

Evaluation of high-resolution computed tomography and pulmonary function tests in patients with chronic hepatitis C virus infection

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Abstract

AIM: To investigate pulmonary involvement via pulmonary function tests (PFT) and high-resolution computed tomography (HRCT) in patients with chronic hepatitis C virus (HCV) infection.

METHODS: Thirty-four patients with chronic HCV infection without diagnosis of any pulmonary diseases and 10 healthy cases were enrolled in the study. PFT and HRCT were performed in all cases.

RESULTS: A decrease lower than 80% of the predicted value was detected in vital capacity in 9/34 patients, in forced expiratory volume in one second in 8/34 patients, and in forced expiratory flow 25-75 in 15/34 patients, respectively. Carbon monoxide diffusing capacity (DLCO) was decreased in 26/34 patients. Findings of interstitial pulmonary involvement were detected in the HRCT of 16/34 patients. Significant difference was found between controls and patients with HCV infection in findings of HRCT ($\chi^2=4.7$, $P=0.003$). Knodell histological activity index (KHA1) of 28/34 patients in whom liver biopsy was applied was 9.0 ± 4.7 . HRCT findings, PFT values and DLCO were not affected by KHA1 in patients with HCV infection. In these patients, all the parameters were related with age.

CONCLUSION: We suggest that chronic hepatitis C virus infection may cause pulmonary interstitial involvement without evident respiratory symptoms.

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INTRODUCTION

Hepatitis C virus (HCV) is a common infectious agent, and it is estimated that 3% of the world population are infected with HCV. It was reported that HCV caused 20% of acute hepatitis and 70% of chronic hepatitis^[1,2]. HCV could be stimulated chronically by immune system^[3,4]. There are few studies about

pulmonary involvement of chronic HCV infection. These have been done with small patient groups and results on the association between chronic HCV infection and pulmonary involvement could not be found from these studies^[5,6].

Although idiopathic pulmonary fibrosis is considered to be idiopathic, inhaled substances are suggested to be responsible for the manifestation of this clinical presentation^[7,8]. Onset of symptoms following a viral infection or common cold in some patients suggests that development of the disease may be due to the injury related to the infection. There is evidence that hepatitis C virus, Epstein-Barr virus (EBV), and adenoviruses may be responsible for the fibrosis^[9-11].

This study was to investigate the relationship between HCV infection and interstitial pulmonary involvement, and to reveal the relationship among involvement and age, sex, cigarette smoking, severity of hepatitis, and respiratory functions.

MATERIALS AND METHODS

Patients and study design

Thirty-four patients with chronic HCV infection at outpatient clinics of our hospital, were included in the study. Written informed consent was obtained from each patient prior to participation. Ten healthy subjects (6 males, 4 females) were enrolled in the study as control group. Their age, sex characteristics, and smoking habit were similar to the patient group.

Diagnosis of chronic HCV infection was established by the 3rd generation ELISA test (AxSYM HCV version 3.0, Abbott, Wiesbaden-Delkenheim, Germany) and liver biopsy. When liver biopsy was impossible (6 cases), HCV RNA positivity was accepted for the diagnosis.

Patients with previous diagnosis of another pulmonary disease, decompensated cirrhosis, congestive heart failure, suspected malignancy, collagen tissue disease, leukopenia ($<3\ 000/\text{mm}^3$), thrombocytopenia ($<80\ 000/\text{mm}^3$), hepatitis B carriers and drug addicts (current and past users) were excluded. Cases having a history of chronic alcoholism were also not included in the study. All the patients did not receive any treatment for HCV infection.

Medical history was recorded and physical examination was performed in cases who fulfilled the above criteria for study entry. Their age, sex and quantity of cigarette smoking (pack-year) were recorded. Chest X-ray was obtained.

Pulmonary function test (PFT), diffusion test and high-resolution computerized tomography (HRCT) were performed in all cases.

Pulmonary function test

Measurements of vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in first second (FEV1), forced mid-expiratory flow rate (FEF25-75), carbon monoxide diffusion capacity (DLCO) and ratio of DLCO to alveolar ventilation (DLCO/VA) were done in accordance with American Thoracic Society criteria^[13] by using the Vmax 22 device (Sensor Medics, Yorba Linda, CA, USA) with single breath diffusion method. None of the patients had received bronchodilator drugs prior to the tests. Measurements were

recorded as the percentage of the predicted value, 80% and above were considered as normal.

High resolution computerized tomography

HRCT images were obtained by the Somatom DRH device (Siemens, Erlangen, Germany), without contrast administration, and with 10 mm interval, 2 mm thick section, 310 mAs, 125 kVp, 4 seconds of imaging time, in bone algorithm, 512x512 reconstruction matrix, and 1 600/-400 parenchymal and 350/50 mediastinal window range.

For evaluation of interstitial involvement with HRCT, the method described by Remy-Jardin *et al*^[13] was used. HRCT scans were evaluated for the presence, distribution, and extent of the following signs: [a] ground-glass attenuation, [b] nodular areas of high attenuation, [c] consolidation, [d] linear areas of high attenuation, classified as nonseptal lines, [e] septal lines, [f] honeycombing, and [g] architectural distortion.

Extension of the involvement was assessed independently for each of the three zones of the thorax defined as follows. The upper zones were above the level of the main carina, the middle zones were between the level of the main carina and the inferior pulmonary veins, and the lower zones were under the level of the inferior pulmonary veins. HRCT scores in the upper, middle, and lower pulmonary zones were determined by visually estimating the extent of the disease in each zone. The HRCT score was based on the percentage of pulmonary parenchyma that showed evidence of each recorded abnormality, and was estimated to be 5% of parenchymal involvement: 25% and below as 1 point, 26%-50% as 2 points, 51%-75% as 3 points, 76% and above as 4 points. The scores for each zone were then added to obtain a global extent score, ranging from 0 to 12, and referred to as the HRCT extent score of each HRCT abnormality. A total score of pulmonary involvement was obtained by summation of the global extent score of all HRCT abnormalities, ranging from 0 to 84, which was the feature referred to as the overall HRCT of disease severity.

Pulmonary interstitial involvement was confirmed with prone position scanning in patients who had HRCT findings. HRCT scans were interpreted in random order by two radiologists without any clinical data, the two observers assessed the scans together to reach a decision by consensus.

Evaluation of liver biopsy

Liver biopsy was performed in 28/34 patients. Histological evaluation of liver biopsy reflecting the activity level of the disease was done according to the Knodell histological activity index (KHA) described by Knodell *et al*^[14]. Inflammation in portal areas, piecemeal appearance and bridging necrosis at periportal areas and necro-inflammatory activity observed in parenchyma were considered in the evaluation of the severity of hepatitis.

Statistical analysis

Quantitative data were presented as mean±SD. Statistical

analysis was performed by Mann-Whitney *U* test for comparison of PFTs of patients with HCV infection and control group, and Fisher's exact (chi-square) test for comparison of HRCT findings. Relation among KHA and age, sex was evaluated by multiple linear regression analysis. HRCT and PFT were considered as dependent variables, KHA and factors possibly affecting pulmonary pathologies including age, sex and amount of cigarette smoking were considered as independent variables, then separate multiple linear regression analyses for HRCT score, VC, FVC, FEV1, FEF25-75, DLCO, DLCO/VA were performed. *P*<0.05 was considered statistically significant.

RESULTS

Thirty-four patients (15 women and 19 men) with a mean age of 47.6±17.5 years (20-72) were enrolled in the study. Eighteen patients had a history of cigarette smoking and the mean amount of cigarette smoking was 16.5±9.7 pack-year. Ten healthy control cases (6 men and 4 women) with a mean age of 46.2±2.6 years (21-65) were enrolled into the study. Four of them had a history of cigarette smoking.

PFT measurements revealed that VC, FVC, FEV1, and FEF25-75 were below 80% of the predicted value in 9/34, 8/34, 5/34 and 15/34 patients with HCV infection, respectively. DLCO was decreased in 26/34 patients and DLCO/VA ratio was decreased in 18/34 patients. But, there was no significant difference between controls and patients with HCV infection in mean PFT parameters (Table 1). KHA values were between 2-16 in 28 patients in whom liver biopsy was performed and the mean KHA was 9.0±4.7 points.

Table 1 Knodell histological activity index (KHA) and pulmonary function tests (mean±SD) in patients with chronic hepatitis C virus infection and controls

| Features | Patients with HCV (n=34) | Controls (n=10) | P |
|-----------------------|--------------------------|-----------------|----|
| KHA | 9.0±4.7 | - | - |
| VC ^a | 86.3±10.9 | 83.6±7.9 | NS |
| FVC ^a | 85.8±12.0 | 80.6±8.3 | NS |
| FEV1 ^a | 86.5±11.0 | 82.3±6.7 | NS |
| FEF25-75 ^a | 78.2±18.8 | 81.7±13.5 | NS |
| DLCO ^a | 66.3±21.3 | 80.7±15.3 | NS |
| DLCO/VA ^a | 77.7±18.0 | 85.2±14.5 | NS |

^a: % predicted; NS: Not significant.

Interstitial pulmonary involvement was found in 16/34 patients with HRCT. Only one case (1/10) had distortion in the controls in HRCT. HRCT findings excluded other causes such as pneumonia, cancer or tuberculosis in patients and control cases. There was a significant difference between controls and patients with HCV infection in HRCT for interstitial involvement ($\chi^2=4.7$, *P*=0.03) (Table 2). All of our

Table 2 High-resolution computed tomography (HRCT) findings in patients with chronic hepatitis C virus infection and controls

| HRCT Findings | Patients with HCV infection | | | Controls | | |
|-----------------------------------|-----------------------------|------|-------------|----------|----|-------------|
| | n | % | HRCT scores | n | % | HRCT scores |
| Ground-glass attenuation | 1 | 2.9 | 2 | 0 | 0 | - |
| Nodular areas of high attenuation | 6 | 17.6 | 3.6±1.5 | 0 | 0 | - |
| Consolidation | 0 | 0 | - | 0 | 0 | - |
| Non-septal lines | 5 | 14.7 | 2.7±1.7 | 0 | 0 | - |
| Septal lines | 4 | 11.7 | 3.9±1.6 | 0 | 0 | - |
| Honeycombing | 0 | 0 | - | 0 | 0 | - |
| Distortion | 0 | 0 | - | 1 | 10 | 2 |

P=0.03, $\chi^2=4.7$.

Table 3 Multiple linear regression analysis of Knodell histological activity index (KHAI) and age and sex in patients with chronic hepatitis C virus infection

| Dependent variable | Independent variables | | | | | | | | |
|--------------------|---------------------------|------|--------|------|-----|--------|-----|---|---|
| | Whole regression equation | | | Age | | | Sex | | |
| | R ² | F | p | β | t | p | β | t | p |
| KHAI | 0.61 | 38.8 | <0.001 | 0.78 | 6.2 | <0.001 | a | a | a |

a: Not significant, R²: squared multiple correlation coefficient, F: F value, β: Partial correlation coefficients, t: t value of regression coefficients.

Table 4 Multiple linear regression analysis of high-resolution computed tomography (HRCT) score, pulmonary function test, Knodell histological activity index (KHAI), age, sex and smoking in patients with chronic hepatitis C virus infection

| Dependent variables | Independent variables | | | | | | | | | | | | | | |
|---------------------|---------------------------|------|-------|------|-----|------|-------|------|-------|-----|---|---|---------|---|---|
| | Whole regression equation | | | KHAI | | | Age | | | Sex | | | Smoking | | |
| | R ² | F | p | β | t | p | β | t | p | β | t | p | β | t | p |
| HRCT score | 0.17 | 5.4 | 0.028 | a | a | a | 0.42 | 2.3 | 0.028 | a | a | a | a | a | a |
| VC | 0.19 | 6.1 | 0.020 | a | a | a | -0.44 | -2.5 | 0.020 | a | a | a | a | a | a |
| FVC | 0.24 | 8.0 | 0.009 | a | a | a | -0.49 | -2.8 | 0.009 | a | a | a | a | a | a |
| FEV1 | 0.25 | 8.6 | 0.007 | a | a | a | -0.50 | -2.9 | 0.007 | a | a | a | a | a | a |
| FEF25-75 | 0.30 | 11.1 | 0.003 | a | a | a | -0.55 | -3.3 | 0.003 | a | a | a | a | a | a |
| DLCO | 0.16 | 4.9 | 0.036 | a | a | a | -0.40 | -2.1 | 0.036 | a | a | a | a | a | a |
| DLCO/VA | 0.22 | 3.5 | 0.047 | 0.55 | 2.2 | 0.04 | -0.66 | -2.6 | 0.015 | a | a | a | a | a | a |

a: Not significant, R²: squared multiple correlation coefficient, F: F value, β: Partial correlation coefficients, t: t value of regression coefficients.

16 patients in whom interstitial pulmonary involvement was found in HRCT had HRCT scores consistent with mild parenchymal abnormalities, there was a negative correlation between HRCT score and DLCO, FVC ($r=-0.364$, $P=0.035$; $r=-0.400$, $P=0.019$, respectively).

Multiple linear regression analysis in which age and sex were considered as independent variables and KHAI was considered as dependent variable, revealed that KHAI was not affected by sex and was related with age, while KHAI was increased with age (Table 3). In order to investigate the possible association between liver pathology (KHAI) and pulmonary data (HRCT, PFT), pulmonary data were considered as dependent variables, KHAI and possible factors affecting pulmonary pathologies including age, sex and amount of cigarette smoking were considered as independent variables, then separate multiple linear regression analyses for HRCT score, VC, FVC, FEV1, FEF25-75, DLCO, DLCO/VA were performed. HRCT score, VC, FVC, FEV1, FEF25-75, DLCO, and DLCO/VA were related with age. HRCT score was positively correlated with age, whereas others decreased with increasing age (negative correlation). When multiple linear regression analysis was used, no significant relation was found between liver pathology and any of the PFT (except DLCO/VA) or HRCT score (Table 4). Although 16 patients had signs consistent with interstitial involvement in HRCT, our findings showed that this was not directly related with liver pathology.

DISCUSSION

In our study, some patients with HCV infection had a mild decrease in PFTs. However, there was no significant difference between patients and controls in PFTs. We determined that there was a significant difference between patients and controls according to the findings in thorax HRCT. The age was related with both pulmonary involvement and liver pathology.

Although the relationship between pulmonary fibrosis and HCV infection was first suggested by Ueda *et al*^[9], Irving *et al*^[15] held on opposite point. In a study, which investigated 300 patients with clinically evident HCV infection for the presence

of pulmonary fibrosis, HRCT assessments revealed a moderate degree of pulmonary fibrosis in 4 cases and severe pulmonary fibrosis in another 4 cases. In all of these 8 cases, there were various degrees of decreases in diffusion capacity that correlated with HRCT findings and less frequently restriction in PFT parameters^[5].

In our study, FEF25-75 was below 80% of the predicted value in a small group of patients (5 patients) with normal FEV1 and VC. Decrease in FEF25-75 and normal VC and FEV1 might be an indicator of an early stage small airway disease. Similar to our findings, Mimori *et al*^[16] stated that in sarcoidosis patients with normal FEV1 and VC, the increase in the ratio of maximum expiratory flow rate at 50% of vital capacity (V50) to maximum expiratory flow rate at 25% of vital capacity (V25) was a finding of the early stage manifestation of small airway disease.

There are contradictory results in the literature about correlations between PFT and HRCT score in patients with pulmonary fibrosis. Also, studies generally revealed a negative correlation between PFT and HRCT score^[5,13,17]. We detected a negative correlation among HRCT, FVC and DLCO in patients with HCV infection.

As HCV infections generally follow a silent course and as they are rarely diagnosed at the acute phase, onset of the disease usually could not be determined^[2]. So, duration of the disease was not investigated among factors that would possibly affect the development of pulmonary involvement. HRCT score and PFT parameters were related with age. In our opinion, because duration of HCV infection may not be accurately determined, age may indirectly be a sign of the duration of the disease.

KHAI was related with DLCO/VA and age in our study. Chronic HCV infection is known to result in moderate to severe disorders in liver, particularly in elderly and alcoholics^[18]. In our patients, neither any of the PFT parameters except DLCO/VA nor HRCT score was affected by KHAI (Table 3). Change in DLCO was probably related with age. Because KHAI is for the evaluation of liver parenchyma, we believe that it does not reflect the intensity of extrahepatic manifestations.

It is clearly revealed that HCV infection does not only affect

the liver, it also has many systemic manifestations. However few studies about its effect on the lung showed that there was an uncertain relationship between HCV infection and pulmonary involvement^[4,18]. We found a negative correlation between HRCT score and DLCO in chronic HCV patients. In some patients (six cases), there was a decrease in DLCO despite normal HRCT findings. Many studies have shown that DLCO could decrease without presence of any radiological finding in the early stage of fibrosis and this decrease might become more significant later^[19-21].

Chronic hepatitis C virus infections may cause mild pulmonary involvement without any pulmonary symptoms resulting in a minimal decrease in PFT. In our study, we found that pulmonary involvement was not related with the degree of liver pathology. The relationship between liver pathology and pulmonary involvement must be investigated in large patient population, and also, it should be detected whether alveolitis can demonstrate the early stage pulmonary involvement. However, we suggest that chronic HCV infection patients, particularly elder ones, might be carefully evaluated by HRCT and DLCO even though they have normal chest X-ray or other PFT parameters.

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