Research Article

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Hepatitis C Genotype Distribution Changing Through Years in the Kahramanmaraş Region

Kahramanmaraş Yöresinde Yıllar İçinde Değişen Hepatit C Genotip Dağılımı

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ABSTRACT

Objectives: Chronic hepatitis C virus (HCV) infection still continues to be a significant health problem in the entire world. In addition to this, knowing about the existing genotypes in a region is highly important in terms of guiding antiviral treatment and understanding the epidemiology in that region. In our study, we examined the varying genotype distribution in our region and affecting factors.

Materials and Methods: To determine the HCV genotype distribution in Kahramanmaraş in Turkey, patients who were determined to be HCV-positive in the last 4.5 years and whose genotypes were studied retrospectively searched from records and included in the study.

Results: Genotype 1 was the most prevalent genotype (47%) in Kahramanmaraş. The second most prevalent (45%) genotype was genotype 3. Additionally, genotypes 2 and 4 were seen at the rates of respectively 2% and 6%. While there was male dominance in genotypes 1, 2, and 3, genotype 4 had female dominance (69%). There was a very high male dominance in genotype 3 (95%), and the mean age of the patients was 26.4.

Conclusion: The epidemiology of HCV may show serious variations at locations that receive intense migration and where increased drug usage is observed. The main point in preventing HCV infection should be the identification and elimination of risk factors.

Keywords: Hepatitis C virus, genotype, risk factors, Kahramanmaraş

ÖZ

Amaç: Kronik hepatit C virüs (HCV) enfeksiyonu tüm dünyada halen önemli bir sağlık sorunu olmaya devam etmektedir. Bununla birlikte bir bölgedeki mevcut genotiplerin bilinmesi anti-viral tedaviye rehberlik etmesi ve o bölgedeki epidemiyolojiyi anlamak için çok önemlidir. Bizde çalışmamızda bölgemizdeki değişen genotip dağılımını ve etki eden faktörleri irdelemeyi amaçladık.

Gereç ve Yöntemler: Kahramanmaraş genelindeki HCV genotip dağılımını belirlemek için son 4,5 yıl içinde bölgemizde HCV pozitif saptanan ve genotip çalışılan hastalar retrospektif olarak kayıtlardan taranarak çalışmaya alındı.

Bulgular: Genotip 1 Kahramanmaraş'ta en yaygın (%47) genotipti. İkinci en yaygın (%45) genotip ise genotip 3'tü. Ayrıca genotip 2 ve 4 sırasıyla %2 ve %6 oranında görülüyordu. Genotip 1,2,3'te erkek hakimiyeti varken genotip 4'te kadın ağırlıklıydı (%69). Genotip 3'te ise ciddi bir erkek hakimiyeti (%95) vardı ve genotip 3 hastaların yaş ortalaması 26,4'tü.

Sonuç: Yoğun göç alan ve artmış uyuşturucu kullanımının olduğu yerlerde HCV epidemiyolojisi çok ciddi değişimler gösterebilmektedir. HCV enfeksiyonunu önlemede temel nokta ise risk faktörlerinin belirlenmesi ve ortadan kaldırılması olmalıdır.

Anahtar Kelimeler: Hepatit C virüsü, genotip, risk faktörleri, Kahramanmaraş

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Introduction

The hepatitis C virus (HCV) may lead to both acute and chronic hepatitis. The acute process limits itself, rarely causes liver failure and usually leads to chronic infection. Chronic HCV infection shows a progressive course for long years, and at the end, it may result in cirrhosis, hepatocellular carcinoma and requirement of liver transplantation. About 15-45% of infected individuals completely recover within the 6 months after infection without any treatment. The remaining 55-85% develop chronic HCV infection. The risk of cirrhosis in individuals with chronic HCV infection within 20 years is between 15% and 30%. There are 399,000 deaths every year in connection to chronic HCV infection and complications. Additionally, approximately 71 million people living with hepatitis C are considered as a global health problem. According to the World Health Organization, the regions most affected around the world are the Eastern Mediterranean Region and Europe, and the prevalence in these regions were estimated respectively as 2.3% and 1.5% for 2015 (1). The prevalence of chronic HCV infection in healthy individuals in Turkey is reported between 0.6% and 2% (2).

HCV is a small RNA virus belonging to the Hepacivirus species in the Flaviviridae virus family. As in other RNA viruses, the genome of HCV also shows differences based on geographical regions. HCV has 7 types and 67 subtypes that are defined. In the entire world, the most prevalent type is genotype 1 (44%), which is followed by genotype 3 (25%) in the second place, genotype 4 (15%) in the third place and genotypes 2, 5 and 6 in decreasing prevalence (3,4). While genotype 1 is the most frequent type on high- and medium-income levels, genotype 4 is the most frequent type on low-income levels (4). Molecular epidemiology studies have shown that these HCV genotypes and subtypes are differently distributed in different parts of the world, and certain genotypes are dominant in some regions. Type 2 in Ghana, type 5 in South Africa, type 6 in Vietnam, type 4 in Egypt and Syria, type 1b in Japan, type 3 in Pakistan and type 1 in Turkey are the most frequently seen genotypes (4).

Genotype 1, especially its subtypes 1a and 1b, are the most prevalent ones in Europe and the USA. Moreover, genotype 3 carries an increasingly higher significance as it is the second most prevalent genotype reported in all European countries except for Italy and Romania (5). While genotype 4 in Central Africa and the Middle East, genotype 5 in South Africa and genotype 6 in Southeast Asia constitute the most frequently distributed regions for these genotypes, genotype 7 was recently determined in Central African immigrants in Canada (6). Especially genotype 3a is the prevalently seen genotype in intravenous drug addicted individuals in Europe and the United States (7).

As the effectiveness of most existing and new treatments shows differences based on the genotype of HCV, it is clinically important to know about the distribution of HCV genotypes. Treatment times and success rates vary based on HCV genotypes and subtypes (8). Additionally, in monitoring the effects of the intense flows of migration towards Turkey and Europe in recent years on the dynamics of hepatitis C, the most suitable instrument will be genotyping. Thus, in our study, we aimed to examine the HCV genotype distribution changing by years in the Kahramanmaraş region and affecting factors.

Materials and Methods

Patients who were admitted to and found to be anti-HCV positive at family health centers, districts, state hospitals and faculty of medicine laboratories in Kahramanmaraş between January 2015 and June 2019 were determined. Among these patients, those for whom HCV RNA and HCV genotyping was made were included in the study. The study was started by obtaining approval from the Local Ethics Board of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University and permission from the Provincial Directorate of Health. The data were provided by the information processing department from the automation system of the relevant hospital. The collected data were analyzed in the computer environment, the data on patients whose genotypes were studied were gathered, and the demographic characteristics of these patients were recorded.

Statistical Analysis

The data were analyzed by using the SPSS 18 statistical software. Data analysis was performed using frequency analysis and chi-square test. All values were considered statistically significant when $p<0.05$.

Results

In the last 4.5 years in our region of study, 2,189 HCV-positive patients were determined, genotypes were studied in 553 of these patients, and the genotypes of 497 were determined. In the other 56 patients, genotypes could not be determined due to HCV-RNA negativity. Three hundred fifty-one (70.6%) of the patients were male, and 146 (29.4%) were female. The mean age of the patients was 42.7±20.8 (range: 18 to 89 years). Genotype 1 was determined in 235 (47%) patients, 8 (2%) patients had genotype 2, 225 (45%) had genotype 3, and 29 (6%) had genotype 4. Among the patients infected with genotype 1, 123 (52%) were male, 112 (48%) were female, and their mean age was 56.8 (range: 21 to 89 years). Additionally, among the genotype 1 patients, the subtype of 8 (3%) was reported as 1a, while the subtype of 45 (19%) was 1b (Table 1). Among the patients infected with genotype 2, 5 (62.5%) were male, 3 (37.5%) were female, and their mean age was 47 (range: 19 to 82 years). Among the genotype 3 patients, 214 (95%) were male, 11 (5%) were female, and the mean age was 26.4 (range: 18 to 72 years). Among these genotype 3 patients, the subtype of 15 (6%) was genotype 3a. Among the genotype 4 patients, 9 (31%) were male, 20 (69%) were female, and the mean age was 53.8 (range: 22 to 68 years). Among these genotype 4 patients, 25 (86%) were of Syrian nationality, while 4 (14%) were Turkish citizens. Moreover, 2 (25%) of the genotype 2 patients were of Syrian nationality. Three (1%) of the genotype 3 patients were of Azerbaijani nationality. The differences in the distributions of the genotypes based on sex were significant ($p<0.001$). We determined that genotype 3 was seen more in the male patients, while genotype 4 was seen more in the female patients (Table 2). Especially the mean age of the genotype 3 patients was significantly lower than those infected with the other genotypes (Figure 1). No genotype 5 or 6 patients were encountered in our region of study.

Discussion

HCV is a virus with high genetic variation. In hepatitis C, genotype determination is an important parameter for treatment selection and determining the duration of the selected treatment. However, in recent times, pangenotypic drugs offered in the market have caused us to question the necessity of looking at genotypes for patients to be treated. Moreover, genotype determination provides us with information on the course of the disease. For example, genotype 1 may show that the disease progresses more severely in these patients, the risk of hepatocellular cancer development is higher in such individuals, and these individuals should be more closely monitored due to this issue (9).

HCV has been divided into seven main genotypes and several subtypes. The geographical distribution of HCV is also heterogenous. While genotypes 1, 2 and 3 have a global distribution, genotypes 4, 5, 6 and 7 are limited with some geographical regions (e.g. South Africa, Southeast Asia, Egypt and Central Africa) (10). In recent studies, it was determined that the most frequently observed type of HCV in Turkey is genotype 1, while the most prevalent subtype is 1b. The distribution of other genotypes in these studies was reported as genotypes 3, 2 and 4 in decreasing order (11,12,13,14).

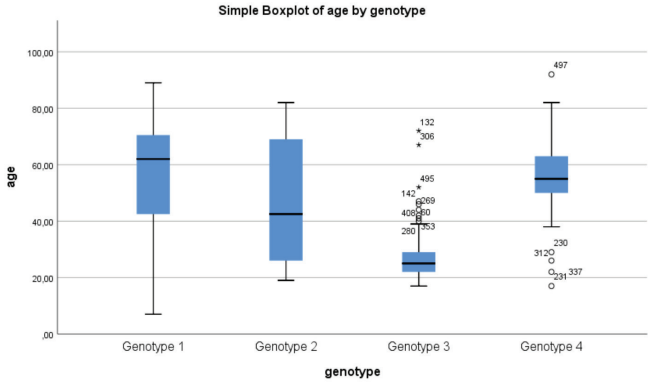

Figure 1. Genotype distribution based on age

In our region of study, in a single-center study by Kirişci et al. (15) conducted in 2013, genotype 1 (60%) was the most prevalent genotype. In the same study, genotype 3 was encountered by 40%, while no other genotypes were observed (15). In a study again in 2013 which only included the data of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University and was presented as a poster at an international conference, 95% genotype 1 and 5% genotype 3 patients were determined, and no other genotypes were encountered. However, in recent years, a serious change has taken place in the genotype distribution in the region.

In our study containing the data of the last 4.5 years and covering the entirety of the aforementioned region, the type that was seen the most frequently was genotype 1 (47%). On the other hand, in comparison to the study in 2013, we observed that the genotype 1 rate decreased (60% vs. 47%). Additionally, the genotype 3 rate was observed to increase from 40% to 45%. These values were similar to those in the world. Furthermore, it was determined that genotype 2 and 4 patients that had not been encountered in the mentioned previous study started to be seen in our region of study. The reasons for these results may be that the province has been rapidly receiving migration from Syria since 2010, and the rate of drug abuse among the youth has increased.

The case is similar to ours in different regions of Turkey. In a genotype study conducted in İzmir in western Turkey by Çetin Duran et al. (16), previously unencountered genotype 5 patients

Table 1. Genotype and subtype distribution

	n	%	Subtype / (n, %)
Genotype 1	235	47.3	1a/8/3 1b/45/19 Undefined subtype/182/77
Genotype 2	8	1.6	2a/1/12.5 2c/1/12.5 Undefined subtype/6/75
Genotype 3	225	45.3	3a/15/6.6 Undefined subtype/210/93.3
Genotype 4	29	5.8	Undefined subtype/29/100
Total	497	100.0	

Table 2. Genotype distribution based on sex

			Genotype				Total	p
			Genotype 1	Genotype 2	Genotype 3	Genotype 4		
Sex	Male	n	123	5	214	9	351	<0.001
		%	35.0%	1.4%	61.0%	2.6%	100.0%	
	Female	n	112	3	11	20	146	
		%	76.7%	2.1%	7.5%	13.7%	100.0%	
Total		n	235	8	225	29	497	
		%	47.3%	1.6%	45.3%	5.8%	100.0%	

were determined, and the authors concluded that the reason for this was the migration received by the region.

Genotype distributions based on age groups may show variations based on the geographical location and societies in which they are seen. Niu et al. (17) reported that genotypes 1 and 2 were seen more in the age group of 40-60, while genotype 3 cases were seen in younger patients. Kartashev et al. (18) showed that genotype 1 patients were mostly in the age group of 45-55, genotype 1a was seen in 55-66-year-olds, genotype 1b was seen in those over 65, genotype 2 was seen in those over 65, and genotypes 3 and 4 were seen in the age group of 45-55. Another study determined that, while the median age of patients infected with genotypes 1, 2 and 4 was 50 and higher, that in those infected with genotype 3 was 41,7. In contrast, in Pakistan, it was determined that all genotypes were mostly seen in the age group of 25-45 (19). A study conducted in Algeria reported that genotype 1 patients could be usually gathered in the age interval of 50-70 (20). The mean age of genotype 1 patients in Turkey was reported in the range of 50-60 (11,21,22). In our study, the mean ages of the genotype 1, 2 and 4 patients were similar to those reported in the aforementioned studies. However, the mean age of the genotype 3 patients in our study was found as 26.4. This value was lower than those reported in Turkey and other countries. This may be explained by the increasingly higher intravenous drug addiction in the young population in our region of study.

Genotype distributions may also vary based on sex. Janahi et al. (23) determined in Bahrain that the frequency of male cases in all genotypes was higher than females. However, the lowest frequency in female patients was seen in genotype 3. Likewise, in a study covering the period of 2008-2015 and Belgium, the prevalence of male cases was higher in all genotypes (24). Kartashev et al. (18) found genotypes 1b and 2 more frequent in women, while they found genotypes 1a, 3 and 4 more frequent in men. In our study, there was a male dominance in all patients of genotypes 1, 1a and 1b. It is seen that the female dominance in the study previously conducted in our region of study turned into a male dominance in recent years. Additionally, the male sex was more prevalent among the genotype 2 and 3 patients. Among the genotype 4 patients, as opposed to the case in the studies mentioned above, the female sex was more prevalent. This may have been caused by the higher rate of the female sex among those migrating from Syria to our region of study. Indeed, 25 of the genotype 4 patients were of Syrian origin, and most of these were female patients.

Study Limitations

Since our study is retrospective, it does not contain much information about HCV transmission risk. The limitations of our study are that genotype could not be checked in all patients with positive anti-HCV, and subtype analysis could not be performed in patients with all genotypes.

Conclusion

It was seen that there have been serious changes in the genotype distribution in comparison to previous studies conducted in our region of study. As in the case in the whole world, the most frequently encountered genotype was also determined in our study as genotype 1, but it was observed that its prevalence decreased in comparison to the past. In this study, genotype 2 and 4 patients, who were not encountered at all in previous studies in our region of study, were determined. This shows that the epidemiology of HCV may change in time especially in regions receiving migration. Therefore, in our region, there is a need to increase social awareness and prevent intravenous drug use.

Ethics

Ethics Committee Approval: The study was started by obtaining approval from the Local Ethics Board of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University and permission from the Provincial Directorate of Health.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.G., M.İ., Design: K.G., Data Collection or Processing: K.G., M.A., A.R.Ş., B.K., Analysis or Interpretation: K.G., B.K., A.R.Ş., M.A., Literature Search: K.G., M.İ., Writing: K.G.

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