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ORIGINAL ARTICLE

Hepatitis C Virus Infection and Chronic Obstructive Pulmonary Disease

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Background and Aims: **A growing pile of evidence supports the notion that pulmonary involvement is one of the extrahepatic manifestations of chronic hepatitis C virus (HCV) infection. The objective of this study was to determine the prevalence of HCV infection in patients with chronic obstructive pulmonary disease (COPD), and *vice versa*.**
Methods: **Two cross-sectional studies were performed: 1. A prevalence study of HCV infection among patients with COPD; 2. A prevalence study of COPD among patients with chronic HCV infection. COPD was diagnosed according to ATS/ERS guidelines. The prevalence of HCV infection in COPD group was compared with the result of a previous study which determined the prevalence of HCV infection in general population. Prevalence of COPD in patients with chronic HCV infection was also compared to those with chronic hepatitis B virus (HBV) infection.**
Results: **The study included 108 patients with COPD, 68 patients with chronic HCV infection, and 60 patients with chronic HBV infection. HCV infection was observed in 8.3% of patients with COPD, and 1.2% of the control subjects (P= 0.000). The prevalence of COPD among patients with chronic HCV and HBV infection was 17.6%, and 5%, respectively (P=0.03). Comparing COPD-positive and -negative chronic HCV patients for risk factors for COPD revealed that only the mean age was higher in COPD-positive patients (60.8±9.1 years *vs.* 46.5±11.5 years, P=0.000). In multivariate analysis, age was found to be the only independent predictor of COPD in HCV group.**
Conclusions: **Patients with COPD have increased prevalence of HCV infection, and patients with HCV infection, have increased prevalence of COPD. COPD may be an extrahepatic disease associated with HCV infection.**
Keywords: **Hepatitis C, Chronic Obstructive Pulmonary Disease, Prevalence, Extrahepatic Manifestation**

Introduction

Hepatitis C virus (HCV) infection is associated with a wide series of extrahepatic manifestations including mixed cryoglobulinemia, lichen planus, porphyria cutanea tarda, B-cell non-Hodgkin's lymphoma (NHL), monoclonal gammopathies, *etc* [1, 2]. A growing pile of evidence supports the notion that pulmonary involvement is one of the extrahepatic manifestations of chronic HCV infection [3-6]. Several reports have suggested an important role for latent viral infections, in particular adenovirus and human immunodeficiency virus (HIV), in the etiology and/or progression of chronic obstructive pulmonary disease (COPD) [7, 8]. Based on these reports, Kanazawa *et al.* have hypothesized that chronic HCV infection might also function as a trigger for inflammation in the lungs, hence, either initiating or exacerbating the development of COPD [5]. Their study revealed that chronic HCV infection might accelerate the decline in lung function in patients who have COPD. In addition, some researchers suggest that airway disease may be related to the underlying chronic inflammatory disorders such as inflammatory bowel disease or autoimmune thyroid disease [9].

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To the best of our knowledge, there is no study has investigated the prevalence of HCV infection among patients with COPD; furthermore, information is scarce on the prevalence of COPD among patients with HCV infection.

In this study, we aimed at investigating any association between HCV infection and COPD by determining the prevalence and risk factors of HCV infection in patients with COPD and *vice versa*.

Materials and Methods

To examine a potential association between HCV infection and COPD, we performed two cross-sectional studies: 1. A prevalence study of HCV infection in a group of patients with COPD, and 2. Another study to determine the prevalence of COPD and any pulmonary disease in patients with chronic HCV infection.

Patients with COPD, consecutively admitted to Chest Diseases Department of Ataturk University Medical School Hospital, from May 2005 to December 2006, were enrolled into the first study. COPD was diagnosed according to the American Thoracic Society (ATS)/The European Respiratory Society (ERS) guidelines [10, 11]. All patients with COPD were screened for HCV infection. Antibodies to hepatitis C virus (anti-HCV) were evaluated by third generation enzyme-linked immunosorbent assay (ELISA) method. Serum HCV-RNA was evaluated in the anti-HCV-positive patients by lightcycler real time polymerase chain reaction (PCR) (Biorad). HCV infection was considered if both anti-HCV and HCV-RNA were positive. As the control population, we used a previous study which determined the prevalence of HCV infection in general population in our region [12]. In addition, patients with COPD were divided into two groups of "HCV-positive" and HCV-negative. The two categories were compared for age, sex, smoking habits, previous hospitalization, exposure to occupational and environmental pollutants, and risk factors for acquisition of HCV infection (blood or blood-products transfusion, major surgery, hemodialysis, occupational exposure to blood or body fluids, sexual behavior, intravenous drug abuse, dental-care procedures, shaving at barber shop, tattooing, body piercing, professional pedicure/manicure), and serum alanine aminotransferase (ALT) levels.

In the second study, 68 consecutive patients with chronic HCV infection, and 60 patients with chronic hepatitis B virus (HBV) infection (as the control group) admitted to Clinical Microbiology and Infectious Diseases Department of the same hospital from 2006 to 2007 were screened for COPD. Chronic HCV infection was considered on the basis of positive serum anti-HCV antibodies by third generation ELISA and positive serum HCV-RNA by real time PCR assay at least for six months and/or liver biopsy consistent with chronic hepatitis. Chronic HBV infection was diagnosed by the presence of hepatitis B surface antigen (HBs Ag) in the serum for six months or more and increased ALT activity (greater than the upper limit of normal) on at least two separate monthly determinations within the last six months and/or liver biopsy. Patients with cirrhosis were excluded from the study. In HCV group, the patients were divided into two categories according to COPD status. These categories were compared for risk factors for COPD (age, sex, smoking habits, exposure to occupational and environmental pollutants). Because of the small number of patients with COPD, we could not perform similar comparison in chronic HBV group.

Statistical analysis

Statistical analyses were performed by SPSS ver 13.0 for Windows® (SPSS Inc, Chicago IL, US). Univariate methods included a Student's t test to compare means of groups for continuous variables, and χ^2 analysis for categorical variables unless Fisher's exact test was required for contingency tables-when more than 20% of the expected values were less than five. $P<0.05$ was considered statistically significant.

Logistic regression analysis was used to assess the independent predictors for COPD in patients with chronic HCV infection.

Results

The first study included 108 patients with COPD. The second study included 68 patients with chronic HCV infection, and 60 control subjects with chronic HBV infection. The characteristics of the patients are shown in Table 1.

In the first study, 13 patients with COPD had anti-HCV antibodies detected by ELISA (12.0 %); nine of them were found HCV-RNA positive by PCR assay. Eventually, the prevalence of HCV infection in this group was 8.3%. We compared the result with a previous study which determined the prevalence of HCV infection in general population in our region [11]. In that study, 568 subjects (50.3% females, 49.7% males) above 14 years of age and

Table 1. Demographic features of patients with COPD, chronic HCV infection and chronic HBV infection.

	COPD group n=108	Chronic hepatitis group		P value
		Chronic HCV infection n=68	Chronic HBV infection (control group) n=60	
Age (mean, year)	64.8±10.6	49.0±12.3	46.5±11.3	
≤30	0 (0%)	6 (8.8%)	5 (8.3%)	
31-40	1 (0.9%	12 (17.6%)	11 (18.3%)	
41-50	11 (10.2%)	18 (26.5%)	17 (28.3%)	0.2
51-60	22 (20.4%)	21 (30.9%)	19 (31.6%)	
61-70	42 (38.9%)	8 (11.8%)	7 (11.7%)	
≥71	32 (29.6%)	3 (4.4%)	1 (1.7%)	
Sex				
Male	81 (75%)	37 (54.4%)	35 (58.3%)	0.6
Female	27 (25%)	31 (45.6%)	25 (41.7%)	
HCV infection	9 (8.3%)	-	-	-
Smoking habits				
Non-smokers	39 (36.1%)	38 (55.9%)	32 (53.3%)	0.86
Ex-smokers	18 (16.7%)	7 (10.3%)	8 (13.3%)	
Smokers	51 (47.2%)	23 (33.8%)	20 (33.3%)	
Pulmonary diseases	-	22 (32.3%)	4 (6.7%)	0.000
COPD		12 (17.6%)	3 (5%)	0.03
Asthma		10 (14.7%)	1 (1.7%)	0.000

older were screened for anti-HCV antibodies, and mean prevalence was 1.2%. The highest prevalence (3.2%) was found in the 40-49 age group (Table 2). Compared with the mean and the highest prevalence rates in the general population, patients with COPD had a significantly higher prevalence rate of HCV infection. In the COPD group, 44.4% of HCV-positive patients had risk factors for acquisition of HCV infection compared with 12.1% of HCV-negative patients (P=0.02). The mean serum ALT level was higher in HCV-positive patients group than those of HCV-negative patients. There were no differences between the two categories for age, sex, smoking habits, previous hospitalization, and exposure to occupational and environmental pollutants. Among patients with COPD, only three had environmental or occupational exposure to various dusts, chemicals, vapors and fumes which are known risk factors for COPD (Table 3). In two of the patients, exposure was occupational-one of them was an overland road worker and the other was a construction worker.

Table 2. Prevalence of HCV infection among healthy population in our region.

Age Group	Prevalence (%)
14-19	0
20-29	0
30-39	2
40-49	3.2
50-59	2.3
≥60	0
Mean	1.2%

In the second study, the prevalence of COPD in patients with chronic HCV infection was 17.6%. In addition, 14.7% of the patients had asthma. Totally, 32.3% of the patients with chronic HCV infection had a pulmonary disease. Among patients with chronic HBV infections (control group) the prevalence of COPD was 5%, and the prevalence of asthma was 1.7%. Totally, 6.7% of the patients had a pulmonary disease. There were no differences for age, sex, and smoking habits between the two groups (Table 1). The patients with chronic HCV infection were further divided into two categories according to COPD status. COPD-positive and negative patients in this group were compared for risk factors for COPD (*i.e.*, age, sex, smoking habits, exposure to occupational and environmental pollutants), by univariate and logistic regression analysis. In univariate analysis, the sex, smoking habits, exposure to occupational and environmental pollutants were

Table 3. Analysis of COPD group according to HCV infection status.

	HCV positive n= 9	HCV positive n= 9	P value
Age (mean, year)	62.7±9.7	65.0±10.8	
≤30	0	0	
31-40	0	1	
41-50	2	9	0.5
51-60	2	20	
61-70	3	39	
≥71	2	30	
Sex			
Male	9 (100%)	72 (72.7%)	0.1
Female	0 (0%)	27 (27.3%)	
Smoking habits			
Non-smokers	1 (11.1%)	17 (17.2%)	
Ex-smokers	3 (33.3%)	48 (48.5%)	0.8
Smokers	5 (55.5%)	34 (34.3%)	
Exposure to occupational or environmental pollutants	1 (11.1%)	3 (3.0%)	0.3
Hospitalization			
<2	0 (0.0%)	6 (6.0%)	
2-4	6 (66.6%)	56 (56.6%)	0.5
4>	3 (33.3%)	37 (37.4%)	
Risk factor for acquisition of HCV infection	4 (44.4%)	12 (12.1%)	0.02
ALT (IU/L)	108.8±106.0	40.15±40.9	0.000

similar in both categories, but patients with COPD had a significantly higher mean age than COPD-negative patients (60.8±9.1 *vs.* 46.5±11.5 years, P= 0.000). COPD-positive patients had a greater proportion (91.7%) of patients over the age of 50 in comparison to COPD-negative patients (37.5%) (Table 4). Likewise, logistic regression analysis revealed that the age was the only independent predictor of COPD among patients with chronic HCV infection (OR: 1.13, 95% CI: 1.04-1.24, P=0.004). Because of the small number of patients with COPD, we could not perform similar comparison in chronic HBV group.

Table 4. Analysis of chronic hepatitis C group according to COPD status.

	COPD positive n=12	COPD negative n=56	P value
Mean Age (year)	60.8±9.1	46.5±11.5	
No (%) of patients			
≤30	0 (0%)	6 (10.7%)	
31-40	0 (0%)	12 (21.4%)	
41-50	1 (8.3%)	17 (30.3%)	0.000
51-60	6 (50%)	15 (26.8%)	
61-70	3 (25%)	5 (8.9%)	
≥71	2 (16.7%)	1 (1.8%)	
Sex			
Male	8 (66.6%)	29 (51.8%)	0.5
Female	4 (33.3%)	27 (48.2%)	
Smoking habits			
Non-smokers	4 (33.3%)	34 (60.7%)	
Ex-smokers	3 (25%)	4 (7.1%)	0.1
Smokers	5 (41.7%)	18 (32.1%)	
Exposure to occupational or environmental pollutants	1 (8.3%)	1 (1.8%)	0.3
Risk factor for acquisition of HCV infection	3 (25%)	19 (33.9%)	0.7

Discussion

It is well-known that patients with HCV infection are at higher risk for development of some extrahepatic conditions. While the association of some extrahepatic conditions with HCV is very clear, for some conditions, the association is strongly suspected and for other conditions it is based only on some anecdotal data. For A few disorders, associations with HCV have been defined on the basis of pathogenesis and higher prevalence of the disrder in patients than in controls (*e.g.*, mixed cryoglobulinaemia, B-cell NHL, monoclonal gammopathies, porphyria cutanea tarda and lichen planus). For other disorders, associations still require confirmation and/or a more detailed characterization with respect to similar pathologies of different etiology or idiopathic nature [2].

A recent study investigated co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans in the USA suggested that HCV-infected subjects had a higher prevalence of diabetes, anemia, hypertension, COPD)/asthma, cirrhosis, hepatitis B and cancer [13]. Another study showed at least one pulmonary alteration evidenced either by pulmonary function tests, carbon monoxide diffusing capacity, or high-resolution computed tomography in 75% of patients with chronic HCV infection [14]. In some cases, pulmonary interstitial involvement may be without evident respiratory symptoms [4]. However, the data on the prevalence of HCV infection among patients with COPD and *vice versa* is scanty.

Our study revealed that patients with COPD have a higher prevalence of HCV infection compared with the control group. One could argue that patients with COPD have an increased risk of exposure to HCV infection because of chronic nature of their diseases and frequent admission to health care facilities and this higher prevalence may be originated from increased risk of exposure. In our study, the frequency of risk factors for acquisition of HCV infection was higher among HCV-positive patients than HCV-negative patients (44.4% *vs.* 12.1%, P= 0.02) (Table 2). However, almost similar frequencies of risk factors for HCV infection were found (25% *vs.* 33.9%) in our COPD-positive and -negative patients with chronic hepatitis C (Table 4).

The results of this study showed that although there were no differences between age, sex and smoking habits, patients with chronic HCV infection had a higher prevalence of COPD than patients with chronic HBV (Table 1). Risk factors for COPD include both host factors and environmental exposures, and the disease usually arises from an interaction between these two types of factors. The major environmental factors are tobacco smoke; heavy exposure to occupational dusts and chemicals (vapors, irritants, fumes); and indoor/outdoor air pollution [15]. In addition, several reports have suggested an important role for latent viral infections, in particular adenovirus and HIV, in the etiology and/or progression of the disease [3]. We did not observe any significant difference but age, in the prevalence of risk factors for COPD in patients with chronic hepatitis C. COPD-positive patients had a higher mean age (60.8±9.1 years) than patients with no COPD (46.5±11.5 years). This finding is in agreement with the fact that the prevalence of COPD increase with

age [15]. In a study from Turkey, the prevalence of COPD among the subjects aged 40 years and older was 15.4% in males and 6% in females-overall 10.6% [16]. However, our prevalence rates for COPD (27.6% in males and 12.9% in females, overall 17.6%) were higher than reported in that study. It can be speculated that, a second cause of the higher prevalence of COPD in older age group may be the result of long-term effect of chronic HCV infection on lung tissue. However, HCV infection cannot be considered as a cause or trigger of COPD without establishing a temporal relationship for the development of each disorder.

The role of gender in the development and progression of COPD is controversial. Historically, COPD has been far more frequent in males than in females, related to patterns of smoking and occupational exposures [15]. Although the majority of our patients were male in both COPD and chronic hepatitis C groups, there were no significant differences for gender between the studied subgroups.

The main finding of the present study was that patients with COPD have increased prevalence of HCV infection. In addition, patients with chronic HCV infection have higher prevalence of COPD. Patients with COPD who have HCV infection have increased prevalence of risk factor for acquisition of HCV too. Patients with chronic HCV infection who have COPD were older. In spite of some negative reports, similar association has been reported between HCV infection and type II diabetes mellitus. In an epidemiological study performed in the USA the risk of type II diabetes mellitus was about three times higher in patients with HCV and over those 40 years old than in HCV-negative subjects; no association with type I diabetes was found [17]. Mason *et al.* suggested that HCV acts as a risk factor independently from liver disease [18]. We speculate that a similar mechanism may be responsible to trigger COPD in some HCV-infected patients.

Conclusions

The data suggest an association between HCV infection and COPD. Patients with COPD had increased prevalence of HCV infection, and those with HCV infection, especially older ones, had increased prevalence of COPD. HCV infection may have some long-term effects on pulmonary tissue and serve as an additional risk factor for the development of COPD. COPD may be an extra-hepatic disease associated with HCV infection. Further studies are needed to clarify the relationship between HCV infection and COPD. The small sample size in the study prevents drawing serious conclusions regarding relation between HBV infection and COPD. However, we believe that this study would induce more comprehensive research.

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