



Original Research

HCV Genotype Distribution of Patients with Chronic Hepatitis C in Istanbul

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Abstract

Objectives: Hepatitis C virus (HCV), which has no protective vaccine, is a common cause of chronic hepatitis, which is a severe public health threat. There are differences in nucleotide and amino acid sequences in different regions of the HCV genome. As a result of these differences, HCV has been shown to have at least seven major genotypes and many subtypes. In Turkey, the prevalence of genotype 1 is between 51.7% and 97.1%, the highest rate among all genotypes, while subtype 1b is the genotype with the highest rate. It is important to detect mixed genotype infection reliably as it causes treatment failure. This study aims to reveal the distribution of the HCV genotypes in our hospital in Istanbul over the years and to contribute to the epidemiological data of Turkey.

Methods: For this purpose, 385 patient samples sent to Sisli Hamidiye Etfal Training and Research Hospital, Clinical Microbiology Laboratory for HCV genotype determination between January 2016 and June 2019 were evaluated retrospectively. Anti-HCV was screened by enzyme immunoassay and confirmation was performed by Line immunoassay. HCV genotyping assays targeting highly conserved 5'UTR and most variable region NS5B regions were used.

Results: The most common genotype was genotype 1 (81.3%) with 313 cases and subtypes 1a and 1b were detected at the rates of 10.9% and 67.8%, respectively. In addition, genotype 3, 2, 4, 5 were detected at the rates of 8.8%, 3.4%, 2.9%, 0.8%, respectively and mixed genotype was found in 2.9% of cases. Although genotype 5 is seen in South Africa, it is found in the Middle East region, albeit at a low rate. In our study, it was observed that genotype 5 was detected in different years from patients of Syrian origin.

Conclusion: In this study, genotype 1 was the most common genotype with a rate of 81.3% and subtype 1b was 67.8%, in accordance with the literature. However, genotypes 3, 2, 4 and 5 were also present at low rates. It is important to monitor these rare genotypes since some of them are dominant in surrounding countries. In addition, 2.9% of HCV mixed genotype was detected and this should be considered concerning management of HCV infection.

Keywords: Epidemiology; HCV genotype; HCV subtype; hepatitis C virus; mixed genotype.

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Hepatitis C virus (HCV) is one of the major causes of chronic hepatitis that has been affecting the entire world since it was first identified by Choo et al. in 1989. HCV is classified within the *Hepacivirus* genus of the *Flaviviridae*

family. The virion consists of an icosahedral capsid encapsulated by a lipid membrane envelope that is 55-65 nm in diameter.^[1] Positive-sense, single-stranded, 9.6 kb long RNA genome of HCV encodes structural and non-structural

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proteins. Structural proteins of the virus are core (C) and envelope proteins (E1 and E2). Non-structural proteins involved in viral replication in the host cell are proteins, such as protease (NS2, NS3, NS4A), helicase (NS3), RNA-dependent RNA polymerase (NS5B).^[2]

HCV is a causative agent of chronic hepatitis commonly found worldwide, infecting more than 170 million people and posing a severe public health threat, especially since there is no protective vaccine.^[3, 4] In Turkey, it is estimated that about 1 million people are infected with HCV.^[5] The virus is usually transmitted through blood transfusion, surgical and dental procedures, intravenous drug use, and sexual intercourse.^[5] According to the World Health Organization data, 3% of the world's population is infected with HCV, mostly in developed countries. Although it generally causes asymptomatic infection, the development of chronic hepatitis (85%), cirrhosis (20%) and hepatocellular carcinoma (1-4%) is important concerning mortality and morbidity.^[6]

One of the important features of HCV is its ability to create genetic diversity through interactions it enters in the host cell. This feature leads to its chronicity in the presence of immune response and the development of resistance against antiviral drugs.^[4] There are differences in nucleotide and amino acid sequences in different regions of the HCV genome.^[7] HCV genotypes display the sequence divergence at 30%–35% of nucleotide sequence while different HCV subtypes of a genotype differ by at least 15% of the nucleotide sequence.^[1, 4] Studies have shown that HCV has at least seven major genotypes and many subtypes.^[8] Genotype 7 was first reported in a Central African immigrant in Canada.^[9] Later, a few more genotype 7 were reported in Central Africa.^[10] It is also important to detect mixed infections safely since they can cause treatment failure.^[3] Determining the geographic distribution of HCV genotypes is critical in the development of rational therapy protocols.^[5] Although the rate and distribution of HCV genotypes differ regionally, 1a, 1b, 2a, 2b, 3a, and 3b are genotypes that are commonly found.^[11] The most common genotype worldwide is genotype 1 and the most common subtype is subtype 1b.^[1, 6] When we look at its distribution around the world, genotype 1 is in North and South America, the genotype 2 is in East Asia, genotype 3 is in Asia and Europe, especially in India and Pakistan, the genotype 4 is in the Middle East and North Africa, genotype 6 is in Southeast Asia and genotype 5 is found in South Africa, although rare.^[12] The most common genotype in our country is subtype 1b, and different genotype rates are observed in different regions.

This study aims to determine the HCV genotypes in our hospital in Istanbul, which is an important tourism center, where population mobility is intense, and to reveal the dis-

tribution by years. Our results will contribute to the epidemiological data of Turkey.

Methods

Three hundred eighty-five patient samples which were sent to Sisli Hamidiye Etfal Training and Research Hospital Clinical Microbiology Laboratory between January 2016 and June 2019 for genotype assay in anti-HCV (+) patients were tested.

Anti-HCV (Elecsys Anti-HCV II, Roche Diagnostics, Germany) was studied using Enzyme Immunoassay (EIA) method for serological diagnosis. When the reactive results were rerun with the same test kit and reactive results were obtained, the confirmation study was performed with Line Immunoassay (INNO-LIA HCV Score, Innogenetics, Belgium). Samples confirmed by LIA were considered as anti-HCV positive.

Genotype assay was performed using HCV-TS test kit (AB Analitica, Italy) between January-June 2016, Abbott RealTime HCV Genotype II (Abbott Diagnostics, Germany) between June 2016-February 2017, and Bosphore HCV genotyping kit v3 (Anatolia Geneworks, Turkey) between February 2017-June 2019. In the EU Analitica system, genotype assay is performed with reverse line blot and reverse transcription of 5'UTR (untranslated regions) region. In the Abbott RealTime HCV Genotype II system, genotype assay is performed by hybridization of 5'UTR regions and amplification of NS5B regions. Genotype assay is performed using Montania 4896 Anatolia Bosphore HCV genotyping kit v3 using the amplification and fluorescence detection method of the HCV genome 5'NS5B region.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics were given as number and percentage for categorical variables, mean, standard deviation, minimum, maximum for numerical variables. The rates in the groups were compared by Chi-Square Analysis and Bonferroni correction was applied. The statistical alpha significance level was considered as $p < 0.05$.

Results

In this study, 385 patients, of which 145 (37.7%) were males and 240 (62.3%) were females, were included. The ages of cases were between 10-91, while the average age was 56.72 ± 17.0 . When we evaluated the cases according to age groups, the majority of the patients were in the adult group, i.e., the group under 20 constituted 1.6% of the total HCV genotypes, and the group over 20 constituted 98.4% of all patients.

In our study, genotype 1 was the most prevalent HCV genotype with a rate of 81.3% (313), followed by genotype 3 at 8.8% (34), genotype 2 at 3.4% (13), genotype 4 at 2.9% (11), genotype 5 at 0.8% (3). Among patients with genotype 1, subtype 1b was the predominant subtype with a rate of 67.8% (261), followed by subtype 1a at 10.9% (42). While 374 cases yielded only one HCV genotype result, 11 cases (2.9%) were determined as mixed genotypes.

There was a statistically significant difference in genotype distribution according to gender. Subtype 1a and genotype 3 were higher in males while subtype 1b was higher in females ($p=0.002$). Genotype distribution by gender is given in Table 1.

A statistically significant difference was found in genotype distribution by age groups; subtype 1a was significantly higher in 0-20 age group, while subtype 1b was higher in all age groups over 20 ($p<0.001$). Genotype distribution by age group is given in Table 2.

When the distribution over the years is evaluated, subtype 1b has been detected at the highest rate for all years. Mixed genotype was detected only in 2018 and 2019, and accordingly, a statistically significant difference was observed in genotype distribution rates by years ($p<0.0083$). Genotype distribution by years is given in Table 3.

Discussion

HCV poses a severe health problem all over the world for several reasons, such as high chronicity rate, inducing severe liver diseases, and having no effective vaccine.^[11]

Depending on the immunological conditions, the infection can be cleared naturally in 20 to 45% of patients infected with HCV, usually in the first six months after exposure.^[6, 13]

The diagnosis is made by serological tests aimed to detect antibodies against recombinant antigens; anti-HCV may not be detected in patients with chronic renal failure and immune deficiency. If there is evidence of chronic liver disease in these patients, the diagnosis is made by displaying genetic material. Detection of HCV RNA and determination of genotype are crucial for early detection and treatment of chronic HCV infection.^[14] Identification of HCV genotypes has importance in antiviral treatment, dose adjustment of antiviral agents, determining the duration of treatment, following the response to the treatment, and predicting the patient prognosis.^[1]

Direct-acting antivirals (DAA) have significantly increased the treatment success of chronic HCV infection. Sustained virological response (SVR) defined as aviremia 12 weeks after the end of treatment.^[13] With the combination of pegylated interferon (IFN)-alpha and ribavirin used in the past, the rates of SVR were observed to be quite low.^[15] With dual treatment, the rates of SVR are between 75-90% in genotypes 2 and 3 and 20-50% in genotypes 1 and 4. With the development of new combination DAA regimes approved by the FDA in late 2014, over 90% cure rates are provided for most patients. Genotype data and, in some cases, the presence of a subtype constitute a very important part of determining the most appropriate DAA selection and duration of treatment.^[13] Regional determination of genotypes is important for establishing epidemiology and treatment protocols.

Various studies have been conducted in our region and our country demonstrating the distribution of HCV genotypes (Table 4). Genotype 1 accounts for 46% of all HCV infections in the world.^[1] It has also been reported that the vast majority of HCV infection in Turkey is caused by genotype 1

Table 1. Genotype distribution by gender

Genotype	Total		Gender				p
	n	%	Male		Female		
			n	%	n	%	
1a	42	10.9	27	18.6	15	6.3	<0.001
1b	261	67.8	83	57.2	178	74.2	0.001
1	10	2.6	2	1.4	8	3.3	0.331
2	13	3.4	4	2.8	9	3.8	0.774
3	34	8.8	20	13.8	14	5.8	0.008
4	11	2.9	4	2.8	7	2.9	1.000
5	3	0.8	1	0.7	2	0.8	1.000
6	-	-	-	-	-	-	
Mixt	11	2.9	4	2.8	7	2.9	1.000
Total	385		145		240		

Table 2. Genotype distribution by age group

Age	Genotype									Total
	1a	1b	1	2	3	4	5	6	Mixt	
0-20										
n	3	1	-	-	-	1	-	-	1	6
%	50.0	16.7	-	-	-	16.7	-	-	16.7	100
21-30										
n	5	11	-	-	3	1	-	-	1	21
%	23.8	52.4	-	-	14.3	4.8	-	-	4.8	100
31-40										
n	4	33	2	1	11	-	-	-	1	52
%	7.7	63.5	3.8	1.9	21.2	-	-	-	1.9	100
41-50										
n	18	24	-	1	8	1	-	-	4	56
%	32.1	42.9	-	1.8	14.3	1.8	-	-	7.1	100
51-60										
n	6	47	1	2	5	3	1	-	1	66
%	9.1	71.2	1.5	3.0	7.6	4.5	1.5	-	1.5	100
61-70										
n	6	72	2	6	5	4	2	-	1	98
%	6.1	73.5	2.0	6.1	5.1	4.1	2.0	-	1.0	100
71-										
n	-	73	5	3	2	1	-	-	2	86
%	-	84.9	5.8	3.5	2.3	1.2	-	-	2.3	100
Total										
n	42	261	10	13	34	11	3	-	11	385
%	10.9	67.8	2.6	3.4	8.8	2.9	0.8	-	2.9	100

Table 3. Genotype distribution by years

	2016		2017		2018		2019	
	n	%	n	%	n	%	n	%
Genotype 1	147	87.5	73	77.6	66	75.0	27	77.1
1a	19	11.3	9	9.6	10	11.4	4	11.4
1b	118	70.2	64	68.1	56	63.6	23	65.7
1	10	6	-	-	-	-	-	-
Genotype 2	5	3	6	6.4	1	1.1	1	2.9
Genotype 3	11	6.5	11	11.7	12	13.6		
Genotype 4	3	1.8	4	4.3	3	3.4	1	2.9
Genotype 5	2	1.2	-	-	1	1.1	-	-
Mixt	-	-	-	-	5	5.7	6	17.1
Total	168	100	94	100	88	100	35	100

and its prevalence ranges from 51.7% to 97.1%.^[20,28] Similar to other data in our country, genotype 1 was found as the most common genotype in the present study, with a rate of 81.3%. Subtype 1b is the most prevalent genotype in Turkey, with prevalence ranging from 97.4% to 52.7%.^[21, 22] In our study, subtype 1b was detected as the most common subtype with a rate of 67.8%. In a study conducted by Sele

et al. in Istanbul in 2015-2016, genotypes 1, 2, and 3 were identified and the subtype 1b ratio was reported as 67%.^[1] In another study from the Istanbul region covering the years 2013-2016, Karabulut et al. identified genotypes 1, 2, 3, 4, and reported subtype 1b at the rate of 38.8%.^[29] In our study, unlike other researches in the Istanbul region, genotype 5 and mixed genotypes were detected.

Table 4. Some of the HCV genotype studies conducted in different centers in our country

Research	Date	Province	n	Genotype (%)								
				1a	1b	1	2	3	4	5	6	Mixt
Abacioğlu et al. ^[16]	1995	İzmir	89	19.1	75.3	-	3.4	-	2.2	-	-	-
Yarkın et al. ^[17]	2000	Adana	72	14.5	82.2	-	3.3	-	-	-	-	-
Özacar et al. ^[18]	2001	İzmir	170	10	81.2	-	2.4	0.6	1.2	-	-	4.7
Bozdayı et al. ^[19]	2004	Ankara	365	11	84	-	-	1	1	-	-	-
Altuğlu et al. ^[20]	2008	İzmir	345	9.9	87.2	-	0.9	1.4	0.6	-	-	-
Aktaş et al. ^[21]	2010	Zonguldak	44	2.6	97.4	-	-	-	-	-	-	-
Gökahmetoğlu et al. ^[22]	2011	Kayseri	146	3.4	52.7	5.5	2.7	-	35.6	-	-	-
Tezcan et al. ^[23]	2013	Mersin	236	1.7	84.7	5.9	2.1	4.2	0.8	-	0.4	-
Kayman et al. ^[24]	2012	Kayseri	375	2.4	57.6	2.4	3.2	1	32	-	-	1.4
Sağlık et al. ^[25]	2014	Antalya	422	14.7	63.3	5.4	3.5	11.1	1.6	-	-	-
Çetin Duran et al. ^[26]	2016	Adana	119	12.6	58.8	-	7.6	16.8	3.4	0.8	-	-
Tiryaki et al. ^[4]	2018	Aydın	182	18.1	69.2	2.2	1.7	7.2	1.7	-	-	-
Cirit et al. ^[27]	2019	Şanlıurfa	312	5.4	54.8	9.2	14.1	3.8	10.3	1.6	-	0.6
This research	2019	İstanbul	385	10.9	67.8	2.6	3.4	8.8	2.9	0.8	-	2.9

HCV: Hepatitis C virus.

When the Middle East region, is considered, HCV has a very high prevalence with 4.7%.^[30] Egypt is the country with the highest HCV prevalence (14.7%) in the world.^[12] In a meta-analysis by Ghaderi-Zefrehi et al., examining the studies investigating the distribution of HCV genotypes in the Middle East countries, it is reported that genotype 1 is the most common in Bahrain, Iran, Israel, Lebanon and the United Arab Emirates (36.59%, 56.66%, 68.02%, 34.93%, 41.36%, respectively). The most common genotype in Syria, Iraq, and Egypt is genotype 4, detected with the ratios of 57.36%, 60.26%, and 86.22%, respectively, and genotype 1 is the second most common in these countries.^[31] It is reported that genotype 4 originated mainly from Central Africa and spread from there to North Africa. Besides, there were also opinions stating that it might be related to population movements during World War II.^[10] In an HCV genotype study examining the years 2004-2006 in Syria, genotype 1 was determined as 28.5%, genotype 2 as 0.8%, genotype 3 as 1.8%, genotype 4 as 59% and genotype 5 as 10%.^[32] In our study, genotype 4 was found at a rate of 2.9%. The follow-up of genotype 4 is important because it is a common genotype in neighboring countries, and it is more resistant and has a longer duration of treatment. The rate of genotype 5 was found at 0.8%. Although genotype 5 is mostly found in South Africa, there are studies reporting that it has been detected at certain rates in Syria, and all three the cases in our study were from Syria.

Mixed genotype HCV infection may develop in 25% of those infected via blood transfusion or intravenous drug

use.^[13] Detection of mixed genotype infection is important as it can cause treatment failures.^[3] Although HCV genotype detection methods are reliable, none of these tests are sufficient to detect mixed infections. If the genotype test method used in the patient with mixed genotype only detects the dominant genotype, since the treatment will be specific to this genotype, this may lead to genotype change and treatment failure. Although there is no clear recommendation in the guidelines, it is reported that pan-genotypic treatment can be used as a precaution.^[33] In studies conducted, the rate of mixed genotype HCV infection was 1.6% in Poland, 5.5% in Pakistan, 7.1% in Brazil, 0.9% in France, 1.1% in Russia.^[3] In a study covering the vast majority of Europe, the prevalence of mixed genotype HCV infection was 0.7% with data from 33 countries between 2000-2015.^[34] In a study conducted by Kùlah et al.^[3] covering 23 centers in Turkey, the rate of mixed genotype HCV infection was found as 1.3%. In studies conducted in different regions of Turkey, it is seen that the ratio of mixed genotype has reached up to 5.1%.^[18, 35] In our study, HCV mixed genotype rate was 2.9%.

It is reported in different studies that HCV genotype rates vary according to genders. In some studies, subtypes 1a and 1b were higher in female patients,^[6] while in some studies, subtype 1b was higher in female patients, subtype 1a and genotype 3 in male patients.^[1, 23] In our study, subtype 1b was higher in female patients, and subtype 1a and genotype 3 were higher in male patients. No significant difference was observed between genders for other genotypes (Table 1).

The prevalence of HCV in children is 54% in low-income countries, 28% in low-middle-income countries, 21% in high-middle-income countries, and 4% in high-income countries.^[12] In our study, the total HCV genotype rate was 1.6% in the group under 20 years of age. While the most common genotype in this age group was detected as subtype 1a, the most common genotype in groups above 20 years was the subtype 1b. In studies conducted, it is seen that the average age for genotype 1b is above 50.^[6, 23] In our data, the average age for genotype 1b is 59.9 and 73.6% of the cases (192/261) were over 50 years old (Table 2).

When the genotype changes by years were evaluated, a statistically significant difference was found only in mixed genotypes. No significant change was found among other genotypes. When we examine the change of subtype 1b over the years, it is seen that it varies between 63.6% and 70.2%. Although the total of genotype 1 showed increasing and decreasing rates over the years, it was found to vary between 75% and 87.5%. Two of the three cases with genotype 5 detected in 2016 and one in 2018. Mixed genotypes were detected only in 2018 and 2019 (Table 3). Due to international travel, tourism, and trade, especially in the past 50 years, migrations and mass human movements have led to the emergence of an unlimited world concept. Approximately 2.3% of the world's population is migrants, with about 740 million internal migrants and 232 million international migrants. When the presence of informal immigrants is added to these figures, the number is much higher. High migration rates to our country, from regions where HCV is endemic, may cause differences in the incidence of the disease and the genotype distribution of HCV.^[1] Since Istanbul is one of the world's travel centers concerning tourism and an important city that receives external and internal migration, it is important to follow HCV genotype changes and epidemiological data.

The limitation of our study is that the genotype distribution was prepared only with the patients' data requested by the clinician. This is likely to have been reflected in the rates in our data.

As a result, subtype 1b was found most frequently in our study. Considering the population mobility in our region, the fact that genotype 4, which is common in the Middle East region, and genotype 5, which can be found in the Middle East, in certain ratios, and mixed genotypes, which can affect treatment decision-making processes, have been identified revealing the necessity to continue to carefully monitor genotype distributions and changes in the future.

Disclosures

Ethics Committee Approval: This study has been approved by the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee, Resolution 2509.

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