ORIGINAL ARTICLE

Frequency of Thyroid Dysfunction Following Interferon Therapy in Patients with Chronic Hepatitis C

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ABSTRACT

Objective: The objective of this study was to assess the frequency of thyroid dysfunction following interferon therapy in patients with chronic hepatitis C.
Study design: Prospective Study
Place and duration: This study was conducted at Medical OPD, Chandka Medical College Hospital Larkana from September 2008 to January 2010.
Material and methods: Fifty cases of chronic hepatitis C ,proven by anti-HCV and HCV RNA positive with baseline TSH, T3 ,T4 within the normal reference range ,who were treated with interferon alfa 3 millions units S/C three times in week and oral ribavirin were included in this study . All patients were assessed for TSH, T3, T4 at 2, 4, 6 months during therapy.
Results: Out of 50 patients, thyroid dysfunction developed in 5 (10%) patients. Out of 5 patients 4 (80%) had hypothyroidism and 1 (10%) patient hyperthyroidism. Males are more affected. HCV RNA became negative in 45 patients, while in 5 patients remained positive. Mean age of presentation is 36.9±10.9.
Conclusion: Screening of T3, T4, TSH is recommended before and during treatment and patients should be informed of the risk of thyroid dysfunction .Treatment of HCV can be continued safely because thyroid dysfunction responds well to treatment.
Key words: Interferon, Chronic Hepatitis c, Thyroid Hormone, Hyperthyroidism, Hypothyroidism.

INTRODUCTION

Hepatitis c virus infection is a worldwide problem and its natural, unfavorable course is still a challenge for the hepatologist. The standard of treatment is combined therapy with interferon-alpha and ribavirin. Treatment of hepatitis c infection often results in many endocrinological disturbances of which thyroid dysfunction is most prevalent[1]. Interferons are a family of naturally occurring, small protein molecules with molecular weight of 15,000-20,000 Da[2]. They are included in three groups, IFN –alfa, IFN-beta, IFN-gamma with different biological effects and variable duration of activity. Ribavirin is a synthetic Guanoside nucleoside analogue that exerts immunomodulatory effects by inducing cytokines in the against HCV infection[3] and is frequently given with IFN in the treatment of chronic hepatitis C patients.

A high prevalence of thyroid gland dysfunction has been reported in hepatitis C virus (HCV) infected patients before and after interferon –Alfa therapy and some data also show a high prevalence of anti-HCV antibody in patients with autoimmune thyroiditis[4]. The development of thyroid disease does not seem to be related to the dose of IFN. In contrast, duration of IFN treatment has been related to the occurrence of thyroid dysfunction. Interferon is currently used widely due to its beneficial effects in patients with chronic hepatitis C , even though multiple reactions can occur[5]. *Schultz et al* first reported interferon –induced thyroid dysfunction in hepatitis patients[6], and *Mayet et al* reported interferon –induced ant-thyroid autoantibody production or elevation of the titer of such antibodies[7]. *Fentiman* firstly reported the occurrence of hypothyroidism after interferon –alfa therapy in 1985[8]. Several studies not only expressed the prevalence of thyroid dysfunction but also assessed anti-thyroid antibodies production in these patients. They showed the elevation of thyroid peroxidase antibody and thyroglobulin antibody levels in patients during interferon –alfa therapy compared with the normal population. It is also estimated that HCV infection itself, especially the one with mixed HCV genotypes and low viral load, is a predisposing factor for autoimmune thyroid dysfunction. Thyroid auto antibodies are present in 20-42% chronic hepatitis c patients sera compared to 5-10% chronic hepatitis B individuals[9,10,11]. Due to the widespread use of interferon in the treatment of these patients, recognition of adverse effects of this drug is

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important. The aim of this study was to determine the rate of thyroid dysfunction in chronic hepatitis C patients, during interferon –alfa therapy.

MATERIAL AND METHODS:

It's a prospective study conducted at Medical OPD tertiary care, Chandka Medical College Hospital Larkana, from September 2008 to January 2010.

Consecutive cases of chronic hepatitis C proven by anti-HCV and HCV RNA PCR positive, normal U/S abdomen, clinically no evidence of thyroid diseases were included in study. Exclusion Criteria were Co-infected with the hepatitis B virus or HIV, Known thyroid disease or decompensated cirrhosis, Immuno suppressive medications, Neoplastic, autoimmune diseases, severe cardiac, pulmonary, or other co-morbid diseases, severe depression or other psychiatric disorders.

All patients signed an inform consent form. Confirmatory tests for anti-HCV positive patients and HCV RNA by PCR. Before the start of the treatment in HCV patients, other Lab: studies including Blood CP & ESR, Serum Proteins, LFTS, RBS, U/S abdomen, were performed. Patients were treated with interferon –alfa , 3 millions units three times in week , and oral ribavirin , 1000 mg /day (wt: <75kg) or 1200 mg /day (wt: >75 kg) ,patients were treated for 24 weeks. Before the patients entered the research, Histroy, Thyroid physical examination was done. These patients were Re-evaluated clinically 2, 4, 6 months interval during treatment. At each visit, the presence and severity of adverse events assessed and routine laboratory testing was performed. Patients underwent screening for thyroid disease when clinically suspicious of thyroid disorder. T3, T4, TSH levels were measured. These were measured by using immunoradiometric (IRMA) and Radio immunometric (RIA) assay method for TSH and T3, T4. Respectively by using kit immunotech of Beckman coulter company. Normal values; TSH: 0.4-7.1 uiu/ml, T3: 2.5-5.8 pmol/l, T4: 11.5-23 pmol/l. The data was analyzed by using SPSS version 12.0. The p-value level of significance was at <0.05.

RESULTS

Fifty (50) diagnostic patients of chronic hepatitis C. out of 50 patients 42(84%) were Males while 8(16%) were Females. During the study period, thyroid gland dysfunction occurred in five patients, so thyroid dysfunction occurred in 10% of chronic hepatitis C patients, who are on treatment of interferon and ribavirin. Although thyroid function of all patients was normal before the starting of interferon –Alfa therapy. The duration to the development of disease, hyper and hypothyroid phases are all quite variable. Out of 5 patients, three (60%) patients showed thyroid dysfunction within two months after the treatment was initiated and two (40%) patients developed thyroid dysfunction four months after the therapy. Out of 5 patients four (80%) patients were males while one (20%) patient is female, so males are more affected than females. Four (80%) patients became hypothyroid while one (20%) patient turnout hyperthyroidism (Table 1), while table 2 shows changes of thyroid hormones before and after interferon therapy.

Table 1:

Gender/ Age(years)	Dysfunctional occurrence. Time(months)	Thyroid gland dysfunction
27 years male	2 months	Hypothyroidism
56 years female	5 months	Hypothyroidism
58 years male	2 months	Hypothyroidism
43 years male	2 months	Hyperthyroidism
20 years male	4 months	Hypothyroidism

Table 2

Patient no : 1	T4 (pmol/l)	T3 (pmol/l)	TSH (uiu/ml)
Before therapy	15	4	1
2 months after therapy	4.1	1.0	38
Patient no: 2			
Before therapy	13	4.2	0.9
5 months after therapy	4	1.1	44
Patient no :3			
Before therapy	12.5	3.5	1
2 months after therapy	3.2	0.9	39
Patients no: 4			
Before therapy	13.5	4.5	0.6
2 months after therapy	35	13	0.09
Patients no: 5			
Before therapy	16	5	0.9
4 months after therapy	3.0	1	38

Mean age of presentation of HCV patients were 36.9±10.9.

HCV RNA by PCR was negative at the end of treatment in 45 (90%) patients, while in 5 (10%) Patients HCV RNA by PCR were positive.

DISCUSSION

Interferon –Alfa, in addition to its antiviral and anti-proliferate activities, acts as an immunomodulatory agent, including autoantibody production and development of autoimmune disease in susceptible patients[12,13]. Interferon –Alfa directly inhibits production, release and metabolism of thyroid hormones. Not only immunomodulation properties of interferon –Alfa have crucial roles in pathogensis, but also genetic predisposition factors are important[14]. Following the initial reporting of hypothyroidism after

interferon –Alfa therapy by *Fentiman and Coworkers in 1985*, many other patients with this complication were reported[4,8,15]. In previous reports, the prevalence of thyroid gland dysfunction varied markedly ranging from 3.4% to 31.4%[10,11.] Another study showed prevalence of thyroid dysfunction was 18.69%. In our study prevalence was 10%.Dalgard and his team found thyroid dysfunction in 11.8%[16], whereas Kee *et al*, found thyroid dysfunction in 12.6% of patients[17]. In our study hypothyroidism is more than hyperthyroidism, it cross ponds to previous study [(18)]. Differences in geographical distribution, genetic variability in the populations studied and even environmental factors such as iodine intake or virus infection could play a major role in the development of thyroid dysfunction after intake of interferon –Alfa therapy. In previous studies, the prevalence of thyroid dysfunction following interferon –Alfa therapy was reported to be 10%. Therefore, it is in accordance with other studies from other countries[4,19]. In our study patients age was lower than other similar studies[14]. Regarding sex, in other studies, it was found that female sex was a risk factor for developing thyroid dysfunction in HCV patients[20]. Our study was in contrast to this finding. But it cross ponds to a study in which males are more than females[21]. On the other hands, our results were similar to a study by *Lisker Melman et al*[22]. Patients who developed overt hypothyroidism during therapy were treated with levothyroxin and hyperthyroidism with propylthyuracil and propranolol, although these findings suggest that antiviral therapy can be continued despite the development of thyroid disorder. In some studies, it was suggested that screening tests before the interferon –Alfa therapy were not necessary and further studies should be performed if clinically indicated[9,11]. Fatigue, depression, decreased appetite, and myalgias were common in patients with overt hypothyroidism, whereas nervousness, rritability, fatigue insomnia and weight loss were common in patients with hyperthyroidism. Although these symptoms are common in chronic hepatitis C patients, they could easily mistaken for adverse effects of HCV therapy, and thyroid dysfunction could have remained undiagnosed, if the patients did not undergo routine screening of TSH level. Therefore, it is recommended that screening for thyroid disease be routinely performed in all patients with HCV infection, who are treated with interferon therapy.

CONCLUSION

According to our results in HCV patients after treatment of interferon- alpha therapy, Hypothyroid is more common. Males are more affected than females. We recommend the assessment of thyroid function tests assay before the treatment and their re-evaluation in 2 or 3 months intervals. Screening for T3, T4, and TSH is recommended before, during interferon-alpha treatment, and patients should be informed of the risk of thyroid dysfunction. Short-termed and rapid onset treatment should be considered to reduce the burden of psychological and physical symptoms contributed by thyroid diseases to patients undergoing interferon treatment. Ninety patients had intact thyroid function at the end of treatment .Treatment of HCV can be safely continued in these patients because thyroid dysfunction responds well to treatment.

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