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Genotype Distribution and Risk Factors in Patients with Chronic Hepatitis C Infection

Kronik Hepatit C Enfeksiyonlu Hastalarda Genotip Dağılımı ve Risk Faktörleri

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Abstract

Objective Hepatitis C virus (HCV) is a common infection around the world and an important public health problem. Determination of HCV genotype is important epidemiologically and for treatment approaches. In this study, the aim was to assess the genotype distribution and associated risk factors for patients monitored at our center in northern Turkey.

Materials and Methods A cross-sectional study was carried out of patients with confirmed HCV infection. Our study retrospectively assessed 175 patients with chronic hepatitis C diagnosis in the Infectious Diseases clinic from 2016-2019 and with antiviral treatment administered. The samples were tested by type specific genotyping assay. The relationship between demographic characteristics and potential risk factors and genotype was investigated.

Results Genotype 1b was identified as the dominant genotype (95%). In 5% of patients, non-1b genotypes were present (genotype 1a, 3 and mixed). Genotype 1b was more common in patients over 50 years of age, while the patients with other genotypes were younger. The most frequent risk factor was identified as surgical intervention history. While young age, transplantation and intravenous drug use were identified as risk factors for development of infection with non-1b genotypes, household HCV contact was significant for genotype 1b.

Conclusion In our study, the dominant genotype was identified as genotype 1b. Among the risk factors in our study, the most frequently identified are surgical interventions and dental treatment. The variation in traditional risk factors will cause an increase in non-1b genotypes. We think it is important to correctly analyze these variations in the global struggle with HCV.

Keywords Hepatitis C, genotype, risk factors, epidemiology, non- 1b genotypes

Özet

Amaç *Hepatit C virusu (HCV) enfeksiyonu tüm dünyada yaygın, önemli bir halk sağlığı sorunudur. HCV genotipinin belirlenmesi epidemiyolojik olarak ve tedavi yaklaşımının belirlenmesinde önemlidir. Bu çalışmada, Türkiye'nin kuzeyinde yer alan merkezimizde takip ettiğimiz hastalarda genotip dağılımının ve ilişkili risk faktörlerinin değerlendirilmesi amaçlanmıştır.*

Materyal ve Metod *Çalışmamızda 2016-2019 yılları arasında Enfeksiyon Hastalıkları Polikliniğinde Kronik hepatit C tanısı almış ve doğrudan etkili antiviral tedavi uygulanmış 175 hasta retrospektif olarak değerlendirildi. Genotip dağılımı belirlenerek hastaların bulaş ve farklı genotipler açısından risk faktörleri analiz edildi.*

Bulgular *Genotip 1b hakim genotip olarak saptandı (%95). %5 hastada 1b dışı genotipler (genotip 1a, 3 ve mix) mevcuttu. Genotip 1b, 50 yaş üstü hastalarda sık iken diğer genotiplere sahip hastalar daha gençti. Risk faktörü olarak en sık cerrahi girişim öyküsü tespit edildi. Genç yaş, transplantasyon ve damar içi uyuşturucu kullanımı 1b dışı genotip ile enfeksiyon gelişimi için risk faktörü olarak saptanırken, ev içi HCV teması genotip 1b için anlamlı bulundu.*

Sonuç *Çalışmamızda hakim genotip, genotip1 b olarak saptanmıştır. Risk faktörleri arasında en sık tespit edilenler cerrahi müdahaleler ve dental girişim öyküsüdür. Geleneksel risk faktörlerindeki değişim 1b dışı genotiplerin artmasına yol açabilir. HCV ile küresel mücadelede bu değişimin doğru analiz edilmesinin önemli olduğunu düşünüyoruz.*

Anahtar Kelimeler *Hepatit C, genotip, risk faktörleri, epidemiyoloji, 1b dışı genotipler*

INTRODUCTION

Hepatitis C virus (HCV) infection is common around the world and is an important public health problem. Nearly 350,000 people die annually due to complications related to chronic hepatitis C (CHC) and hepatitis C is one of the important causes in patients requiring liver transplantation.[1,2,3] To date, seven genotypes and more than 80 subtypes of HCV have been identified.[4,5] Type 1, 2 and 3 HCV infections are common around the world. Type 4 is common in the Middle East and Africa and is responsible for 80% of all HCV infections in these countries.[6] Genotypes 5 and 6 are found in South Africa and Southeast Asia.[7] In Turkey, the reported HCV seroprevalence is 0.6-1.6% and the dominant genotype is 1b.[8] Studies in recent years show that other genotypes are rapidly increasing in our country.[9] Different genotypes display differences in terms of epidemiology, pathogenesis and treatment response. As a result, genotype analysis is determined as standard before treatment. HCV is transmitted by percutaneous contact, transfusion of blood/blood products, infected tissue and organ transplantation or common use of contaminated injectors. Transmission is possible at lower rates from infected mothers at birth or from infected partners by sexual transmission.[10] The treatment at increasing rates of hepatitis C patients in society has caused infection especially in risk groups to come to the agenda. It is reported that the genotype distribution in these groups may display differences compared to the normal population.[11] Determination of risk factors and genotype distributions are important in terms of creating appropriate treatment algorithms.[12] Additionally, it will ensure determination of priorities when developing health strategies to intervene against this infectious disease. This study aimed to determine the HCV genotype distribution and risk factors for patients monitored with CHC diagnosis.

2. METHODS

2.1 Patients

Our study included patients receiving chronic hepatitis C diagnosis from the Infectious Diseases clinic from 2016-2019 with direct-acting antiviral treatment administered. Patient files were retrospectively investigated. All patients were anti-HCV and HCV RNA positive. While 56.6% of patients received new diagnosis, the remaining patients were treatment experienced and were followed by us since 2016.

2.2. Methods

The demographic information of patients, pretreatment quantitative HCV RNA values, genotype analyses, hepatitis B co-infection presence, cirrhotic status, and presence of hepatocellular cancer were recorded. Additionally, patients were questioned about risk factors before treatment and information was recorded on a patient form. This patient form questioned the risk factors of potential parenteral exposure to blood or blood products (surgical operation, injuries requiring hospital intervention, transfusion of blood or blood products), hemodialysis, tattoos, intravenous drug use (IVDU) history, multiple partner sex, perinatal risk factors, dental treatment, household contact with HCV-infected person and being a health worker.

2.3. Clinical virology analyses

The anti-HCV and HbsAg tests were serologically evaluated with the ELISA method (Abbott Laboratories, USA). Quantitative HCV-RNA real-time PCR tests were completed using a COBAS AmpliPrep/COBAS Taqman 48 system (Roche, Branchburg, NJ, USA). When determining HCV genotype, Bosphore HCV genotype (Anatolia Geneworks, Turkey) real-time PCR method was used according to the manufacturer's instructions.

2.4. Statistical analysis

Statistical analyses were performed with Statistical Package for Social Sciences (IBM SPSS for Windows, Ver.22). Means and standard deviations were obtained for continuous variables while categorical variables were summarized using frequency and percentage. The student's t-test was applied to assess differences between numerical variables. The chi-square test was used to compare categorical vari-

ables. In case of a significant difference between the parameters evaluated, logistic regression analysis was applied. The level of significance was defined as P value < 0.05.

2.5. Ethics

The study was approved by the Regional Clinical Research Ethics Committee (registration number: 2020/122) and was conducted according to the Helsinki Declaration.

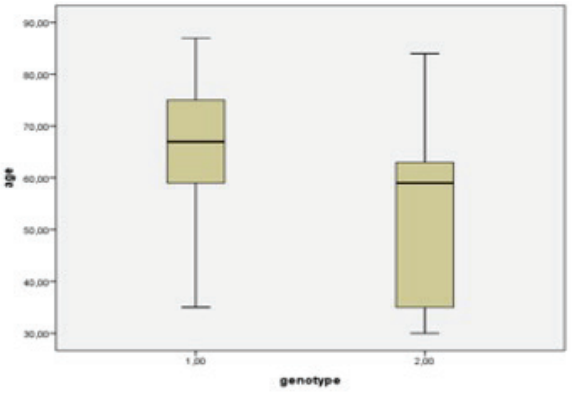
3. RESULTS

This study included 175 patients who were anti-HCV positive and HCV RNA positive. The mean age of patients was 66± 11.2 years (age interval 30 - 87), 96 were female (55%) and 79 were male (45%). Fourteen patients (8%) were in the 30-50 years age interval, while the remaining 161 patients (92%) were over 50 years of age. Genotype analysis identified that 166 patients (95%) had genotype 1b, while 9 patients (5%) had non-1b genotypes. Five patients had genotype 3, 2 patients had genotype 1a and 2 patients had mixed genotypes. Mixed genotypes were genotype 3 + 4 and genotype 1b + 3. One hundred and twenty-nine patients (74%) were noncirrhotic and 46 patients (26%) were cirrhotic. One of the cirrhotic patients had genotype 1a, one had mixed genotype (3+4) and all other patients had genotype 1b. Mean HCV RNA values were 2882380 IU/mL in the genotype 1b group and 5492404 IU/mL in the non-1b genotypes (Table 1). Though the mean HCV RNA levels were numerically different, there was no statistical significance present.

Table 1: Genotype distribution and patient characteristics

Identified genotypes	Genotype 1a	Genotype 1b	Genotype 3	Mixed Genotype
Number (%)	2 (1)	166 (95)	5 (3)	2 (1)
Mean age	56	66	50	59.5
Gender (n/%)				
Females	2 (100)	91 (55)	2(40)	1(50)
Males	-	75 (45)	3 (60)	1 (50)
Mean HCV level (IU/ml)	4290115	2883280	4611800	8847786

When mean age is assessed, there was a significant difference between patients with genotype 1b and non-1b (P<0.05). Patients with non-1b genotypes comprised a younger population (Graph 1).



Graph 1: Age distribution for genotype 1b (1) and other genotypes (2)

Among risk factors questioned, 46% had surgical history, 35% had dental treatment (17.5% non-clinician interventions), 20% had positivity in the family, 17.5% had transfusion history for blood and blood products, 4.6% had hemodialysis and 0.5% were determined to be intravenous drug addicts (Table 2).

Table 2: Reported risk factors for HCV transmission

Risk factor	Number (%)
Surgical operation	82 (46)
Dental procedures	61 (35)
HCV-positive household contact	35 (20)
Transfusion of blood and blood products	31 (17.5)
Hemodialysis	8 (4.6)
Transplantation	2 (0.5)
IVDU*	2 (0.5)
*IVDU: Intravenous drug use	

The distribution of risk factors, age and gender according to genotype is shown in Table 3. Those with HCV positive household contact were statistically significantly high for genotype 1b, while those with risk factors of IVDU and transplantation history were statistically significantly high

for non-1b genotypes (P<0.01) (Table 4). In other words, young age, transplantation history and IVDU were identified to be risk factors for having higher rates of non-1b genotype.

Among risk factors, tattoo, acupuncture history, perinatal transmission and being a health worker were not identified. Objective data could not be obtained when questioning multiple partner sex probably due to concerns with tradition.

Table 3: Distribution of age, sex and risk factors according to genotype 1b and other genotypes

	Genotype 1	Other genotypes	P
Age	66.86 (± 10.32)	53.44 (± 18.29)	0.04
Sex			0.50
Female	92	4	
Male	74	5	
Surgical operation			0.12
Operation +	80	2	
Operation -	86	7	
Dental Procedures			0.40
Dental Procedures +	59	2	
Dental Procedures -	107	7	
HCV-positive household contact			< 0.01
HCV-positive household contact +	30	5	
HCV-positive household contact -	136	4	
Transfusion of blood and bloodproducts			0.58
Transfusion of blood and blood products +	30	1	
Transfusion of blood and blood products -	136	8	
Hemodialysis			0.49
Hemodialysis +	8	0	
Hemodialysis -	158	9	
Transplantation			< 0.01
Transplantation +	1	1	
Transplantation -	165	8	
IVDU*			< 0.01
IVDU +	0	2	
IVDU -	166	7	
*IVDU: Intravenous drug use			

Table 4: Logistic regression analysis of risk factors

	β	S.E	df	p	Odds ratio	95% CI	
						Lower	Upper
Age	-0.09	0.03	1	< 0.01	0.90	0.85	0.96
HCV positive household contact	-1.72	0.70	1	0.01	0.17	0.04	0.70
Transplantation	-3.02	1.46	1	0.03	0.04	0.00	0.853
IVDU*	-24.36	28420.73	1	0.99	0.00	0.00	-
*IVDU : Intravenous drug use							

4. DISCUSSION

Determination of the HCV genotype distribution is important in terms of monitoring the molecular trace of the virus and to create correct eradication policies. Currently, the development of new treatment choices has ensured differentiation of treatment approaches. As a result, determination of genotype before treatment of patients still preserves its importance. Petruzelli et al[13] assessed the global distribution of HCV genotypes. In the study, they reported that the dominant genotype for Europe, Asia and America was genotype 1b. In neighboring countries where healthy data can be obtained, like Greece, Georgia and Iran, genotype 1 is dominant, while genotype 3 has notable rates in Iran. The distribution of other genotypes may display regional variations in the same continent and countries. Our country is located geographically between two different continents and genotype 1b is observed to be dominant. HCV genotype 1b has been reported in studies conducted in Turkey between 66.7-100%. Our hospital is in the north of our country; it is located in the Central and Eastern Black Sea region. In our study, similarly, 95% genotype 1b and 5% other genotypes were identified. Though common genotypes were determined in many countries, monitoring requires a dynamic process. Varying epidemiological characteristics, migrations, effective treatment of the traditional patient group with more potent agents, prevention of the spread of dominant genotypes by treat-

ment and differentiation of transmission routes have resulted in changes to the genotype profile.[14] In recent years, a globally reducing trend was reported for genotype 1, with an increase in the frequency of genotype 3. In Turkey, a significant increase is present for the frequency of non-1b genotypes.[15] Intravenous drug use has become a significant risk, especially.[16,17]

One of the problems with HCV is the presence of mixed genotypes. A multicenter study in our country reported 1.3% rate for the mixed genotype.[18] In our study, there were 2 patients with mixed genotype of genotype 1b+3 and 3+4. Our patient with genotype 3+4 identified also had hepatitis B co-infection and was understood to have multiple and intense contact in terms of diseases transmitted by blood in their anamnesis. The other patient was not identified to have any additional risk factor. Our information about mixed genotypes is limited and there is a need to determine clinical approaches.

HCV prevalence is higher among those over the age of 50 and it is recommended that this age group be screened for HCV.[19] In our study, similarly, 92% of patients were over the age of 50. While genotype 1b was identified in patients over 50 years of age, non-1b genotype patients were in a significantly lower age group. This situation leads to consideration that traditional transmission routes like problems with aseptic procedures and sexual transmission, which were significant in the past for HCV, were more significant in the older age group, while additional risk factors came to the agenda for the younger group. The strict administration of safe blood transfusions and sterile procedures, and pregnancy screening have reduced the traditional HCV transmission routes and caused an increase in different transmission routes.[20,21] Among the risk factors questioned in our study, the most frequently identified are surgical interventions and dental treatment, similar to other studies in our country.[22,23] In recent years, the frequency of transmission has gradually increased with the use of iv drugs. It was reported that 8.5% of HCV-infected individuals were intravenous drug users and they comprised 23% of new infections.[24] In Turkey, the IVDU rate for patients infected with HCV is 1.3-3.1%.[23] A low rate was identified in our study. However, we think this rate was lower than in reality due to reasons like the lack of current data, social problems in this group, and difficulty or lack of desire to access the health services.

During questioning of risk factors, the risk factor of more than one sexual partner could not be assessed due to not receiving objective responses linked to traditional reasons in our country. Our study had a household contact history of 20%. The role of intrafamilial HCV transmission is controversial. It is seen that household contacts are more in sexual partners and siblings. Apart from the sexual route, horizontal contact or perinatal contact may develop as a result of common family behavior and life monitoring. Bayomy et al. reported 20% in their studies.[25] This rate is the same as the rate in our study. Egypt is a country where HCV prevalence is high. Although it is lower in our country, life style may be similar. Another study investigating intrafamilial transmission in Italy linked positive rates to the presence of other risk factors.[26] As a result, living with a HCV positive individual may be a factor that increases the risk. However, this risk increases with the presence of other risk factors.

Hepatitis C virus (HCV) infection is frequent in dialysis patients and is associated with increasing morbidity and mortality. Nosocomial transmission is a significant risk and it is necessary to apply infection control precautions strictly. The Centers for Disease Control and Prevention stated that more than 50% of all HCV epidemics related to health care occurred in hemodialysis units from 2008 to 2015.[27] The HCV rate for hemodialysis patients is reported to be between 4-20%. Genotypes 1 and 3 are the most commonly reported genotypes in dialysis patients.[28] According to data from the end of 2018 from the national nephrology association in Turkey, there was 3.47% anti-HCV positivity present.[29] In our study, 4.6% were iden-

tified to have this risk factor and the genotype profile was not different to society.

Logistic regression analysis identified age, transplantation history and household HCV contact as significant factors in terms of genotype 1b and other genotypes. The increase in age by one year increases the odds of being infected with genotype 1 by 0.90 times. In addition, home contact increases the risk of being infected with genotype 1 by 0.17 times. Advanced age and home contact are significant risk factors for becoming infected with genotype 1. In patients with a history of transplantation, the risk of non-genotype 1b infection increases by 0.04 times. Risk analysis could not be performed for intravenous drug use, even though significant, due to the low numbers and the lack of patients with different genotypes.

The low number of patients with risk factors such as iv drug use is a limiting aspect of our study.

5. CONCLUSION

In our study, the dominant genotype was defined as genotype 1b. Among the risk factors in our study, the most frequently identified are surgical interventions and dental treatment. We think that transmission routes may differ especially in the young population and genotype follow-up is important.

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Conflicts of interest statement

None of the authors report any conflict of interest related to the manuscript.

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