Research Article

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Seven-year Genotype Distribution Among Hepatitis C Patients in a City in the Central Anatolia Region of Turkey

İç Anadolu Bölgesinde Bir Şehirde Hepatit C Hastalarının Yedi Yıllık Genotip Dağılımları

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ABSTRACT

Objectives: Hepatitis C virus (HCV) is an important viral agent of hepatitis, cirrhosis and hepatocellular carcinoma. In our study, we aimed to determine the HCV genotype distribution among patients with HCV who presented to our hospital in a city in the Central Anatolia Region of Turkey.

Materials and Methods: Results of 480 patients who were positive for HCV RNA and whose serum samples were sent to our laboratory from various inpatient and outpatient clinics of the hospital with a pre-diagnosis of hepatitis C between January 2010 and May 2017 were retrospectively screened. In HCV genotype determination, a commercially available kit (Ampliquality HCV-TS, AB Analitica®, Italy) based on Reverse Line Blot was used in accordance with the manufacturer's recommendations. Genotype distributions were analyzed by years and by age. The first and only one test results of the same patients were evaluated.

Results: Of the patients whose genotyping was made, 260 (54.2%) were female and 220 (45.8%) were male. It was found that 396 (82.6%) of 480 patients were with genotype 1b, 17 (3.5%) - genotype 1a, 15 (3.1%) - genotype 3a, 14 (2.9%) - genotype 1, 9 (1.9%) - genotype 4, 8 (1.7%) - genotype 2, 6 (1.3%) - genotype 2b, 5 (1.0%) - genotype 1a/1b, 4 (0.8%) - genotype 2a/2c, 3 (0.6%) - genotype 4a, 1 (0.2%) - genotype 3, 1 (0.2%) - genotype 5a and 1 (0.2%) patient was with genotype 6.

Conclusion: In chronic HCV patients admitted to our hospital, genotype 1b, which had the highest prevalence in our country, was detected with a rate of 82.6%. In addition, the presence of rare genotypes 5a and 6 in our country has been shown.

Keywords: Hepatitis C, reverse hybridization, genotype

ÖZ

Amaç: Hepatit C virüsü (HCV), hepatit, siroz ve hepatosellüler karsinomun önemli bir viral etkenidir. Çalışmamızda, İç Anadolu Bölgesi'nde bir şehirde, hastanemize başvuran HCV ile enfekte hastaların HCV genotip dağılımlarını saptamayı hedefledik.

Gereç ve Yöntemler: Ocak 2010-Mayıs 2017 tarihleri arasında, laboratuvarımıza hastanenin çeşitli klinik ve polikliniklerinden hepatit C ön tanısı ile serum örneği gönderilen ve HCV RNA pozitifliği olan 480 hastanın sonuçları retrospektif olarak tarandı. HCV genotip tayininde, ters hibridizasyon (Reverse Line Blot) temeline dayanan ticari bir kit (Ampliquality HCV-TS; AB Analitica®, İtalya), üretici firma önerileri doğrultusunda kullanıldı. Genotip dağılımları yıllara ve yaşlara göre incelendi. Aynı hastaların ilk ve tek test sonucu değerlendirmeye alındı.

Bulgular: Genotiplemesi yapılan hastaların 260'ı (%54,2) kadın, 220'si (%45,8) erkek idi. Toplam 480 hastanın 396'sı (%82,6) genotip 1b, 17'si (%3,5) genotip 1a, 15'i (%3,1) genotip 3a, 14'ü (%2,9) genotip 1, 9'u (%1,9) genotip 4, 8'i (%1,7) genotip 2, 6'sı (%1,3) genotip 2b, 5'i (%1,0) genotip 1a/1b, 4'ü (%0,8) genotip 2a/2c, 3'ü (%0,6) genotip 4a, 1'i (%0,2) de genotip 3, genotip 5a ve genotip 6 olarak bulunmuştur.

Sonuç: Hastanemize başvuran kronik HCV hastalarında en sık; ülkemizde de en yüksek prevalansa sahip olan: genotip 1b, %82,6 oranıyla saptanmıştır. Ayrıca, ülkemizde az görülen genotip 5a ve genotip 6'nın varlığı gösterilmiştir.

Anahtar Kelimeler: Hepatit C, reverse hibridizasyon, genotip

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Introduction

Hepatitis C virus (HCV) infection is an important public health problem due to its chronicity risk up to 80% and its complications, such as cirrhosis and hepatocellular carcinoma, that may occur in advanced stages. It is estimated that more than 170 million people are infected with HCV in the world (1).

HCV is the only member of the Hepacivirus genus and belongs to the *Flaviviridae* family. The positive polarity, enveloped RNA genome of 30-60 nm in diameter; encodes 10 proteins (5'-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-3') (2). Six major genotypes and more than 80 subtypes have been identified since HCV was first diagnosed in the late 1980s. All genomes of the genotypes are different from one another at the rate of ≥30% at the nucleotide level while the sub-types under a certain genotype typically differ at that of 15% to 25% (3,4).

In recent years, a new variant called genotype 7 has been identified in patients in Canada and Belgium (4). HCV genotypes have a worldwide distribution and each genotype is classified into several subtypes with about 20% sequence variation (5).

The RNA dependent RNA polymerase enzyme is prone to make mistakes; it causes mutations in glycoprotein and other genomes. The high mutation rate and genomic heterogeneity of the viral genome has a decisive effect on the effectiveness of treatment (5).

The gold standard of genotyping is whole-genome sequencing analysis. This method is relatively expensive, and instead the protein coding regions such as 5'UTR, NS5B, and core region are used in the new-generation tests (6).

Epidemiologic studies have suggested that HCV genotypes are differently distributed between geographical areas, however, genotype 2 is less prevalent than genotype 1 throughout the world. Genotype 3a is more prevalent in South Asia, Australia, and Iran; genotype 4 in the Middle East, and Middle and North Africa; genotype 5a in South Africa; genotype 6a in Hong Kong and Vietnam; genotype 1b in South and East Europe; genotype 1a in North America and Europe (7,8,9,10).

It has been reported in studies performed until today that genotype 1b was the most prevalent genotype in Turkey (11,12). Determining the prevalence of genotypes and their geographical variation is also important in terms of prognosis and treatment.

In our study, we aimed to determine the genotype distribution among hepatitis C patients followed up in our hospital and the potential variation of HCV transmission in our region within the years and ages.

Materials and Methods

We retrospectively analyzed medical records of 480 patients, who were diagnosed with acute hepatitis C between January 2010 and May 2017 via anti-HCV (ELISA; Abbott Laboratories, the U.S.) and HCV RNA [real-time polymerase chain reaction (PCR); COBAS® TaqMan® 48 Analyzer, Roche Diagnostics, the U.S.]. In determining HCV genotype, a commercial kit (Ampliquality HCV-TS; AB Analitica®, Italy), which is based on Reverse Line Blot and called "line prob assay" (LiPA), was used in accordance with the manufacturer's recommendations. This test is based on the fact that the 5'UTR region of HCV RNA is amplified and hybridized with the oligonucleotide primers of the nucleic acids produced. In this test, all the six major HCV genotypes and certain HCV subtypes (1, 1a, 1b, 1a/1b, 2, 2a/2c, 2b, 3, 3a, 4, 4a, 5a, 6, 6a, or 6b) can be detected. The manufacturer identifies its detection sensitivity as 98.1% and its specificity as 100%. We used bands formed in the way that the probes specific for various HCV genotypes are embedded around the nitrocellulose strips. The genotype distribution was reviewed by years. The first and only test results of the same patients were evaluated.

Statistical Analysis

For the data analysis, a software program, SAS University Edition 9.4, was utilized. In the data evaluation, analysis of variance (ANOVA) and a chi-square test were used; a p value of less than 0.05 was considered statistically significant.

Results

Of the patients whose genotyping was made, 260 (54.2%) were female and 220 (45.8%) were male (Table 1). The average age of the patients was calculated as 59.2. It was found that 396 (82.6%) of the 480 patients were with genotype 1b, 17 (3.5) - genotype 1a, 15 (3.1%) - genotype 3a, 14 (2.9%) - genotype 1, 9 (1.9%) - genotype 4, 8 (1.7%) - genotype 2, 6 (1.3%) - genotype 2b, 5 (1.0%) - genotype 1a/1b, 4 (0.8%) - genotype 2a/2c, 3 (0.6%) - genotype 4a, 1 (0.2%) - genotype 3, 1 (0.2%) - genotype 5a and 1 (0.2%) patient was with genotype 6 (Table 2).

Discussion

The HCV genotypes determine the choice of treatment and the duration of the selected treatment. For HCV genotype 1, either the rate of response to interferon treatment is lower or the risk of progression of hepatocellular carcinoma is higher compared to other genotypes. Response to treatment in infected patients with HCV genotype 1 and 4 is lower than in those with genotype 2 and 3 and treatment duration is longer (5).

Table 1. Distribution of genotypes by sex and mean age

Genotype	1a	1b	1a/1b	1	2a/2c	2b	2	3a	3	4a	4	5a	6	Total (%)
Number	17	396	5	14	4	6	8	15	1	3	9	1	1	480 (100)
Female %	7 41.2	225 56.8	4 80.0	6 42.9	3 75.0	0 0	4 50	3 20.0	1 100.0	1 33.3	5 55.6	0 0	1 100.0	260 (54.2)
Male %	10 58.8	171 43.2	1 20.0	8 57.1	1 25.0	6 100.0	4 50	12 80.0	0 0	2 66.7	4 44.4	1 100.0	0 0	220 (45.8)
Mean Age	60.8	60.4	60.0	65.3	63.3	28.5	56.1	40.7	46.0	51.7	51.1	49.0	74.0	59.2

Currently, there are many methods used for HCV genotyping. However, the gold standard of genotyping is the sequence analysis of the core, E1, NS5b and 5'-UTR regions and phylogenetic analysis made afterwards (6,30,31).

However, the methods of sequence analysis require special equipment and experienced personnel. Therefore, it can be performed only in specific labs. We can count the other methods such as genotyping performed using PCR made by targeting the core or NS5b regions with genotypic primers; genotyping performed using restriction fragment length polymorphism (RFLP) made by clipping 5'UTR region with the restriction enzymes after PCR amplification; genotyping made by targeting 5'UTR, C, E1, NS3, or NS5b; genotyping by reverse hybridization after PCR with type-specific probes; and serotyping performed using C, E2 or NS4 region peptides (30,31).

These methods used in performing HCV genotyping studies can determine major genotype groups but nonetheless, it is stated that their discriminatory power among the subtypes is not as effective as phylogenetic analysis (6).

In our study, we also used a commercial kit based on reverse line blot. In this test, based on the amplification of the 5'UTR region of HCV RNA and hybridization of the resulting nucleic acids with oligonucleotide primers, dark colored bands formed by probes specific for different HCV genotypes attached to nitrocellulose strips were evaluated.

When the four main genotypes (Turkey posthoc) were statistically compared, the average ages of patients with genotype 1 and genotype 2 (p=0.0003), genotype 1 and genotype 3 (p=0.0001) and genotype 1 and genotype 4 (p=0.0452) were found to be different from each other. The age distribution by genotypes is presented in Figure 1. When the four main genotypes were compared by gender using a chi-square test, there was a statistically significant difference among them (p=0.0491). According to our study, the average age of patients with genotype 1 was higher than 60 years (n=432) as in other countries. The highest reported HCV prevalence in the world was in Egypt, where the prevalence of infection increases steadily with age, and high rates of infection are observed among persons in all age groups (32).

In conclusion, it was found that genotype 1b, which has the highest prevalence in Turkey, is also the most prevalent genotype in our region by 82.6%. The high incidence of genotype 1b remained the same within the years, yet the ranking of other genotypes changed. In addition, the presence of genotype 5a and genotype 6, which are rare genotypes in Turkey, has been reported.

In Turkey, there are many studies conducted at various times related to HCV genotyping. These studies have been done using many different methods such as reverse hybridization, PCR, RFLP, sequence analysis, pyrosequencing and LiPA. The results of these studies are presented in Table 3. In their study investigating the distribution of HCV genotypes in 7 regions of Turkey by evaluating 7002 patients with chronic HCV infection using LiPA method, Altindis et al. (13) found that 67.7% of patients had type 1b, 7.7% had type 1, and 5.5% patients had type 1a. In their study including 422 HCV RNA-positive patients performed in Antalya, Sağlik et al. (15) determined that 63.3% of subjects had genotype 1b, 14.7% had genotype 1a and 11.1% had genotype 3a. In their study, Oztürk et al. (18), using the method of pyrosequencing of 639 samples, found genotype 1b in 86.7% and genotype 2 in 9.3% of patients in Antakya and genotype 1b in 55.2% and genotype 3 in 26% in Adana. Altuglu et al. (12) investigated serum samples collected from 535 patients with chronic HCV infection and reported that infection with subtype 1a and subtype 1b was observed in 12.9% and 80.4% of patients, respectively. In studies performed in Turkey, the incidence of genotype 1b has

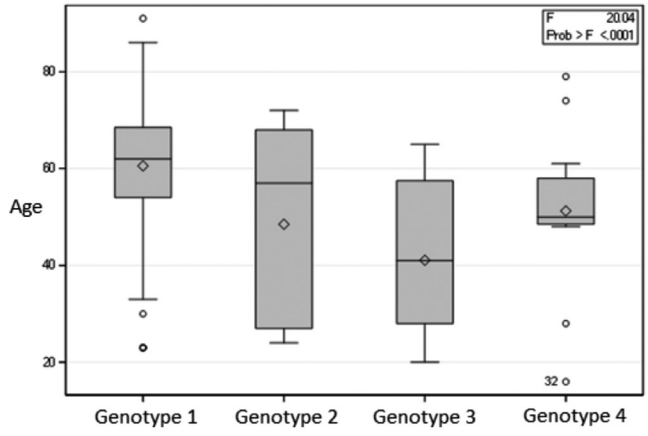

Figure 1. Age distribution by genotypes (ANOVA)

Table 2. Distribution of hepatitis C virus genotypes by years

	Genotype 1				Genotype 2			Genotype 3		Genotype 4		Genotype 5	Genotype 6
Year	**1a**	**1b**	**1a/1b**	**1**	**2a/2c**	**2b**	**2**	**3a**	**3**	**4a**	**4**	**5a**	**6**
2010	0	60	0	3	2	0	0	3	1	0	2	0	0
2011	0	76	1	1	1	1	1	1	0	0	3	0	0
2012	1	75	2	2	0	0	3	1	0	0	1	1	1
2013	1	57	1	1	0	0	3	2	0	0	0	0	0
2014	1	20	0	2	1	1	0	0	0	0	1	0	0
2015	0	23	0	0	0	0	0	1	0	0	1	0	0
2016	9	57	1	4	0	1	1	4	0	3	1	0	0
2017	5	28	0	1	0	3	0	3	0	0	0	0	0
Total	17	396	5	14	4	6	8	15	1	3	9	1	1
Percent (%)	3.5	82.6	1.0	2.9	0.8	1.3	1.7	3.1	0.2	0.6	1.9	0.2	0.2

Table 3. Hepatitis C virus genotype distributions according to studies conducted in Turkey

Location	Time	Researcher	Method	Number	1	1a	1b	1a/1b	2	2a	2b	2a/2c	3	3a	4	4a	5	6	Other
Multi-centered	2009-2014	Altindis et al.(13)	LiPA	7002	7.7%	5.5%	67.7%	0.2%	3.6%	-	0.1%	1.1%	6.7%	-	7.4%	-	0.1%	0.02%	0.13% (mix)
Istanbul	2016-2017	Oral Zeytinli et al. (14)	LİPA	554	-	22.9%	56.3%	0.5%	-	-	-	0.5%	16.9%	-	0.5%	-	-	-	0.1% (1b/4) Unknown (1.9%)
Antalya	2009-2013	Sağlik et al. (15)	LiPA	422	5.4%	14.7%	63.3%	-	2.6%	-	0.9%	-	-	11.1%	1.4%	-	-	-	0.2% (4e), 0.2% (mix)
Kayseri	2010-2011	Kayman et al. (16)	PCR	375	62.4%	-	-	-	3.2%	-	-	-	1.1%	-	32.0%	-	-	-	-
Adana	1996-2013	Kuscu et al. (17)	Different methods	369	78.3%	-	-	-	6.2%	-	-	-	14.6%	-	0.8%	-	-	-	-
Antakya	2010-2012	Oztürk et al. (18)	Pyrosequencing	324	-	0.3%	86.7%	-	9.3%	-	-	-	0.9%	-	2.8%	-	-	-	-
Adana	2010-2012	Öztürk et al. (18)	Pyrosequencing	315	-	3.5%	55.2%	-	14.6%	-	-	-	26.0%	-	0.6%	-	-	-	-
Mersin	2013	Tezcan et al. (11)	LiPA	236	3.8%	1.7%	84.7%	2.1%	0.4%	-	1.3%	0.4%	-	4.2%	0	0.8%	-	0.4%	-
Bursa	2010-2012	Agca et al. (19)	Reverse hybridization	231	92.6%	-	-	-	0.4%	-	-	-	3.9%	-	3.1%	-	-	-	-
Izmir	2005-2010	Altuglu et al. (12)	RFLP	215	-	12.9%	80.4%	-	1.5%	-	-	-	3.7%	-	1.5%	-	-	-	-
Sivas	2008-2009	Celik et al. (20)	Reverse hybridization	178	-	9.0%	88.2%	-	0	1.12%	-	-	1.7%	-	-	-	-	-	-
Nevşehir	2011-2014	Borcak et al. (21)	PCR	170	45.1%	-	37.0%	-	14.5%	-	-	-	1.2%	-	0.6%	-	-	-	-
Antalya	2011-2013	Çekın et al. (22)	RFLP- Sequence analysis	148	8.8%	12.8%	60.8%	-	4.1%	-	-	-	11.5%	-	2.0%	-	-	-	-
Kayseri	2011	Gökahmetoğlu et al. (23)	Pyrosequencing	146	5.5%	3.4%	52.7%	-	-	2.7%	-	-	-	-	21.9%	4.8%	-	-	8.9% (4d)
Eastern Anatolia Region	2011-2014	Aktas et al. (24)	Pyrosequencing	108	-	8.3%	87.0%	-	-	-	-	-	-	3.7%	-	-	-	-	1% (4d)
Kahraman-maraş	2010-2012	Kirisci et al. (25)	PCR	100	60.0%	-	-	-	-	-	-	-	40.0%	-	-	-	-	-	-
Manisa	2002-2005	Sanlidag et al. (26)	Sequence analysis	100	-	2.0%	90.0%	-	-	2.0%	-	-	-	-	-	5.0%	-	-	-
Diyarbakır	2007-2008	Ozbek et al. (27)	LiPA	74	4.1%	-	87.8%	-	2.7%	-	-	-	2.7%	2.7%	-	-	-	-	-
Adıyaman	2013-2016	Akgun et al. (28)	Sequence analysis-PCR	71	4.2%	8.4%	71.8%	-	-	-	11.3%	-	-	4.2%	-	-	-	-	-
Konya	2010-2012	Demircili et al. (29)	LIA	65	-	1.5%	90.8%	3.1%	-	-	-	1.5%	-	1.5%	1.5%	-	-	-	-
Gaziantep	2010	Karslıgil et al. (30)	Sequence analysis	51	-	9.8%	78.4%	-	-	7.8%	-	-	-	2.0%	-	-	-	-	2% (4c)

LiPA: Line prob assay, PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism, LIA: Line immunoassay

been reported in the range of 37-90.8% and the most commonly detected genotype was found to be genotype 1b. It is followed by genotype 1a, genotype 4, and genotype 3 respectively. Genotype 4a, genotype 5 and genotype 6, which are rare genotypes, were detected at various rates.

Conclusion

In this study, we determined the distribution of HCV genotypes in our region, which is crucial for treatment regulations and in identifying prognosis and made a contribution to the epidemiologic data in the way of evaluating its trend within the last seven-year period.

Ethics

Ethics Committee Approval: There is no ethics committee approval because the study is retrospective.

Informed Consent: Since the study was retrospective, the patient's consent was not taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.T., Design: U.T., M.B., Data Collection or Processing: B.F., Analysis or Interpretation: M.Ö., Literature Search: B.S.G., Writing: U.T.

Conflict of Interest: There is no conflict of interest between authors.

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