

Frequency of restrictive pulmonary function tests in patients with chronic Hepatitis C

Original Article

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ABSTRACT

Introduction: Hepatitis C infection is a common health problem worldwide and is the major cause of chronic liver disease in Pakistan. Common complications of chronic hepatitis C infection are cirrhosis, asities, and hepatocellular carcinoma. Also, hepatitis C virus (HCV) infection¹ is associated with several extrahepatic manifestations including interstitial lung fibrosis. It has been found that the frequency of pulmonary fibrosis is increased in patients with cirrhosis of the liver as the stage of cirrhosis advances. This lung fibrosis can cause a restrictive pattern of pulmonary function tests. This study was conducted to determine the frequency of restrictive pulmonary function in patients with different stages of chronic hepatitis C infection, based on Child-Pugh classification.

Method: Ninety-nine patients of age range 20 to 80 years, both males and females having chronic hepatitis C infection and interferon negative patients, were enrolled from outpatient and inpatient departments of medicine, Mayo Hospital Lahore. Patients were divided into three groups according to Child's criteria. Pulmonary function tests were performed on patients to look for FEV₁/FVC ratio. FEV₁/FVC ratio greater than 80 was considered as restrictive pulmonary function.

Results: Out of 99 patients, 32% were found to have a restrictive pattern of pulmonary functions.

Conclusion: Chronic hepatitis C infection is associated with a restrictive pattern of pulmonary function, suggestive of pulmonary fibrosis.

Keywords: Liver Cirrhosis, Pulmonary fibrosis, Respiratory Function Tests, Hepatitis C

INTRODUCTION

Chronic liver disease is a worldwide health issue. It has several etiologies like viruses, alcohol, autoimmune hepatitis, Wilson's disease, nonalcoholic fatty liver disease, hereditary hemochromatosis, primary biliary cirrhosis, and alpha-1 antitrypsin deficiency.[1] In the western world, alcohol is the leading cause of chronic liver disease while in

Pakistan hepatitis B (HBV) and hepatitis C (HCV) viruses account for the majority of the cases with chronic liver disease.[2]

HCV is an RNA virus belonging to the flavivirus family and is more common in Pakistan than HBV infection. Currently there are seven different genotypes of the HCV. Acute hepatitis C infection is less common and accounts for 15-20 percent of cases while the remaining 80-85% cases progress to chronic infection. The spontaneous recovery rate of acute infection depends upon the genotype and genetics of HCV. There are at least 6 different genotypes of the HCV, which are further subdivided into a and b. At the nucleotide level, they have more than 30 differences in structure. Genotype 1 is more prevalent worldwide and 50-60 % of patients in the US have genotype 1. In the US 10-15 % of patients have genotype 2, while genotype 3 is more common in Pakistan, India, Thailand, Australia. In the CC genotype of IFNL (IL28B) spontaneous recovery rate is 64 percent while genotype CT or TT has a 24 % and 6 % spontaneous recovery rate. If the chronic infection is left untreated, 20 % of these will develop cirrhosis over a period of 20-40 years and once cirrhosis is there, life expectancy is decreased to 95 % and 81 % at 5 and 10 years respectively. Other complications of cirrhosis like ascites develop in 25% of patients over a decade and life expectancy is further reduced to 50% at 5 years. Among these cirrhotic patients, 2-5 % develop hepatocellular carcinoma per year.[3]

Hepatitis C infection has several extrahepatic



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manifestations that include lichen planus, mixed cryoglobulinemia, membranoproliferative glomerulonephritis, autoimmune thyroiditis, lymphocytic sialadenitis, porphyria cutanea tarda, monoclonal gammopathy, autoimmune idiopathic thrombocytopenia, and cirrhotic cardiomyopathy.[3,4] With chronic hepatitis C infection, there is a 20-30 percent increase in risk to develop non-Hodgkin lymphoma in the future. Infection with genotype 1 increases the risk to develop the end-stage renal disease while genotype 3 is associated with hepatic steatosis. Besides, Pulmonary complications develop in many patients, which include hepatic-pulmonary syndrome, Porto pulmonary syndrome, right ventricular systolic dysfunction, and interstitial pulmonary fibrosis.[5]

Idiopathic pulmonary fibrosis (IPF) is the hardening and scarring of lung parenchyma due to chronic inflammation. It is defined as a specific form of chronic progressive interstitial pneumonia of unknown cause occurring primarily in the elderly, limited to lungs, and having histological and radiological features of usual interstitial pneumonia after exclusion of other causes. It seems that the pathophysiology of fibrosis is similar both in the lung and liver. However, there is some genetic predisposition to trigger lung fibrosis.[6,7]

Other causes of lung fibrosis are viral infections like adeno and herpes viruses, pulmonary tuberculosis, rheumatoid arthritis, connective tissue diseases like systemic sclerosis and polymyositis, vasculitis, sarcoidosis, environmental exposure to asbestos, silica dust, and the cotton industry. Furthermore, radiation therapy to the chest wall or lung fields and few drugs like nitrofurantoin, methotrexate, cyclophosphamide, amiodarone, etanercept, and adalimumab can also lead to interstitial lung fibrosis. [8]

The present study is designed to determine the frequency of restrictive pulmonary function tests in patients with different grades of chronic hepatitis C infection based on Child-Pugh criteria in the Pakistani population as there are very few studies on this subject. Early detection of lung fibrosis in these patients will assist to improve the management of lung fibrosis in terms of early initiation of drugs like Pirfenidone as well as LTOT and noninvasive ventilation like BiPAP.

MATERIALS AND METHODS

Objectives

The study was carried out to find out the frequency of restrictive pulmonary function test pattern according

to Child's-Pugh classification.

Settings

This study was carried out at the South Medical ward of Mayo hospital Lahore, affiliated with King Edward medical university from January 2016 to June 2016.

Inclusion Criteria

Patients between 20 to 80 years of age presenting to the medical outpatient department or admitted to the South medical ward, having established chronic liver disease based on viral serology (anti HCV antibody), PCR for HCV RNA, and ultrasonography were included in this study.

Exclusion Criteria

Patients with respiratory pathologies (pulmonary tuberculosis, chronic obstructive airway disease, primary lung tumor or lung metastasis), chronic systemic disorders (sarcoidosis, rheumatoid arthritis) and connective tissue disorder(systemic sclerosis, polymyositis) were excluded.

Method

Informed consent was obtained and patients were recruited from the outpatient and inpatient department. Baseline investigations, abdominal ultrasonography, PT / ATT, serum albumin, viral serology, PCR for HCV RNA were performed on all patients to classify according to the Child-Pugh stage. Pulmonary function tests (PFTs) were performed on all patients and were categorized as a restrictive or obstructive pattern of PFT. The PFTs were performed in pulmonology department of Mayo Hospital Lahore. FEV1/FVC ratio of more than 80 percent was labeled as a restrictive pattern. Interstitial lung fibrosis was diagnosed as per recommendations of the American Thoracic Society.

Child-Pugh grades

A score of less than 7 was grade A, a score between 7-9 was grade B while a score of more than 9 was labeled as grade C based on parameters like bilirubin, PT, serum albumin, ascites grade, and hepatic encephalopathy grade.

Data Analysis

Data was entered in SPSS version 22 descriptive statistics, means, and standard deviations were calculated.

RESULTS

This study included 99 patients from both genders. There were 57 males (57.57%) while 42 were females (42.42%) as shown in Table 1. The mean age was 54.2 ±6.49 years for males while 52.39±5.52 years for females as shown in table 2.

Mean FEV1 was 94.05±28.07 for males and 93.06±27.08 for females. While mean FVC was

106.28±20.22 for males and 103.28±20.24 for females.

Out of 57 male patients, 18 patients showed FEV1/FVC ratio consistent with a restrictive pattern of pulmonary function test, and six male patients showed an obstructive pattern. Among 42 female patients, 15 patients showed restrictive and 2 patients showed an obstructive pattern.

When looked at different stages of chronic liver disease according to Child's Pugh criteria, eight patients were in stage A, ten in stage B while fifteen patients were in stage C. This suggests that as stages of chronic liver disease advances there is a progressive increase in the frequency of restrictive pattern from stage A to C.

DISCUSSION

Hepatitis C virus was discovered in 1989 and has hepatotropic and lymphotropic features that can cause hepatic as well as extrahepatic disease or manifestations. Mixed cryoglobulinemia and non-Hodgkin's lymphoma are the most common extrahepatic conditions that are frequently associated with hepatitis C infection and this virus has several direct effects on the lung as well which include exacerbation of asthma and COPD, interstitial Pneumonitis, and pulmonary fibrosis while indirect effects are cirrhosis and its long term complications like hepato-pulmonary syndrome, Porto-pulmonary hypertension, mixed cryoglobulinemia, Sicca syndrome, non-Hodgkin B-cell lymphomas, autoimmune thyroid disease and polymyositis. [3,4,9,10]

A study conducted in 2008 by Hamid S et al. documented that 49 percent of Pakistani patients with cirrhosis have some evidence of lung fibrosis on the HRCT chest.[2]

Masood M et al. in 2011 showed in their study on Pakistani patients that, as the grade of chronic liver disease advances, the frequency of fibrosis increases on HRCT chest. These study results are similar to that but instead of HRCT chest, pulmonary function tests were performed and this shows that with the advancement of the grade of liver disease, there is a progressive worsening of restrictive PFT suggesting fibrosis.[11] Ohta et al. tested anti HCV antibodies in patients with IPF and found that prevalence was 12.4 %.[12] While Irving et al. conducted a study on the British population and found only two patients positive for HCV antibody out of 62 patients. So they concluded that HCV infection was no more prevalent in British patients with IPF than in the general population.[13] Meliconi et al. tested the same

Gender	No	%age
Male	57	57.57
Female	42	42.42

Table 1: Gender wise distribution of subjects

Gender	Mean age (yrs.)	SD	Min	Max
Male	54.2	6.49	37	71
Female	52.39	5.52	39	69

Table 2: Age wise distribution of subjects

	Parameter	Male	Female
1	FVC L/min	106.28±20.22	103.28±20.24
2	FEV1 L/min	94.05±28.07	93.06±27.08
3	FEV1/FVC ratio%	90.27±7.73	91.06±6.94

Table 3: Restrictive and obstructive PFT and gender

	Parameter	Male	Female
1	FVC L/min	106.28±20.22	103.28±20.24
2	FEV1 L/min	94.05±28.07	93.06±27.08
3	FEV1/FVC ratio%	90.27±7.73	91.06±6.94

Table- 4 Spirometry results hypothesis in Italy. Antibodies to HCV were measured

in 60 patients with IPF, as well as 13 patients without interstitial lung disease, and found no difference in prevalence in both groups.[14] Similarly, Ferry et al. monitored the presence of lung disease in 300 patients with chronic HCV infection and found that 8 patients showed signs of interstitial lung fibrosis by high-resolution CT (HRCT).[15] A recent retrospective cohort study was performed on 6150 Japanese HCV-infected patients and 2050 hepatitis B-virus infected patients (as a control group). The mean observation period was 8.0 years and cumulative rates of IPF development in the HCV group were 0.3% at Year 10 and 0.9% at Year 20. The prevalence of IPF was slightly higher in the HCV group compared with the HBV group.[16] Abbas et al. conducted a similar study in Egypt in 2015. They studied 20 patients recently diagnosed with chronic hepatitis C virus infection and without any previous pulmonary disease. They performed both HRCT chest and pulmonary functions on each patient and found that 11 out of 20 patients showed evidence of lung fibrosis on the HRCT chest (55% and 10 out of these 11 patients had evidence of a restrictive pattern of PFT (91 %) suggesting that PFT can be a reasonable substitute of HRCT in this particular population of patients, This can be cost-effective and radiation exposure to patients can also be avoided.[17] The discrepancy between these results has several explanations. The first is geographical differences in the prevalence of HCV infection, which is high in Japan, Pakistan, and low in northern Europe. Secondly, people who volunteer blood donors are generally not at risk for hepatitis viruses; thus, they do not represent the most appropriate. Furthermore, genotyping was not studied in all of these studies, the HCV genome should be considered concerning this discrepancy. Interferon-based therapy should also be considered concerning the link between pulmonary fibrosis and HCV. IFN has been used successfully to treat chronic HCV infection in past till the discovery of better oral drugs which have more than a 95% success rate. That is why injection interferon is rarely used nowadays because it can cause pulmonary complications. Interstitial pneumonia and sarcoidosis are well-documented complications of IFN therapy.[18,19] The exact mechanism of HCV in the pathogenesis of interstitial Pneumonitis is not understood, but chronic immune activation and inflammation that is induced by HCV infection may be involved. Because HCV induces chronic inflammation and fibrosis in the liver, HCV is believed to have similar functions in the lung and might be mediating the pathogenesis of pulmonary fibrosis. The other possible mechanism is

Clas	No	Restrictive	Obstructive
A	36	8	2
B	33	10	3
C	30	15	3

Table-5: Child class and restrictive PFT

that antigens and antibodies from the bowel or other organs enter portal circulation and are not separated sufficiently in patients with severe liver dysfunction. Immune complexes that are formed by these antigens and antibodies enter the systemic circulation and accumulate in the glomeruli or lung.[18] Conversely, some conditions, such as mixed cryoglobulinemia and sicca syndrome, are seen in HCV infection and can involve the lung with or without clinical symptoms. Some patients may present with dyspnea of exertion, dry cough, interstitial lung fibrosis, pleural effusions, or hemoptysis, which can be a consequence of alveolar hemorrhage.[9,15,20]

Conclusion

Chronic hepatitis C infection can cause impairment in pulmonary functions. We recommend that PFTs should be made a part of medical follow-up of patients with Child-Pugh B and C.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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