Healthcare Related Risk Factors Account for the Majority of HCV Transmissions in Middle Black Sea Region of Turkey: A Case-Control Study

Sağlık Hizmetleriyle İlişkili Risk Faktörleri Türkiye'nin Orta Karadeniz Bölgesinde HCV Bulaşlarının Büyük Çoğunluğundan Sorumludur: Bir Vaka-Kontrol Çalışması

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ABSTRACT Objective: This case-control study was designed to determine the risk factors for hepatitis C virus transmissions in Middle Black Sea Region of Turkey. **Material and Methods:** One hundred and ninety-three anti-HCV positive patients were eligible for the study and the number of patients in control group was 190. The individuals in each group were questioned for the factors having a possible role in transmission of hepatitis C virus. The data was evaluated statistically by Chi-square and logistic regression analysis. **Results:** Among cases, 78% of patients were females. There was no significant difference in terms of gender and average ages between two groups. Taking surgery, endoscopy, coronary angiography, number of the pregnancies and deliveries into consideration, no statistical difference was found between the case and control groups. However, logistic regression analysis revealed that the following risk factors were related to HCV infection: history of blood transfusion before year 1996 (Odd's Ratio (OR)= 4.5), uterine curettage and/or delivery in a hospital (OR= 2.4), hospitalization for more than one week (OR= 2.7) and previous dental care (OR= 1.8). **Conclusion:** Apart from blood transfusions, hospitalization and medical procedures like dental care, curettage or delivery in a hospital were important risk factors for hepatitis C infection in Tokat region. These risk factors should be eliminated with effective sterilization and disinfection strategies in order to prevent the spread of HCV.

Key Words: Hepatitis C; risk factors; transmission

ÖZET Amaç: Bu vaka-kontrol çalışması, Türkiye'nin Orta Karadeniz Bölgesindeki hepatit C virüsü bulaşları için risk faktörlerini saptamak amacıyla tasarlandı. **Gereç ve Yöntemler:** Anti-HCV testi pozitif olan 193 hasta çalışma için uygundu ve kontrol grubundaki hasta sayısı 190'dı. Her gruptaki bireyler, hepatit C virüsü bulaşında olası rol oynayabilecek faktörler açısından sorgulandı. Veriler Ki-kare ve lojistik regresyon analizi ile istatistiksel olarak değerlendirildi. **Bulgular:** Vakaların %78'i kadındı. İki grup arasında, cinsiyet dağılımları ve ortalama yaşlar bakımından anlamlı fark yoktu. Cerrahi, endoskopi, koroner anjiyografi, gebeliklerin ve doğumların sayısı dikkate alındığında, vaka ve kontrol grupları arasında istatistiksel fark saptanmadı. Bununla birlikte, lojistik regresyon analizi aşağıdaki risk faktörlerinin HCV enfeksiyonu ile ilişkili olduğunu açığa çıkardı: 1996 yılından önce kan transfüzyonu öyküsü (Odd's Oranı (OR): 4.5), hastanede rahim küretajı ve/veya doğum (OR0= 2.4), bir haftadan uzun süren hastanede yatış (OR= 2.7) ve geçmişte diş tedavisi olma (OR= 1.8). **Sonuç:** Kan transfüzyonları dışında, hastanede kalış ve diş tedavisi, hastanede küretaj veya doğum gibi tıbbi işlemler de Tokat bölgesinde hepatit C enfeksiyonu için önemli risk faktörleriydi. HCV'nin yayılmasını önlemek için bu risk faktörleri etkili sterilizasyon ve dezenfeksiyon stratejileri ile saf dışı edilmelidir.

Anahtar Kelimeler: Hepatit C; risk faktörleri; iletim

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Hepatitis C virus (HCV) causes a serious infectious disease that may lead to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). It is estimated that approximately 130 million people

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are infected with HCV globally. The HCV prevalence and the routes of transmissions may vary in different countries and regions of the world. For instance, HCV prevalences are similar in Turkey and in United States of America (USA), being between 1-1.9%; however, routes of transmission, age-specific prevalence and risk factors for HCV differ considerably.[1,2]

HCV is mainly transmited by parenteral route. In developed countries such as in the USA, the intravenous (IV) drug abuse accounts for nearly 2/3 of HCV transmissions. However, globally various other risk factors come to forefront in respect to routes of HCV transmissions.[1,3,4] For instance, unsafe parenteral injections are the primary factor for HCV transmissions in countries like Egypt and Pakistan.[5] In studies from Turkey, the rate of IV drug abuse as a risk factor for HCV transmission was very low.[6,7] In view of all these facts, this case control study was designed to determine the risk factors of hepatitis C infection in Tokat, a province located in the middle-interior Black Sea Region of Turkey.

MATERIAL AND METHODS

This research is a case-control study. The anti-HCV positive patients who applied to Gaziosmanpasa University Hospital outpatient clinic of Infectious Diseases and Clinical Microbiology between January 2005 and March 2008 constituted the case group. The control group consisted of anti-HCV negative patients who applied either to our or to internal medicine outpatient clinic with diseases other than hepatitis, or the adult female patients who were stationary-monitored at Tokat Maternity and Child Care Hospital. The patients undergoing hemodialysis were not included in the study. One hundred ninety-three and 190 patients were allocated for the case and control groups, respectively. An informed consent was obtained from each participant. The study was performed through anti-HCV enzyme immunoassay (Abbott, Axsym) method. Cases and the individuals in the control group were questioned in terms of the following risk factors which were deemed to have a possible role in transmission of hepatitis C virus: history of procedures like surgery, endoscopy, coronary angiography, and history of blood transfusion, dental care, IV drug abuse, hospitalization for more than one week. Besides these, only for women, number of pregnancies and deliveries, number of uterine curettage and history of delivery in a hospital setting were examined. Tooth extraction was not considered as a risk factor, on the other hand, treatment-related dental procedures, i.e. dentures, fillings etc. were considered as risk factors associated with dental care.

The data were analyzed statistically with the SPSS 11.5 program. When comparing the frequencies of risk factors between the groups, Chi-square analysis (when necessary Fisher's exact test) was performed. Multiple logistic regression modeling was done to identify the independent risk factors for HCV infection. Only those risk factors that were statistically significant on univariate analysis were included in the model.

RESULTS

The mean age of 193 anti-HCV positive patients was 52.1 ± 9.8 years whereas it was 50.5 ± 10.5 years in the control group. The female patients constituted 78% and 77% of the case and control groups, respectively. HCV RNA test could not be performed for 11 patients in the case group. HCV RNA was positive in 159 out of 182 patients (87.4%). Upon the review of age distribution of cases, it was observed that number of cases below 29 years and above 70 years were quite low (3.1% and 3.1%, respectively) and that the highest number of cases was in the age group 50-59 (50.8%) followed by the age group 40-49 (24.1%) (Figure 1).

There was no significant difference in terms of gender distribution and average ages between the case and control groups. During the statistical analysis, "curettage" and "delivery in the hospital" were evaluated separately and together since these two birth-related procedures have similar risk in terms of HCV. IV drug abuse was not detected as a risk factor in either in the case group or control group. As a result of Chi-square analysis, no difference was observed among the case and control groups in respect to surgery, blood transfusions after 1996, number of pregnancies and deliveries, en-

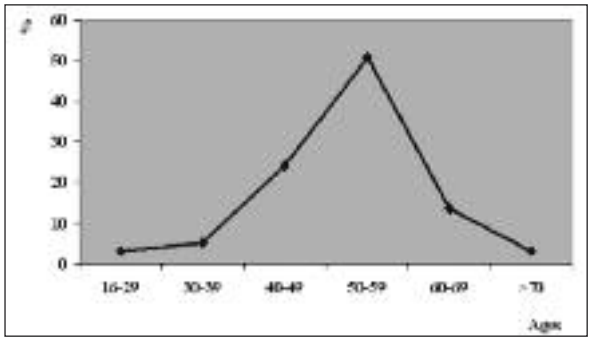

FIGURE 1: Frequency of hepatitis C by age groups.

doscopy and coronary angiography. However, it was found that the following variables distributed differently among two groups and were significantly related to increased risk for hepatitis C infection in the logistic regression analysis: blood transfusions before 1996, undergoing three or more curettages, hospitalization for more than one week, history of curettage and/or delivery in the hospital and dental care (Table 1). The Odds ratios calculated at the confidence range of 95% for the risk factors are presented in Table 2.

DISCUSSION

HCV-infected people serve as a reservoir for transmission to other healthy people. Moreover, HCV is responsible for approximately 27% of cirrhosis and 25% of HCC cases worldwide.[1] The epidemiological pattern of HCV varies in different regions and periods. For instance, Turkey and USA are included in the same section on the world map with respect to anti-HCV prevalence (1-1.9%); however, age-specific prevalence and routes of the transmission differ considerably.[1,2] HCV prevalence is at the highest level in the population aged between 30-49 years in USA; this indicates that transmission occurred mostly in the last 20-40 years and usually diagnosed at young ages.[8,9] According to several sudies from Turkey, HCV seroprevalence among adult population has been estimated as 1.15%.[10] However, there are regional differences in terms of HCV prevalence, for example a recent population-based study performed in Tokat province located in Middle-Black Sea Region of Turkey revealed that the HCV prevalence in adults was 2.1%.[11]

In the present study, it was determined that the number of patients increased after 40 years of age. The highest number of patients were in the age group 50-59 (50.8%) and 67.5% of the patients were above 50 years of age. These findings complied with the study of Karaca et al.[7] which included 320 patients. Accordingly, unlike the developed countries, it may be stated that risk of HCV infection in Turkey was quite high 40-60 years ago.

TABLE 1: Distribution of risk factors for hepatitis C among cases and controls.

	Cases		Controls		
	N (%)	Total (n)[c]	N (%)	Total (n)[c]	p
Number (F/M)[a]	193 (151/42)		190 (147/43)		0.830
Mean Age ± SD[b]	52.1 ± 9.8		50.5 ± 10.5		0.120
Dental Care	121 (65.1)	186	103 (55.1)	187	0.040*
Hospitalization	109 (61.2)	178	78 (41.7)	187	<0.001*
Curettage or delivery in the hospital	126 (89.4)	141	115 (79.3)	145	0.040*
Three or more curettages	50 (34.0)	147	34 (23.3)	146	0.040*
Curettage	106 (72.6)	146	91 (62.8)	145	0.088
Delivery in the hospitals	80 (58.0)	138	73 (51.4)	144	0.241
Surgery	113 (59.5)	190	107 (56.6)	189	0.570
Endoscopy	19 (10.6)	180	23 (12.3)	187	0.718
Coronary angiography	12 (8.9)	135	10 (10.2)	98	0.911
Blood transfusions before 1996	35 (18.5)	189	9 (4.7)	190	<0.001*

* indicates statistically significant difference between groups (p< 0.05)

[a]Female/Male,

[b]Standard deviation,

[c]the n numbers vary due to insufficient data of the risk factors in the case and control groups.

TABLE 2: Results of logistic regression analysis performed for Hepatitis C in the case and control groups.

Risk factors	B	OR*	95% Confidence Interval
Curettage or delivery in the hospital	0.91	2.4	1.1-5.0
Hospitalization	1.0	2.7	1.6-4.6
Dental Care	0.63	1.8	1.1-3.1
Blood transfusion before 1996	1.43	4.50	1.7-11.8

* Odd's ratio, Estimated relative risk.

HCV is mainly transmitted by percutaneous route. As a result of cohort studies and acute case-control studies, the primary percutaneous risk factors for HCV were as follows: blood and blood product transfusions, solid organ transplantation from infected donors, IV drug abuse, unsafe therapeutic injections and profession-related contacts such as needle stick. Delivery from an infected mother, sexual intercourse with infected partner or with multiple-partners are the factors which are less accountable for the transmissions.[1,4,12,13] According to Center for Disease Control (CDC), new cases of HCV infections in USA are related to following factors: IV drug abuse in 68%, sexual intercourse with infected partner or with multiple-partners in 18% and profession-related contacts in 4%. It was indicated that nosocomial, iatrogenic or perinatal transmissions can be responsible from only 1% of cases for acute hepatitis C and no risk factors could be determined in 9% of such cases.[4] In one study from USA allocating a large sample representetive of the country in between 1999-2002 indicated that IV drug abuse was the most important risk factor in almost half of all anti-HCV positive patients. In this study, blood transfusions before 1992 and sexual history of 20 or more sex partners in a lifetime were determined as other important risk factors.[8] Unlike the developed countries, in Turkey, HCV transmissions were mostly related to percutaneous routes other than IV drug abuse. Patients who applied to Istanbul University, Faculty of Medicine Hospital between 1996-2002 were evaluated in an uncontralled study which did not have a control group. In this study, Karaca et al. reported that 98% of 320 HCV patients had a history of surgery and 39.7% had a history of blood transfusion. Other important risk factors were determined as follows: dental procedures (27.5%), abortus (21.2%), long term hospitalization (11.6%), history of jaundice (4.6%), history of IV drug abuse (3.1%) and history of suspected sexual contact (1.5%). Unlike our study, 31 patients (10%) who received hemodialysis treatment were also included in that study. In this study, rates of surgery and blood transfusion were higher than the rates detected among our cases. This may be due to fact that the studied patients were from various regions. Consequently, the study of Karaca et al.[7] indicated that IV drug abuse was very low in frequency and HCV was transmitted by other parenteral routes in Turkey.

Yildirim et al.[6] compared 151 HCV positive patients who applied to Istanbul University, Cerrahpasa Faculty of Medicine Hospital with the control group in terms of risk factors. In that study, it was determined that the following risk factors were observed significantly more common than the control group: surgery, frequent dental care, dental extraction, blood tranfusions, multiple-partners and sexual intercourse. In this study, the history of surgery was detected in 68.9% of HCV positive cases and a history of blood transfusion was detected in 21.2% similar to the rates in our cases. However, the rates of surgery were not found to be different among cases and controls in our study while there was a difference regarding blood transfusions before 1996, when blood banks began screening for HCV in Turkey. The difference for surgery may be explained with regional differences. In that study, in accordance with our study, dental care was found as an important risk factor. Besides, Yildirim et al,[6] investigated other risk factors such as circumcision, tatoing, acupuncture, sharing toothbrushes and razor blades, IV drug abuse and having a proffession as a healthcare worker. It was observed that the rates of these factors were not higher than that of the control group. However, curettage was not examined as a risk factor in this study.

In a study on people applying to first-line healthcare institutions, it was reported that HCV prevalence varied in various regions of Greece.[14] One thousand sixty one subjects with a history of blood

transfusion, hospitalization, IV drug abuse or abortus (medical or paramedical) were included in this study. It was found that the aforemetioned risk factors -except abortus- were associated with HCV infection. In fact, the investigators detected that HCV infection had a higher rate in patients with a history of abortus, however this was not found to be statistically significant. In the study, in addition to these factors, more than five deliveries, dental procedures and alcohol abuse were also found to be associated with HCV infection.[14]

In France, Karmochkine et al.[15] reviewed the risk factors for 450 HCV seropositive patients who did not have any blood transfusions or IV drug abuse and compared them with the control group. The HCV-related risk factors determined as a result of multi-variant analysis were as follows: hospitalization, abortus, gastrointestinal endoscopy, non-hospital therapeutic applications (i.e. wound care, intravenous or intramuscular injections, varicose ven sclerotherapy, acupuncture, intranasal cocaine usa), contact sports, esthetic treatments, professional manicure and pedicure. As it may be seen, hospitalization and medical treatments performed outside the hospital are among the important risk factors for HCV as also revealed by our study.

A case-control study from Poland investigated the risk factors other than IV drug abuse for chronic hepatitis C on 194 patients and the multi-variant analysis revealed that blood transfusions, working in health sector, minor surgical interventions, hospitalization and dental procedures increased the risk of HCV infection.[16] In this study, even though minor surgical procedures were examined, curettage was not reviewed as a separate risk factor. However, hospitalization, dental care and blood transfusions were detected as important risk factors similar to our study.

Unlike the studies performed in Turkey and in other countries, dominance of females was detected in our study. This may be due to regional differences or as revealed by our study, unlike men, women were exposed to the risk factor unique for female gender (such as curettage or delivery in the hospital and the nosocomial route). According to the findings of our study, HCV infection risk in women increases 2.4 fold in case of curettage and/or delivery in the hospital.

In our study, dental care, uterine curettage, delivery in the hospital and hospitalization were shown to be responsibe from HCV transmission. These findings indicate that HCV transmission in our region was primarily associated with medical procedures. We presume that risk of HCV infection increases due to insufficient infection control precautions in the hospitals or doctors' offices. It was seen in our study that the risk of HCV infection did not increase in patients who had previous surgery. This may be due to the fact that sterilization-disinfection and infection control regulations are obeyed in the operating room settings and are followed strictly in our region. However, compliance to these regulations decreases in the procedures performed outside the operating rooms i.e. delivery by vaginal route. Curettage and dental treatment applications are mostly performed at the doctors' offices where sterilization-disinfection techniques are usually inappropriate and chemicals were used for this purpose in these units. Increase in the risk may be still explained by the failure of infection control precautions in different procedures such as injections.

As a consequence, dental procedures, uterine curettage, delivery in hospitals and hospitalization are the risk factors largely accounting for HCV transmissions in our region. These healthcare-related risk factors are preventable in nature.

REFERENCES

1. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13(17):2436-41.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5(9):558-67.
3. Williams I. Epidemiology of hepatitis C in the United States. Am J Med 1999;107(6B):2S-9S.
4. Alter MJ. Prevention of spread of hepatitis C. Hepatology 2002;36(5 Suppl 1):S93-8.
5. Wong T, Lee SS. Hepatitis C: a review for primary care physicians. CMAJ 2006;174(5):649-59.
6. Yildirim B, Tahan V, Ozaras R, Aytekin H, Mert A, Tabak F, et al. Hepatitis C virus risk factors in the Turkish community. Dig Dis Sci 2005;50(12):2352-5.
7. Karaca C, Cakaloğlu Y, Demir K, Ozdil S, Kaymakoğlu S, Badur S, et al. Risk factors for the transmission of hepatitis C virus infection in the Turkish population. Dig Dis Sci 2006;51(2):365-9.
8. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144(10):705-14.
9. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341(8):556-62.
10. Mıstık R. [Examination of the epidemiology of viral hepatitis in Turkey publications]. Tabak F, Balık I, Tekeli E, editörler. Viral Hepatit 2007. 1. Baskı. İstanbul: Ohan Matbaası; 2007. p.10-50.
11. Yildirim B, Barut S, Bulut Y, Yenişehirli G, Ozdemir M, Cetin I, et al. Seroprevalence of hepatitis B and C viruses in the province of Tokat in the Black Sea region of Turkey: A population-based study. Turk J Gastroenterol 2009;20(1):27-30.
12. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.
13. Tahan V, Karaca C, Yildirim B, Bozbas A, Ozaras R, Demir K, et al. Sexual transmission of HCV between spouses. Am J Gastroenterol 2005;100(4):821-4.
14. Lionis C, Vlachonikolis IG, Skliros S, Symeonidis A, Merkouris BP, Kouroumalis E. Do undefined sources of hepatitis C transmission exist? The Greek study in General Practice. J Viral Hepat 2000;7(3):218-24.
15. Karmochkine M, Carrat F, Dos Santos O, Cacoub P, Raguin G. A case-control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. J Viral Hepat 2006;13(11):775-82.
16. Chlabicz S, Grzeszczuk A, Prokopowicz D. Medical procedures and the risk of iatrogenic hepatitis C infection: case-controlled study in north-eastern Poland. J Hosp Infect 2004;58(3):204-9.