

Distribution of viral genotypes and extrahepatic manifestations in patients with chronic hepatitis C in Eastern Turkey

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Background/aim: To investigate the distribution of viral genotypes, the extrahepatic manifestations, and the relationship between genotypes and extrahepatic manifestations in patients with chronic hepatitis C.

Materials and methods: The study included 62 treatment-naïve patients with chronic hepatitis C infection. Genotype determination was performed by DNA sequencing analysis. To investigate extrahepatic manifestations, the patients' data, recorded prospectively during the pretreatment period, were analyzed.

Results: Genotype determination was successful in 74.2% of the cases. All patients were infected with hepatitis C virus (HCV) genotype 1b. At least 1 extrahepatic manifestation was identified in 37.1% of the patients. The most frequent clinical manifestations were type II diabetes mellitus (8.1%) and arthralgia or arthritis (8.0%). There was no relationship between extrahepatic manifestations and fibrosis or transaminase levels, but female sex and advanced age were risk factors. Because all patients were infected with the same genotype, the relationship between extrahepatic manifestations and genotype could not be examined.

Conclusion: HCV genotype 1b is predominant in patients with chronic hepatitis C in the Eastern Anatolian Region of Turkey. In total, 37.1% of the patients had at least 1 extrahepatic manifestation. Female sex and advanced age were risk factors for having extrahepatic manifestations.

Key words: Chronic hepatitis, hepatitis C virus, genotypes, extrahepatic manifestations

1. Introduction

The hepatitis C virus (HCV) is one of the major causes of liver cirrhosis, liver cancer, and chronic illnesses all over the world. According to a report of the World Health Organization, more than 280,000 deaths from chronic liver illness in 2001 were linked to HCV infection (1). HCV is in the family *Flaviviridae* and the genus *Hepaciviridae*. HCV isolates are classified as genotypes and subtypes. Six genotypes and more than 80 subtypes have been identified. These differ in nucleotide sequence by more than 30% over the complete virus genome. A number of subtypes, which differ in nucleotide sequence by more than 20%, have also been described (2). The genotypes of HCV show a distinct geographical distribution. Genotype 1b, which accounts for 40%–80% of isolates all over the world, is the most widespread genotype. Genotypes 1a, 1b, and 2a are the predominant genotypes in the United States and West Europe. Genotype 4 is the predominant genotype in the

Middle East. Types 5 and 6 are largely confined to South Africa and South East Asia (2). In Turkey, the predominant genotype is 1b (66.7%–100%) (3–5).

Genotypes are important epidemiological markers of HCV and predictors of therapeutic response. Patients infected with genotype 1b are less likely to have a sustained virological response than those infected with genotypes 2 and 3. It is known that the sensitivity of first- and second-generation enzyme-linked immunosorbent assay (ELISA) tests is influenced by the infecting genotypes. However, the role of HCV genotypes in clinical features, severity, and progression of liver disease and extrahepatic manifestations is controversial. Possible links to more severe liver disease and hepatocellular carcinoma have been reported for HCV genotype 1b. HCV-related cirrhosis and hepatocellular carcinoma can occur over a short period in some patients, whereas others have no complications despite a longer period of infection. In addition, it is known that genotype

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1b causes an earlier reappearance of more serious hepatitis in liver transplant recipients (2,6,7).

Some extrahepatic disorders including essential mixed cryoglobulinemia (EMC), lichen planus, type II diabetes mellitus (DM), thyroid dysfunctions, thrombocytopenia, porphyria cutanea tarda, local lymphocytic sialadenitis, Mooren ulcers, vasculitic neuropathy, glomerulonephritis, and polyarteritis nodosa can be accompanied by chronic HCV infection. Idiopathic pulmonary fibrosis, pancreatitis, pericarditis, and amyloidosis can also be associated. Up to 30%–70% of the patients might develop at least 1 extrahepatic manifestation during the course of the disease. As a consequence of chronic infection, an accumulation of circulating immune complexes may be the cause of the extrahepatic disorders. However, the exact mechanism is not known (8,9). The literature on the relation between HCV genotypes and extrahepatic manifestations is controversial and ambiguous (10–13).

The aims of this study were to investigate the distribution of HCV genotypes and extrahepatic manifestations, and to identify the relationship between the genotypes and extrahepatic manifestations among patients with chronic hepatitis C in the Eastern Anatolian Region of Turkey

2. Materials and methods

The study included treatment-naive patients with chronic hepatitis C infection admitted to the Department of Infectious Diseases and Clinical Microbiology of Atatürk University Medical School during the period from November 2008 to April 2010. Chronic HCV infection was considered on the basis of positive serum anti-HCV antibodies by third-generation ELISA assay (Dia.Pro Diagnostic, Italy), and positive serum HCV-RNA by a real-time polymerase chain reaction (PCR) assay (Artus HCV RG RT-RCR Kit, Germany) for at least 6 months and/or liver biopsy consistent with chronic hepatitis. HCV genotyping was performed by pyrosequencing technology, a real-time sequence analysis method based on the detection of pyrophosphate that is released during the synthesis of nucleic acid, on a PyroMark Q24 sequence analyzer (Germany) as described by the protocol of the manufacturer.

The patients' demographic features and disease histories were recorded. All patients were subjected to physical examinations for their general status and symptoms related to extrahepatic manifestations. Complete urine tests; blood tests including fasting blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), partial thromboplastin time (PTT), alpha-fetoprotein, and thyroid hormone levels; and an abdominal ultrasonography were performed on all patients. HBsAg, HBeAg, anti-HBs, anti-HBe, anti-HBc total, and anti-HIV antibodies were also measured

by the ELISA method (Dia.Pro Diagnostic). The patients with hepatitis B virus–HCV coinfections were excluded from the study. Patients were assigned a diagnosis of DM if they were using oral hypoglycemic medication or insulin, or if they had random glucose greater than 200 mg/dL, fasting glucose greater than 126 mg/dL, or glycosylated hemoglobin A1c (HbA1c) above than 6.5% on 2 occasions. Peripheral blood smear and respiratory functions tests were performed if deemed necessary. A liver biopsy was performed in 30 patients diagnosed with chronic HCV infection who gave their informed consent beforehand. A biopsy was not performed if the patient refused the procedure.

Serum antinuclear antibody (ANA), antismall muscle antibody (ASMA), antiliver kidney microsomal antibody-1 (LKM-1), antimitochondrial antibody (AMA), and antithyroid antibodies were investigated by an immunofluorescence method (Euroimmun, Lübeck, Germany).

Cryoglobulins were determined qualitatively. Ten milliliters of whole blood was incubated in a Benmari incubator at 37 °C for 30 min and then centrifuged at 3000 rpm for 10 min. A 5-mL serum sample was kept at 4 °C for 3 days. The sera were checked every 30 min on the first day and once a day thereafter. The presence of a cryoprecipitate was considered positive.

2.1. Statistical analysis

Statistical analysis was performed with SPSS 18.0 (SPSS Inc., USA). Quantitative data were expressed as mean \pm SD and Student's t-test was employed for comparison. For nonparametric variables Mann–Whitney tests and Wilcoxon's signed ranks tests were used, and $P \leq 0.05$ was considered significant.

3. Results

This study included 62 patients with chronic hepatitis C, 32 (51.6%) males and 30 (48.4%) females. The mean age was 49.74 ± 11.61 years. Viral genotype could be determined in 46 patients (74.2%). Genotype 1b was the sole genotype. A total of 23 patients had 1 or more extrahepatic manifestations. Of the patients who had extrahepatic manifestation, 15 (65.2%) were female and 8 (34.8%) were male ($P < 0.05$). The characteristics of the patients are shown in Table 1.

Type II DM was the most common extrahepatic manifestation. No patient had cryoglobulinemia. The distributions of extrahepatic manifestations are shown in Table 2.

Because all patients were infected with genotype 1b, the relation of extrahepatic manifestations to genotypes was not ascertained. Extrahepatic manifestations were more common at advanced ages and in female patients. Although the mean ALT values were not different, the

Table 1. Characteristics of patients (mean \pm standard deviation).

	Patients with extrahepatic manifestations (n = 23)	Patients without extrahepatic manifestations (n = 39)	P
Age, years	53.0 \pm 8.2	43.86 \pm 14.8	<0.05
Sex, female, n	15 (65.2%)	15(38.5%)	<0.05
ALT (U/L)	5.09 \pm 37.7	52.68 \pm 38.0	>0.5
HCV-RNA (copies/mL)	13,055 \times 10 ⁶ \pm 26,355 \times 10 ⁶	19,042 \times 10 ⁸ \pm 851,293 \times 10 ⁸	<0.05
Biopsy, n Fibrosis	15	15	
FO	6.7%	20%	<0.05
FI	53.3%	40%	<0.05
F3	40%	40%	>0.05

mean HCV-RNA value was greater in patients having extrahepatic manifestations than in those not having extrahepatic manifestations. There was no case of hepatocellular carcinoma or cirrhosis in our patient population, but 60% of them had moderate liver fibrosis. Liver fibrosis scores were also different among patients with and without extrahepatic manifestations (Table 1).

4. Discussion

In this study, genotype determination could be done in 46 of the 62 patients, and all were genotype 1b. Various studies report a failure to determine HCV genotype in 0%–44% of patients (14–17). Genotype determination rates vary by sample handling procedure and analysis method. According to the results of many other studies, genotype 1b is the most prevalent (66%–100%) HCV genotype in Turkey, and our findings are compatible with these results

Table 2. The distributions of extrahepatic manifestations.

Extrahepatic manifestations	Females, n (%)	Males, n (%)	Total, n (%)
Type II DM*	3 (10)	2 (6.2)	5 (8)
Depression	2 (6.6)	1 (3.1)	3 (4.8)
Arthralgia	2 (6.6)	1 (3.1)	3 (4.8)
Pruritus	2 (6.6)	1 (3.1)	3 (4.8)
Asthma	1 (3.3)	1 (3.1)	2 (6.2)
COPD**	1 (3.3)	1 (3.1)	2 (6.2)
Arthritis	2 (6.6)	0 (0)	2 (6.2)
ANA positivity	1 (3.3)	0 (0)	1 (3.2)
Anti-LKM-1 positivity	0 (0)	1 (3.1)	1 (3.2)
Hypothyroidism	1 (3.3)	0 (0)	1 (3.2)
Cryoglobulinemia	0	0	0
Total	15 (24.2)	8 (12.9)	23 (37.1)

*: Diabetes mellitus, **: chronic obstructive pulmonary disease.

(3–5,14–20). In a comprehensive survey, 87.2% of the patients had genotype 1b, 9.9% had genotype 1a, 0.9% had genotype 2, 1.4% had genotype 3, and 0.6% had genotype 4 (18). In another study from İstanbul, genotypes 1b, 3a, 4e, 2a/2c, 1a, and 4 were found in 76.9%, 9.6%, 5.7%, 3.8%, 1.9%, and 1.9% of the patients, respectively (19). Genotypes 2 and 3 were more common in younger patients.

Today, the clinical significance of HCV genotypes is still debatable. However, it is accepted that HCV genotype determination is important in predicting treatment response and defining the duration of the treatment and the dosage of antiviral drugs (6,7,21). The relationship of the genotypes with clinical features, extrahepatic manifestations, and prognosis is controversial. Some studies have shown an association between liver illness, hepatocellular carcinoma, and cirrhosis and genotype 1b (2,7). In a study from Turkey there was no relation between HCV genotypes and age, sex, transmission history, ALT level, or liver histopathology (3). It is suggested that genotypes 1b and 2 appear in older age groups in comparison with 1a, 3, and 4 and that HCV genotype has no relation with the levels of AST and ALT (2,19,22). Because all of our patients were infected with genotype 1b, we could not investigate any relationship for these parameters. Since multiple hosts and viral factors can contribute to variations in the natural history of diseases, it is hard to see the role of the viral genotype as an independent factor. In this study, there was no relation between extrahepatic manifestations and liver fibrosis score. Moreover, HCV-RNA levels were lower among the patients who had extrahepatic manifestations than those who did not (Table 1).

According to different studies, 40%–74% of patients infected with HCV might develop at least 1 extrahepatic manifestation during the course of the disease (13,23–25). In the present study, the rate was 37.1%, and it increased with age. Extrahepatic manifestations were more prevalent among female patients. The limitation of this study is the lack of a control group. Although some studies revealed

a female preponderance, there are also other studies that showed no sexual difference, or a male preponderance (26–28).

EMC is one of the most prevalent extrahepatic manifestations in this patient population, with prevalences of 3%–54% (8,9). The rates are lower (0%–32%) in studies from Turkey (29–31). Our study also supports these lower rates. Clinical manifestations in cryoglobulinemic patients are purpura, skin ulcers, Raynaud's phenomenon, systemic vasculitis, glomerulonephritis, and neuropathy. None of these were detected in our patient population. A prior study suggested that genotype 2c has a strong relation with EMC, while genotype 1b seems to prevent its onset (13). In considering our unique 1b genotype, it is not surprising to see no cryoglobulinemia in this study.

The association of pruritus with chronic HCV infection is reported to be 10%–15% in the literature. Pruritus during HCV infection is accepted as an immunological phenomenon and is generally seen in patients with more advanced histological lesions; reports on response to antiviral treatment are inconsistent (9,26,31–33). Pruritus was an uncommon manifestation in our cases. In contrast to some previous reports, pruritus resolved spontaneously after antiviral treatment in the patients who had treatment response.

Functional thyroid disorders and autoimmune thyroiditis can accompany chronic HCV infection or develop during antiviral treatment (6). As many as 13% of HCV-infected patients (especially older women) have hypothyroidism, and up to 25% have thyroid antibodies independent of the stage of liver disease (9,30). Hypothyroidism was noted in 1 patient in this study (1.6%). However, we could not detect thyroid antibodies.

There are numerous reports about the association between chronic HCV infection and type II DM, which is attributed to severe liver damage and fibrosis, or is independent of the degree of fibrosis (34,35). In this study, type II DM was the most prevalent extrahepatic disease, and 4 of 5 patients with DM had severe fibrosis.

Arthralgia and arthritis are other common extrahepatic manifestations in patients with chronic HCV infection. The exact mechanism of arthritis has not been determined, but it is thought to be a local inflammatory response to synovial tissue damage caused directly by viral invasion or indirectly by deposition of cryoglobulin. In comparison with other reports, prevalences of arthralgia and arthritis were much lower in this study (24,36).

Depressive disorders can be found in 50% of patients with HCV infection and can potentially be exacerbated by interferon-alpha treatment (31,37). Depression also has a

negative effect on treatment compliance. Our rate of 4.8% is lower than those of previous studies.

Several studies suggest that anti-HCV antibody prevalence is higher among patients with chronic obstructive pulmonary disease (COPD) than those without COPD (11,38). In a previous study from Erzurum, anti-HCV prevalence was 8.3% among these patients (11). Otherwise, the prevalence of COPD was 17.6% among patients who had the anti-HCV antibody. In this study, 6.2% of the patients had a diagnosis of COPD. The coexistence of COPD and HCV infection was lacking in other reports (28,39).

As a virus-induced autoimmune phenomenon, persistent HCV infection triggers production of a number of organ-specific and nonorgan-specific autoantibodies. The diversity of autoantibodies in the sera of patients with HCV-related chronic liver disease has been shown. In our study, ANA and anti-LKM-1 positivity was 1.6%, which is much less than in other literature reports. The titers of these autoantibodies seem to be independent of HCV genotypes or HCV-RNA load (40). Because of the limited number of patients with autoantibodies, we could not perform an investigation of this link. Some studies indicate a link between HCV infection and non-Hodgkin lymphoma, Sjögren's syndrome, amyloidosis, or pancreatitis (41,42). These disorders were not encountered in our study population.

In recent years, the relation between extrahepatic manifestations and HCV genotypes has been investigated (12,13). In a prior study, the genotype 2c was related to EMC, carpal tunnel syndrome, and autoimmune thyroiditis, whereas, on the contrary, genotype 1b seemed to prevent EMC (12). The association of extrahepatic manifestations with the genotypes could not be determined in another study (13). Due to the fact all our patients were infected with the same genotype, the relationship between extrahepatic manifestations and genotype could not be examined in this study.

In conclusion, as throughout all of Turkey, the predominant HCV genotype is 1b in the Eastern Anatolian Region. Chronic HCV infection is accompanied by some extrahepatic manifestations in 37% of the patients. The most prevalent extrahepatic manifestation in the study region is type II DM. An association between EMC and HCV infection was not determined in this study. Female sex and advanced age are risk factors for extrahepatic manifestations. Because genotype 1b was the unique genotype in this study population, the relationship between extrahepatic manifestations and genotype could not be examined.

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