBV/HCV co-infection also showed that the virological profiles of patients with HBV/HCV co-infection could be extremely diverse (33). Indeed, evidence shows that both viruses can simultaneously inhibit each other; however, the history of infection can play a significant role in determining the dominant virus (4, 34). It seems that these mutual interplays of HCV and HBV need to be confirmed by studies with longer follow-up periods (11).

5.1. Conclusion

Study findings showed the low prevalence of HBV/HCV co-infection in Mashhad, Iran. Moreover, the findings highlight the importance of long-term monitoring of both HBV and HCV for the purpose of accurate diagnosis and effective treatment. The roles of innate and acquired immunities in viral replication and clinical outcomes still deserve further investigations. Moreover, further studies are needed to determine the most effective antiviral agents for the management of HBV/HCV co-infection.

Acknowledgments

This study was financially supported by Research and Technology Deputy of Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch, Mashhad, Iran. The authors would like to appreciate the personnel of the Central Diagnostic Laboratory of Razavi Khorasan Branch of ACECR, Mashhad, Iran, for their kind assistance.

References

- 1. Hassanjani-Roshan M-R, Taheri H. Frequency of chronic active hepatitis in asymptomatic HBV carriers in Babol, Iran. *Arch Iran Med.* 2002;**5**(2):90–100.
- 2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis.* 2005;**5**(9):558–67.
- Brass V, Moradpour D. New insights into hepatitis B and C virus coinfection. *J Hepatol*. 2009;**51**(3):423–5. doi: 10.1016/j.jhep.2009.06.003. [PubMed: 19596479].
- Liaw YF. Hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. J Gastroenterol. 2002;37 Suppl 13:65–8. [PubMed: 12109669].
- Genesca J, Esteban JI, Alter HJ. Blood-borne non-A, non-B hepatitis: hepatitis C. Semin Liver Dis. 1991;11(2):147–64. doi: 10.1055/s-2008-1040432. [PubMed: 1653459].
- Chu C-M, Sheen I-S, Liaw Y-F. The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B. *Gastroenterol.* 1994;107(1):189–95.
- Jamma S, Hussain G, Lau DT. Current Concepts of HBV/HCV Coinfection: Coexistence, but Not Necessarily in Harmony. *Curr Hepat Rep.* 2010;9(4):260–9. doi: 10.1007/s11901-010-0060-4. [PubMed: 21258658].
- 8. Liaw Y-F. Role of hepatitis C virus in dual and triple hepatitis virus infection. *Hepatol*. 1995;**22**(4):1101–8.
- Fathimoghaddam F, Hedayati-Moghaddam MR, Bidkhori HR, Ahmadi S, Sima HR. The prevalence of hepatitis B antigen-positivity in the general population of Mashhad, Iran. *Hepat Mon.* 2011;11(5):346–50. [PubMed: 22087159].
- Ghezeldasht SA, Hedayati-Moghaddam MR, Shamsian K, Fathimoghadam F, Bidkhori HR, Rezaee SA. Prevalence of Hepatitis C Virus Infection in General Population of Mashhad, Northeastern Iran. *Iran J Pub Health.* 2017;46(3):408–13.
- Saravanan S, Velu V, Nandakumar S, Madhavan V, Shanmugasundaram U, Murugavel KG, et al. Hepatitis B virus and hepatitis C virus dual infection among patients with chronic liver disease. *J Microbiol Immunol Infect*. 2009;42(2):122–8. [PubMed: 19597643].
- Crespo J, Lozano J, De la Cruz F, Rodrigo L, Rodriguez M, San Miguel G. Prevalence and significance of hepatitis C viremia in chronic active hepatitis B. Am J Gastroenterol. 1994;89(8).

- Liang TJ, Bodenheimer HC, Yankee R, Brown NV, Chang K, Huang J. Presence of hepatitis B and C viral genomes in US blood donors as detected by polymerase chain reaction amplification. *J Medvirol.* 1994;42(2):151–7.
- Liu CJ, Liou JM, Chen DS, Chen PJ. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. J Formos Med Assoc. 2005;104(11):783–91. [PubMed: 16496056].
- Reimer J, Lorenzen J, Baetz B, Fischer B, Rehm J, Haasen C, et al. Multiple viral hepatitis in injection drug users and associated risk factors. J Gastroenterol Hepatol. 2007;22(1):80–5. doi: 10.1111/j.1440-1746.2006.04358.x. [PubMed: 17201886].
- Roshandel G, Semnani S, Abdolahi N, Besharat S, Kashtkar AA, Joshaghani HR. The prevalence of Co-infection with HCV and HDV in HBV infected patients in Golestan province of Iran [In Persian]. J Gorgan Univ Med Sci. 2008;9(4):61–5.
- Fong TL, Di Bisceglie AM, Waggoner JG, Banks SM, Hoofnagle JH. The significance of antibody to hepatitis C virus in patients with chronic hepatitis B. *Hepatology*. 1991;14(1):64–7. [PubMed: 1648540].
- Fattovich G, Tagger A, Brollo L, Pontisso P, Realdi G, Ferroni P, et al. Liver disease in anti-HBe positive chronic HBsAg carriers and hepatitis C virus. *Lancet.* 1989;334(8666):797–8.
- 20. Barros H, Miranda HP, Silvestre F. Hepatitis C virus antibodies in asymptomatic chronic carriers of hepatitis B surface antigen. *Acta Med Port*. 1994;7:30–4.
- Bruix J, Calvet X, Costa J, Ventura M, Bruguera M, Castillo R, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet*. 1989;**334**(8670):1004–6.
- 22. Simonetti RG, Camma C, Fiorello F, Cottone M, Rapicetta M, Marino L, et al. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case-control study. *Ann Intern Med.* 1992;**116**(2):97–102. [PubMed: 1309286].
- 23. Liaw YF, Chen YC, Sheen IS, Chien RN, Yeh CT, Chu CM. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *Gastroenterol*. 2004;**126**(4):1024–9.
- Osella AR, Misciagna G, Guerra VM, Chiloiro M, Cuppone R, Cavallini A, et al. Hepatitis C virus (HCV) infection and liver-related mortality: a population-based cohort study in southern Italy. The Association for the Study of Liver Disease in Puglia. *Int J Epidemiol*. 2000;**29**(5):922–7. [PubMed: 11034979].
- Marcellin P. Hepatitis B and hepatitis C in 2009. *Liver Int*. 2009;29 Suppl 1:1-8. doi: 10.1111/j.1478-3231.2008.01947.x. [PubMed: 19207959].
- Fattovich G, Tagger A, Brollo L, Giustina G, Pontisso P, Realdi G, et al. Hepatitis C virus infection in chronic hepatitis B virus carriers. *J Infect Diseas*. 1991;163(2):400–2.
- 27. Liaw YF, Lin SM, Sheen IS, Chu CM. Acute hepatitis C virus superinfection followed by spontaneous HBeAg seroconversion and HBsAg elimination. *Infection*. 1991;**19**(4):250-1. [PubMed: 1917039].
- Sheen IS, Liaw YF, Deng-Yn, Chu CM.Lin. Role of hepatitis C and delta viruses in the termination of chronic hepatitis B surface antigen carrier state: a multivariate analysis in a longitudinal follow-up study. J Infect Diseas. 1994;170(2):358–61.
- 29. Sato S, Fujiyama S, Tanaka M, Yamasaki K, Kuramoto I, Kawano S. Coinfection of hepatitis C virus in patients with chronic hepatitis B infection. J Hepatol. 1994;**21**(2):159–66.
- 30. Zarski JP, Bohn B, Bastie A, Pawlotsky JM, Baud M, Bost-Bezeaux F, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol.* 1998;**28**(1):27–33.
- Ohkawa K, Hayashi N, Yuki N, Masuzawa M, Kato M, Yamamoto K, et al. Long-term follow-up of hepatitis B virus and hepatitis C virus replicative levels in chronic hepatitis patients coinfected with both viruses. J Med Virol. 1995;46(3):258–64. [PubMed: 7561800].

- Sheen IS, Liaw YF, Chu CM, Pao CC. Role of hepatitis C virus infection in spontaneous hepatitis B surface antigen clearance during chronic hepatitis B virus infection. *J Infect Dis.* 1992;165(5):831–4. [PubMed: 1314869].
- 33. Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, Saitta C, et al. Longitudinal evaluation reveals a complex spectrum of virolog-

ical profiles in hepatitis B virus/hepatitis C virus-coinfected patients. *Hepatology*. 2006;**43**(1):100–7. doi: 10.1002/hep.20944. [PubMed: 16323213].

 Liaw YF. Concurrent hepatitis B and C virus infection: Is hepatitis C virus stronger?. J Gastroenterol Hepatol. 2001;16(6):597-8. [PubMed: 11422609].