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ORIGINAL ARTICLE

Prevalence of chronic hepatitis C virus (HCV) infection in patients with idiopathic pulmonary fibrosis

Abd El Monaem Rabea [a], Mohamad Zidan [a], Rasha Daabis [a,*], Perihan El Sayed [b], Sally Samir [a]

[a] *Department of Chest Diseases, Faculty of Medicine, Alexandria University, Egypt*
[b] *Department of Internal Medicine (Hepatology Unit), Faculty of Medicine, Alexandria University, Egypt*

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KEYWORDS

Hepatitis C virus;
Idiopathic pulmonary fibrosis;
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Pulmonary function testing;
Severity;
High resolution CT score

Abstract *Introduction:* Pathogenic sequences leading to the development of idiopathic pulmonary fibrosis (IPF) are unclear; but one theory is that, in a genetically susceptible host, there is a "triggering agent or event inducing an inflammatory reaction in the lung that perpetuates itself and causes parenchymal fibrosis". One potential source for a self-perpetuating triggering event could be a chronic viral infection. For this reason, evidence for an association between IPF and chronic viral infection has been sought by many investigators for several different viruses, including HCV.

Objective: To estimate the prevalence of chronic hepatitis C virus infection in patients with idiopathic pulmonary fibrosis via detection of HCV antibodies in selected patients in comparison to the control group.

Patients and methods: In this study we evaluated 30 patients diagnosed with idiopathic pulmonary fibrosis according to diagnostic criteria of American Thoracic Society (ATS) in comparison to 60 healthy control subjects. All enrolled subjects underwent a serologic test for HCV infection by detecting hepatitis C surface antigen (HCVsAg) by a third-generation enzyme-linked immunosorbent assay (ELISA) test. All patients had undergone dyspnea severity assessment by the mMRC score, routine laboratory testing including arterial blood gases (ABGs), pulmonary function testing (PFTs), chest-X-ray, high resolution CT scan (HRCT), liver ultrasonography and bronchoscopy (when needed).

Results: 9 IPF patients were positive for HCV (30%), while 17 control subjects were positive for HCV (28.3%) ($p = 0.869$). In HCV positive IPF patients there were more severe dyspnea as assessed by the mMRC score ($p = 0.042^*$), lower FVC ($p = 0.011^*$), SaO_2% and PaO_2 were significantly lower ($p \leqslant 0.001^*$ for both parameters), and more severe HRCT scanning score ($p = 0.012^*$), in comparison to HCV negative IPF patients. There was significant negative

* Corresponding author.
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correlation between the HRCT score and FVC ($p = 0.011^*$) in HCV positive IPF patients, there was significant negative correlation between liver cirrhosis and PaO_2 ($p = 0.023^*$), $PaCO_2$ ($p = 0.002^*$) in HCV positive IPF patients.

Conclusion: Despite the fact that we couldn't confirm the hypothesis that HCV can be a causative agent in the development of IPF, however, we have shown that HCV can be a predisposing factor for the development of a more severe form of IPF. Therefore screening IPF patients for the presence of underlying HCV infection can have important therapeutic and prognostic implications in those patients.

Introduction

IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP (usual interstitial pneumonia) [1].

The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and ILD associated with environmental exposure, medication, or systemic disease [1,2].

The incidence of IPF was estimated at 10.7 cases per 100,000 per year for men and 7.4 cases per 100,000 per year for women in a population-based study from the county of Bernalillo, New Mexico [3], the most recent estimated prevalence of IPF is 1.6–1.7/10,000 [4].

Hepatitis C virus (HCV), a ribonucleic acid (RNA) virus, is now recognized as the major cause of non-A, non-B transfusion-associated hepatitis. With improved diagnostic techniques, HCV infection is increasingly identifiable and is recognized as being associated with conditions other than hepatitis [5,6].

Chronic hepatitis C affects an estimated 170 million people worldwide and causes approximately 350,000 deaths each year [7]. The overall prevalence positive for antibody to HCV in Egypt by released Egyptian Demographic Health Survey [EDHS] 2008* was 14.7% [8]. The diverse HCV studies conducted among different general population subgroups, regardless of design or methodology, consistently report a very high HCV prevalence, as high as 41% in some studies [9].

Since HCV is well known to induce chronic inflammation and fibrosis in the liver, it was thought that HCV may play a similar role in the lung and may be involved in the pathogenesis of pulmonary fibrosis [10]. The pathogenic sequences leading to the development of IPF are unclear; but one theory is that, in a genetically susceptible host, there is a "triggering agent or event inducing an inflammatory reaction in the lung that perpetuates itself and causes parenchymal fibrosis" [11]. One potential source for a self-perpetuating triggering event could be a chronic viral infection [12]. For this reason, evidence for an association between IPF and chronic viral infection has been sought for several different viruses, including HCV [13].

An association between HCV infection and IPF was initially supported by seroepidemiological data, which revealed a higher prevalence of anti-HCV antibodies in patients with IPF [14]. 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 [15].

To our knowledge, there are only few studies that investigated the association between IPF and HCV infection as a risk factor, the present study aimed at investigating the prevalence of chronic hepatitis c virus (HCV) infection in patients with idiopathic pulmonary fibrosis.

Subjects and methods

Study design

A case control study was conducted in the Chest Diseases Department, Faculty of Medicine, Alexandria University. The study protocol was approved by the ethics committee of the University and all study subjects were informed about the study and their written consent was obtained.

Study subjects

The study protocol included 30 IPF patients, diagnosed according to diagnostic criteria of American Thoracic Society (ATS) with the following exclusion criteria: (1) patients with other chronic pulmonary diseases. (2) Secondary causes of IPF such as (congestive heart failure, suspected malignancy, collagen tissue diseases, occupational lung diseases. (3) Chronic liver diseases due to chronic hepatitis B virus infection, chronic alcoholism or autoimmune hepatitis. (4) History of treatment with interferon in HCV positive patients.

Patients were compared with 60 age and sex matched control subjects

Laboratory investigations including

1. Complete liver profile including: aspartate aminotransferase (AST), alanine aminotransferase (ALT) [16], Bilirubin [16], Serum albumin [17], prothrombin time and international normalized ratio (PT/ INR) [17].
2. Diagnosis of HCV infection by a third-generation enzyme-linked immunosorbent assay (ELISA) test (Ortho Diagnostic System, Raritan, New Jersey, USA) [18].
3. Investigations to exclude secondary causes of IPF e.g. Collagenic profile in the form of rheumatoid factor (RF), LE cells, anti-nuclear antibody (ANA), and anti-double strand DNA (anti-Ds. DNA) [19].