Original Article

Effects of Interferon on Thyroid

Effects of Interferon Alpha on Thyroid Functions during Treatment of Chronic Hepatitis C

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ABSTRACT

Objective: The aim of the study was to assess the incidence, types and risk factors of thyroid dysfunction and thyroid autoimmunity, and to correlate the laboratory parameters with clinical findings.
Study Design: Prospective clinical trial
Place and Duration of Study: This study was conducted at General hospital, Lahore from March, 2011 to December 2011.
Materials and Methods: The study enrolled sixty diagnosed patients of chronic hepatitis C with normal baseline thyroid hormone levels (TSH, FT3, FT4). Anti-thyroid peroxidase antibodies (anti-TPO-Ab) were also assayed. Baseline results were compared with those obtained during and at the end of interferon-alpha (IFN- α) and ribavirin combination therapy.
Results: Incidence of thyroid dysfunction was 10%. Six patients (10%) developed thyroid dysfunction. Subclinical hypothyroidism was more common. Four female patients developed hypothyroidism and 2 patients showed hyperthyroidism. The overall incidence of anti thyroid peroxidase antibodies (anti-TPO-Ab) before treatment was 1.7% which became 5% at the end of therapy.
Conclusion: Female sex and anti-thyroid peroxidase antibodies (anti-TPO-Ab) either present before or during treatment at are at risk of developing thyroid dysfunction, so all the patients of chronic hepatitis C should be screened for thyroid functions and anti-thyroid peroxidase antibodies (anti-TPO-Ab) before treatment with interferon-alpha (IFN- α) & ribavirin combination therapy, and be monitored during and after treatment.
Key Words: Interferon Alpha. Autoimmunity. Anti-thyroid peroxidase antibodies, HCV..

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INTRODUCTION

Chronic hepatitis C is a liver disease caused by hepatitis C virus (HCV). The hepatitis C virus was recognized in 1989 and since then hepatitis C virus (HCV) has been considered as a major public health problem all over the world including Pakistan.[1] Hepatitis C virus produces liver infection in more than 180 million people worldwide[2]. In Pakistan about 10 million people have the hepatitis C virus (HCV) infection, although accurate epidemiological information for chronic hepatitis C virus (HCV) infection is still not available[3]. These patients are more prone to develop hepatocellular carcinoma due to constant infection[4]. At least 250,000 deaths per year are due to hepatitis C[5]. Factors known to increase the progress to cirrhosis include, old age at HCV acquirement, male sex, heavy alcohol intake, and co-infection with either Hepatitis B or HIV[6]. Treatment for chronic hepatitis C has become better over the last decade and it is generally recommended in patients under the age of 70 years[7]. The purpose of the treatment is to achieve an undetectable HCV-RNA six months after treatment[8]. Interferon alpha (IFN) in combination with Ribavirin has been used in the treatment and become standard treatment for Chronic Hepatitis C since French consensus conference in 2002[9]. Interferons (IFNs) were discovered and named by Isaacs and Lindenmann in 1957 who observed that virus-infected culture formed a protein that reacted with cells, making them resistant to infection by other viruses[10]. Interferon-alpha regular or pegylated in combination with ribavirin is used and this results in sustained virological response in about 80% of cases with genotype 2 and 3 CHC infection and 40-50% in genotype 1 infection.[11,12]

Adverse effects of IFN treatment include flu-like symptoms, fever, malaise, muscle aches, neuropsychiatric symptoms and endocrinal dysfunction[13, 14]. The most important endocrine gland affected is thyroid gland[13, 14]. Hypothyroidism or hyperthyroidism may occur in up to 5-20% of patients especially in those with anti-thyroid antibodies present before treatment with interferon alpha and ribavirin[15]. Interferon alpha treatment may activate the production of different types of auto-antibodies such as antinuclear

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antibodies (ANA), thyroid peroxidase antibodies (TPO) and anti thyroglobulin (TGA) antibodies[16].

Thyroid dysfunction is the most common autoimmune disorder related with Interferon alpha treatment and the occurrence of thyroid dysfunction due to interferon alpha was recognized in 1985 in patients who underwent interferon alpha treatment for carcinoid tumors and breast cancer[17]. The important factors that play role in the development of thyroid disease during Interferon alpha therapy are female gender and presence of thyroid auto-antibodies particularly anti-thyroid peroxidase antibodies(TPO-Ab) prior to treatment[18].

The common form of thyroid autoimmunity is the presence of thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab). The newer immunoassays have improved sensitivity to detect thyroid peroxidase antibodies (TPO-Ab) than the older assays[19].

MATERIALS AND METHODS

60 patients of either sex were enrolled for the study. Written consent, for participation in the study, was taken from each patient.

Inclusion criteria: Diagnosed patients of Chronic Hepatitis C (CHC) with normal thyroid functions.

Exclusion criteria: Abnormal thyroid function tests before the treatment and the co-existence of other disease that need chronic drug therapy. Serum levels of TSH, FT4, FT3 and TPO-Ab were assayed using enzyme immunoassay test kits, catalog no, BC-100I, 1008,1006 Biocheck inc, 323 Vintage park. All patients were assessed clinically too. Patients were treated with interferon alpha and ribavirin by their physician. The duration of treatment was 24 weeks and all patients were tested for thyroid hormones and thyroid peroxidase auto-antibodies (TPO-Ab) at week 0, 12 and 24 of treatment with Interferon alpha and ribavirin.

Data Analysis: The data was analyzed using SPSS 16.0 (Statistical Package for Social Sciences). Mean ± S.D is given. Frequencies and percentages are given for qualitative variables. Graphs are presented for both quantitative and qualitative variables. Paired sample t-test is applied to observe pair wise differences for normally distributed quantitative variables. A p-value of <0.05 was considered as statistically significant [20].

RESULTS

Among 60 patients participated in the prospective clinical study, 26 were males with mean age 41.77±8.53 and 34 females with mean age 42.71±8.36 years. The overall mean age was 42.30±8.37 years (Table.1).

Table No.1: Distribution of cases by age and gender

	Male		Female		Total	
Age (Years)	N	%	N	%	N	%
31 – 40	15	57.7	20	58.8	35	58.3
41 – 50	8	30.8	9	26.5	17	28.3
51 – 60	3	11.5	5	14.7	8	13.3
Total	26	100.0	34	100.0	60	100.0
Mean	41.77±8.53		42.71±8.36		42.30±8.37	

After treatment with interferon alpha and ribavirin for 24 weeks, fifty four (90%) were having normal thyroid functions. Six patients (10%) developed thyroid dysfunction biochemically, four patients(6.6%) developed hypothyroidism, all were females with age ranging from 35-58 years. two patients(3.4%) developed hyperthyroidism. When the test of normality was performed by using Shapiro-Wilk test the results were deviating from the normality with p-value< 0.001. Among thyroid function tests the value for FT3 was raised by 2.013± with p-value 0.999. The value for FT4 was declined by 0.13± 0.36 pg/ml with p-value 0.006 which was insignificant statistically. Thyroid auto-antibodies (TPO-Ab) were present in 1.5% of patients before the start of treatment and in 5% after the treatment with p-value. 0.662 , which was insignificant statistically.(table 2)

Table No.2: Thyroid function tests of the patients showing thyroid dysfunction

Age (years)	Gender	TSH		FT3		FT4		TPO-Ab	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
50	Female	2.4	6.8	1.151	1.139	0.94	0.41	10.6	85.47
52	Female	2.69	8.35	1.45	0.83	0.96	0.22	0.79	15.70
58	Female	2.84	10.41	1.4	0.89	0.83	0.29	5.58	125.62
57	Female	2.65	8.32	2.60	1.124	0.87	0.295	8.30	15.40
54	Female	0.42	0.99	1.43	4.36	1.87	3.37	80.59	92.50
45	Male	0.85	0.32	2.78	4.61	1.15	3.92	17.58	23.22

All the patients enrolled for study were examined clinically before starting treatment and after the completion of treatment with interferon alpha and ribavirin. Ten patients(16.7%) were having cold sensitivity with p-value<0.001.Tremors, heat intolerance and mental slowness was observed in 2, 1 and 2 patients respectively with p-value>0.005.

DISCUSSION

Treatment of Chronic Hepatitis C with Interferon alpha and ribavirin may lead to many adverse effects. Abnormal function of thyroid gland is a known side effect or complication during IFN alpha and ribavirin combination therapy. Thyroid dysfunction is more common in females, and hypothyroidism occurs more frequently, and resolves after the end of therapy. IFN interacts with specific receptors present on the cell surfaces and leads to activation of various signaling pathways via very complex sequence of interactions and activation of gene transcription.

In present study the baseline thyroid functions i.e. serum TSH, FT3 and FT4 were normal in all sixty patients participating in study. Baseline (week 0) results were compared with those obtained at weeks 12 and 24 of therapy. Biochemical thyroid dysfunction (TD) developed in 6 patients (10%) out of 60 patients. Hypothyroidism was common as compared to hyperthyroidism. The incidence of hypothyroidism was 6.6% and 4.3% of the patients in the study developed hyperthyroidism. Also all hypothyroid patients were females i.e. four patients (6.6%). Two patients developed hyperthyroidism, one male (3.3) and one female (3.3%). In most of the patients, these disorders occurred during the early course of treatment as has been reported in various studies. Interferon alpha induces a rush of immune reactions in the body.

This is related to immuno-modulatory properties of Interferon (IFN) which induces non-organ specific antibodies causing thyroid dysfunction. Recent reports suggest that Interferon alpha has direct toxic effects on thyroid gland, along with immuno-modulatory mechanisms. The level of thyroid peroxidase antibodies rose from 1.7% at baseline to-5.00% at the end of treatment,i.e.24 weeks, also these antibodies were detected in those female patients who had a higher mean age group which, is characteristic of autoimmune thyroiditis. These results suggest that female patients with Chronic Hepatitis C receiving Interferon alpha therapy are more prone to develop thyroid abnormalities. All the above findings support the view that Interferon alpha therapy in patients with Chronic Hepatitis C accentuates and makes clinically manifest pre-existing autoimmune thyroid abnormalities. We cannot exclude genetic factors to play an important role in the risk for thyroid dysfunction (TD).

In the present study the enrolled patients were assessed clinically too. It was found that all patients were free from any symptom regarding thyroid gland before starting the treatment. At the end of therapy it was found that no patient undergoing IFN alpha therapy showed overt thyroid dysfunction; only subclinical hypothyroidism and hyperthyroidism was observed.

Lastly, thyroid dysfunction caused by interferon alpha and ribavirin combination therapy is a common finding in these patients. Interferon can lead to the appearance of different manifestations of thyroid disease, ranging from subclinical hypothyroidism to overt hypothyroidism or hyperthyroidism. Female gender and the presence of anti-thyroid antibodies are important predisposing factors that may cause thyroid dysfunction . Permanent hypothyroidism is more common and this may necessitate hormone replacement therapy. Thyroid function tests should be checked before the start of treatment and periodically during the treatment and at least once in the six months following IFN alpha treatment.

CONCLUSION

Treatment with Interferon alpha in the patients of Chronic Hepatitis C is associated with thyroid dysfunction and thyroid autoimmunity. The mechanism of interferon induced thyroid dysfunction (IITD) is not very clear but it may be due to the direct toxic effect of interferon alpha on thyroid gland or may be immune mediated. long-term follow-up of patients with thyroid dysfunction due to interferon alpha thyroid is necessary to determine its relation to sustained virological response (SVR).

Conflict of Interest: The study has no conflict of interest to declare by any author.

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