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## Mutual Relationship of Hepatitis C Virus Infection with Hepatitis B

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The present study has been carried out to investigate whether or not there is an increased risk of Hepatitis B Virus (HBV) infection in persons having Hepatitis C Virus (HCV) infection. Never interferon therapy taken anti-HCV positive cases and controls have randomly been studied. In anti-HCV positives, HCVRNA via polymerase chain reaction and in HBsAg positives, HBVDNA via molecular hybridization have been studied. HCVRNA positivity has been detected in 74 of 102 cases with anti-HCV positivity. Although eight cases of HBsAg carrierity (3.63), four cases of chronic hepatitis B (1.81), three cases of HCVRNA positivity (1.36) and one case of anti-HCV positivity alone (0.45) have been detected in 220 controls, only four cases of HBsAg carrierity and no case of chronic hepatitis B have been detected in 74 cases of HCVRNA positivity ( $p>0.05$ ) and no case of carrierity or chronic infection of HBV has been detected in 28 cases of anti-HCV positivity alone ( $p>0.05$ ). Beside that, 24 cirrhosis, five hepatocellular carcinoma, two membranoproliferative glomerulonephritis one of which is together with rheumatoid arthritis and cirrhosis, two lichen planus, three asthma, one prolymphocytic leukemia together with cirrhosis, one idiopathic thrombocytopenic purpura, one bronchiectasis, one monoclonalgammopathy of unknown significance and two cases of non-Hodgkin's lymphoma have been detected in 102 cases of anti-HCV positivity. Although the highly suspected relationship between HCV and many autoimmune diseases and malignancies, HCV is not a facilitating agent of HBV, either having chronic infection or being a carrier of it.

**Key words:** Hepatitis C virus, hepatitis B virus, immunity

**INTRODUCTION**

Hepatitis C and B Virus (HCV and HBV) infections affect a significant part of the world's population. Both of the viruses are believed not to be directly cythopathic and outcome of their infections is influenced by status of the immune system. An energetic response of the natural immunity may allow controls of the viruses. For example, rapid development of specific neutralizing antibodies may be essential for the clearance of acute hepatitis B and C. Immunologic factors such as Human Leukocyte Antigens (HLA) may take role in the susceptibility to infection by HCV and HBV (Mateescu *et al.*, 2004; Cotrina *et al.*, 1997). Correlations between HLA polymorphism and clinical outcome for some viral infections have been reported (Steel *et al.*, 1988). HCV persists in patients without any apparent evidence of immune deficits, depending on virus or host-related factors. The recent studies have revealed that both cellular and humoral immunity appear to be active, despite the progression of the disease (Mateescu *et al.*, 2004). The chronic phase of HBV infection is often associated with an abnormal and weak T-cell response and viral persistence. Additionally in patients with chronic HBV and HCV infections, an inverse relationship in the replicative activity of the two viruses has been reported (Pontisso *et al.*, 1996). In another study, the HCV core protein is able to inhibit HBV *in vitro* and serines at positions 99 and 116 are essential for such inhibition (Squadrito *et al.*, 2002). In this study we have tried to understand whether or not HCV increases the risk of either having chronic infection or being a carrier of HBV.

**MATERIALS AND METHODS**

This study has been performed during the previous four months, including September, 2005 in the hospitals of Mersin and Dumlupinar Universities. Anti-HCV positive and never interferon (INF) therapy taken cases and controls have randomly been taken into the study among the cases coming for any complaint to our gastroenterology polyclinic. In all patients and controls, anti-HCV, HBs Ag, anti-HBs and liver function tests and alpha-fetoprotein have been studied. Additionally abdominal ultrasonographies have been performed to exclude same additional pathologies. In anti-HCV positive cases, HCV RNA via polymerase chain reaction and in HBs Ag positive cases, HBV DNA via molecular hybridization have been studied. Additional fine needle aspiration biopsies have been performed via tru-cut needle with number 16 in suspected cases from cirrhosis or HCC. The diagnoses of NHL and MPGN have been performed via lymph node biopsies, one from inguinal and

one from superficial cervical lymph nodes and renal biopsies under the guide of computed tomography, respectively. Dermalologic consultations have been wanted from the required cases. Additional consultations have been obtained in required cases. Statistically analyses were performed by SPSS software statistical program (version 10.0, Chicago, USA). Significance of differences between the patient and control groups was determined by unpaired t-test. A probability value of less than  $p = 0.05$  was considered significant.

**RESULTS**

Among the never INF therapy taken anti-HCV positive 102 cases, there have been 74 patients with HCV RNA positivity, now. The mean age of 28 HCV RNA negative cases, 16 female and 12 male, has been  $49.39 \pm 16.57$  years (range 14-77). Again the mean age of 220 control cases, 134 female and 86 male, has been  $49.74 \pm 15.27$  years (range 13-87). On the other hand, the mean age of 74 cases with HCV RNA positivity, 41 female and 33 male, has been  $59.94 \pm 10.84$  years (range 39-87). Although eight cases of HBsAg carrierity (3.63%), four cases of chronic hepatitis B (1.81), three cases of HCV RNA positivity (1.36%) and one case of anti-HCV positivity alone (0.45%) have been detected in 220 controls (Table 1), only four cases of HBsAg carrierity and no case of chronic hepatitis B, diagnosed according to the negative results of HBV DNA detected via molecular hybridization, have been detected in 74 cases of HCV RNA positivity ( $p > 0.05$ ). Additionally, no case of HBsAg carrierity and chronic hepatitis B has been detected in 28 cases of anti-HCV positivity alone ( $p > 0.05$ ). In addition to them, 24 cases of cirrhosis, five cases of hepatocellular carcinoma, two cases of membranoproliferative glomerulonephritis one of which is together with rheumatoid arthritis and cirrhosis, two cases of lichen planus, three cases of asthma, one case of polymphocytic leukemia together with cirrhosis, one case of idiopathic thrombocytopenic purpura, one case of bronchiectasis, one case of fibromyalgia, one case of

Table 1: Comparisons of alone anti-HCV positive, HCV RNA positive and control groups

	Alone anti-HCV positive group	HCV RNA positive group	Control group
Number	28	74	220
Mean age	$49.39 \pm 16.57$ (range 14-77)	$59.94 \pm 10.84$ (range 39-87)	$49.74 \pm 15.27$ (range 13-87)
Female/male	16/12	41/33	134/86
Number of HBsAg carriers	0	4	8
Number of chronic hepatitis B cases	0	0	4
HBsAg carrierity (%)	0*	5.40*	3.63
Chronic hepatitis B (%)	0*	0*	1.81

\* $p < 0.05$  (Statistically significant than control groups)

**Table 2: Comparison of cases with HCVRNA positivity and negativity**

	74 patients with HCVRNA positivity	28 patients with anti-HCV positivity alone
Cirrhosis	24	0
Hepatocellular carcinoma	5	0
Membranoproliferative glomerulonephritis	2	0
Rheumatoid arthritis	1	0
Asthma	1	2
Prolymphocytic leukemia	1	0
Non Hodgkin's lymphoma	2	0
Fibromyalgia	0	1
Monoclonal gammopathy of unknown significance	0	1
Idiopathic thrombocytopenic purpura	1	0
Bronchiectasis	1	0
Lichen planus	1	0

**Table 3: The extrahepatic disorders reported with chronic hepatitis C**

Antiphospholipid syndrome	Idiopathic pulmonary fibrosis
Aplastic anemia	Idiopathic thrombocytopenic purpura
Autoimmune hemolytic anemia	IgA deficiency
Autoimmune thyroiditis	Lichen planus
Chronic tiredness syndrome	MALToMa
Behçet's syndrome	Membranoproliferative glomerulonephritis
Carotid atherosclerosis	Membranous glomerulonephritis
CREST syndrome	Mixed cryoglobulinemia
Dermatomyositis	Mooren's corneal ulcerations
Diabetes mellitus	Multiple myeloma
Fibromyalgia	Non Hodgkin's lymphoma
Guillain-Barre syndrome	Neurocognitive problems
Hypertrophic cardiomyopathy	Pancreatitis
Hypocholesterolemia	Polyarteritis nodosa
Polymyositis	Sjögren's syndrome
Porphyria cutanea tarda	SLE
Rheumatoid arthritis	Uveitis
Sialadenitis	Waldenström's macroglobulinemia

Monoclonalgammopathy of Unknown Significance (MGUS) and two cases of non-Hodgkin's lymphoma have been detected among all of 102 anti-HCV positive cases. As a big difference, except two cases of asthma, one case of fibromyalgia and one case of MGUS all of the others have been detected in HCVRNA positive patients (Table 3).

### DISCUSSION

HCV and HBV infections are frequently seen diseases of gastroenterology polyclinics. For instance, there are estimated to be 350 million carriers of HBV, worldwide. Chronic hepatitis B occurs in 5 to 10% of infecteds (Feder *et al.*, 1996; Lee, 1997). On the other hand, some studies have shown that the carrier state of HCV is higher than that of HBV (Kemp *et al.*, 1998). But here we have detected rates of carrier states of HBV and HCV as 3.63 and 0.45%, respectively, in the control group. HCV infects individuals by parenteral route (Anonymous, 1998) and 75 to 85% of the infected become persistent. Here, we have observed the rate of HCV RNA positivity as 72%. Progressive hepatic fibrosis and cirrhosis develop in 20 to 30% of patients with chronic hepatitis C. This rate has been observed as 23% in anti-HCV

positive cases in our study. Anti-HCV positivity persists for years. The presence of HCVRNA is used to show the viral activity. Viremia can be intermittent in the first year of infection and the presence of HCVRNA should be considered when attempting to determine the outcome of a HCV infection (Villano *et al.*, 1999). Viral clearance may be defined as one positive anti-HCV test and two negative HCV RNA tests at least six months apart. Persistence is defined as continued HCV RNA positivity over a one-year period. In addition, the degree of liver damage can be semiquantitatively assessed by a system used to score liver biopsies (Knodell *et al.*, 1981).

The mechanisms that determine viral clearance or persistence in chronic viral hepatitis have not clearly been identified, yet. Recent advances in molecular genetics have permitted detection of variations in immune response, often associated with polymorphism in human genome. Eventually, it has been strongly thought that disease severity can't be solely attributed to the virulence of microbial agents. In acute HCV and HBV infections, early host immune response is one of the determinants of viral persistence. Class I HLAs, which present foreign antigens to Cytotoxic T-lymphocytes (CTL), are integral components of this response. Various Major Histocompatibility Complex (MHC) alleles, that are correlated with more favorable outcomes in viral hepatitis, have been identified in diverse populations. The DRB1\*1302, A\*0301, DR2, DR6 and DR13 alleles are correlated with better HBV outcomes, whereas DQB1\*0301, DQB1\*0201, DQB1\*03, DQA1\*03, DRB1\*01, DRB1\*0101, DRB1\*0301, DRB1\*04, DRB1\*0401, DRB1\*11, DRB1\*12, DRB1\*1101, DRB1\*1104, DRB1\*1302, DRB3\*03, DRQ1\*1101, DQA1\*03, DQA1\*0501, DQB1\*0302, A\*1101, B\*57, Cw\*0102, DR15 alleles are correlated with better HCV outcomes (Abbas *et al.*, 1997; Ahn *et al.*, 2000; Aikawao *et al.*, 1996; Almarri and Batchelor, 1994; Alric *et al.*, 1997). On the other hand, some studies have shown correlation between specific alleles and less favorable clinical outcomes of HBV and HCV infections.

In addition to playing a crucial role in control of the hepatitis viruses' infections, T cell responses are also responsible for the liver injury during acute and chronic phases of viral hepatitis (Ichiki *et al.*, 2005). In chronic liver disease and cirrhosis, immune defense against viral infections depends on effective cellular immune responses, derived mainly from T-helper 1-related cytokines. T-helper 2 can inhibit efficient immune function by secretion of several cytokines, such as interleukin-10 and Tissue Growth Factor (TGF)- $\beta$  1. In a particular study, serum TGF- $\beta$  1 levels have been found as higher in both cirrhosis and Chronic Hepatitis C (CHC) groups than Chronic Hepatitis B (CHB) and control groups ( $p < 0.05$ ), which may be indicating that the elevated TGF- $\beta$  1 levels in patients with CHC and cirrhosis may have a role in the pathogenesis and chronicity of these diseases (Kirmaz *et al.*, 2004).

In addition to the hepatic involvement, HCV seems to be related with mixed cryoglobulinemia, Sjögren's syndrome, rheumatoid arthritis and membranoproliferative glomerulonephritis like many autoimmune disorders and non-Hodgkin's lymphoma and hepatocellular carcinoma like malignancies. Thirty six reported extrahepatic, prominently autoimmune, disorders which are thought to be related with HCV infection are shown in Table 2 (Lunel, 1994; Marcellin *et al.*, 1995; Pawlotsky *et al.*, 1994; Pawlotsky *et al.*, 1995; Tran *et al.*, 1992; Haddad *et al.*, 1992; Nobuyuki, 1998). Here we have also diagnosed a large variety of autoimmune disorders and even malignancies in anti-HCV positive patients, which may indicate possible immunologic and even malignant triggering mechanism of HCV.

Although the previously reported inverse relationship between replicative activities of HBV and HCV (Pontisso *et al.*, 1996) in one hand and the frequently detected previous or present HBV infection in chronic HCV patients (Vardareli *et al.*, 2003) on the other hand, here we couldn't find any increased or decreased risk of HBsAg carrierity or chronic infection of HBV in cases with anti-HCV positivity alone or together with HCV RNA positivity. Similarly, in some other studies they have been found that HCV has not affected the induction of primary and memory HBV-specific CD8 (cluster of differentiation) responses (Boni *et al.*, 2004) and HCV core protein is not able to inhibit HBV *in vivo* (Squadrito *et al.*, 2002).

As a conclusion, lesions of the viral hepatitis have been found to depend on state of the immune system. It is possible that the genetically determined factors are critical in eliminating hepatitis virus infections and differences in host susceptibility to them. As a result although the suspected relationship between HCV and HBV under the light of some previous studies and

although the highly probable associations of many autoimmune disorders and even malignancies with HCV, we couldn't find any increased risk of HBsAg carrierity or chronic hepatitis B in anti-HCV positive cases alone or together with HCV RNA positivity.

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