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ORIGINAL ARTICLE

Thyroid Dysfunction in Patients with Chronic Viral Hepatitis B and C during Alpha Interferon Therapy

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Background and Aims: **Thyroid dysfunction has been reported in patients with chronic viral hepatitis B and C before and after alpha interferon (IFN-α) therapy and a high prevalence of anti hepatitis C virus (anti-HCV) antibodies in patients with autoimmune thyroiditis has been shown. The aim of this study was to determine the rate of thyroid dysfunction in hepatitis B virus (HBV) and HCV infected patients during IFN-α therapy and to compare them.**

Methods: **In this prospective study, many patients with hepatitis B and C who had undergone IFN-α therapy were studied. Eighteen cases of HBV and fifty-eight cases of HCV entered the study. Thyroid weight measurement, thyroid functional test and anti-thyroid antibodies assay were performed when the study initiated and were repeated after two, four and six months.**

Results: **Thyroid dysfunction was not seen in the HBV group. Only 6 (10.3%) cases of thyroid dysfunction were seen in HCV group (5 hypothyroidism and 1 thyroiditis). Four cases of them had positive levels of thyroid peroxidase antibody (Tpo Ab) before IFN-α therapy. In the HBV group, only 1 (5.5%) patient had positive levels of Tpo Ab. However, at the end of the study, 3 (16.7%) patients had positive levels of Tpo Ab. In the HCV group, at the beginning of the treatment, 8 (13.8%) patients had Tpo Ab; but at the end of study, 14 (24.1%) cases became positive. During the IFN-α therapy, mean weight of thyroid gland in both HCV and HBV groups were significantly increased ($P<0.005$ and $P<0.001$ respectively). There were not any relationships between thyroglobulin (Tg) Ab levels and duration of IFN-α therapy.**

Conclusions: **Patients with HCV are more susceptible to thyroid dysfunction during IFN-α therapy than patients with HBV. As a result, screening of thyroid gland function and Tpo Ab titers in all patients with HCV before and during IFN-α therapy may be necessary. However, this needs further studies in HBV patients.**

Keywords: **Interferon Alfa, Thyroid, Hepatitis B, Hepatitis C**

Introduction

A high prevalence of thyroid gland dysfunction has been reported in hepatitis C virus (HCV) infected patients before and after interferon-alfa (IFN-α) therapy and some data also show a high prevalence of anti HCV antibody in patients with autoimmune thyroiditis [(1)]. But this prevalence is very low in patients infected with hepatitis B virus (HBV) [(2)]. IFN-α has important effects on the cell mediated immunity such as activation of macrophages, regulation natural killer cells and cytotoxic T cells activity. Furthermore, it has a relationship with cytokine production and major histocompatibility complex (MHC) system. Anti viral effects of IFN-α was discovered in 1957 [(1)]. The interferons are classified based on structural and biochemical characters into four groups: α, β, δ, and γ. Despite a broad range of immunological effects, the role of IFN-α in the pathogenesis of autoimmune thyroid diseases remains uncertain [(1)]. Fentiman firstly reported the

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occurrence of hypothyroidism after IFN-α therapy in 1985 [3]. This fact was followed by multiple studies and prevalence of thyroid gland dysfunction was reported to be about 11% in 1991 [1].

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 (Tpo Ab) and thyroglobulin (Tg) Ab levels in patients during IFN-α therapy compared with the normal population [2, 4, 5]. In Iran, viral hepatitis is an important and common disease. The prevalence of HBV and HCV based on antibodies assay are about 2-3% and 0.3%, respectively [6].

Due to the widespread use of IFN-α in the treatment of these patients, recognition of adverse effects of this drug is important. The aim of this prospective study was to determine the rate of thyroid dysfunction in HBV and HCV patients, during IFN-α therapy in Tehran Hepatitis Center and to compare them. As we know this study is done for the first time in Iran.

Materials and Methods

This interventional study was performed on 76 patients with hepatitis (58 HCV and 18 HBV) in Tehran Hepatitis Center, between March 2002 and May 2003. Our sampling methods were according to a study by Imigawa *et al.* [5].

All patients signed an inform consent form. The Ethical Committee of Tehran University of Medical Sciences approved the study protocol.

Confirmatory tests for anti HCV (enzyme-linked immunosorbant assay ELISA) positive patients were recombinant immunoblot assay (RIBA) and HCV RNA (polymerase chain reaction PCR). If HCV RNA was positive, qualitative PCR for the determination of HCV genotype was performed. If genotypes 1b or 1a were found, liver biopsy was recommended. However, if genotype 3a was found, IFN-α therapy without liver biopsy was started. Also in the HBV group, following tests were performed: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), hepatitis B surface antibody (HBsAb), hepatitis B e antibody (HBeAb) and hepatitis B core antibody (HBcAb). Further studies included qualitative and viral loading PCR for the detection of HBV DNA. In these patients, indications of liver biopsy were as follows: positive HBeAg and elevation of liver function test. Before the start of the treatment in both HCV and HBV patients, other studies including liver sonography, platelet count and serum protein electrophoresis were performed. Treatment started only in non cirrhotic patients with sufficient status. All serologic tests were performed in Tehran Blood Transfusion Organization.

An endocrinologist visited the patients and reviewed history and thyroid functional test and performed thyroid physical examination. If the previous studies were unremarkable, the patient entered the research. These patients were re evaluated in 2, 4, 6 month intervals. In all patients we measured serum levels of T_3 and T_4 using RIA with a normal range of 80-160 ng/dl and 5-12 µg/dl, respectively.

Thyroid stimulating hormone (TSH) measurements were made via immunoradiometric assay (IRMA) with a normal range of 0.3-3 mIu. Tpo Ab and Tg Ab were assayed via ELISA (DRG-test, Germany). Tpo Ab positive titers were considered those higher than 50 mIu and in Tg Ab higher than 100 mIu. Thyroid weight was assessed by physical examination. Statistical analyses were performed using SPSS, ver 11.0. Variables were compared by means of statistical repeated measure and ANOVA. For statistical analysis, we used Friedman test which is a non-parametric statistical test in order to detect differences in treatments across multiple test attempts.

Results

Seventy six patients, 15 (19.7%) women and 61 (80.31%) men, were included in this study (eighteen patients (23.6%) with HBV (6 women and 12 men; mean age± SD: 27.7±4.7 yr) and fifty eight patients (76.4%) with HCV (9 women and 49 men; mean age± SD: 37.9± 10.97 yr)). During the study, thyroid gland dysfunction occurred in six HCV patients (Table 1). As Table 1 shows, thyroid dysfunction occurred in 10.3 % of HCV patients.

Although thyroid function of all patients were normal before the IFN-α therapy, three patients showed thyroid dysfunction two months after the treatment was initiated and three cases developed thyroid dysfunction four months after the therapy.

Table 1. Characters of six HCV patients with occurrence of thyroid gland dysfunction during the IFN therapy.

Patient	Age	Sex	Dysfunctional occurrence Time (months)	Thyroid gland dysfunction
1	28	Male	2	Hypo
2	34	Male	4	Hypo
3	57	Female	4	Hypo
4	59	Male	2	Hypo
5	44	Male	2	Hyper
6	19	Male	4	Hypo

Five of these 6 patients became hypothyroid and the remaining case developed thyroiditis-associated thyrotoxicosis which was confirmed by radioactive iodine absorption. In the HBV group, thyroid dysfunction was not seen. Thyroid tests results in six patients with thyroid dysfunction are shown in Table 2. Before treatment, positive levels of Tpo Ab were found in 8 (13.8%) patients with HCV which increased to 14 (24.1%) cases after 6 months.

Table 2. Thyroid test results in six HCV patients with occurrence of thyroid gland dysfunction during IFN therapy.

	T4 (µg /dl)	T3 (ng/dl)	TSH (mIu)	T3Ru (%)	Tpo-Abs (mIu)	Tg-Abs (mIu)
Patient 1. before therapy	9	140	1	27	(+) 120	(+) 230
2 months after therapy	4.5	64	37	21	(+) 120	(+) 230
Patient 2. before therapy	8.5	128	0.9	28	(+) 150	(+) 200
4months after therapy	3.5	80	45	17	(+) 200	(+) 300
Patient 3. before therapy	10.1	147	0.7	30	(+) 100	(+) 150
4months after therapy	4.3	87	40	21	(+) 200	(+) 200
Patient 4. before therapy	9.6	139	31	26	(+) 140	-
2 months after therapy	3.2	90	36	20	(+) 540	-
Patient5. before therapy	10.9	160	0.3	30	(-) <50	(-) <100
2 months after therapy	13.3	253	0.1	37	(-) <50	(-) <100
Patient6. before therapy	8.5	100	0.7	28	(-) <50	(-) <100
4months after therapy	4.5	86	30	22	(+) 150	(+) 150

According to the results, before IFN-α therapy, positive levels of Tpo Ab were found in four HCV patients but increased to five cases after therapy (Table 2). Before and after the treatment, positive levels of Tg Ab were found in 5 (8.6%) and 8 (13.8%) cases, respectively. In patients with HBV, no relationship was found between Tpo and Tg Ab levels and duration of IFN-α therapy.

Post-treatment TSH levels in patients with HCV increased significantly compared to pre-treatment values (P<0.02) while it decreased in HBV patients; however, this decrease was not significant (Table 3). Nonetheless, TSH levels in euthyroid HCV patients did not change significantly at the end of the treatment. Mean thyroid gland weight in HBV and HCV patients significantly increased after treatment compared to before treatment (P<0.001 and P<0.005, respectively) (Table 3). Mean age of HCV and HBV patients are shown in Table 3.

Table 3. TSH levels and mean of thyroid gland weight in HCV and HBV patients before and after treatment.

Patients	Mean age (yr)	TSH (mIu)		Thyroid gland weight (g)	
		Before	After	Before	After
HCV	37.9±10.9	0.81±0.7	0.9±0.3a	20.6±2.3	20.8±2.1b
HBV	27.7±4.7	1.7±0.6	1±0.4	19.3±2.1	20.36±2.4c

a: P<0.02, b: P<0.005, c: P<P<0.001

Discussion

IFNs have been shown to modulate immune responses by increasing natural killer cell activity, enhancing cytotoxic lymphocyte maturation and increasing HLA class I expression in infected cells [7]. Also, IFNs modulate the suppressor activity of T lymphocytes [4]. However, the role of IFN-α in the pathogenesis of autoimmune thyroid diseases remains uncertain [8]. IFN-α directly inhibits production, release and metabolism of thyroid hormones. Not only immunomodulation properties of IFN-α have crucial roles in pathogenesis, but also genetic predisposition factors are important [9]. Following the initial reporting of hypothyroidism after IFN-α therapy by Fentiman and coworkers in 1985, many other patients with this complication were reported [1, 3, 5, 6, 10]. In previous reports, the prevalence of thyroid gland dysfunction varied markedly ranging from 3.4% to 31.4% [4, 5]. 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 IFN-α therapy [9]. In previous studies, the prevalence of thyroid dysfunction following IFN-α therapy was reported to be 8-12% and in our study was reported to be 10.4%. Therefore, it is in accordance with other studies from other countries [1, 11].

There was a significant difference between our study and other studies in HBV patients' age which could be related to the vertical transmission route in Iran. However HCV patients' age in our study was lower than other similar studies [6].

In other studies, it was found that female sex was a risk factor for developing thyroid dysfunction in HCV patients [12]. Our study was in contrast to this finding. On the other hands, our results were similar to a study by Lisker-Melman *et al.* [8]. In the present study, after the start of IFN-α therapy, Tpo Ab

increased from 13.8% to 24.1%. Our overall results are in agrreement with other studies [3, 4, 10, 12].

The effect of Tg Ab in the development of thyroid dysfunction is lower than Tpo Ab and also in the present study, after the start of IFN-α therapy, Tg Ab increased from 8.6% to 13.8% which showed no significant relationship and are in agreement with other similar studies [2, 4, 5, 10]. In our study, thyroid dysfunction was present in 6 (10.2 %) patients with HCV and hypothyroidism and thyroiditis were found in five and one cases, respectively. Thyroid dysfunction induced by IFN-α therapy was not present in any of the 18 patients with HBV. Before treatment, positive levels of Tpo Ab and Tg Ab were found in 1 (5.5%) and 1 (5.5%). During the therapy, positive levels of Tpo Ab and Tg Ab were found in 3 (16.7%) and 2 (11%) cases of HBV patients respectively. However, their relationship was not significant.

Fernandez *et al.* found positive levels of Tpo Ab and Tg Ab in 5 % and 3 % of patients with HBV and revealed a 3 % thyroid dysfunction during the therapy (sample size: 41 patients) [2]. In a study by Deutsch *et al.* 7 (4 %) of the 170 patients with HBV revealed thyroid gland dysfunction [13]. In another study by Preziati *et al.* on 51 patients with HBV who underwent IFN-α therapy, initially positive levels of Tpo Ab and Tg Ab were found in zero and 5 (9.8 %) patients, respectively [4].

After the start of the treatment, only 27 cases were followed up. Positive levels of Tpo Ab and Tg Ab were found in 11.1 % and 14.8 % of patients, respectively. In this study, hypothyroidism was not found while hyperthyroidism was found in one patient [4]. According to previous studies, patients with HCV are more susceptible to thyroid dysfunction than those with HBV after treated with IFN-α.

In some studies, it was suggested that screening tests before the IFN-α therapy were not necessary and further studies should be performed if clinically indicated [2, 5]. There was a significant difference between the prevalence of HBV and HCV thyroid dysfunction. In the present study, thyroid gland dysfunction was not found in any of the HBV patients compared with other studies. However, it seems that this discrepancy was solved through an increased sample size in privious studies. Our study exclusively revealed a relationship between thyroid gland weight and duration of IFN-α therapy. As we observed, there was a significant raise of thyroid weight in the course of time. This change is most probably due to the irregularity of thyroid hormone synthesis or release pathway. However, in long-term follow up of the patients, thyroid goiter may be found. Physical examination is less sensitive compared to thyroid weight suggested by ultrasound.

According to our results in HCV patients, we recommend the assessment of thyroid function tests and Tpo Ab assay before the treatment and their re-evaluation in 2 to 3 month intervals. Further research will determine the management of HBV patients.

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