Chronic obstructive pulmonary disease and hepatitis C

Evgeni V. Mekov1, Rosen E. Petkov1, Dimitar T. Kostadinov1, Krasimir A. Antonov2, Deian T. Jelev2

1 Clinical Center for Pulmonary Diseases, St. Sofia Hospital for Pulmonary Diseases, Medical University of Sofia, Sofia, Bulgaria
2 Clinic of Gastroenterology, St. Ivan Rilski University Hospital, Medical University of Sofia, Sofia, Bulgaria

Correspondence:
Evgeni V. Mekov, Clinical Center for Pulmonary Diseases, St. Sofia Hospital for Pulmonary Diseases, Medical University of Sofia, 19, Acad. Ivan Geshov Blvd., 1431 Sofia, Bulgaria
E-mail: dr_mekov@abv.bg
Tel: +359888320476

Received: 17 July 2016
Accepted: 10 Oct 2016
Published Online: 31 Jan 2017
Published: 27 June 2017

Key words: COPD, hepatitis C, HCV, comorbidity


BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a preventable, treatable disease with significant extrapulmonary manifestations that could worsen the course of the disease in some patients. An epidemiological study shows a prevalence of COPD in Bulgaria of 11.2% (23.7% in current smokers, 21% in former smokers, 6.6% in non-smokers), which is similar to the global COPD prevalence of 11.7% among people aged >30 years.

The prevalence of hepatitis C in Bulgaria is 1.5%, whereas worldwide prevalence is 2.8%. Hepatitis C virus is a small single stranded RNA virus of the Flaviviridae family, which is a major cause of liver cirrhosis and hepatocellular carcinoma worldwide.

Hepatitis C virus (HCV) infection, in turn, is connected to a large number of extraphepatic manifestations such as mixed cryoglobulinemia, lichen planus, porphyria cutanea tarda, B-cell non-Hodgkin’s lymphoma, monoclonal gammopathy, etc. An increasing body of evidence supports the possibility of pulmonary involvement as extraphepatic manifestations of chronic HCV infection.

AIM

The aim of this article was to review literature on the prevalence of HCV in COPD and vice versa, the pathogenetic link and the consequences of their mutual existence.

HCV IN COPD

The available studies on the prevalence of HCV in COPD are scant and have small sample sizes.

Erol et al. reported a prevalence of HCV infection of 8.3% in patients with COPD (n=108). Forty-four point four percent of patients with HCV and COPD had risk factors for viral infection (such as blood transfusions, surgery, hemodialysis, exposure to blood or biofluids, risky sexual behavior, use of intravenous drugs, dental treatments, tattoos), while in the control group with no HCV, risk factors were found in 12.1% of patients. The two groups were matched in age, gender, smoking status and number of previous hospitalizations.

The incidence of HCV in 187 patients with COPD, according to another study, was 7.5% (95%CI...
Lung function in this study showed correlation with increased local levels of IL-8, as well as increased levels of inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α) which can increase further in exacerbation. There is also neutrophilic inflammation in HCV could facilitate systemic inflammation in HCV could facilitate the occurrence of COPD. COPD is characterized by increased levels of inflammatory cytokines (IL-1β, IL-6, IL-8, and TNFα) which can increase further in exacerbation. There is also neutrophilic inflammation with increased local levels of IL-8, as well
as NF-kB and 15-lipoxygenase. In addition, the bronchial epithelium in COPD expressed an increased amount of monocyte chemoattractant protein-1 and IL-8, which is a leukocyte attractant and contribute to increased levels of neutrophils in the sputum.

At molecular level, the most likely link is IL-8, which is crucial in the pathogenesis of COPD. HCV increases the level of IL-8 in endothelial cells by transcriptional activation and stabilization of the mRNA and the level of IL-8 in turn is correlated with the replication of HCV. In addition, HCV nuclear nucleocapsid protein increases IL-8 by p-38 and gC1qR (receptor protein, which is involved in the complement system - C1).

IL-8 has a chemotactic effect on inflammatory cells such as neutrophils through CXCR receptors 1 and 2, which increases pulmonary inflammation. It could directly induce bronchoconstriction and contribute to bronchial hyperresponsiveness, as well as indirectly through stimulation of neutrophil attraction and activation. Serum and intrahepatic cytokines, in particular IL-8 in patients with HCV, are increased. The expression of IL-8 can inhibit the antiviral activity of IFN and correlates with the degree of liver fibrosis and portal inflammation in HCV.

The number of lymphocytes in bronchoalveolar lavage (BAL) in patients with HCV is increased, which implies involvement of HCV infection in the development of lymphocytic alveolitis. Thus HCV may contribute to the development of lung parenchymal destruction. Except for increased numbers of lymphocytes, other studies showed an increased number of lymphocytes and neutrophils as well as increased neutrophils only in the BAL of patients with HCV. An increased number of CD2+, CD3+, CD4+ and HLA-DR+ T-lymphocytes has also been reported. However, these results are based on small sample sizes and in asymptomatic patients with no clinical and radiological data of pulmonary disease.

Cytotoxic CD8+ T-lymphocytes increase in viral infection and activate a series of inflammatory pathways which results in release of inflammatory mediators. CD8+ cells are also involved in pulmonary inflammation in COPD as their number is increased and correlates inversely with lung function.

CD8+ T lymphocytes contribute to dysregulation of M2 muscarinic receptors whose main function is to inhibit the release of acetylcholine and prevent bronchoconstriction. CD8+ lymphocytes increase the level of IFN, which reduces the expression of M2-receptors in the parasympathetic neurons in the airways and increases bronchial hyperresponsiveness.

Last, but not least, smoking-related diseases such as COPD are of great concern in the HIV-infected population which is commonly associated with HCV. The prevalence of COPD is higher in patients with HIV when compared to the general population. HAART therapy has led to changes in HIV-related pulmonary diseases which prolong survival. COPD is emerging as a new source of morbidity and mortality in HIV-infected patients.

SECONDARY INVOLVEMENT OF THE LUNG IN HCV

Secondary involvement of the lung in HCV is associated on one hand with the development of liver cirrhosis and portal hypertension and on the other - with the development of autoimmune diseases which are prevalent in patients with HCV.
vasculature may represent another mechanism of lung involvement (Fig. 1). Chronic liver disease may lead to lung injury because of changes in liver metabolism due to circulating inflammatory mediators and/or changes in blood flow due to pulmonary hypertension.

Liver cirrhosis (due to HCV) could lead to hepatopulmonary syndrome (vasodilatation) and portopulmonary hypertension (vasoconstriction).

Hepatopulmonary syndrome (HPS) is represented by the triad of liver disease (liver dysfunction), pulmonary vasodilation and impaired arterial oxygenation (hypoxemia). The prevalence of HPS in patients with chronic liver disease is 10-15%. The clinical presentation varies from asymptomatic course to shortness of breath, cyanosis and finger clubbing. Platypnea (dyspnoea occurring when getting up from a lying position) and orthodeoxia (lowering of PaO2>3 mm Hg when getting up from a lying position) are common in patients with HPS due to pulmonary vasodilatation, mainly in the lower lung lobes due to gravity.

Pulmonary vasodilation is a major cause of hypoxemia in HPS. It leads to a mismatch between ventilation and perfusion due to increased perfusion and unchanged ventilation, which makes impossible the diffusion of the oxygen from the alveolar space to the center of abnormally dilated capillaries and oxygenation of hemoglobin. In addition, hypoxic vasoconstriction in patients with chronic liver disease and increased pulmonary blood flow also contributes to the mismatch between ventilation and perfusion.

Portopulmonary hypertension (PPH) is characterized by the tetrad: increased pulmonary pressure (>25 mm Hg at rest), increased pulmonary vascular resistance (>240 dyn.s.cm-5), normal wedge pressure (<15 mmHg) and portal hypertension (>10 mm Hg). In most patients with PPH, portal hypertension is preceding 4-7 years on average. The pathogenesis of the structural changes is not entirely clear, but include pulmonary vasoconstriction, remodeling of the muscle layer on the wall of pulmonary arteries and in situ microthrombosis and/or thromboembolic lesions. Although pathological changes are similar to those shown in primary pulmonary hypertension, PPH is characterized by increased cardiac output.

It is notable that HIV-HCV co-infected patients have higher prevalence of PAH, which could worsen the prognosis.

Last but not least, HCV infection leads to chronic liver inflammation and liver fibrosis. It is possible that HCV plays a similar role in the lung and is involved in the pathogenesis of pulmonary fibrosis.

**PULMONARY COMPLICATIONS OF INTERFERON THERAPY**

Interferon (IFN) therapy shows good results in HCV. This discovery was followed by reports of IFN-associated pulmonary complications. Most of them are reporting of cases, which impedes determination of the prevalence. They include interstitial pneumonitis, ARDS, sarcoidosis, pulmonary hypertension and pleural effusions. According to two large studies the frequency of IFN-associated interstitial pneumonitis is 0.2-0.3%. Pulmonary complications of HCV therapy without IFN are still under study.

**CONCLUSION**

COPD patients have increased prevalence of HCV and patients with HCV, especially older ones, have increased prevalence of COPD. COPD patients have an increased risk of acquiring HCV infection due to the chronic nature of the disease and frequent medical treatment as well as presence of classical risk factors for HCV. However, patients with HCV infection don’t have increased prevalence of risk factors for COPD, despite the presence of COPD. HCV infection has long-term effects on lung tissue and is an additional risk factor for the development of COPD. The presence of HCV is associated with an accelerated loss of lung function in COPD patients, especially in current smokers. COPD could represent extrahepatic manifestation, associated with HCV infection. The most likely pathogenetic link between both diseases is systemic inflammation.

Secondary involvement of the lung in HCV is associated on the one hand with the development of liver cirrhosis and portal hypertension, and on the other - with the development of autoimmune diseases which are prevalent in patients with HCV. Liver cirrhosis can cause hepatopulmonary syndrome and portopulmonary hypertension, which further worsen the prognosis of patients with HCV and COPD.

Interstitial pneumonitis is a well-described complication of therapy with IFN, but the association with other reported complications is questionable.

**CONFLICT OF INTEREST**

Mekov E – Chiesi: travel grant for ERS 2015, Astra Zeneca, speaker.

Antonov K and Jelev D - fees as local advisory board members and/or research funding from Gilead, Abbvie, MSD, Roche, Novartis, Johnson & John-

Folia Medica I 2017 I Vol. 59 I No. 2
son, Idexx, Norgine and ACPS - Applied Clinical Pharmacology Services, GSK.

REFERENCES


Хроническая обструктивна болезнь лъгките и гепатит С

Евгени В. Меков1, Росен Е. Петков1, Димитр Т. Костадинов1, Красимир А. Антонов2, Деян Т. Желев2

1 Клинический центр лёгочных заболеваний, Специализированная больница лёгочных заболеваний „Св. София“, Медицинский университет - София, София, Болгария
2 Клиника гастроэнтерологии, Университетская больница „Св. Иван Рилски“, Медицинский университет - София, София, Болгария

Адрес для корреспонденции: Евгени В. Меков, Клинический центр лёгочных заболеваний, Специализированная больница лёгочных заболеваний „Св. София“, Медицинский университет, бул., „Акад. Иван Гешов“ 19, София 1431, Болгария
E-mail: dr_mekov@abv.bg
Тел.: +359888320476
Дата получения: 17 июля 2016
Дата приемки: 10 октябрь 2016
Дата онлайн публикации: 31 януари 2017
Дата публикации: 27 юни 2017

Ключевите слова: ХОБЛ, гепатит С, HCV, коморбидность


Хроническая обструктивна болезнь лъгките (ХОБЛ) е предотвратима, лечима болезнь со значителни венеъшни проявлението, които могат оказат отрицателно въздействие на протекването на заболяването у някои пациенти. С друга страна, инфициране с вирус гепатит С (HCV) е свързно с рядом венеъшни проявлението, свързани с HCV инфицирането. У пациенти с ХОБЛ проявява HCV, а у пациенти с HCV, особено у пожилите, проявява распространение и короткотрайно развитие ХОБЛ. HCV инфициране оказва долгоасмотрено въздействие на венеъшната тъкан и я е допълнителен фактор на риска на развитието на ХОБЛ. Наличието на HCV е свързано с похабено развитие на венеъшна функция у пациенти с ХОБЛ, особено у активни курици. ХОБЛ може привести к венеъшни проявлението, свързани с HCV инфицирането. Целят на тази статия е допълнителен обзор информацията, свързана с распространението на HCV и ХОБЛ, и с друга страна, установяване на патогенна връзка и последствия на взаимното проявяне.