Dumlupınar Üniversitesi
Sayı:9
Fen Bilimleri Enstitüsü Dergisi
Aralık 2005

HEPATITIS C VIRUS INFECTION MAY ALWAYS TERMINATE WITH CHRONIC MANIFESTATIONS OF IT IF LIFE SPAN OF THE HUMAN BEING WOULD BE ENOUGH

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ABSTRACT

Background: It seems that hepatitis C virus (HCV) infection is more common in elderlies. Its outcome is probably influenced by status of immune system. We have tried to understand whether or not there is an increase in prevalence of HCV infection by aging and if so could it be explained by a time period, at least in some of infecteds, required for virus until onset of clinical manifestations.Patients and methods: Patients with anti-HCV positivity, never treated with interferon (INF), have been taken, randomly and prospectively. Additionally anti-HBs, HBsAg, routine hematologic and biochemical tests, alpha-fetoprotein, urinalysis, and abdominal ultrasonography have been performed in all cases. In anti-HCV positives, HCVRNA via polymerase chain reaction and in HBsAg positives, HBVDNA via molecular hybridization have been studied. Tissue samples and additional radiographic films, including computed tomography, have been obtained in required cases.Results: We have taken anti-HCV positive and never INF therapy taken 92 cases into study. Sixtysix of 92 patients have been positive for HCVRNA. Rates of HCVRNA positivity have been 14.28 % under the age of 40 years, 68.88 % between the ages of 40 and 59 years, and 85.00 % at and above the age of 60 years. Additionally, 19 cases of cirrhosis, four HBsAg positivity in the absence of HBVDNA positivity, 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 fibromyalgia, one monoclonalgammopathy

of unknown significance (MGUS), and two cases of non-Hodgkin's lymphoma have been detected in 92 cases with anti-HCV positivity. 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 cases. Conclusion: As a result, prevalence of HCVRNA positivity increases by age and anti-HCV positive individuals should be followed-up during their life span for high risk of even delayed-onset hepatic and multisystemic manifestations.

Keywords: Hepatitis C virus infection

ÖZET

Hepatit C virüs (HCV) enfeksiyonu yaşlılarda daha sık gibi görünmektedir. Enfeksiyon sonucu muhtemelen immün sistem tarafından belirlenmektedir. Biz HCV enfeksiyonu prevalansının yaşla birlikte artış gösterip göstermediğini ve eğer gösteriyor ise bu sürenin, enfeksiyonun klinik bulgularının ortaya çıkması için gerekli bir sürenin varlığı ile izah edilip edilemeyeceğini anlamaya çalıştık. Çalışmaya gastroenteroloji polikliniğine herhangibir şikayetle başvuran, daha önce interferon (INF) tedavisi almamış, HCV antikor (anti-HCV) pozitif hastalar rastgele ve prospektif olarak alındı. Anti-HCV yanında tüm hastalardan hepatit B virüs yüzey antijeni ve antikoru (sırasıyla HBs Ag ve anti-HBs), alfa-fetoprotein, rutin hematolojik ve biyokimyasal testler ve idrar analizi istendi. Anti-HCV pozitif vakalarda polimeraz zincir reaksiyonu ile HCV RNA ve HBs Ag pozitif vakalarda moleküler hibridizasyon ile HBV DNA çalışıldı. Gereken vakalarda doku biyopsileri alındı ve bilgisayarlı tomografiyi de içeren ilave radiyografik görüntülemeler yapıldı. Toplam 92 anti-HCV pozitif, INF tedavisi almamış hasta çalışmaya alındı. Hastaların toplam 66'sında HCV RNA pozitifliği tespit edildi. HCV RNA pozitifliği oranı 40 yaş altında %14.28, 40-59 yaşları arasında %68.88 ve 60 yaş ve üzerinde %85 olarak tespit edildi. Ek olarak, toplam 19 siroz, beş hepatosellüler karsinom, dört HBs Ag taşıyıcılığı, birisi romatoid artrit ile birlikte sirozlu olmak üzere iki membranoproliferatif glomerulonefrit, iki liken planus, üç astım, bir siroz ile birlikte prolenfositik lösemi, bir idiyopatik trombositopenik purpura, bir bronşektazi, bir fibromyalji, bir önemi bilinmeyen monoklonal gammopati ve iki non-Hodgkin lenfoma vakası, toplam 92 anti-HCV pozitif birey arasında tespit edildi. Büyük bir fark olarak, iki astım, bir fibromyalji ve bir önemi bilinmeyen monoklonal gammopati vakası haricindeki tüm vakalar HCV RNA pozitif bireyler arasında tespit edildi. Sonuç olarak, HCV RNA pozitifliği yaşla birlikte artış göstermektedir ve anti-HCV pozitif bireyler, hayatları boyunca geç ortaya çıkabilen karaciğer ve multisistemik tutulum riski nedeniyle takip edilmelidirler.

Anahtar kelimeler: Hepatit C virüs enfeksiyonu

INTRODUCTION

Hepatitis C virus (HCV) infection is an under-diagnosed and prevalent bloodborne illness, resulting with cirrhosis in up to 25% of those infecteds. While the overall prevalence in the United States is 1.7%, high-risk populations may have up to a prevalence of 80%. About 170 million people are estimated to be chronically infected, worldwide. Additionally, it is the leading cause of hepatocellular carcinoma (HCC) and liver transplantation in developed countries. In addition to the hepatic involvement, it seems to be related with mixed cryoglobulinemia, Sjögren's syndrome (SS), rheumatoid arthritis (RA), non-Hodgkin's lymphoma (NHL), and membranoproliferative glomerulonephritis (MPGN) like many autoimmune disorders and malignancies (1), and a wide variety of extrahepatic involvement of HCV has been reported (2). HCV is believed not to be directly cythopathic and the host immune response is responsible for the viral clearance and cellular injury. Immunologic factors such as human leukocyte antigens (HLA) may take role in the susceptibility to infection by HCV.

According to our experiences, HCV infection seems to be more frequent in elderlies. Here, we have tried to understand whether or not there is an increase in the prevalence of HCV infection by aging and if so, whether or not it could be explained by a time period required for the virus until the onset of clinical manifestations, at least in some the patients.

PATIENTS and METHODS

Patients with anti-HCV positivity have been taken into the study among all of persons coming our gastroenterology polyclinic with any reason, randomly and prospectively. All the medical history of the patients including previous interferon (INF) therapy has been learned, and previously INF therapy taken patients have been excluded from the study. In all of the patients, beside anti-HCV test, anti-HBs, HBs Ag, liver function tests including alkaline phosphatase, gamma-glutamyl transferase, aspartate and alanine transaminases, albumin, globulin, direct and indirect bilirubins, alpha-fetoprotein, lactic dehydrogenase, cholesterol, and prothrombin time, routine hematologic and biochemical tests, erythrocyte sedimentation rate, and urinalysis have been performed. Additionally an abdominal ultrasonography has been performed for all cases. In anti-HCV positive cases, HCV RNA via polymerase chain reaction (PCR) method and in HBs Ag positive plus elevated transaminase levels having cases HBV DNA via molecular hybridization method have been studied, respectively. Additional fine needle aspiration biopsy has been performed in suspected cases from cirrhosis or HCC. The diagnosises of NHL and MPGN has been performed via lymph node biopsy and renal biopsy, respectively.

RESULTS

We have taken anti-HCV positive and never INF therapy taken 92 cases into the study, and previously INF taken eight cases have been excluded from the study. Sixty-six of 92 patients have been found as positive for HCV RNA and 26 as negative. The mean age of 26 cases with HCV RNA negativity, 15 female and 11 male, has been found as 49.39 +/- 16.57 years (range 14-77). On the other hand, the mean age of 66 cases with HCV RNA positivity, 37 female and 29 male, has been calculated as 59.94 +/- 10.84 years (range 39-87). The rates of HCV RNA positivity have been found as 14.28% under the age of 40 years (one case in seven), 68.88% between the ages of 40 and 59 years (31 cases in 45), and 85.00% at and above the age of 60 years (34 cases in 40). Additionally, 19 cases of cirrhosis, four cases of HBs Ag positivity in the absence of HBV DNA positivity, five cases of HCC, two cases of MPGN, two cases of lichen planus, one case of RA together with cirrhosis and MPGN, three cases of asthma, one case of prolymphocytic leukemia together with cirrhosis, one case of idiopathic thrombocytopenic purpura, one case of bronchiectasis, one case of fibromyalgia, one case of monoclonalgammopathy of unknown significance (MGUS), and two cases of NHL have been detected among all of 92 anti-HCV positive cases. As a great difference, only two cases of asthma, one case of fibromyalgia, and one case of MGUS have been detected among the HCV RNA negative patients, all of the others have been detected in HCV RNA positive group.

DISCUSSION

HCV is the leading cause of cirrhosis, hepatocellular carcinoma, and probably autoimmune disorders and even malignancies (1). In a current study, HCV has been detected in the majority (76.4%) of HCC cases in Italy. Similarly, five HCC cases has been detected among 92 anti-HCV positivite cases in our study. Additionally, the before mentioned 25% risk of cirrhosis in infected patients with HCV has been determined as 20.65% in our study. HCV

infects individuals by the parenteral route (3), and 75% to 85% of the infecteds become persistent, at least under the light of current knowledge. But the increasing prevalence of HCV RNA positivity by age may indicate that it may eventually terminate with chronic manifestations in every infected if the life span of the individual permits. The anti-HCV persists for years after HCV infection, even in those individuals who present with HCV RNA negativity. Viremia can be intermittent in the first year of infection and the presence of HCV RNA should be considered when attempting to determine the outcome of an acute HCV infection (4). The degree of liver damage can be semiquantitatively assessed by a system used to score liver biopsies (5). In addition to the hepatic involvement, HCV seems to be related with mixed cryoglobulinemia, SS, RA, and MPGN like many autoimmune disorders and NHL-like malignancies. There are 36 reported extrahepatic, prominently autoimmune, disorders which are thought to be related with HCV infection (6-12), they are shown in table 1. High prevalences of mixed cryoglobulinemia have been reported with chronic hepatitis C (13,14). Its prevalence increases by the duration of infection, for example, the duration of infection is nearly two-fold longer in cases with mixed cryoglobulinemia (15). The prevalence of MPGN is approximately 30% in chronic hepatitis C plus type II cryoglobulinemia cases (7). In an autopsy study performed on 188 Japanese dominantly cirrhotic patients with chronic HCV infection, it has been detected that the prevalence of histological accumulation of immunecomplexes in glomeruli is importantly higher than the prevalence of symptomatic GN (11). The prevalence of histological GN has been found as 54.8% ,and the prevalence of MPGN as the most frequently seen type as 11.2%. But only 12.2% of cases, especially the MPGN having ones, have been symptomatic for GN during the year just before death.

According to a widely discussed hypothesis, the cause of extrahepatic involvement of HCV is the extrahepatic tropism, especially the lymphotropism of the virus. The lymphotropism is thought to be the important factor for the development of B-cell non-Hodgkin's lymphoma (B-NHL) and the production of autoantibodies. In long term follow up studies, B cell malignancies have been detected in 4-6% of cases with chronic hepatitis C plus type II cryoglobulinemia (16,17). The prevalence of chronic hepatitis C has been found as higher in B-NHL cases than the controls in six studies performed in Italy and Japan (9-32% versus 0.0-3.1%) (18-23). Until now HCV is not accepted as an oncogenic virus. But in a study, it is reported that core proteins of HCV takes role in the malign conversion of cells (24). Additionally, oncogenesis and hypermutation of Ig in infected cells with HCV have been shown in a study (25). In addition to above, it has been shown that splenic lymphoma associating with chronic hepatitis C regresses parallel to the regression of viremia achieved by antiviral therapy (26). Additionally, although the detection of HCV specific CD4+ and CD8+ lymphocytes in lesions of lichen planus, they couldn't be detected in blood (27). The prevalence of HCV has been found as higher in patients with porphyria cutanea tarda in South Europa, America, and Japan. This finding supports the idea that HCV is a precipitating factor for porphyria cutanea tarda (28) with unknown mechanisms, because infection does not decrease the activity of hepatic uroporphyrinogen decarboxylase which is actually decreased in cases with active porphyria cutanea tarda (29).

The pathogenesis of the HCV infection is not completely understood yet. HCV is believed not to be directly cythopathic, and the host immune response is responsible for the viral clearance and cellular injury. 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 (30). Propably the genetically determined factors are also critical in eliminating hepatitis virus infections and differences in host susceptibility to infectious disease, and eventually the disease severity can't be attributed solely to the virulence of microbial agents. Immunologic factors such as HLAs may take role in the susceptibility to HCV (31). Class I HLAs, which present foreign antigens to cytotoxic T-lymphocytes (CTL), are integral components of the early host immune response. Various major histocompatibility complex (MHC) alleles that are correlated with more favorable outcomes in cases of viral hepatitis have been identified in diverse populations. The 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 (32-36).

INF together with ribavirin are widely used for the treatment of chronic hepatitis C, now ,and the reporteds efficacies of the therapy range from 40 to 85%. Three of the previously INF therapy taken eight cases have been detected as HCV RNA negative, now, but one of the three cases has been cirrhotic. The long term benefits of INF therapy will be seen in the future.
As the conclusion, the mechanisms that determine viral persistence of HCV have not clearly been identified yet. But the increasing prevalence of HCV RNA positivity by age may indicate that it may eventually terminate with chronic manifestations in every infected patient if the life span of the individual permits. As a result, the anti-HCV positive individuals should be followed-up during all of their life span due to the high risks of hepatic and multisystemic, even delayed-onset, manifestations of HCV.

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Table 1

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	NonHodgkin'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

The extrahepatic disorders reported with chronic hepatitis C