

Does hepatitis C virus enhance prevalence of idiopathic pulmonary fibrosis and affect its severity? An Egyptian study

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Background Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of pulmonary fibrosis characterized by gradual loss of pulmonary function. Despite rigorous research, the etiology of IPF has remained unknown. Viruses, for example, hepatitis C virus (HCV), had been implicated in IPF etiology; however, data on the prevalence of HCV infection in IPF patients were limited.

Aim of the study Our aims were to assess the prevalence of HCV antibodies in IPF patients and to assess the relationship between severity of pulmonary and hepatic dysfunction.

Materials and methods IPF patients were prospectively enrolled from Chest Department, Assiut University Hospital. HCV antibodies were detected using the third-generation enzyme-linked immunosorbent assay. Patients' pulmonary and hepatic functions were evaluated.

Results HCV antibodies were significantly higher in IPF patients than in controls (29.4 vs. 14%, $P = 0.04$). Patients with HCV had significantly more severe hypoxemia and lower diffusing capacity for carbon monoxide than those without HCV (47.7 ± 11.3 vs. 54 ± 18.7 , $P = 0.03$ and

52.7 ± 8.4 vs. 67.3 ± 9.5 , $P = 0.01$, respectively). There was no significant difference between HCV-positive IPF patients and HCV-negative IPF patients regarding spirometric parameters and liver function parameters.

Conclusion This higher prevalence of HCV and its effect on pulmonary functions in IPF patients may contribute in IPF pathogenesis, which hopefully will allow currently available antiviral drugs or novel therapeutic approaches to treat or modify the course of this devastating disease.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive invariably fatal condition that severely compromises pulmonary function [1]. Major advances have been made in understanding the pathogenesis of the inflammatory and fibrotic mechanisms at work in IPF. The exact triggers, which initiate this fibrotic process, remain unknown. Viruses, for example, hepatitis C virus (HCV), have long been suspected of playing a role in the immunopathogenesis of IPF [2,3]. In the last years, the epidemiology of IPF has been changed, where we noticed increasing numbers of patients with IPF who are younger than expected [4]. In our locality, HCV infection is a common infection; moreover, Egypt has the largest burden of HCV infection in the world, with a 10% prevalence of chronic HCV infection among persons aged 15–59 years [5]. Several Egyptian series studied the prevalence of IPF in patients with chronic hepatitis C [6,7]. However, studies demonstrating HCV prevalence in IPF patients were limited.

Hence, our aims were to assess the prevalence of HCV antibodies in IPF patients and to assess the relationship between the severity of pulmonary and hepatic dysfunction.

Materials and methods

Study design

This prospective study was carried out at Assiut University Hospital (AUH), Egypt. The study was approved by the Ethics Committee of AUH and informed consent was obtained from all participants before enrollment.

Study population

IPF patients admitted to Chest Department, AUH, during the period between January 2014 and June 2014 were enrolled in this study. Diagnosis of IPF was made according to the ATS/ERS/JRS/ALAT statement 2011 [8]. Fifty controls had no pulmonary diseases and were sex and age matched with patients. These controls were selected randomly from relatives of the patients. Patients with evidence of acute exacerbation of IPF, interstitial lung diseases other than IPF, other chest diseases, chronic hepatitis B, and coinfection with HCV and hepatitis B virus (HBV) were excluded.

All patients were subjected to the following.

- (1) Thorough medical history and clinical examination.
- (2) Pulmonary function test using spirometry to measure forced vital capacity (FVC), % predicted

of FVC, forced expiratory volume in the first second (FEV₁), and FEV₁/FVC ratio.

- (3) Diffusion capacity of the lung for carbon monoxide (DLCO%) using single-breath method.
- (4) Arterial blood gas (ABG) analysis by measuring pH, PaCO₂, PaO₂, and SaO₂.
- (5) Liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, albumin, bilirubin, and prothrombin time).
- (6) Serological tests for HBV and HCV infection (anti-HCV antibodies and HBsAg).
- (7) Abdominal ultrasound.

The degree of pulmonary restriction of IPF patients was classified according to % predicted of FVC [9]:

- Mild: predicted FVC below lower limited normal but at least 70%.
- Moderate: predicted FVC below 70% and at least 50%.
- Severe: predicted FVC below 50% and at least 34%.
- Very severe: predicted FVC below 34%.

Methods

Venous blood sample of 3–5 ml was obtained from each participant. Samples were collected and centrifuged immediately. Serum samples were frozen at –70°C until assayed. Anti-HCV antibodies were detected using the third-generation enzyme-linked immunosorbent assay (AiD anti-HCV ELISA) (Diagnostic Automation Group, Sunnyvale, California, USA) and HBsAg was tested by ELISA (AiD HBsAg ELISA) (Beijing Wantai Biological Pharmacy Enterprise Co. Ltd, Beijing, China) in accordance with the protocol of the manufacturer.

Statistical analysis

All statistical analyses were conducted using SPSS for Windows, version 17 (SPSS Inc., Chicago, Illinois, USA). The continuous data were expressed as mean ± SD and were compared using Student's *t*-test. Categorical variables were expressed as percentage and compared using the χ^2 -test. For all analyses, *P* value less than 0.05 was considered statistically significant.

Results

During the period between January 2014 and June 2014, 104 patients with IPF were admitted to Chest Department; 30 of them had HCV and only two patients had HBV. The remaining patients were seronegative for viral hepatitis. HBV patients were excluded from this study.

Hence, the study included 102 IPF patients; 22 were male patients and 80 were female patients with a mean

age of 48.7 ± 5.3 years (range 20–66 years). The control group was formed of 37 women and 13 men with a mean age of 47.5 ± 7.6 years. HCV infection was significantly higher in IPF patients than in controls (29.4 vs. 14%, *P* = 0.04).

Table 1 shows the characteristics of the IPF patients with and without HCV infection. We noticed that HCV-positive IPF patients were younger than those IPF patients without HCV infection but with no statistical significance. In addition, there were no significant differences between the two groups with respect to sex ratio and smoking (Table 1).

Regarding ABG, patients with HCV infection had significantly more severe hypoxemia as compared with those without HCV (47.7 ± 11.3 vs. 54 ± 18.7, *P* = 0.03). In addition, DLCO% was significantly lower in patient with HCV than in patients without HCV (52.7 ± 8.4 vs. 67.3 ± 9.5, *P* = 0.01). With respect to spirometric findings, % predicted of FVC was not significantly altered but showed a tendency toward decreased values in IPF patients with HCV infection (*P* > 0.05) (Table 1).

Among HCV-positive IPF patients, there was decrease in the % predicted of FVC and DLCO% in cirrhotic patients than in those without liver cirrhosis; however, these differences were not statistically significant. In addition, ABG parameters showed no significant difference between both groups (Table 2).

Table 3 shows no significant differences between HCV-positive IPF patients with moderate and severe pulmonary restriction regarding liver function parameters and sonographic liver pattern changes.

Table 1 Characteristics of IPF patients with and without HCV infection

| Variables | IPF patients without HCV (n = 72) | IPF patients with HCV (n = 30) | <i>P</i> |
|-------------------------|-----------------------------------|--------------------------------|----------|
| Age (mean ± SD) (years) | 55.4 ± 11.5 | 47 ± 11.4 | 0.368 |
| Sex [n (%)] | | | |
| Male | 16 (22.2) | 6 (20) | 0.373 |
| Female | 56 (77.8) | 24 (80) | |
| Smoking [n (%)] | | | |
| No | 68 (94.4) | 28 (93.3) | 0.764 |
| Yes | 4 (5.6) | 2 (6.7) | |
| Blood gases (mean ± SD) | | | |
| pH | 7.4 ± 0.1 | 7.5 ± 0.1 | 0.249 |
| PaO ₂ | 54 ± 18.7 | 47.7 ± 11.3 | 0.03 |
| PaCO ₂ | 41.4 ± 9.6 | 37.1 ± 9 | 0.06 |
| SaO ₂ | 86.3 ± 8.5 | 83.1 ± 11.7 | 0.141 |
| HCO ₃ | 30 ± 6.5 | 29 ± 4.9 | 0.483 |
| DLCO (%) | 67.3 ± 9.5 | 52.7 ± 8.4 | 0.01 |
| FVC (% predicted) | 64.4 ± 11.6 | 58.2 ± 10.8 | 0.931 |

DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HCV, hepatitis C virus; IPF, idiopathic pulmonary fibrosis.

Table 2 Pulmonary function and ABG parameters of HCV-positive IPF patients according to the severity of liver disease

| Variables | IPF, HCV patients without liver cirrhosis (n = 22) | IPF, HCV patients with liver cirrhosis (n = 8) | P |
|-------------------|--|--|-------|
| FVC (% predicted) | 60 ± 12.5 | 56 ± 11.8 | 0.872 |
| DLCO (%) | 54.2 ± 4.8 | 49.3 ± 6.2 | 0.860 |
| Hypoxemia | 50 ± 3.2 | 45 ± 6.1 | 0.06 |
| Blood gases | | | |
| pH | 7.5 ± 0.06 | 7.4 ± 0.05 | 0.132 |
| PaO ₂ | 56.2 ± 17.6 | 45.6 ± 7.4 | 0.064 |
| PaCO ₂ | 39.4 ± 8.5 | 40.2 ± 13.4 | 0.798 |
| SO ₂ | 87.2 ± 8.3 | 82.2 ± 10.2 | 0.087 |
| HCO ₃ | 27 ± 6.2 | 30.7 ± 5.9 | 0.264 |

ABG, Arterial blood gas; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HCV, hepatitis C virus; IPF, idiopathic pulmonary fibrosis.

Table 3 Liver function parameters and sonographic liver pattern in HCV-positive IPF patients according to the severity of pulmonary restriction

| Variables | Moderate pulmonary restriction (n = 8) | Severe pulmonary restriction (n = 22) | P |
|--------------------------------------|--|---------------------------------------|-------|
| AST (mean ± SD) (IU/l) | 66.4 ± 46.5 | 62.6 ± 95.4 | 0.858 |
| ALT (mean ± SD) (IU/l) | 90.2 ± 48.8 | 75.5 ± 82.8 | 0.429 |
| Serum albumin (mean ± SD) (g/dl) | 3.3 ± 7.9 | 32 ± 6.8 | 0.935 |
| Serum bilirubin (mean ± SD) (µmol/l) | 19.4 ± 16.2 | 20.1 ± 37.3 | 0.931 |
| INR (mean ± SD) | 1.1 ± 0.4 | 1.3 ± 0.4 | 0.623 |
| Abdominal ultrasound [n (%)] | | | |
| Normal | 2 (25) | 6 (25) | 0.343 |
| DHP | 4 (50) | 10 (41.7) | |
| LC | 2 (25) | 8 (33.3) | |

IPF, idiopathic pulmonary fibrosis; ALT, alanine transaminase; AST, aspartate transaminase; HCV, hepatitis C virus; INR, international normalized ratio; DHP, diffuse hepatic pathology; LC, liver cirrhosis.

Discussion

In this study, we tried to answer whether HCV infection affects the prevalence and has a role in the pathogenesis of IPF. The present study showed significant higher prevalence of chronic HCV infection in IPF patients (29.4%) compared with healthy controls (14%). This result was within the range of the previous estimates for the prevalence of HCV infection in IPF patients, where Ueda *et al.* [10] detected anti-HCV antibodies in 28.8% of patients with IPF. In addition, Meliconi *et al.* [11] reported a higher prevalence of HCV antibody in patients with IPF compared with the general population. However, Irving *et al.* [2] was unable to find any connection between HCV and IPF. These controversial results may be explained by the geographical differences and other factors where people from Japan and Mediterranean countries are more susceptible to HCV than those from northern Europe [12].

This high prevalence of HCV antibodies among IPF patients may suggest a possible role for HCV infection in the pathogenesis of IPF. HCV is a well-known cause of liver fibrosis, and it could potentially provoke similar abnormalities in the lung, mainly because of its lymphotropism, which can induce chronic immune activation and inflammation [13]. Viral infections including occult ones may play a pathogenetic role as cofactors in the development of fibrosis. This hypothesis is based on the assumption that this inflammatory agent (HCV) disrupts the normal healing process, thereby making the lung to be highly susceptible to injurious triggers [14]. Chronic HCV infection may contribute to the immune responses that modulate the pathogenic processes underlying pulmonary disorders – for example, accumulation to lung tissue of immunoglobulin and/or immune complex or direct involvement of HCV-RNA [15]. Idilman *et al.* [16] reported an increased bronchoalveolar lavage neutrophil count in individuals with chronic HCV hepatitis. This finding suggests that HCV may have the potential to induce an alveolitis leading to fibrotic changes in the lung [15].

Our findings were in agreement with previous studies, which reported that HCV infection was complicated by a number of extrahepatic manifestations including restrictive lung diseases [17,18]. In addition, some conditions, such as mixed cryoglobulinemia and sicca syndrome, are observed in HCV infection and can involve the lung [19,20].

The higher prevalence of HCV infection in IPF patients may be explained in part by acquiring the HCV through frequent hospitalization, injections, or other ancillary factors; especially, we have not been able to determine whichever happened first. However, this hypothesis can be refuted because of the lack of the number of patients infected with HBV, despite being subjected to the same factors.

The mean age of IPF patients in our study was younger than that reported in the literatures that stated IPF is common in elderly [4]. In addition, HCV-positive IPF patients were younger age compared with those without infection in our series. This may reflect the background rate (10%) of HCV infection among persons aged 15–59 years suggesting that HCV may implicate in pathogenesis of IPF [5].

The current study revealed that HCV-positive IPF patients had significant reduction in PaO₂ and DLCO% compared with IPF patients without HCV infection. Erturk *et al.* [21] demonstrated abnormal DLCO% results that occurred early in HCV infection

suggesting a high rate of subclinical pulmonary destruction in patients with chronic HCV infection.

We speculated that the underlying mechanism predisposing to more severe hypoxemia and impairment of gas exchange may be chronic immune activation and inflammation-induced HCV infection causing accelerated decline of pulmonary function [18,22]. Moreover, polymyositis, a complication of chronic HCV infection, can also impair respiration through weakened respiratory muscles [23]. Saleh *et al.* [6] demonstrated that HCV-related cryoglobulinemia may have an impact on both gas exchange and airway parameters. In addition, pulmonary vascular dilatation and ventilation perfusion mismatch that occurs in cirrhotic patients may be another explanation of decreased oxygen level [23].

In agreement with the study by Saleh *et al.* [6], our study found that the severity of pulmonary involvement was not parallel to the liver impairment; thus, patient management and prediction of disease outcome can be subject to marked variability.

Conclusion

This higher prevalence of HCV and its effects on pulmonary functions in IPF patients may contribute in IPF pathogenesis, which hopefully will allow currently available antiviral drugs or novel therapeutic approaches to treat or modify the course of this devastating disease. However, further studies should be performed to determine whether there is a causal relationship between HCV infection and IPF. In addition, screening for early parenchymatous lung changes in patients with HCV is recommended.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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