THYROID DYSFUNCTION INDUCED BY RECOMBINANT INTERFERON-ALPHA THERAPY FOR CHRONIC ACTIVE TYPE C HEPATITIS

Nayyar Chaudhry, Samina Ghayur, *,Abdus Sattar*,Rizwan Hashim,* Aamer Ijaz**, Farooq Ahmad Khan*

Abstract

Objective: The aim of this study was to assess the frequency and types of thyroid dysfunction that develops during IFN-α therapy in patients of Chronic Hepatitis C.
Study Design: Case control study
Place and Duration of Study: Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi.
Methods: The study was carried out on a total of 50 patients of chronic hepatitis C on recombinant IFN-α therapy. In addition 50 patients with chronic hepatitis C, not on any antiviral treatment, were included as controls. After informed consent, clinical history was obtained, physical examination was done and findings recorded on a pre-designed proforma. Blood sampling was done for thyroid profile at the beginning of interferon therapy, at 12 weeks and finally at 24 weeks.
Results: Thyroid dysfunction (TD) was observed in 14% (n=7) of the patients on antiviral therapy for CHC (n=50).Amongst these seven patients with TD, hypothyroidism was observed in 5 and hyperthyroidism in 2 patients. In contrast the frequency of thyroid dysfunction observed in control group (n=50) was 2%.
Conclusion: The frequency of thyroid dysfunction in patients of chronic hepatitis C treated with interferon approaches 14%, with hypothyroidism being the more commonly observed pattern.

Keywords : Hepatitis C, Interferon therapy, Thyroid dysfunction.

Article

INTRODUCTION

Viral hepatitis remains a very common and formidable health problem all over the world affecting approximately 2% of the world population1. Treatment of hepatitis C has evolved over the last 15 years. Till today, it remains based on interferon as an immune modulator2.
Interferons are a family of naturally occurring small protein molecules that are produced and secreted by cells in response to viral infections or to various synthetic and biologic inducers1. Autoimmune thyroid disease is one of the reported adverse effects of interferon-α therapy in patients with chronic hepatitis C. Through its immunomodulatory properties, IFN-α seems to act through major histocompatibility complex class 1 antigens to produce antithyroid antibodies and thyroid disease; a direct inhibitory effect on thyrocytes may be presumed in subjects who develop hypothyroidism without autoimmunity2,3. The overall prevalence of thyroid dysfunction in such patients is reported to be 3% to 15% in various international studies. Destructive thyroiditis associated with transient early thyrotoxicosis followed by hypothyroidism has also been seen. Risk factors for developing thyroid disorder are presence of pre-existing autoimmune thyroditis (such as positive antimicrosome or anti thyroperoxidase (TPO) antibodies before treatment) and female gender; the latter directly associated with increasing age4,5. Combination therapy employing interferon and ribvarin is not generally believed to increase the risk of dysthyroidism compared to monotherapy with interferon6. Similarly pegylated interferon is not believed to be a risk factor compared to standard interferon7. Though IFN-α induced thyroid disorders can usually be controlled with medication these disorders are not always reversible. Data regarding the long term outcome of this complication to date however is scarce8.

Due to the paucity of available data regarding the development of TD in IFN-α treated chronic hepatitis C (CHC) patients in our population and since we have a higher prevalence of genotype III of hepatitis C virus in our population, there is a need to carry out further studies to assess the pattern of thyroid dysfunction that develops in our chronic hepatitis C patients, while they are receiving interferon therapy.

MATERIALS AND METHODS

This case control study was conducted in the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi. It comprised 50 patients of chronic hepatitis C on recombinant IFN-α therapy along with 50 patients of chronic hepatitis C, not on any antiviral treatment, included as controls, employing non-probability convenience sampling.

Patients reporting to AFIP reception for PCR of HCV RNA and who were being worked up for interferon therapy for chronic hepatitis C were included in the study whereas patients found to have thyroid dysfunction at the beginning of interferon treatment, those who were unable to complete antiviral treatment for the duration of six months due to any reason, and those who did not report back for repeat sampling at specified time periods were excluded. All the participants were explained about the test procedure and the requirements/significance of repeated sampling during the period of interferon treatment. Written consent was obtained from every patient at this stage. The patients were thoroughly examined. The presence or absence of clinical manifestations of thyroid dysfunction was noted. All the findings were noted in the patients' Proforma. Along with that, the findings of hormonal investigations including serum TSH & T4 were also endorsed for the patients for whom they were already available. Estimation of serum TSH levels was done at the start of antiviral treatment to rule out pre-existing thyroid dysfunction. The patients were instructed to report back at 12 and 24 wks of interferon therapy for repeat sampling, the laboratory request forms with specified dates of the next visit were handed over to each patient.

The patients were seated comfortably for about 15 minutes before sampling for thyroid profile. Five ml of blood was collected in plain tube. Thyroid profile analysis included serum TSH, Free T4 and Total T3.

The tubes were properly labeled and the specimens were transported to the processing room within half an hour of collection and allowed to clot at room temperature. Serum was separated by centrifugation at a relative centrifugal force of 2000-3000 g for 15 minutes. During the 24 weeks treatment serum TSH was used as the first line test to screen patients with thyroid dysfunction. Patients found to have symptoms of thyroid dysfunction or abnormal TSH levels were evaluated further by free T4 and total T3 estimation, as indicated.

Hormonal analysis (SerumTSH, Free T4, and Total T3) was done for the patients and the controls, enrolled for the study. It was carried out in batches, utilizing Chemiluminescence Immunoassay technique, a type of indicator labeled immunoassay, on Immulite 2000, an automated, random access, immunoassay analyzer.

The data was stored and compiled for statistical analysis using Statistical Package for Social Sciences SPSS version 11.0. Mean and Standard deviation (SD) were calculated for numerical data including age, and thyroid profile (Serum TSH). Frequency and percentage were calculated for qualitative data including thyroid status and the types of thyroid dysfunction.

RESULTS

A total of 64 patients of Chronic Hepatitis C on recombinant interferon-α therapy (Group A) were registered initially. However, twelve patients did not report back during the follow up visits, additionally two were found to have deranged thyroid profile at the outset, and therefore were excluded from the study. Likewise out of the initial 58 patients without interferon treatment, who served as controls (Group B, n=50), eight were dropped as they failed to report at the specified time periods. In group A (n=50), the mean age of the patients was 36 ± 16 years (mean ± SD). Regarding gender distribution, group A comprised of 40(80%) male patients and 10 (20%) female patients (Fig 1).

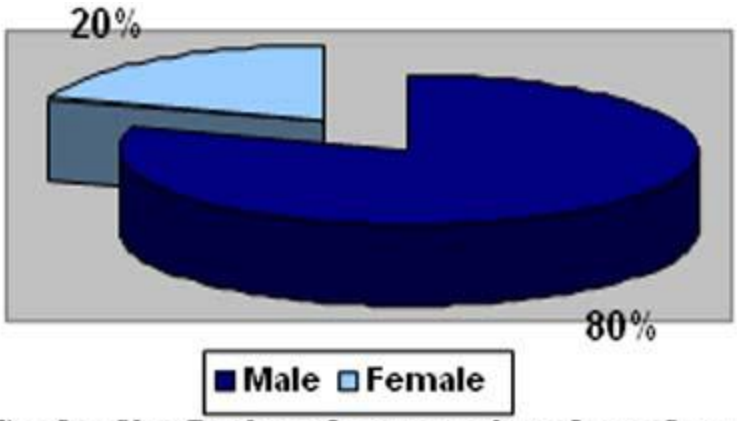

Fig 1: Gender distribution of group on interferon therapy (n=50)

Control group (n=50) consisted of 39 (78%) male and 11 (22%) female patients, with mean age of the patients being 30 ± 10 years (mean ± SD), a pattern of distribution almost similar to that of the patient group.

Biochemical thyroid dysfunction (TSH < 0.4 or > 4.0 miU/L) was observed in 7 (14%) of the 50 patients (Fig 2).

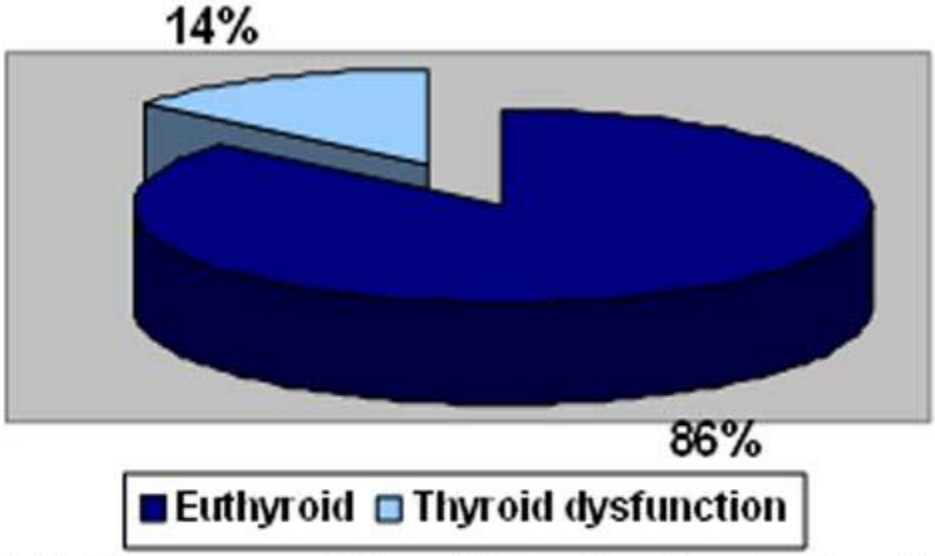

Fig 2: Frequency of thyroid dysfunction in chronic hepatitis C patients on interferon therapy (n=50).

Amongst these seven patients, 3 were males, and 4 were females. Hypothyroidism was seen in 5 and hyperthyroidism in 2 patients (Table).

Table: Thyroid dysfunction development in chronic hepatitis C patients on Interferon treatment (n=7).

Category	Hypothyroid	Hyperthyroid
Type of thyroid dysfunction	5	2
Pattern of thyroid dysfunction Overt Subclinical	1 4	1 1

Moreover 2 out of these 7 patients developed symptomatic thyroid disease, one female patient with characteristic features of hypothyroidism (weight gain, cold intolerance and somnolence) and another male patient with typical symptoms of hyperthyroidism (fine tremors, palpitations, heat intolerance). Such peculiar features were not observed in the rest of the patients. Although vague symptoms like lethargy and fatigue were observed, yet they were only transient, typically occurring only after the dose of IFN.

Regarding the time to onset of thyroid dysfunction, 3 patients were found to have deranged thyroid functions 3 months after initiation of IFN therapy. The other 4 patients were detected at the last sample (24 wks).

Comparison of CHC patients in the two groups at 24 weeks revealed development of thyroid dysfunction in only 1 patient (2%) in control group relative to the patient group (14%) (Fig. 3),

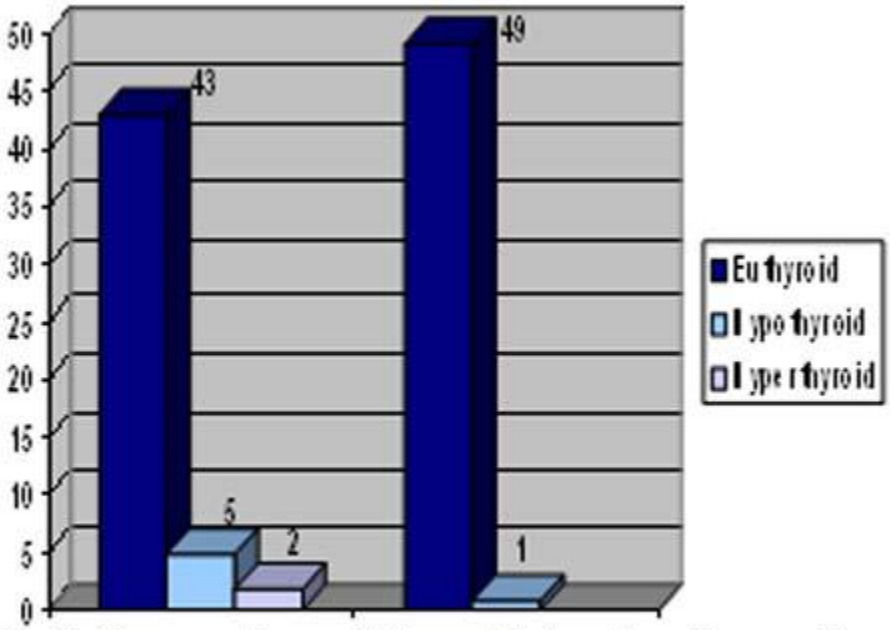

Fig 3: Comparison of thyroid dysfunction pattern in patient group (n=50) and control group (n=50).

indicating a statistically significant difference in the observed values (p=<0.027) (Fig 4).

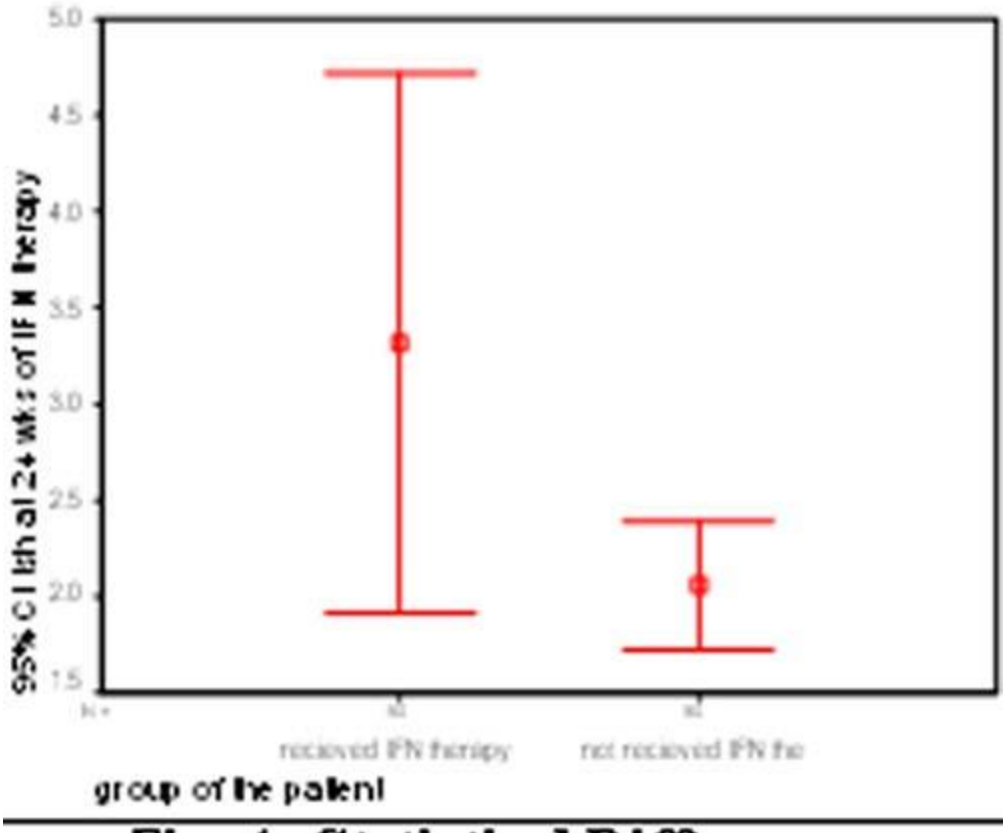

Fig. 4: Statistical Difference.

DISCUSSION

The development of thyroid dysfunction in patients on IFN-α therapy for chronic hepatitis C has been highlighted by a number of international studies, although the pattern and type of the findings have been found to be variable. A few local studies have also targeted certain features of hepatitis C treatment, but local data on the pattern/frequency of thyroid dysfunction in these patients is scarce. In different studies carried out worldwide, the incidence of thyroid dysfunction developed during interferon-α therapy, has been 6-15% approximately9. Frequency of TD observed in IFN-α treated CHC patients in our study was 14%. This variability can be explained on the basis of ethnic origin, age and gender ratio in the studied populations and the duration of interferon-α therapy. In one study carried out on 225 patients, overt thyroid dysfunction appeared in 6.7% of the patients10. In another study 5.2% patients were found to have developed clinical/ subclinical thyroid disorder, whereas de-novo appearance of TPO antibodies was observed in 6% of subjects9. Antonelli and colleagues, in a study on 630 consecutive patients with chronic hepatitis C, found that these patients are more likely to have hypothyroidism (13%; n=82)10. Dalgard and co-workers have shown biochemical thyroid dysfunction to develop in 11.8% of 254 patients in their study11.

Hypothyroidism, in our study, was clearly the more common pattern (72%) of TD in patients on combination antiviral therapy. The incidence of hypothyroidism in general population is around 2-5%12. It has been suggested by various studies worldwide that the virus itself may also play a causal role in the development of hypothyroidism in IFN treated patients as the prevalence is higher than in the general population13. To further add to the complexity of the situation, hypothyroidism is even more frequently observed in patients having combination therapy of IFN-α and ribavirin (RBV) (as opposed to IFN-α treated alone). Whilst HCV itself, also, is well known to induce a higher prevalence of auto-antibody, this may not necessarily translate into hypothyroidism (either clinical or subclinical)14. To overcome this problem we studied the pattern of thyroid dysfunction in HCV patients who did not receive recombinant interferon treatment (Group B), in parallel with patients of

HCV on antiviral treatment (Group A), for direct comparison.
Hypothyroidism affected only 2% (n=1) patient in the control group, confirming the findings that IFN-α and ribavirin (RBV) therapy may be causative factors for the occurrence of TD in the study group. The pathogenesis remains poorly understood but IFN-α is thought to have a direct inhibitory effect on thyrocytes preventing hormonogenesis and secretion. Another postulate is immunomodulation of the immune system caused by recombinant interferon- α in the presence of hepatitis C infection, which leads to the development of thyroid auto-antibodies with complete destruction and consequently permanent hypothyroidism in genetically susceptible individuals15.
Although recombinant IFN-α treated hepatitis B patients also may develop hypothyroidism, its prevalence is much lower than that of the patients with chronic hepatitis C. This suggests that the hepatitis C virus or its genome itself also plays an essential part in the development of thyroid dysfunction. The virus has been postulated to induce thyroid auto-antibodies by generating high endogenous IFN levels triggering off autoimmune thyroid disease in susceptible individuals, similar to Coxsackievirus. This virus and others have been shown to induce a higher level of endogenous IFN-α level which have also been associated with other auto-immune diseases such as type 1 diabetes. When IFN-α is administered exogenously, this effect is accentuated. It is indeed possible but purely speculative that exogenous IFN-α synergizes with the endogenous source, exaggerating the effect on the thyroid thus causing additional hypothyroidism16.
Presence of anti-TPO antibodies prior to interferon therapy and preexisting autoimmune disorders have also been implicated by various other studies to be another risk factor for development of hypothyroidism19. These assays should be proposed before initiating antiviral treatment in patients with chronic hepatitis C, however the autoantiboby profile of the patient groups was not a part of our study therefore it is not possible to comment on the contributory part played by anti TPO antibodies in the causation of thyroid dysfunction or otherwise.
In our study, the number of patients who developed hyperthyroidism (n=2) in group A, is too small to arrive at any definitive conclusion. Goitre was absent in both the cases and thyrotoxicosis resembling Graves disease was not observed. Hyperthyroidism in these patients was mild and resolved spontaneously with IFN dose reduction. This was presumed to be IFN-α/autoimmune mediated. Radioactive iodine uptake scans are required in such cases for definitive diagnosis. However these tests were beyond the scope of our study and, therefore, were not performed. Symptomatic treatment using beta-blockers is generally indicated. Interruption of the antiviral treatment should be discussed systematically, balancing the risks and benefits for each individual patient18.

CONCLUSION

The study signifies that patients with Chronic Hepatitis C have a definite tendency to develop thyroid dysfunction while on recombinant IFN-α therapy. The pattern of most commonly observed is hypothyroidism. Comprehensive longitudinal studies are required if the long term outcome of the recombinant IFN-α treatment in chronic hepatitis C patients is to be fully appreciated.

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