pISSN 2287-2728
eISSN 2287-285X

CMH

http://dx.doi.org/10.3350/cmh.2013.19.1.45
Clinical and Molecular Hepatology 2013;19:45-50

Original Article

Clinical and epidemiological characteristics of Korean patients with hepatitis C virus genotype 6

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Background/Aims: The distribution of hepatitis C virus (HCV) genotypes varies geographically. In Korea, genotypes 1 and 2 comprise more than 90% of HCV infections, while genotype 6 is very rare. This study compared the clinical and epidemiological characteristics of patients with genotype 6 HCV infection with those infected with HCV genotypes 1 and 2.

Methods: This was a prospective, multicenter HCV cohort study that enrolled 1,173 adult patients, of which 930 underwent HCV genotype analysis, and only 9 (1.0%) were found to be infected with genotype 6 HCV. The clinical and epidemiological parameters of the genotypes were compared.

Results: The patients with genotype 6 HCV had a mean age of 41.5 years, 77.8% were male, and they had no distinct laboratory features. A sustained virologic response (SVR) was observed in four (67%) of six patients who received antiviral therapy. Risk factors such as the presence of a tattoo (n=6, 66.7%), more than three sexual partners (n=3, 33.3%), and injection drug use (n=3, 33.3%) were more common among genotype 6 patients than among genotypes 1 or 2.

Conclusions: The epidemiology and treatment response of patients infected with genotype 6 HCV differed significantly from those with genotypes 1 or 2, warranting continuous monitoring. **(Clin Mol Hepatol 2013;19:45-50)**

Keywords: HCV; Genotype; Epidemiology; Treatment; Korea

INTRODUCTION

Hepatitis C virus (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide. It is estimated that 3% of the world population is chronically HCV infected. HCV is a member of the genus Hepacivirus in the family Flaviviridae and shows a high degree of genetic heterogeneity.[1] Sequencing of HCV isolates has identified six major genotypes and more than 83 subtypes.[2] The HCV genotype is one of the most important predictors of a sustained virologic response (SVR) after antiviral treatment.

Abbreviations:

HCV, hepatitis C virus; SVR, sustained virologic response; HCC, hepatocellular carcinoma; IDU, intravenous drug use; RVR, rapid virologic response; HBsAg, hepatitis B virus surface antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

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Received : Oct. 5, 2012 / **Revised :** Nov. 20, 2012 / **Accepted :** Dec. 4, 2012

There are geographic differences in the distribution of HCV genotypes.[3] HCV genotypes 1 to 3 are widely distributed globally, whereas genotypes 4 to 6 are limited to less-developed regions: genotype 4 in Egypt and Africa; genotype 5 in South Africa; and genotype 6 in Southeast Asia, South China, Hong Kong, and Taiwan.[2,4] The geographic distribution is associated with the transmission route. For example, genotypes 1a, 1b, and 3a are transmitted through blood transfusion and intravenous drug use (IDU) and are the dominant genotypes in Western countries.[1] Genotypes 4 and 6 HCV infections in underdeveloped regions are often transmitted by undefined domestic routes, such as acupuncture, folk remedies, tattooing, and piercing.[5]

The major HCV genotypes in Korea are genotypes 1b and 2a/c,[6] while few studies have examined genotypes 3, 4, and 6 in Korea. Recently, we reported the rarity of HCV genotype 6 infection in Korean patients in a prospective, multicenter, HCV cohort study. Therefore, we compared the clinical characteristics and epidemiology of Korean patients infected with HCV genotype 6 with those of genotypes 1 and 2.

MATERIALS AND METHODS

Study design and population

A prospective, multicenter HCV cohort enrolled 1,173 adult patients positive for anti-HCV antibody using a third-generation enzyme immunoassay at five university hospitals from January, 2007 to December, 2011. HCV genotyping was conducted in 930 patients in the cohort, and nine were found to be infected with genotype 6 HCV. The diagnostic categories of the HCV-related liver disease comprised acute hepatitis C, spontaneous recovery from past infection with positive results for anti-HCV and negative for serum HCV ribonucleic acid levels (RNA) without antiviral treatment, chronic hepatitis C, liver cirrhosis, and HCC. Liver cirrhosis was diagnosed based on the histological and radiological findings and clinical features of portal hypertension, including thrombocytopenia <100,000/mm^3, gastroesophageal space varices, and ascites. The diagnosis of HCC was made histologically or from typical radiological findings, including arterial enhancement and venous wash-out on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) in hepatic nodules.

All patients provided written informed consent and the study was approved by the Institutional Review Board of each hospital.

Laboratory tests and Questionnaire survey

A real-time polymerase chain reaction (PCR) assay was used to quantify HCV RNA, using manufacturer-provided protocols, reagents, and software (Abbott Molecular, Des Plaines, IL). HCV genotyping was conducted using the INNO-LiPA HCV II assay (Innogenetics, Zwijnaarde, Belgium), which is a hybridization-based line probe assay. The 5′-untranslated region and core region of the HCV genome were amplified using nested PCR with biotinylated primers, based on the manufacturer's instructions.[7]

Blood biochemistry performed at enrollment included anti-HCV, serum HCV RNA levels, hepatitis B virus surface antigen (HBsAg), anti-HBs, white blood cell count, hemoglobin, platelet count, aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, gamma glutamyltransferase, albumin, creatinine, and alpha fetoprotein.

A trained research coordinator at each hospital interviewed each subject using a standardized questionnaire, which included socio-demographics (age, gender, education, and occupation), health behavior (smoking and drinking), and a medical history including accompanying diseases (cancer, thyroid disease, psychiatric disease, diabetes, kidney disease, cerebrovascular disease, and cardiovascular disease). In addition, the patients were asked about their lifetime experience of theoretical risk factors for HCV infection, such as acupuncture, dental procedures, diagnostic endoscopy, surgery, tattooing, piercing, needle-stick injury, blood transfusion, hemodialysis, a diagnosis of hemophilia, IDU, familial history of HCV-related liver disease, living with an HCV carrier, and number of sex partners.

Completed questionnaires and clinical data were collected and entered into an electronic case report form at the Korean HCV cohort study group homepage (http://www.hcvcohort.or.kr).

Statistical analysis

Categorical variables were compared using the chi-square test and continuous variables using Student's *t*-test. Continuous variables were compared among the three groups using analysis of variance (ANOVA). A significant portion of data were missing due to the nature of the questionnaire survey. For analysis, missing data were treated using the SPSS missing values options. SPSS version 18 was used for all statistical analyses (SPSS, Chicago, IL)

http://dx.doi.org/10.3350/cmh.2013.19.1.45

RESULTS

The prevalence of genotype 6 HCV infection in Korean patients

The prevalence of HCV genotypes in the Korean HCV cohort is summarized in Table 1. Genotypes 1-4, and 6 HCV were found in 52.8% (n=491), 45.3% (n=421), 0.8% (n=7), 0.2% (n=2), and 1.0% (n=9), respectively. All genotype 6 subgenotypes were genotype 6c.

Clinical and epidemiological characteristics of genotype 6 HCV-infected patients

The comparison of the clinical and epidemiological characteristics of genotypes 1, 2, and 6 is summarized in Table 2. The genotype 6 HCV-infected patients had a mean age of 41.5 years, which was significantly younger than those with genotype 1 (54.4 years) or 2 (57.2 years) (P<0.001). Moreover, the proportion of male genotype 6 patients (77.8%) was higher than that of genotype 1 (54.2%) or 2 (42.0%) (P<0.001). The diagnostic distribution and baseline laboratory results of genotype 6 patients were similar to those with genotype 1 or 2 (Table 2).

Among the genotype 6 patients, the exposure history to possible risk factors associated with HCV infection was as follows: dental procedure (n=7, 77.8%), diagnostic endoscopy (n=7, 77.8%), acupuncture (n=8, 88.9%), surgery (n= 1, 11.1%), tattooing (n=6, 66.7%), piercing (n=2, 22.2%), more than three sex partners (n=3, 42.8%), blood transfusion before 1995 (n=1, 11.1%), and IDU (n=3, 33.3%). Interestingly, the proportion of IDU was significantly higher in genotype 6 patients (33.3%) than in either genotype-1 (7.2%) or -2 (3.1%) patients (P<0.001), while the proportion that underwent remote blood transfusions before 1995 was lower in the genotype 6 group (Table 2).

Antiviral therapy against HCV was administered to six patients, of which four achieved a SVR (Table 3). During the mean follow-up period of 2.9 years, there was no mortality, and one patient (patient #4) progressed from chronic hepatitis to liver cirrhosis (Table 3). Patient #4 had a peculiar course. After 3 months of therapy with peginterferon α2a with ribavirin, he discontinued the antiviral therapy for economic reasons. After 2.3 years, retreatment with peginterferon α2a and ribavirin for 6 months resulted in viral relapse; at this time, the viral genotype was retested and showed genotype 1b instead of genotype 6c. He denied any risk behavior related to possible reinfection with HCV during the follow-up period. Therefore, he might initially have been co-infected with genotypes 6c and 1b, with genotype 6 dominant, and after antiviral treatment for 6 months, genotype 6 HCV might have been cleared, while genotype 1c remained and became predominant. This may suggest that the antiviral response of genotype 6 infection is better than that of genotype 1 infection.

DISCUSSION

We identified genotype 6 HCV in about 1% of Korean patients with chronic HCV infection, especially in young males with a history of IDU and tattooing. The laboratory findings of genotype 6 infection did not differ significantly compared with those of genotype 1 or 2. Antiviral therapy was administered to six of the nine patients and a SVR was achieved in 67%.

The reported prevalence of genotype 6 among HCV-infected patients was 49% in Myanmar, 47.1% in Vietnam, 37.1% in Hong Kong, and 18-31% in Thailand.[2,4] In addition, several previous small-scale studies reported that genotypes 1b (about 50%) and 2a/c (about 50%) were dominant in Korea.[6,8] A recent study of the HCV genotypes in Korean blood donors found genotypes 1b, 1a , 2a/c, 2b, 3a, and 4 in 47.7, 1.3, 35.0, 2.3, 1.6, and 0.1%, respectively, but none with genotype 6.[9] In comparison, in this study, 1% of the chronic liver disease patients were infected with genotype 6 HCV, confirming the rarity of this genotype in Korea.

The mean age of the genotype 6 patients in our study was significantly younger and the proportion of males was higher than in those with genotype 1 or 2. There was no HCC or liver

Table 1. The prevalence of HCV genotypes in Korea

Genotype	Subgenotype	Respective numbers of patients (%) (n=930)	Subtotal
1	1b, 1a, 1, 1c, 1a/b	422 (45.4), 28 (3.0), 25 (2.6), 13 (1.3), 3 (0.3)	491 (52.8)
2	2a/c, 2, 2a, 2b	266 (28.6), 78 (8.4), 66 (7.0), 11 (1.2)	421 (45.3)
3	3a, 3	5 (0.6), 2 (0.2)	7 (0.8)
4	4	2 (0.2)	2 (0.2)
6	6c	9 (1.0)	9 (1.0)

http://dx.doi.org/10.3350/cmh.2013.19.1.45

Table 2. Comparison of the clinical characteristics of patients with HCV genotypes 1, 2, and 6

	Genotype 1 (n=491)	Genotype 2 (n=421)	Genotype 6 (n=9)	*P*-value
Sociodemographics, n (%)				
Age (yr)*	54.4±12.7	57.2±12.4	41.5±7.8	<0.001
Female	225 (45.8)	244 (58.0)	2 (22.2)	<0.001
Education above high-school level (n=908)	329 (68.8)	269 (65.3)	5 (55.6)	0.407
Occupation (n=899), Yes	362 (75.6)	334 (83.1)	7 (77.8)	0.024
Smoking (current or former)	267 (54.8)	188 (44.9)	7 (77.8)	0.003
Alcohol drinking (current or former)	277 (57.2)	202 (48.7)	7 (77.8)	0.013
Diagnosis, n (%)				
Acute hepatitis	25 (5.1)	15 (3.6)	1 (11.1)	0.334
Pulmonary hypertension	1 (0.2)	0 (0)	0 (0)	
Chronic hepatitis	325 (66.2)	313 (74.3)	8 (88.9)	0.013
Liver cirrhosis (LC)	92 (18.7)	56 (13.3)	0	0.035
Hepatocellular carcinoma (HCC)	48 (9.8)	37 (8.8)	0	0.552
LC + HCC	140 (28.5)	93 (22.1)	0	0.018
Biochemistry				
White blood cell count* /μL	5,271.9±2081.3	5,131.1±1,704.3	5,166.6±1,361.2	0.558
Platelets* ×1,000/μL	164.2±74.5	167.7±69.3	161.0±53.8	0.755
Albumin* g/dL	4.0±0.5	4.1±0.4	4.3±0.3	0.198
Total bilirubin* mg/dL	0.9 (0.6-1.2)	0.8 (0.6-1.1)	1.0 (0.7-1.5)	0.139
AST† IU/L	51.0 (31.0-83.0)	49.0 (28.0-90.0)	82.0 (38.0-643.5)	0.558
ALT† IU/L	52 (27.0-93.0)	47.0 (23.0-98.0)	162.0 (42.5-726)	0.105
HCV RNA >600,000 IU/mL	243 (49.4)	144 (34.2)	5 (55.5)	1.000
Risk factors, n (%)				
Intravenous drug use (n=928)	35 (7.2)	13 (3.1)	3 (33.3)	<0.001
Needle stick injury (n=771)	46 (11.1)	21 (6.2)	0 (0)	0.041
Transfusion before 1995 (n=907)	78 (16.3)	81 (19.6)	1 (11.1)	0.612
Tattooing (n=915)	162 (33.3)	164 (39.9)	6 (66.7)	0.022
Living with HCV carrier	3 (0.5)	4 (1.0)	0 (0)	0.466
Hemodialysis (n=908)	4 (0.8)	3 (0.7)	0 (0)	0.118
≥Three sex partners (n=865)	133 (29.1)	72 (18.3)	3 (33.3)	<0.001
Dental procedure (n=910)	452 (93.8)	379 (92.4)	7 (77.8)	0.146
Endoscopy (n=914)	409 (84.7)	359 (86.9)	7 (77.8)	0.504
Acupuncture (n=913)	399 (82.3)	349 (85.1)	8 (88.9)	0.471
Piercing (n=909)	164 (34.1)	159 (38.8)	2 (22.2)	0.239
Surgery (n=904)	201 (42.1)	183 (44.9)	1 (11.1)	0.106

*Mean±SD; †Median (interquartile range).

cirrhosis in the genotype 6 patients; this might be related to their younger age. Seto et al found genotype 6 in 28.9% of a chronic HCV cohort in Hong Kong, and there was no significant difference between genotypes 6 and 1 patients in terms of laboratory results, development of cirrhotic complications, and mortality during a mean follow-up of 5.4 years.[10] In a clinical study of 308 chronic hepatitis C Southeast Asian American patients, Nguyen et al found that genotypes 6 (41%) and 1 (42%) were common,

http://dx.doi.org/10.3350/cmh.2013.19.1.45

Table 3. The results of liver biopsies and treatments of HCV genotype 6 patients at enrollment

Patient	Age (yr)	Sex	Follow-up (yr)	Dx	New LC	Death	US	Liver biopsy	Tx	Regimen	Tx duration (wk)	RVR	EVR	SVR	Relapse
1	34	M	2.15	AH	N	N	Normal	N	N						
2	50	M	4.15	CH	N	N	CLD, Fatty liver	Y (A1, F1)	Y	IFN + Ribavirin	13	N	N	N	
3	53	M	3.95	CH	N	N	Normal	N	N						
4	45	M	4.66	CH	Y	N	Normal	Y (A1, F2)	Y	1st: PegIFN α2a+Ribavirin	16	N	Y	N	Y
										2nd: PegIFN α2a+Ribavirin	22	Y	Y	N	Y
5	47	M	3.06	CH	N	N	CLD	N	Y	PegIFN α2b+Ribavirin	24	N	Y	Y	N
6	31	M	1.54	CH	N	N	Normal	N	Y	PegIFN α2b+Ribavirin	52	NC	Y	Y	N
7	43	M	1.56	CH	N	N	Fatty liver	N	Y	PegIFN α2b+Ribavirin	48	NC	Y	Y	N
8	35	F	N	CH	N	N	Normal	N	N						
9	36	F	1.96	CH	N	N	Fatty liver	Y (A1, F3)	Y	PegIFN α 2b+Ribavirin	23	NC	Y	Y	N

Fibrosis scores: F0=no fibrosis, F1=portal fibrosis without septa, F2=portal fibrosis with few septa, F3=numerous septa without cirrhosis, F4=cirrhosis.
Activity scores: A0= no activity, A1=mild activity, A2=moderate activity, A3=severe activity.
AH, acute hepatitis; CH, chronic hepatitis; LC, liver cirrhosis; CLD, chronic liver disease; FU, follow-up; Dx, diagnosis; Tx, treatment; Y, yes; N, no; NC, not checked; US, ultrasonography; IFN, standard interferon; PegIFN, peginterferon; EVR, early viral response; RVR, rapid viral response; SVR, sustained viral response.

but there were no major differences in the clinical features of the different genotypes or in the development of HCC or liver cirrhosis between the genotypes.[11]

In our study, the most common risk factors in patients with genotype 6 were acupuncture (n=8, 88.9%), dental procedures (n=7, 77.8%), endoscopy (n=7, 77.8%), tattooing (n=6, 66.7%), IDU (n=3, 33.3%), and more than three sex partners (n=3, 33.3%). Interestingly, the proportion of IDU was significantly higher in patients with genotype 6 than in the other genotypes. This result is compatible with the Hong Kong study,[10] in which a significantly larger proportion of genotype 6 patients were injection drug users compared with genotype 1 patients (28.2 vs. 8.7%), while genotype 1 patients had a greater proportion of remote blood transfusion than genotype 6 patients (71.7 vs. 56.4%), as seen in other studies.[12,13] There were trends to higher proportions of tattooing and more than three sex partners in genotype 6 patients. In addition, the genotype 6 subtype was 6c in all patients; this is also prevalent in Thailand. HCV genotype 6c in Korea might have been imported from Thailand, although we did not ask about a history of travel to Thailand.

The HCV genotype is a major predictor of the response to antiviral therapy. Studies have reported a SVR of 62.5-85.7% for genotype 6 after 24-48 weeks of antiviral therapy. This was better than the SVR in genotype 1 patients (29.2-52.4%).[2,14] A recent randomized trial including 105 treatment-naïve genotype 6 patients in Vietnam found no significant difference in the SVR rates in patients treated with peginterferon α2a/ribavirin for 48 versus 24 weeks (71% vs. 60%, respectively; P=0.24).[15] Among those patients with a rapid virological response (RVR), the SVR was in 86% (48-week treatment) and 75% (24-week treatment) (P=0.45), whereas following a non-RVR, only 8% of the cases had an SVR with 48-week treatment. Another study from Thailand reported that the SVR rate in genotype 6 patients was 76.5% and 24-week treatment using a response-guided strategy was recommended.[16] In our study, six patients were treated with antiviral therapy, with a SVR in four (66.6%); the median duration of treatment was 23 weeks. Although we examined few patients, the SVR rate was comparable to those reported elsewhere.

This study had several limitations. First, the number of subjects was too small to draw any conclusive results, because genotype 6 is very rare in Korea. Second, we relied on a questionnaire survey to evaluate risk factors, creating a recall bias. Third, some people did not want to answer questions about private issues, such as IDU or sexual relationships, which resulted in missing data. Although we investigated the lifetime exposure to each risk factor, a

http://dx.doi.org/10.3350/cmh.2013.19.1.45

history of exposure to a risk factor did not necessarily indicate the cause of the HCV infection.

In conclusion, genotype 6 HCV was found in about 1% of HCV-infected patients in our study group, mainly in middle-aged men with a history of IDU, multiple sex partners, and tattooing. The baseline clinical characteristics of genotype 6 and the other HCV genotypes are similar, and most of the patients presented with chronic hepatitis, rather than cirrhosis or HCC. Antiviral therapy resulted in a SVR rate of 67%, intermediate between the SVRs of genotypes 1 and 2. In addition, the only subtype of genotype 6 found was 6c, which is prevalent in Thailand. Since HCV epidemiology is dynamic, further study of the epidemiological and clinical characteristics of the HCV genotypes in Korea is warranted.

Acknowledgements

This study was supported by a research grant from the Korea National Institute of Health (KNIH: Extramural fund, Grant No. 83 in 2012). We are grateful to the devoted research coordinators and collaborator: Sung Ho Hwang, Da Seol Lee, Min Young Kim, Won Hee Jeong, Eun Hee Park, Young Soon Kim, Ye Young Lee, and Mi Kyong Kang, and Jae Ho Kim.

Conflicts of Interest

The authors have no conflicts to disclose.

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