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Distribution of HCV Genotypes in Patients of with Chronic Hepatitis C in the Eastern Anatolia Region

Doğu Anadolu Bölgesindeki Kronik Hepatit C Hastalarında HCV Genotiplerinin Dağılımı

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ABSTRACT

Objectives: Hepatitis C is a blood-borne virus affecting a large number of people all over the world. Hepatitis C virus (HCV) is one of the important causative agents of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Its viral genotypes variability affects response to interferon treatment. Therefore, identification of viral genotypes is key to management and treatment of hepatitis C infection. In our region, there has been no study on genotyping of the virus yet. This study was designed to determine the prevalence of HCV genotypes in our region.

Materials and Methods: This study was conducted on the serum specimens of patients with chronic hepatitis C in the provinces of the Eastern Anatolia Region who attended Atatürk University between January 2011 and February 2014. Anti-HCV antibodies in the serum specimens were identified using an enzyme immunoassay kit (Dia. Pro Diagnostic Bioprobes Srl, Milan, Italy) and automatic analyzer, (Radim/Alisei®, Calenzano-Firenze, Italy). HCV-RNA load was detected by quantitative PCR (Qiagen©, Germany). HCV genotypes were determined by pyrosequencing method using Pyromark Q24 kit and automatic analyzer (Qiagen©, Germany).

Results: Four different HCV subgenotypes including 1b (87.0%), 1a (8.3%), 3a (3.7%) and 4d (1%) have been identified in seven different provinces within the Eastern Anatolia Region. Genotype 1 was found to be the most common major genotype.

Conclusion: The prevalence of HCV genotypes in patients in the Eastern Anatolia Region was reported for the first time. We assume that the results obtained from this study may contribute to regional epidemiological data on HCV genotypes and to the treatment strategies for patients with hepatitis C in our region. (Viral Hepatitis Journal 2014; 20(3): 91-94)

Key words: Hepatitis C virus, Anti-Hepatitis C Virus, Hepatitis C Virus genotypes, enzyme immunoassay, quantitative PCR, pyrosequencing

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ÖZET

Amaç: Hepatit C virüsü (HCV) kan yoluyla bulaşan, tüm dünyada geniş kitleleri etkileyen, kronik hepatit, siroz ve hepatoselüler karsinom gibi hastalıkların önemli etkenlerinden biridir. Hepatit C virüsünün genotipik değişkenliği hepatit C hastalarının takibinde ve tedavisinde yol gösterici olmaktadır. Daha önce Doğu ve Kuzey-Doğu Anadolu bölgesi hastalarında hepatit C virüs genotiplendirilmesiyle ilişkili bir sonuç verilmemiştir. Bu çalışma, yöremizdeki hastalarda hepatit C virüs genotip prevalansının belirlenmesi amacıyla planlanmıştır.

Gereç ve Yöntemler: Bu çalışma Doğu Anadolu bölge illerinden Ocak 2011-Şubat 2014 tarihleri arasında Atatürk Üniversitesi Araştırma Hastanesine başvuran kronik hepatit C hastalarının serum örnekleri üzerinde gerçekleştirilmiştir. Anti-HCV antikorları enzim immunoassay kitleri (Dia. Pro Diagnostic Bioprobes Srl, Milano, Italy) ile otomatik analizörde (Radim/Alisei®, Calenzano-Firenze, Italy); HCV-RNA yükü kantitatif PCR (Qiagen©, Germany) ile araştırıldı. HCV genotipleri pirosekanslama yöntemi ile (Pyromark Q24 kit, Qiagen©, Germany) kitleri ve otomatik analizörü kullanılarak araştırılmıştır.

Bulgular: Bu çalışmada, Doğu Anadolu bölgesi sınırları içindeki yedi farklı ilde yaşayan kronik hepatit C'li olgularda 1b (%87,0), 1a (%8,3), 3a (%3,7) ve 4d (%1) olmak üzere dört farklı HCV subgenotipi tespit edilmiştir. Bölgemizde en yaygın ana genotipin genotip 1 olduğu görülmüştür.

Sonuç: Doğu Anadolu illerindeki kronik hepatit C'li hastalarda HCV genotiplerinin prevalansı ilk kez bildirilmiştir. Bu çalışmanın, HCV genotiplerine ilişkin bölgesel epidemiyolojik verilere ve bölgemizdeki HCV'li hastaların tedavi stratejilerinin belirlenmesine katkı sağlayacağını düşünüyoruz. (Viral Hepatit Dergisi 2014; 20(3): 91-94)

Anahtar kelimeler: Hepatit C virüsü, Anti-Hepatit C Virüsü, Hepatit C Virüsü genotipleri, enzim immunoassay, kantitatif PCR, pirosekanslama

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Introduction

Hepatitis C virus (HCV) is a member of the genus Hepacivirus in the Flaviviridae family. It causes various important clinical pictures such as chronic hepatitis, cirrhosis and hepatocellular carcinoma (1). Approximately 200 million people in the world are infected with HCV and are at risk of developing above cited diseases. It has been suggested that HCV-associated end-stage liver disease and/or hepatocellular carcinoma account for more than half of adult liver transplantation cases in Western countries, and that HCV-associated diseases is expected to exponentially increase in the near future (2). The natural course of hepatitis C virus infection varies from person to person. It has been stated that approximately 20-30% of infected persons get rid of the virus from their bodies in the acute phase, and the remaining of infected persons may develop chronic hepatitis which could progress to cirrhosis and liver cancer in 20-30 years (3). The current treatment for HCV infection is made by administration of PEG-interferon-α in combination with ribavirin (RBV). A favorable response to this treatment is achieved in about 50% of patients (4).

HCV is a single-stranded positive-sense virus with a genomic RNA molecule approximately 9.600 nucleotides in length. There are significant differences in nucleotide and amino acid sequences in the different regions of the HCV genome. This heterogeneous virus is divided into six major genotypes and about 80 subtypes, according to the mutational differences from the reading, lack of RNA polymerase (5). The prevalence of predominant genotypes is varied in HCV-infected people living in different geographies. The most common genotypes are 1, 2 and 3 throughout the world. HCV subtypes 1a and 1b are common in the US and Europe. In Japan, genotype 1b is responsible from approximately 1/4 of HCV-infected patients. Genotypes 2a and 2b are relatively common in North America, Europe and Japan, and genotype 2c is found commonly in Northern Italy. HCV genotype 4 has been reported to be prevalent in North Africa and the Middle East, and genotypes 5 and 6 in South Africa and Hong Kong (6). It has been reported that HCV prevalence was between 2% and 3% in the world and between 1% and 1.9% in Turkey, but genotype 1 is most common (68-94%) and least responsive to current therapies (7).

Clinical course of the disease, response to treatment in HCV-infected patients varies depending on HCV genotypes. As an example, individuals with genotype 1b are less likely to respond well to IFN treatment, besides, the risk of developing hepatocellular carcinoma is high (8). This study is planned to contribute to the determination of the treatment process and to the treatment strategies by identifying the HCV genotypes in infected patients in our region.

Materials and Methods

Patients

This study was conducted on serum specimens of 108 patients (59 males, 49 females; median age: 50.6 years; range:20-76 years) admitted to Atatürk University Research Hospital one of the provinces of the Eastern Anatolia Region between January 2011 and February 2014.

Serologic Tests

Anti-HCV antibodies in the serum specimens were investigated using an enzyme immunoassay kit (Dia. Pro Diagnostic Bioprobes Srl, Milano, Italy) and automatic analyzer, (Radim/Alisei®, Calenzano-Firenze, Italy) according to the manufacturer's recommendations.

Purification of Hepatitis C Virus-RNA and PCR

Hepatitis C Virus-RNA was purified by QIAsymphony DSP Virus/Pathogen Midi Kits (Qiagen, Germany) from 1000 µL of serum specimens taken from each patient.

PCR reaction was used in the amplification of HCV core and 5 'UTR regions that are very well protected for genotyping. In the RNA samples, cDNA and PCR reaction of these two regions was performed by a one-step RT-PCR. QIAGEN PyromarkOneStep RT-PCR Kit (Qiagen, Germany) was used in the reaction. PCR-1 and PCR-2 reaction mixes (5X RT-PCR buffer 10 µL, dNTP 2 µL, HCV primer pair 2 µL, RT-PCR enzyme mix 2 µL, water 29 µL and template RNA 5 µL) for two different regions of the HCV genome to be be amplified were prepared according to the manufacturer's protocol. PCR cycles: 50 °C for 30 minutes 1 cycle (reverse transcription), 95 °C for 15 minutes 1 cycle (HotStarTaq DNA Polymerase activation), 94 °C for 30 seconds, 58 °C for 30 seconds, 72 °C for 30 seconds 45 cycles and finally 1 cycle 10 minutes at 72 °C (final extension). The same temperature cycles were used in both PCR reactions. Amplification products of different portions of the HCV genome (240 bp in PCR-1 and 180 bp in PCR-2) were obtained at the end of the reaction. The products were kept on ice packs ready to be used as template for sequenced.

HCV Genotyping

In pyrosequencing analysis, Pyromark Q24 (Qiagen©) devices and kits were used. Four different sequencing primers (HCV-S1, S2, S3 in PCR-1 and HCV-S4 in PCR-2) were used for the sequencing process. Immobilization of PCR-1 and PCR-2 products was achieved by binding to sepharose streptavidin coated beads (2 µL) in binding buffer (40 µL) and ultrapure water (28 µL). Subsequently, single-stranded DNAs were obtained by incubating in 70% ethanol for 5 seconds, in denaturation solution for 5 seconds, and in the wash solution for 10 seconds. Then, the DNAs were incubated at 80 °C for 2 minutes in solution plates containing four sequencing primers. After this preparation, plates containing sequencing primers that were hybridized with DNA were placed in pyrosequencing device. At the end of the process, the results from the process pyrosequence were evaluated in comparison with databases (HCV database: http://hcv.lanl.gov).

Results

As seen in Table 1, four different HCV subgenotypes belonging to three major genotypes were detected in a total of 108 HCV-RNA-positive cases. The most common subgenotype was found to be 1b in our region, as is the case with throughout Turkey.

The distribution of HCV genotypes in patients from the provinces of the Eastern Anatolia Region is shown Table 2. The genotypes distributed as 1a, 1b, 3a and 3b in Erzurum; 1a, 1b and 3a in Ağrı; 1b and 3a in Iğdır; 1a and 1b in Erzincan, and only 1b in the others.

Discussion

The prevalence of HCV genotypes varies among human living in different geographical regions. The number of studies on the distribution of HCV genotypes in our country started from the middle of the 1990s and 2000s to the present day has increased steadily. Genotype 1 is common in all regions of our country.

Table 1. Distribution of Hepatitis C Virus (HCV) genotypes in patients with chronic hepatitis C in our region

Genotypes	n	%
1b	94	87.0
1a	9	8.3
3a	4	3.7
4d	1	1.0
Total	108	100.0

Table 2. Distribution of Hepatitis C Virus (HCV) genotypes in patients from the provinces of Eastern Anatolia region

Cities	n	1a	1b	3a	4d
Erzurum	69	7 (10.14)	60 (86.96)	1 (1.45)	1 (1.45)
Iğdır	14	-	12 (85.7)	2 (14.3)	-
Ağrı	9	1 (11.1)	7 (77.8)	1 (11.1)	-
Erzincan	6	1 (16.7)	5 (83.3)		-
Kars	6	-	6 (100.0)	-	-
Muş	3	-	3 (100.0)	-	-
Tunceli	1	-	1 (100.0)	-	-

Data presented as n (%) of patients

In İzmir, which is one of the provinces of the Aegean Region, Abacioglu and colleagues, found in 2005 that the predominant genotype was 1b (75.3%), followed by 1a (19.1%) 2 (3.4%), and 4 (2.2%) (9). They also reported that distribution of HCV genotypes in patients with chronic liver disease were affected by various factors such as age, gender, blood transfer history, and alanine aminotransferase (ALT) levels. In a study conducted in İzmir, in 2001, Özacar and colleagues (10) reported that genotype 1b was observed in 81.2% of subjects with chronic hepatitis, genotype 1a in 10.0%, genotypes 2a/2c in 1.8%, genotype 3a in 0.6%, genotype 4c/4d in 0.6%, and mixed genotype was observed in 4.7% of patients with chronic hepatitis. Erensoy and colleagues (11) also found the prevalence of 66.6% of genotype 1b and 33.3 genotype 1a, in district İzmir, in 2002. Altuglu and colleagues (12), in another study conducted in İzmir, in 2008, reported that they identified genotype 1b in 87.2% of patients, genotype 1a in 9.9%, genotype 3 in 1.4%, genotype 2 in 0.9% and genotype 4 in 0.6% of subjects. The prevalence of HCV genotypes has been reported from different provinces of the Aegean Region. In their study including 100 subjects in Manisa, in 2009, Sanlidag and colleagues (13) reported that genotype 1b was determined in 90 patients (90%), genotype 4a - in five patients (5%), genotype 1a - in two patients (2%) and genotype 2a - in two patients (2%). In Afyonkarahisar, in 2009, Çiftçi and colleagues (14) found genotype 1 in 91.2% of individuals and genotype 4 in 8.8%. Kalaycı and colleagues (15) found genotype 1b, 1a, 4 and 1c in 63.3%, 20%, 13.3%, and 3.3% of patients, respectively. In a study conducted in Ankara, in the Central Anatolia Region, on 365 patients with chronic hepatitis C, Bozdayi and his colleagues (16) determined genotype 1b in 84% of cases, 1a - in 11%, 2 in 3% and genotype 3 and 4 - in 1% of subjects. They have also reported that among 36 patients receiving hemodialysys, 28 (78%) had genotype 1b and the rest (22%) had genotype 1a. In Kayseri, in 2011, Gökahmetoğlu et al. (17) detected genotype 1, genotype 4 and genotype 2 in 90 (61.7%) 52 (35.6%), and 4 (2.7%) patients, respectively. In Konya, in a study by Ural et al. (18) all patients with hepatitis C (n=80) were found to have genotype 1b. In another study from the Central Anatolia Region, Çelik et al. (19), reported genotype 1b in 88.2%, genotype 1a in 9.0%, genotype 2a in 1.1% and genotype 3 in 1.7% of HCV isolates from infected cases in 2010 in Sivas.

In a study from Zonguldak, a city in the Black Sea Region, evaluating the HCV genotype profiles of patients with chronic hepatitis C in 2010, Aktaş et al. (20) reported that 97.4% of patients had genotype 1b and 2.6% had genotype 1a. In another study from the Black Sea Region, Buruk et al. (21) reported genotype 1b (87.5%) as the most prevalent genotype in the Black Sea provinces followed by genotypes 1a (5.3%), 2 (1.6%), 3 (4.9%) and 4 (0.7%).

In a study from Diyarbakır, a city in the Southeast Anatolia Region, Yarkın and Hafta (22) reported in 2000 that genotype 1 was most common, accounting for 82.2% of infections. Genotype 1a was detected in 14.5% and genotype 2a in 3.3% of subjects genotype 2a. In the same province in 2009, Özbek et al. (23) have reported that genotype 1b was most common, accounting for 87.8% of infections, followed by 2, 3 and 3a (2.7%, 2.7%, 2.7%, respectively. In Gaziantep, Karslıgil et al. (24) detected five genotypes (1b (78.4%), 1a (9.8%), 2 (7.8%), 3 (2.0%) and 4 (2.0%)) in 51 patients with hepatitis C. More recently (in 2013), Kirişçi et al. (25) detected genotype 1 in 60%, genotype 2 in 40% of 100 patients infected with HCV in Kahramanmaraş.

In the Marmara Region, in their study conducted in 2010 in Istanbul Kücüköztaş and colleagues (26) detected six genotypes (1b, 3a, 4e, 2a/2c, 1a and 4) in 52 patients with chronic hepatitis C and they stated that the most prevalent genotype was b1 (76.9%). Altındiş and et al. (27) identified genotype 1b in 92.4%, genotype 1a in 5.7%, and genotype 2 in 1.9% of soldiers in the Northern Cyprus in 2006.

According to the studies mentioned above, HCV genotypes in our country were distributed approximately range from 60 to 100% for 1b, 2 to 30% for 1a, 1 to 8% for 2, 1 to 10% for 3, and 2 to 36% for 4. In our study, four different HCV subgenotypes (1a, 1b, 3a and 4d) belonging to three major genotypes (1, 3 and 4) were detected in a total of 108 HCV RNA-positive cases from the seven provinces of the Eastern Anatolia Region. The most common subgenotype was found to be 1b, as is the case throughout Turkey. The genotypes were distributed as 1a, 1b, 3a and 3b in Erzurum; 1a, 1b and 3a in Ağrı; 1b and 3a in Iğdır; 1a and 1b in Erzincan and only 1b in the other cities. The number of different genotypes is most probably affected by the low number of cases in other provinces, except in Erzurum. Only genotype 4 was found to be lower than the average in Turkey.

As shown, in all of the studies done in our country has determined that 1b is the most prevalent genotype among the genotypes of HCV in patients with hepatitis C. However, we have observed that the distribution of the genotypes varies significantly in other countries. In 2011, Sievert and colleagues (28) reported that genotype 1 was common in Australia, China, Taiwan and other North Asian countries; genotype 6 in Vietnam and other Southeast Asian countries; genotype 3 in India and Pakistan; genotype 4 in the Middle Eastern countries such as Egypt, Saudi Arabia and Syria.

RBV in combination with pegylated interferon α (PEG-IFN-α) is recommended for standard treatment of chronic hepatitis C infection (29,30,31). This combination therapy has greatly improved the sustained virological response rate, particularly in difficult-to-

treat cases. Determination of sustained virological factors such as, host, virus and treatment-related factors provides important information about the mechanisms of action of RBV and IFNα. So far, a large number of permanent and non-permanent important determinants have been identified for the treatment of hepatitis C (30). Elderly, cirrhosis or advanced fibrosis, excess weight, obesity, diabetes, lowlevels of ALT, cholesterol, hemoglobin and platelets, insulin resistance, and the level of hepatic steatosis are the important factors associated with host. In addition, among the main factors associated with the virus are HCV genotype, pretreatment viral load and the first virological response. Treatment dose of RBV and PEG-IFN-α is an important factor for treatment. Antiviral therapy is administered for 48 weeks in patients infected with genotype 1 and 4 and the number of viruses in the blood decreases within 24 weeks. Genotype 2 or 3 is more sensitive to combination therapy of RBV and PEG-IFN-α than genotype 1 or 4, allowing shorter duration of treatment (24 weeks) (30).

As a result, the frequency of the HCV genotypes in patients with chronic hepatitis C in the Eastern Anatolia Region is consistent with that of Turkey except for genotype 4 with a low rate. We think that the results of this regional study will contribute to the national epidemiological data.

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