
ORIGINAL ARTICLE

Thyroid Dysfunction in Chronic Hepatitis C Patients Treated with Pegylated Interferon Alpha 2a and Ribavirin Combination Therapy and its Predisposing Factors

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ABSTRACT

Background: Pakistan carries one of the world's highest burdens of the chronic hepatitis C and mortality due to liver failure. Chronic hepatitis C is treated with pegylated interferon alpha and ribavirin combination therapy. Changes in the thyroid function are common side effects of this antiviral treatment. Interferon alpha treatment can induce thyroid dysfunction in 2.5% to 20% of the treated patients.

Study Design: Descriptive case series

Methods: This study was conducted in Medical Unit II, Jinnah hospital Lahore from April 2013 to September 2013 and 220 chronic hepatitis C patients were included in this study. They were started on pegylated interferon and ribavirin combination therapy for 6 months. Thyroid stimulating hormone (TSH) levels were measured at the start and after completion of this therapy. Factors leading to thyroid dysfunction including female gender, HCV genotype and smoking were also recorded in these patients.

Results: Out of 220 patients enrolled in this study, 35 patients (15.91%) developed thyroid dysfunction in which 30 patients (13.64%) were hypothyroid while 5 patients (2.27%) were hyperthyroid. Out of these 35 patients, 23 patients (65.71%) were females.

Conclusion: Thyroid dysfunction is a common side effect of interferon and ribavirin combination therapy. Only female gender was found to be a risk factor for the development of thyroid dysfunction.

INTRODUCTION

Hepatitis C virus (HCV) infection is the major cause of chronic liver disease throughout the world. Overall 25% of the patients ultimately develop cirrhosis and a significant proportion of it develop hepatocellular carcinoma (HCC).¹ Pakistan carries one of the world's highest burden of chronic hepatitis C and mortality due to liver failure and hepatocellular carcinoma.² A survey conducted by Pakistan Medical Research Council (PMRC) in 2009 showed that the prevalence of hepatitis C among healthy population of Pakistan was 4.9%. Thyroid dysfunction is one of the commonest endocrine manifestation of chronic hepatitis C infection exacerbated by interferon based treatment.³ The spectrum of thyroid diseases ranges from production of thyroid auto antibodies to dysfunctions such as hypothyroidism, Grave's disease and destructive thyroiditis.⁴

Thyroid changes are seen in 2.5% to 20% of the patients treated with interferon therapy, these side effects can interfere with effective management of HCV.^{5,6} Almost all side effects of interferon alpha treatment are due to its effects on immune system and data suggests that in addition to its immunomodulatory mechanism, interferon alpha also participates thyroiditis by direct thyrotoxicity.⁶ Hepatitis C virus is both a hepatotropic as well as lymphotropic virus and can modulate T cell and B cell antibody response, affecting most commonly the thyroid gland.⁷ However morphological evidence of hepatitis C virus replication in thyroid cells in immune competent patients has not been demonstrated.⁸ There are many risk factors reported which contribute to the thyroid dysfunction in patients with hepatitis C on interferon therapy including thyroid peroxidase antibodies, HCV genotype⁹, female gender and smoking¹⁰. Many

local studies show incidence of thyroid dysfunction in patients on interferon and ribavirin therapy but there is no data available on frequency of contributing factors to thyroid dysfunction.

MATERIAL AND METHODS

Two hundred and twenty patients (220) were selected in which 107 patients (48.63%) were males and 113 patients (51.36%) were females. They were started on pegylated interferon alpha 2a and ribavirin combination therapy. Thyroid function tests were measured at baseline and at the end of treatment.

Sample size

Sample size of 220 cases was calculated with 95% confidence level, 3.5% margin of error and taking expected percentage of hyperthyroidism i.e. 7.5% (least among all factors) of thyroid dysfunction in chronic hepatitis C patients on interferon and ribavirin therapy

Sample Selection

INCLUSION CRITERIA

1. Patients of either gender between 20 years to 60 years of age.
2. All newly diagnosed patients of chronic hepatitis C planned to receive treatment with pegylated interferon and ribavirin combination therapy.
3. Patients having normal thyroid function tests before starting treatment.

EXCLUSION CRITERIA

1. Patients having hemorrhagic ascites, jaundice or history of upper gastrointestinal bleeding.
2. Patients of thyroid dysfunctions as diagnosed by abnormal TSH levels or patients on antithyroid treatment.
3. Patients of diabetes mellitus (known cases or new cases having fasting blood sugar >126mg/dl or random blood sugar > 200mg/dl).

Operational Definitions

Chronic Hepatitis C patients

Patients with quantitative PCR detected for HCV RNA.

Pegylated Interferon and Ribavirin combination therapy

Pegylated interferon alpha 2a in the dose of 180 microgram subcutaneous once weekly for 6 months and ribavirin in the dose of 800 to 1200mg daily for 6 months.

Thyroid Dysfunction

Abnormal TSH i.e. either hyper or hypo. The reference range is 0.3-5.0 mIU/L.

Hypothyroidism= < 0.3 mIU/L

Hyperthyroidism= > 5.0 mIU/L

Factors contributing to thyroid dysfunction

1. Female gender
2. Smoker (smoked > 100 cigarettes up-to presentation)
3. HCV genotype 1 (detected by PCR)

RESULTS

In this study, 220 patients were enrolled in which 107 (48.63%) were male and 113 (51.36%) were female. Their mean age was 35.05 years.

Table 1:

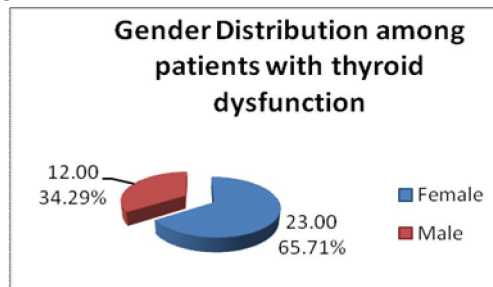
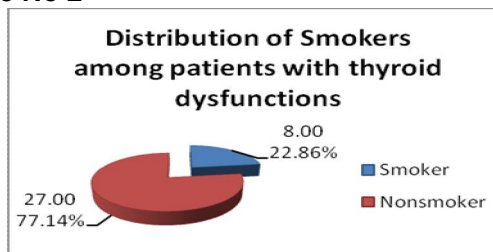


Table No 2

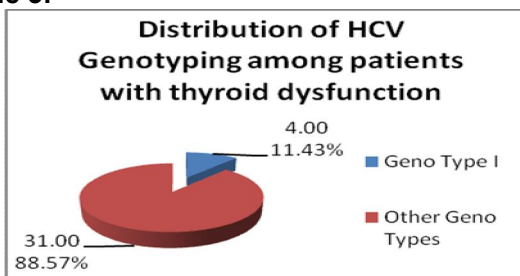


They were followed for thyroid dysfunction after 6 months of treatment with pegylated interferon alpha and ribavirin combination therapy. Out of these 220 patients, 35 patients (15.91%) developed thyroid dysfunction in which 30 patients (13.64%) had hypothyroidism out of which 11 (10.28%) were male and 19 (16.81%) were female. Remaining 5 patients (2.27%) had hyperthyroidism in which 1 (0.93%) was male and 4 (3.54%) were female. Results regarding frequency of predisposing factors are outlined in tables mentioned below.

Out of 220 patients, thyroid dysfunction was present only in 35 patients (15.91%). Among these patients, 23 patients (65.71%) were females and only 12 patients (34.29%) were males.

Out of 35 patients, only 8 patients (22.86%) were smokers and all smokers were males.

Table 3:



Out of 35 patients with thyroid dysfunction, only 4 patients (11.43%) were reported to have HCV genotype 1.

DISCUSSION

The most successful treatment of chronic hepatitis C virus infection is the combination therapy of pegylated interferon and ribavirin but this treatment can lead to many systemic side effects. Occurrence of thyroid dysfunction is one of the most common side effects of this combination therapy. Interferon induced thyroid dysfunction (IITD) may be of autoimmune or non autoimmune type. Autoimmune type IITD includes thyroid autoantibodies, Hashimoto's thyroiditis and Grave's disease.^{11,12} while non autoimmune type IITD includes destructive thyroiditis and non autoimmune hypothyroidism.¹³ Two hundred and twenty patients were enrolled in this study with the mean age of 35.05 years.

Zehui et al¹⁴ conducted a study on 592 patients where mean age was 39.2 years comparable to our mean age group. The development of thyroid dysfunction during interferon and ribavirin combination therapy is reported to be about 4.7% to 27.8% in most of the studies.^{15,16,17} A study conducted by Andrade et al¹⁵ showed the frequency of thyroid dysfunction in 27.69% patients at 24 weeks of treatment with interferon alpha and ribavirin while a local study conducted by Amina et al¹⁶ showed thyroid dysfunction in 18.69% of the patients after antiviral therapy, out of which 8.4% developed hypothyroidism and 7.5% developed hyperthyroidism. The results of our study is equivalent to these international studies as in this study, 35 (15.91%) out of 220 patients developed thyroid dysfunction after 6 months of interferon and ribavirin combination therapy. Hypothyroidism was more common than hyperthyroidism as shown in

most of the previous studies. Out of 35 patients with thyroid dysfunction, 30 patients (13.64%) developed hypothyroidism while only 5 patients (2.27%) developed hyperthyroidism. Among these 35 patients with thyroid dysfunction, 23 (65.71%) were females while 12 (34.29%) were males. Out of 23 females, 19 (16.81%) were reported to have hypothyroidism while 4 (3.54%) had hyperthyroidism. Out of 12 male patients with thyroid dysfunction, 11 (10.28%) developed hypothyroidism while only 1 (0.93%) patient developed hyperthyroidism.

Many risk factors are reported in different studies which can predispose to the development of thyroid dysfunction in patients on interferon and ribavirin combination therapy like female gender, baseline positive thyroid antibodies, HCV genotype 1, smoking, family history of thyroid diseases, body mass index and liver fibrosis.^{6,9,10,15} In this study, we studied 3 contributing factors i.e, female gender, smoking and genotype 1 to see whether these factors have any association with development of thyroid dysfunction in patients on interferon and ribavirin combination therapy.

In current study, only female gender showed an association with thyroid dysfunction with this combination therapy as among the 35 patients who developed thyroid dysfunction, 65.71% were females and 34.29% were males. Kwong et al¹⁸ reported in a study conducted on 461 patients receiving interferon and ribavirin combination therapy that female gender was significantly associated with thyroid dysfunction ($P < 0.001$ odds ratio (OR) = 2.85; 95% confidence interval (CI) = 1.6–5.1). There was no significant association seen between thyroid dysfunction and smoking as out of 35 patients who developed thyroid dysfunction, only 8 patients (22.86%) were smokers. Waleed et al⁹ conducted a study on 54 patients out of which 4 patients (7.4%) developed thyroid dysfunction. Among these 4 patients, 3 patients (75%) had genotype 1. However, there seemed no association between thyroid dysfunction and genotype 1 in present investigation, as only 4 patients (11.43%) out of 35 patients had genotype 1 while 31 (88.57%) had other genotypes.

This study suggests that thyroid dysfunction is a common complication of interferon alpha and ribavirin combination therapy in chronic hepatitis C patients. Therefore, thyroid function tests should be done at baseline i.e, at the start of treatment and should also be monitored during and at end of

therapy to diagnose these patients at an early stage. There are many contributing factors that can increase the risk of development of thyroid dysfunction in patients on interferon and ribavirin combination therapy as shown in previous studies. But in our study, only female gender has found to be a risk factor for the development of thyroid dysfunction in these patients.

CONCLUSION

Thyroid dysfunction is a common side effect of pegylated interferon and ribavirin combination therapy. Monitoring of thyroid function tests during the therapy can help in early detection and treatment of these patients. Females have an increased risk of developing thyroid dysfunction with this combination therapy.

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