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Original Article

The Prevalence of Hepatitis C Virus (HCV) Infection and Genotypes in Patients with Hemophilia and Other Blood Coagulopathies in Mashhad, Iran

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Abstract

Background and Aim: Patients with blood coagulopathies treated with multiple transfusions have a high risk to acquire some viral infections such as hepatitis C. This research was aimed to identify hepatitis C virus (HCV) infection prevalence, and the viral genotypes among patients with hemophilia and other inherited coagulopathies in Mashhad, Iran.

Methods: Medical records of 760 patients with inherited coagulopathies including hemophilia were reviewed in Sarvar Clinic of Mashhad. Plasma samples were subjected to detect antibodies against HCV (anti-HCV) by enzyme-linked immunosorbent assay. HCV RNA and genotypes were determined by a real-time polymerase chain reaction (PCR) method.

Results: Totally 128 individuals (16.8%) including patients with hemophilia (n=116) and individuals with other coagulopathies (n=12) were found to be seropositive for anti-HCV. They comprised 122 men and six women with a mean age of 31.6 ± 10.5 years. The PCR results were available for 118 patients, of whom 86 individuals (72.9%) were found to have detectable HCV RNA in their serum. The most frequent genotypes were 1a and 3a (49.1% and 35.8%, respectively). HCV genotypes were not significantly correlated with the patients' age (p=0.477) as well as with the serum levels of alanine aminotransferase (p=0.655) and aspartate aminotransferase (p=0.332).

Conclusion: The patients with blood coagulation disorders had a greater prevalence of HCV infection in comparison with the general population in our region. The most common subgenotypes of HCV were 1a, and 3a, respectively. These results could assist professionals to choose more efficient approaches for the management of their patients.

Keywords: Blood Coagulation Disorders; Genotype; HCV Infection; Iran; Prevalence.

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Introduction

Hepatitis C virus (HCV) infection is a global health problem affecting 71 million people worldwide. In 2015, it is estimated that 1.75 million people were newly infected with HCV and 399 000 deaths occurred due to disorders related to chronic hepatitis C such as cirrhosis and hepatocellular carcinoma (1).

Iran has been considered as an area with a low frequency of HCV infection. According to a systematic review by Mirminachi et al., the overall prevalence of seropositivity for antibodies against HCV (anti-HCV) and HCV viremia was 0.6% and

0.4%, respectively, in the general Iranian population (2).

Another systematic review estimated previously the overall prevalence of HCV infection as 0.5% among Iranian blood donors (3). However, some healthcare-related contacts are suggested to be responsible for a significant portion of HCV spreading in Iran. In comparison with the general population, the odds ratio of HCV infection was estimated to be 39.3 (95% CI: 25.7-60.2) among Iranian populations at high risk of healthcare-related exposures (4). Populations with frequent blood transfusion are at higher risk of several transfusion-transmitted infections including viral hepatitis. (5). In comparison with the general population, higher prevalence rates of anti-HCV have been reported among patients with blood disorders such as hemophilia in Middle East and North Africa countries.(6)

Another systematic review estimated a total HCV prevalence of 20.0% (95% CI: 16.4-23.9%) among Iranian multi-transfused patients; the rate for hemophiliacs was reported as 6.0% to 90.0%, with a median of 54.0% (4). In fact, patients with inherited coagulopathies such as hemophilia are at extreme risk of HCV infection because of their lifelong requirements of blood transfusion.

HCV has been classified into some major genotypes and subtypes based on genomic heterogeneity (7). Determination of HCV genotypes may have important implications for the prognosis and anti-viral therapies and may show the routes of acquisition. HCV genotype 1 (G1) has been found to be the most frequent in the world (46-49%), followed by G3 (18-22%), G4 (13-17%), G2 (11-13%), and G5 and G6 (together < 5%) (8, 9).

The distribution of HCV genotypes varies based on geographical regions as well as on the demographic differences in the affected populations. HCV G1 to G3 distribute all over the world but G4 to G6 are restricted to certain geographical regions (8). In Iran, both large-scale surveys and systematic reviews indicated that the highest proportion of HCV infection is associated with G1 and G3 (4, 10-12).

Regarding HCV subgenotypes, subtype 1a (39-45%) followed by 3a (27-40%) and 1b (11-13%) are the most predominant reported subtypes in our country (10-13). However, the subgenotypes frequency differences have been reported among HCV-positive Iranian patients with hemophilia and other inherited bleeding disorders (58-65%, 18-19%, and 14-15%, respectively) (14, 15).

In Mashhad, Northeastern Iran, a big city with a significant low prevalence of HCV infection among the general population (0.42%, 95% CI: 0.17-0.87%) (16), the same rates were reported for 1a (39.2%) and 3a (40%) subtypes followed by 1b (10.9%) (17).

Nevertheless, there is no adequate data of patients with congenital bleeding disorders in this city regarding HCV genotypes distribution. The present study was performed to determine the prevalence of HCV infection and the distribution of viral genotypes in patients with hemophilia and other inherited blood coagulopathies in Mashhad, Iran.

Methods

In this cross-sectional study, the medical records of all 760 patients with congenital bleeding disorders were reviewed in the Sarvar Clinic of Mashhad, Iran, in 2011.

The participants included the patients with hemophilia A or B and other blood coagulopathies such as Von Willebrand disease, factor V deficiency, and platelet disorders. The serum samples of patients were tested routinely to detect common transfusion-transmitted viral pathogens using enzyme-linked immunosorbent assay (DiaPro Diagnostic Bioprobes Srl, Italy, for antibodies against HCV).

The seropositive specimens were further tested by a polymerase chain reaction (PCR) method to confirm current HCV infection, and HCV-RNA positive samples were assessed to determine virus genotypes by a real-time PCR assay (artus® HCV RG RT-PCR, QIAGEN GmbH, Germany, and Genotype Assay Kit, Novin Gene, Iran). Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were also measured and a value of 40 mg/dl was considered as upper normal limits for both tests.

Statistical Analysis

Using SPSS version.16.0 software, data were described as percentages or mean ± standard deviations. Interrelation between HCV genotypes and some independent factors was assessed using the chi-square test, and if required, Fisher's exact test, p-values less than 0.05 were considered statistically significant.

Results

Serum HCV antibodies were detected in 128 of 760 patients (16.8%). The range of seropositive patients' age at the time of the study was 2-64 years.

The demographic and clinical data of hemophilia and blood coagulopathies patients with anti-HCV seropositivity in Mashhad, Iran has been shown in Table 1. One-hundred thirteen patients had clotting factor deficiencies and 15 individuals were suffering from blood platelet disorders. Abnormal high levels of serum AST and ALT were observed in 23.9% and 27.4% of the 117 HCV seropositive patients, respectively.

The PCR results were available for 118 individuals, of whom HCV RNA was detected in 86 patients (72.9%). The genotyping data were available in 53 of 86 HCV-RNA positive patients, presented subtypes 1a (49.1%) and 3a (35.8%) as the most frequent viral subgenotypes (Figure 1). The mean of ages was the same in the patients infected with HCV subtypes of 1a (33.3±10.2) and 3a (31.1±10.4, p=0.477).

No significant difference was observed between the patients with HCV subtypes of 1a and 3a regarding the frequency of abnormal levels of serum ALT (40.0% vs. 33.3%, p=0.655) and AST (36.0% vs. 22.2%, p=0.332). .

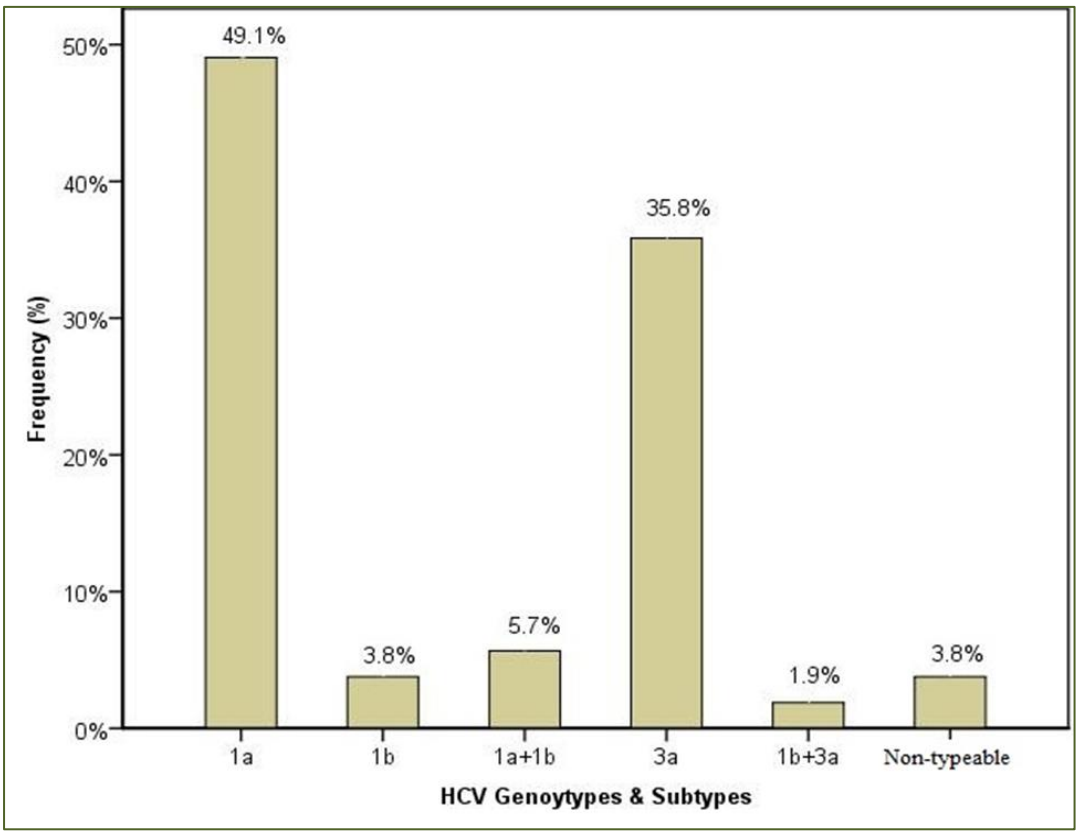

Figure 1. Distribution of HCV genotypes in hemophilia and blood coagulopathies patients in Mashhad, Iran

Table 1. Demographic and clinical data of hemophilia and blood coagulopathies patients with anti-HCV seropositivity in Mashhad, Iran

Variables	Number	Percent (%)
Age (years, Mean, SD, n = 127)	31.6	10.5
Gender (n = 128)		
Men	122	95.3
Women	6	4.7
Type of bleeding disorder (n = 128)		
Hemophilia A	75	58.6
Hemophilia B	30	23.4
Other factors deficiencies	8	6.3
Platelets disorders	15	11.7
Serum ALT (mg/dl, n = 117)		
<= 40	85	72.6
> 40	32	27.4
Serum AST (mg/dl, n = 117)		
<= 40	89	76.1
> 40	28	23.9
Serum HbsAg (n = 107)		
Negative	105	98.1
Positive	2	1.9
Serum anti-HIV (n = 113)		
Negative	112	99.1
Positive	1	0.9
Serum HCV RNA (n = 118)		
Positive	86	72.9
Negative	32	27.1
HCV subgenotypes (n = 53)		
1a	26	49.1
1 b	2	3.8
3a	19	35.8
Mixed	4	7.6
Non-typeable	2	3.8

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase, HbsAg: Surface antigen of hepatitis B virus; HIV: Human immunodeficiency virus; SD: Standard deviation

Discussion

Patients with hemophilia and other coagulopathies who are treated with multiple transfusions are at higher risk of HCV infection (5). A meta-analysis in 2009 demonstrated that the overall prevalence of anti-HCV seropositivity among Iranian patients with hemophilia is as high as 40.8% (18). In the present study, HCV antibodies were detected in the serum samples of 16.8% of patients with blood coagulopathies in Mashhad, northeast of Iran, with 72.9% HCV viremia among anti-HCV seropositive individuals. These rates of anti-HCV seropositivity and active HCV infection were significantly higher than those reported among the general population of this city (0.7% and 0.4%, respectively) (16).

Nevertheless, HCV infection prevalence among our patients was significantly lower than the average rate (54.0%) reported for hemophiliacs in our country (4).

According to the global health sector strategies on viral hepatitis, HCV diagnosis is one of the important steps to reach the goal of viral hepatitis ending in the world by 2030 (19). Furthermore, based on the World Health Organization guidelines, detection of HCV genotypes is needed to choose the appropriate direct-acting antiviral drugs for the treatment of the patients (20). In our population, subtype 1a (49.1%) was the most common HCV type followed by 3a (35.8%), mixed (7.6%), 1b (3.8%) and unclassified genotypes (3.8%). The distribution of HCV subgenotypes in this survey was generally similar to those reported previously from other parts of Iran; however, the prevalence rate of subtype 3a in our study was higher than that detected by the other investigations. For instance, Samimi-Rad et al. in 2016 reported that subtypes 1a (65.0%), 3a (18.7%), and 1b (14.5%) were the most frequent HCV subgenotypes in 229 HCV positive patients with inherited bleeding disorders at a major referral clinic of Tehran, north of Iran (14). In 2010, another study among 367 Iranian HCV-positive patients with inherited coagulopathies, identified subtype 1a as the most HCV subgenotype (58.0%), followed by 3a (18.5%) and 1b (14.7%) (15). Assarehzadegan et al. found a similar distribution of HCV genotypes among hemophilia patients in Ahvaz, southwest Iran, during 2008-2009. However, the rate of infection with HCV 1b (26.1%) was more common than HCV 3a (11.9%) (21). In contrast, a survey from Mazandaran province, north of Iran, performed between 2009-2011, reported a higher rate of HCV infection with subtype 3a as compared to 1a among all 135 HCV RNA-positive patients (51.1% vs. 27.4%) as well as a subgroup of 33 HCV-positive patients with hemophilia (75.8% vs. 21.2%) (22). In 2011, another study from Fars province, south of Iran, showed the higher rate of HCV infection belonging to subtype 3a (40.9%) in comparison with 1a (26.2%) and 1b (8.7%) (23). These discrepancies could be partly due to the differences in the routes of transmission, and various socioeconomic factors (10,14). For example, Ziyaeyan et al. believed that finding a higher proportion of subtype 3a than 1a in their HCV-positive patients referred to a major tertiary teaching hospital in Shiraz, southern Iran, maybe because of a considerable percentage of injecting drug users (38.8%) in their region (23).

The pattern of HCV genotypes among our patients seems to be comparable with western countries where subtypes 1a and 3a are dominant among people with HCV infection (9). In Iran's neighboring countries, however, diverse patterns have been reported. In a study conducted during January to December 2006 in Pakistan, in the neighborhood of Eastern Iran, most of the hemophilia patients with HCV infection demonstrated subtype 3a (38%), though the virus type could not be determined in 52.4% of positive individuals (24). On the other hand, G4 is the most common HCV type reported among hemophilia patients in some of our neighboring Arab countries like Iraq (25), Jordan (26), and Lebanon (27).

In the current study, mixed genotypes were detected in 7.6% of the patients which was compatible with previous reports (11, 22). Keshvari et al., detected mixed HCV genotypes among 6.2% of Iranian patients with blood coagulopathies (15). Infection with two or more HCV subgenotypes might happen in high-risk groups with multiple exposures to the virus such as hemophilia, thalassemia, hemodialysis patients, and intravenous drug abusers (12, 22).

In this study, we could not find any significant interrelation between infection with different HCV subgenotypes and patients' age as well as abnormal serum levels of aminotransferase. Similarly, another study from Iran reported no significant association between patients' age and the liver biochemical profile and HCV genotypes among patients with congenital bleeding disorders patients with chronic HCV infection (15).

Conclusion

Our study revealed a higher rate of HCV infection prevalence among patients with inherited coagulopathies than the general population in Northeastern Iran. In accordance with other parts of the country, the most common subgenotypes of HCV were 1a and 3a subtypes. It seems that more strict

preventive measures should be taken into account in our country to reduce HCV spread, especially among multi-transfused patients. These measures may include HCV screening using more sensitive methods to detect infection during the window phase, implementing more effective virus inactivation or virus removal techniques in blood centers, and developing new treatment plans for the patients affected with this virus.

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Ethics

This survey was scientifically and ethically approved by the Research and Technology Deputy of Academic Center for Education, Culture, and Research (ACECR), Razavi Khorasan Branch, Mashhad, Iran (No. 92.48.3072).

Conflict of Interest

The authors declared that they have no conflict of interest.

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