FREQUENCY OF THYROID DYSFUNCTION DURING TFT IN INTERFERON AND RIBAVIRIN THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Objective: To determine the frequency of thyroid dysfunction among patients of chronic hepatitis C (HCV) infection receiving combination of interferon-alpha and ribavirin therapy.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Medicine, PNS Shifa Naval Hospital Karachi, from September 2012 to March 2013 over a period of six months.

Patients and Methods: In this study, 170 diagnosed patients of chronic HCV (confirmed by anti-HCV and HCV RNA-positive) presenting to medical OPD with normal thyroid functions were recruited. All patients fulfilled inclusion and exclusion criteria. They were prescribed IFN-alpha 2b (3 million units subcutaneously 3 days a week) and oral preparation of antiviral drug ribavirin (800 to 1200 mg daily in divided doses according to weight). At the end of 12 weeks of combination antiviral therapy, their thyroid profile was worked up. Serum TSH, free T4 and T3 levels were determined by chemiluminescence technique in chemical pathology lab of the hospital. Statistical analysis was done on SPSS 17.

Results: Out of 170 patients, 83 (48.82%) were females and 87 (51.18%) were males with the age ranging from 22–46 years (mean ± SD: 33.86 ± 5.32). After 12 weeks of antiviral therapy, thyroid functions were normal in 156/170 (91.76%) patients, whereas in 14/170 (8.24%) cases thyroid dysfunction was observed. Out of those patients having thyroid dysfunction, 10/14 (71.42%) were hypothyroid whereas 4/14 (28.58%) had hyperthyroidism.

Conclusion: Managing patients of chronic HCV with combination antiviral therapy comprising IFN-alpha 2b and ribavirin can cause thyroid dysfunction. These patients should be monitored before and during treatment to avoid complications and poor compliance.

Keywords: Chronic hepatitis C, Interferon, Ribavirin, Thyroid dysfunction.

INTRODUCTION

Hepatitis C virus (HCV) is currently the chief cause of chronic liver disease, including chronic hepatitis and cirrhosis, and hepatocellular carcinoma worldwide. Almost 170 million people are likely to be infected with HCV around the world with a global prevalence of 3%. Major cause of HCV infection includes transfusion of blood and blood products, sharing needles and injections and other parenteral contamination[1]. On the other hand, frequency of HCV tends to stabilize or have downward trend in recent years. However, HCV remains the most common chronic blood borne infection in the United States[2]. Current therapy for treatment of chronic HCV includes combination of INF and ribavirin for 6 months. The biochemical and virological response with this therapy is achieved in about 40% cases.

Thyroid dysfunction is a recognized side effect of interferon therapy particularly in women[16,17]. Anti-thyroid antibodies were found in 5% to 17% of patients with HCV infection and thyroid disorder, however primarily hypothyroidism occurs in about 2% to 13% of patients and up to 25% have detectable thyroid antibodies[3,4].

However, it is still controversial that whether or not the occurrence is greater than in age and sex-matched controls[5,6]. Patients with chronic hepatitis due to other causes also reported with thyroid antibodies and thyroid disorders but the occurrence appears greater in those with chronic HCV infection[7,8]. Only a few patients (1% to 7 %), who were treated with IFN

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therapy, also developed painless thyroiditis[8,9]. An increase in serum concentration of anti-thyroid antibodies and having normal thyroid functions was also observed with an estimate relative risk of 4.4% and an incidence of 5-12% in HCV patients[10,11].

It was also noticed that genetically susceptible individuals were more prone to develop IFN induced thyroid disease[11,12]. Most of the patients having INF induced hypothyroidism recover after the completion of therapy and treatment can be continued with regular monitoring and follow up. However, treatment must be stopped in patients with marked derangement in thyroid profile and having severe symptoms. All the patients, having chronic HCV, taking antiviral therapy must be explained regarding risk of developing thyroid abnormalities and necessary screening for thyroid antibodies and thyroid profile is suggested before starting, during the course and after the completion of antiviral therapy[13].

PATIENTS AND METHODS

This cross-sectional study was conducted at PNS Shifa Naval Hospital, Karachi from September 2012 to March 2013 over a period of 6 months after seeking approval from hospital ethical committee. Before the commencement of interferon and ribavirin therapy, all patients had persistently raised serum alanine transferase (ALT) by International Federation of Clinical Chemistry (IFCC), positive anti-HCV antibodies by ELISA and positive HCV-RNA by polymerase chain reaction (PCR) with normal thyroid functions (TSH, T3 and T4 were within normal range). Exclusion criteria included decompensated liver disease, previous treatment with interferon or ribavirin, history of pre-existing goiter, thyroid or any other endocrine disorder, any autoimmune disease, severe cardiac or pulmonary disease, history of malignancy or using immunosuppressant and steroids or pregnancy. One hundred and seventy diagnosed patients of non-cirrhotic chronic HCV were selected by consecutive non-probability sampling technique after getting informed consent. All patients were given standard antiviral treatment with conventional interferon alpha 2b (in a dose of 3 million units subcutaneously 3 days in a week) and oral ribavirin (1000–1200 mg) daily in divided doses according to patient's weight and were asked to report back for repeat thyroid profile analysis after 12 weeks.

Venous blood samples were collected for thyroid profile including serum thyroid stimulating hormone (S. TSH), serum free thyroxine (S. Free T4) and serum triiodothyronine (S.T3) using full aseptic measures. Samples were immediately transported to pathology department, PNS Shifa hospital and were kept in closed bottles held in vertical position. Thyroid profile analysis was done by chemiluminescence technique. The tests were carried out under supervision of chemical pathologist and the results were entered in a designated proforma. Patients with serum TSH in the range of 0.72–4.2 uiu/ml, serum free T3 in the range of 2.57 – 4.43 pg/ml and serum free T4 in the range of 0.93–1.7 ng/dl were labelled as euthyroid. Patients with serum TSH levels less than 0.72 uiu/ml, serum FT3 more than 4.43 pg/ml and serum FT4 more than 1.7 ng/dl were labelled as hyperthyroid. Patients with serum TSH levels more than 4.2 uiu/ml, serum FT3 less than 2.57 pg/ml and serum FT4 less than 0.93 ng/dl were diagnosed as hypothyroid.

All data collected was entered in SPSS version 17. It comprised of quantitative variables like age of patient, serum TSH, T3 and T4 levels at baseline and 12 weeks; and qualitative variables i.e. gender and thyroid disorder (outcome).

Descriptive statistics, mean and standard deviation were calculated for quantitative variables (age of patient, serum TSH, T3 and T4 levels at baseline and 12 weeks). Frequencies and percentages were presented for qualitative variables (gender and thyroid dysfunctions associated with interferon alpha and ribavirin therapy). Results were presented with the help of tables. Paired sample t test was applied for basal and 12 weeks post treatment thyroid profile levels (TSH, T3 and T4). Chi-square test was used for gender and thyroid dysfunction association. p value <0.05 was taken as significant.

RESULTS

In our study, a total of 170 patients were selected. Of those, 83 (48.82%) were females and 87 (51.18%) were males. The age among all subjects ranged from 22 – 46 years (mean ± SD= 33.86 ± 5.32). Thyroid profile was assessed at baseline and 12 weeks of anti-viral therapy. Mean and standard deviation for TSH, T3 and free T4 at baseline and after treatment are displayed in (table-1). The results were found in significant (p>0.05).

At 12 weeks of interferon alpha and ribavirin therapy, thyroid function was normal in 156/170 (91.8%) patients, whereas in 14/170 (8.2%) cases thyroid dysfunction was observed. Out of these 14 patients, 10 (71.4%) were hypothyroid whereas 4 (28.6%) were found to have hyperthyroidism.

Out of 10 (71.4%) hypothyroid patients, 3 (30%) were males and 7 (70%) were females. Whereas, out of 4 (28.6%) hyperthyroid patients, 1(25%) was male and 3 (75%) were females. Crosss tabulation of gender and thyroid dysfunction as shown in table-3 showed no difference.(p>0.05)

Table-1: Mean and Standard deviation for serum TSH, T3 and free T4 at baseline and after treatment.

S. No	At baseline			At 12 weeks after treatment			*p* value
	Parameter	Mean	SD	Parameter	Mean	SD	
1	TSH	1.80	0.43	TSH	1.99	1.25	0.047
2	T3	3.19	0.31	T3	3.13	0.528	0.281
3	FT4	1.364	0.12	FT4	1.35	0.250	0.630

Table-2: Cross tabulation of gender and thyroid dysfunction.

Parameter		Thyroid dysfunction		Total	*p*- value
		Yes	No		
Gender	Male	4	79	83	0.11
	Female	10	77	87	
Total		14	156	170	

DISCUSSION

The development of thyroid disease during interferon and ribavirin therapy in patients with hepatitis C virus has been well-established. Significant research has been carried out to study the relationship of thyroid dysfunction and interferon therapy[14]. Interferon related thyroid dysfunction can be mediated by immune and non-immune mechanism[15]. Interferon causes immune modulation and also has direct damaging effects on thyroid gland. HCV infection also causes thyroid dysfunction. Ribavirin adds to thyroid disease, caused by interferon, by modulating T helper 1 (Th 1) and T helper 2 (Th 2) subset balances, by activating type 1 cytokine in HCV specific immune response. In literature, the incidence of abnormal thyroid function ranges from 25% to 34.3% with a mean incidence of 6.6%[16]. In a local study, thyroid dysfunction was observed in 18.69% patients receiving antiviral therapy with interferon and ribavirin[17]. These studies concluded that frequency of hypothyroidism was more than hyperthyroidism (3.8 vs. 2.8%), and females were more affected than males (13.0 vs. 3.0%) [16].

In this study, the incidence of thyroid dysfunction among 170 patients of chronic hepatitis C, undergoing 12 weeks of anti-viral treatment was 8.24%. According to previous studies the incidence was in between 3.9–33.33%[18]. Our results were consistent with most of the studies carried out in the past. Moreover, 5.88% of patients had hypothyroidism and 2.36% of patients had hyperthyroidism. Hypothyroidism was found to be more common in this study as is the case in most of the studies both local and international[19,20].

Important risk factors associated with increased probability of INF induced thyroid dysfunction were female gender and the presence of thyroid auto antibodies before the initiation of therapy[21].

Hence, it is suggested to perform a routine screen for thyroid disease in all chronic hepatitis C patients, before starting antiviral therapy.

Despite the development of thyroid disorders (overt and sub-clinical), patients completed their antiviral therapy with Interferon alpha and ribavirin. Although these findings suggest that antiviral therapy can be continued despite the development of thyroid disorder, however the impact of continuing the antiviral therapy on the quality of life is still to be determined.

CONCLUSION

Standard anti-viral treatment of chronic HCV that is interferon-alpha (IFN-alpha) and ribavirin causes thyroid dysfunction (both hyperthyroidism and hypothyroidism). These patients should be closely monitored with thyroid profile before the start of therapy, during and after completion of the treatment to detect thyroid disorders and complications related to it. This can result in improved patient compliance.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

AUTHORS CONTRIBUTION

Imtiaz Ali, Muhammad Umer Siddiqui, Muhammad Rashid Ahmed and Ghulam Hussain Ibrahim, data collection, analysis and manuscript. Syed Parvez Asghar and Muhammad Zafar Ali, technical advisor and supervision

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