Thyroid Dysfunction Related to Interferon in Turkish Patients with Viral Hepatitis: Incidence and Influencing Factors

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ABSTRACT

Objective: Interferon therapy is widely used for patients with chronic viral hepatitis B and C (CHB-C). It is known that thyroid gland dysfunction (TD) may develop secondary to interferon treatment, but different frequencies of TD development are reported in the literature. For this reason, we aimed to investigate the incidence of TD developing secondary to interferon treatment in patients with CHB-C treated in our clinic and possible influence factors.

Methods: A total of 93 CHB-C patients treated with interferon were included in this study. Tests of thyroid functions (TSH, FT3, FT4), thyroid auto-antibodies (Anti-Tg, Anti-TPO) were done before starting interferon treatment, during and after treatment. Patients who did not have normal thyroid gland functions were not included in this study.

Results: TD was observed to develop in a total of 20 patients (21.5%). TD had developed in the first 6 months after initiation of interferon therapy. In 18.3% of these patients the condition was temporary, while 3.2% patients required treatment for TD. The most frequently seen condition are subclinical types. Age (over 40 years) (OR: 7.25 95% CI = 1.46–35.80, P = 0.015) and gender (female) (OR: 5.83 95% CI = 1.31-25.76, P = 0.020) were found to be statistically significant independent risk factors in TD development.

Conclusion: Although TD secondary to interferon treatment in patients with CHB-C may develop in a substantial rate, most of these are temporary and do not require TD treatment. Independent risk factors in TD development were found to be gender and age.

Keywords: Chronic viral hepatitis, interferon, thyroid gland dysfunction

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INTRODUCTION

Chronic viral hepatitis consist a group of diseases widely seen all over the world and which may result in hepatic failure, cirrhosis, or hepatocellular carcinoma, while chronic viral hepatitis B and C (CHB-C) are the most frequently seen types.

Although there are newly developed anti-viral agents with direct effects in CHB-C treatment, interferon (α-2a,-2b) and antiviral nucleoside analogues (ribavirin) are routinely accepted as standard therapeutic agents.

Among these standard agents, some unwanted effects such as hematologic changes (anemia, neutropenia, thrombocytopenia), flu-like symptoms, fever, depression and endocrinologic disorders may be seen due to interferon (1-3). The most frequently seen and known effect on the endocrinologic system, apart from the liver, is dysfunction of the thyroid gland. In many studies on this dysfunction, different results were reported on the incidence of TD between 3% - 35% (4-7).

Although the thyroid gland dysfunction is believed to be mediated by auto–antibodies, the exact mechanism is not known. In some studies, TD was shown to develop more frequently in patients with chronic hepatitis C (CHC) in comparison with patients with chronic hepatitis B (CHB), which suggested that causes of viral origin may be effective in the development of TD (8).

In various researches; gender, presence of thyroid auto–antibodies and ethnic factors were shown to be associated with TD developing due to IFN (7-11).

CHB-C is a frequently encountered health problem in our country and similar to global procedures, interferon is widely used in its treatment. When the literature is examined, the number of studies showing the incidence of TD developing due to IFN use in patients with CHC in Turkey is scarce and data evaluating CHB-C patients together is missing. For this

reason, we aimed to investigate the incidence of TD developing secondary to interferon use in patients with CHB-C and associated risk factors.

METHODS

Patients

File records of patients diagnosed as having CHB-C and were treated and followed-up between 2010-2015 years in private SANKO hospital were examined retrospectively. The main inclusion criteria of this study were age over 18 years, being treated with IFN due to CHB-C for at least 4 weeks, absence of known thyroid disease before IFN treatment, and thyroid gland functions in the normal range. The patients with HIV infection, presence of other hepatic disorders (Wilson's disease, alcoholic – autoimmune liver disease), and those with abnormal thyroid gland function tests before treatment were excluded from study.

The diagnosis of CHB-C was based on clinical, laboratory, USG and histopathological findings. Hepatitis B and C markers (HBsAg, HBeAg, anti-HBcIgM, anti-HBcIgG, anti-HBe, anti-HBs, anti-HCV) were measured from patient peripheral blood samples by microparticle ELISA method (Abbott-Architec i2000sr, USA), measurement of levels of HBV-DNA, HCV-RNA and HCV genotyping were done with Real-Time PCR device.

The patients who were included in the study were classified in two groups according to viral types as follows;

Group 1

A total of 46 patients with a diagnosis of chronic hepatitis B (CHB) were designated as group 1. Twenty two were females and 24 males, with an age range of 20-61 years (mean 37.4±10.3 years). In patients with CHB; Pegillated interferon alpha 2b were administered via the

subcutaneous route (<40 kg: 50 mcg/week, 40-64 kg: 80 mcg/week, 65-75 kg 100 mcg/week, 76-85 120 mcg/week, >80 kg 150 mcg/week) in a period of 48 weeks.

Group 2

A total of 47 patients with a diagnosis of chronic hepatitis C (CHC) were designated as group 2. Sixteen of these patents were females and 31 males, with an age range of 18-71 years (mean 52.6±12.5 years). 44 patients (93.6%) was of the genotype1b, while the other 3 patients had genotypes 2, 3 and 4 subtypes.

In patients with CHC; pegillated interferon alpha 2b was administered via the subcutaneous route (<40 kg: 50 mcg/week, 40-64 kg: 80 mcg/week, 65-75 kg 100 mcg/week, 76-85 120 mcg/week, >80 kg 150 mcg/week) and Ribavirin was given via the oral route (<64 kg 800 mg/day, 65-85 kg 1000 mg/day, >85 kg 1200 mg/day) as a combination therapy. This combination treatment was given for 48 weeks for genotypes 1 and 4, while it was given for 24 weeks for genotypes 2 and 3.

Evaluation of Thyroid Functions

Medical history query, physical examination and tests of thyroid functions [free triiodothyronin (FT3), free thyroxin (FT4), thyroid stimulating hormone (TSH)] and thyroid auto - antibodies [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG)] were done for all patients before IFN treatment.

FT3, FT4, TSH measurements were done by ultra–sensitive immune chemoluminescence non-competitive assay (ICMA) (Immnulite 2500 DPC, USA).

The reference range was; 0,55-4,78 mIU/ml for TSH, 0.8 - 2.0 ng/dL for FT3, 0,89-1,76 ng/dl for FT4, <35 Iu/ml for anti - TPO, and <40 Iu/ml for anti - TG.

During treatment with IFN, histories of the patients were evaluated every 3 months, with physical examination and TSH measurements. Those with an abnormal TSH level were

considered as patients in whom TD had developed and levels of FT3, FT4, anti-TPO, anti-TG were measured. These patients were followed–up at more frequent (every 6 weeks) intervals. Patients in whom TD had developed were classified according to tests of thyroid functions as follows: overt hypothyroidism (TSH level over normal and FT3-FT4 levels under normal limits), subclinical hypothyroidism (TSH level over normal limits and FT3-FT4 in normal limits), subclinical hyperthyroidism (TSH level below normal limits and FT3-FT4 levels in the normal range) and overt hyperthyroidism (TSH level below the normal limits and FT3-FT4 level over the normal limits).

While treatment of patients in whom overt hypothyroidism or overt hyperthyroidism have developed was started immediately, appropriate treatment for patients in whom subclinical hypothyroidism or subclinical hyperthyroidism had developed, appropriate treatment was decided according to symptoms, physical examination findings and differences in laboratory measurements.

Statistical analysis

Analysis of the data was done with PASW® Statistics 18 software (SPSS Inc., Chicago, IL, USA). In the evaluation of data, mean, standard deviation, median, minimal and maximal values were used as descriptive statistical methods. Shapiro-Wilk test was used for determination of normal. Inter – group comparisons for qualitative data was done with chi – square test, and student test was used for continuous variables. Logistic regression analysis was done in order to define independent factors associated with TD development. $p < 0.05$ was considered as statistically significant.

RESULTS

A total of 93 patients with CHB-C (47 CHC, 46 CHB) were included in this study, who met the inclusion criteria. Thirty eight of them were females (F), 55 were males (M), aged between 18-71 years (mean; 44.8±13.7 years).

Of these 93 patients, TD development was observed in 20 (15F, 5M) (21.5%). Eleven of them (7 F, 4 M) had CHB, and 9 (8 F, 1 M) had CHC, with an age range of 30-71 years (mean; 49.7±11.5 years). While the frequency of TD occurrence did not show statistically significant differences in terms of type of chronic viral hepatitis (p= 0.57), it was significantly higher in group 2 and in whole of the group in female gender (group 1; p=0.2, group 2; p= 0.0001, whole study group; p= 0.0004).

The mean age of patients with CHB in group 1 was 37.4±10.3 years, and the mean age of patients with CHC in group 2 was 52.6±12.5 years and this difference between the groups is statistically significant ($p<0.00001$). In patients in whom TD had developed, statistically significant differences were not found in terms of age in their groups and in the whole study group (p=0.06, p=0.09, p=0.07).

TD was detected in the 3rd month after initiation of therapy in 10 patients, in the 6th month in 4 patients, and in the 12th month in 6 patients. In other words, TD had developed in the first 6 months after initiation of interferon therapy in 14 patients (70%). Nine of them had CHB, and 5 had CHC, with no statistically significant differences between the two groups (p= 0.2).

At the time of first diagnosis, the type of TD was overt hyperthyroidism in 1 patient, subclinical hyperthyroidism in 9 patients, subclinical hypothyroidism in 7 patients, and overt hypothyroidism in 3 patients. Among the 14 patients who were diagnosed to have TD in the first 6 months, 7 had subclinical hyperthyroidism, 5 had subclinical hypothyroidism, 1 had overt hyperthyroidism and 1 had overt hypothyroidism.

Patients in whom TD had developed were followed-up for 24 months after IFN therapy was completed. At the end of 24th month, 17 patients (13 F, 4 M) in whom TFTs had returned to normal were considered to have temporary type, and 3 patients (2 F, 1 M) in whom TFTs had not returned to normal were considered to have permanent type TD.

Among 17 patients with temporary type TD (after IFN therapy was completed) TFTs returned to normal in the 6th month in 9 patients, in the 12th month in 6 patients, and in the 18th month in 2 patients. Medication use was needed in only 3 patients (2 with overt hypothyroidism, 1 with overt hyperthyroidism) during the follow-up period.

In the 3 patients with permanent type TD (2 F, 1 M), one had overt hypothyroidism (F, CHB), and the other two had subclinical hyperthyroidism (M, CHB; F, CHC).

Before IFN therapy thyroid auto–antibodies (anti–TPO and / or anti–TG) were high in 9 of 93 patients (7 with CHC, 2 with CHB), while thyroid auto–antibodies (anti–TPO and / or anti–TG) were high initially in 5 of 20 patients in whom TD had developed (3 CHC, 2 CHB) and this was statistically significant (p=0.008).

Genotyping of patients with CHC was done and 44 (93.6%) were found to have genotype 1b while 3 patients had different genotype (genotypes 2, 3 and 4). All of the patients in whom TD had developed were in the 1b genotype.

In the 3-year follow-up of patients with CHB in terms of hepatitis treatment; a complete response was observed in 26 patients (56.5%), 13 patients had a recurrence and 7 patients were unresponsive to treatment while among 11 patients in whom TD had developed, a complete response was observed in 5 patients (45%), recurrence in 5 patients and 1 patient was unresponsive to treatment. There were no statistically significant differences between patients in whom TD had or had not developed in terms of response to hepatitis treatment (p= 0.33).

In the 3-year follow-up of patients with CHC in terms of hepatitis treatment; a complete response was observed in 29 patients (61%), recurrence was observed in 10 patients and 8 patients were observed to be unresponsive to treatment, while among 9 patients in whom TD had developed, 5 (55%) showed a complete response, 3 showed recurrence and 1 patient was unresponsive to treatment. There were no statistically significant differences between patients in whom TD had or had not developed, in terms of response to hepatitis treatment (p= 0.58).

Some of the data showing the findings that were mentioned are presented in Table 1.

All the study group (CHB-C) and both groups (CHB and CHC) were separately examined with multiple regression analysis in terms of the association of independent factors such as gender, age (below 40 years and above 40 years), thyroid auto–antibodies (present or absent), viral type, and response to hepatitis treatment with development of TD. Among these, age and gender were statistically significant variables and age (over 40 years) (OR: 7.25 95% CI = 1.46–35.80, P = 0.015) and female gender (OR: 5.83 95% CI = 1.31-25.76, P = 0.020) were found to be independent risk factors in TD development.

Evaluation of risk factors which could be associated with thyroid dysfunction with multiple regression analysis are presented in Table 2.

DISCUSSION

When the literature is reviewed (4-7), incidence of TD developing secondary to IFN therapy in patients with chronic viral hepatitis is observed to be in a broad range such as 3-35%. These different results may be related with many factors such as genetic predispositions of patients included in studies, regional – ethnic differences, different TD definitions, treatment regimes, viral types and genotypes. The incidence of TD in patients with CHB-C treated with

PEG-IFN was 21.5% (23.9% for CHB and 19.5% for CHC) in the present study. Although this result is higher than that reported by a meta–analysis (13) (approximately 6%), it may be considered similar to the incidence (16.8%) found in the study by Barut S. et al (12) in Turkey.

Although TD is believed to develop via auto–antibodies during IFN therapy, the exact mechanism is still unknown. In some studies, it was shown that TD more frequently developed in patients with CHC in comparison to patients with CHB, which has suggested that causes of viral origin may be effective in TD development (8). There are also studies which had suggested that CHC infection may be responsible for thyroid auto-immunity independently from IFN therapy (14, 15). On the other hand, TD was observed to develop more frequently, albeit insignificantly, in patients with CHB in our study (23.9% for CHB and 19.5% for CHC). This result may have originated from the absence of homogeneity between two patient groups, in terms of independent risk factors such as gender and age which are effective in TD development (this is partly due to comparison of patients with CHB and CHC not being a primary aim of our study).

When patients in whom TD have developed are evaluated, TD is observed to develop in the first 3 months after initiation of interferon therapy, while this rate is 70% in the 6th month. Although most of these are patients with CHB (9 with CHB and 5 with CHC), a significant difference was not found between these two groups. We found the rate of TD development in patients with CHC on the 6th month as 55%. While this is a lower rate than that found by Yan Z. et al. (7) in patients with CHC (88.2%), it is seen that most of TD development during IFN therapy in our study both in the whole group and in patients with CHC starts in the first 6th month.

At first diagnosis, 45% of the patients had subclinical hyperthyroidism, and 35% had subclinical hypothyroidism, in terms of type of TD. In other words, 80% of patients had a

subclinical form of TD. When subclinical and overt types of TD were counted under one heading as hypothyroidism and hyperthyroidism, they included equal numbers of patients. While hypothyroidism was the most frequently encountered form in many of the studies (7, 16, 17), hyperthyroidism was most frequently reported in the study by Hsieh MC. et al (18).

Patients in whom TD had developed were followed-up for 24 months after IFN treatment was completed. At the end of 24th month, TFTs had returned to normal in 17 patients (85%), while 3 patients (15%) still had TD. Of these 17 patients (after IFN therapy was completed) TFTs had returned to normal in 9 at the 6th month, in 6 patients at the 12th month, and in 2 patients at the 18th month. Use of medications was required in only 3 patients (2 with overt hypothyroidism and 1 with overt hyperthyroidism) during the follow-up. In patients in who TD persisted at the end of 24 hours, 1 had overt hypothyroidism and the other 2 had subclinical hyperthyroidism, and their appropriate treatment and controls were continuing.

If we summarize these results, it may be told that TD is mostly in subclinical forms and improved in time without requiring treatment. These findings are similar to former studies (7, 19).

As we have mentioned before, gender and age are among factors that are effective in TD development. Especially in terms of gender, presence of a more reactive immune system in females in comparison to males may explain more frequent occurrence of TD associated with IFN, but while many studies support this (7,10,11,18) some studies did not find a significant association (12,20,21). Age (over 40 years) and female gender were found to be statistically independent risk factors in TD development in our study.

When former studies are examined, results showing that factors such as CHC genotype, thyroid auto-antibodies, and response to IFN therapy may be effective in TD development are observed to be reported (12, 16-22).

Genotype evaluation of patients with CHC in our study were done, 93.6% of all patients and all of the patients in whom TD had developed were found to have genotype 1b. Genotype 1b is the most prevalent genotype in patients with CHC in our country, and our study group is in accordance with this. Pavan MH. et al. (23) have reported that TD development was more frequent in CHC genotype 1. As most of our study group had genotype 1b, a statistical analysis could not be done between genotype and TD development.

The prevalence of thyroid auto-antibodies was reported to be between 20%-30% in patients with CHC, and the presence of anti-TPO or anti-TG anti-bodies was reported to be associated with TD developing due to IFN (11, 24, 25). Thyroid auto-antibodies measured before IFN therapy was 9.6% in the whole group (14.9% in patients with CHC), and this ratio was 25% in patients in whom TD had developed. This difference was statistically significant, but the presence of thyroid auto–antibodies was not found to be significant as an independent risk factor in multiple regression analysis. When studies where the thyroid auto–antibody prevalence was reported between 20-30% in patients with CHC are considered, 14.9% that was found in our study may be accepted as similar.

When the association of TD development with IFN therapy is evaluated separately in patients with CHB and CHC, statistically significant differences were not found in both groups (For CHB; p= 0.33, For CHC; p= 0.58). When evaluated with multiple logistic regression analysis, response status to IFN therapy was not found as a significant risk factor for TD development. While there are studies with similar results (12,26), in the study by Tran HA. et al (27), a significant association was found between TD development and response to IFN therapy.

The main limitations of our study were its being a retrospective and uni-center study, relatively low numbers of patients in CHB and CHC groups, and lack of investigation of some factors (viral load, degree of hepatic fibrosis, body mass index, tests of liver function) that

could have been effective in TD development. In spite of these limitations, we believe that our results provide important information on the incidence of TD developing during IFN therapy in a region where CHB-C is commonly seen in Turkey and on follow-up results of these patients, and contribute to the literature both globally and in Turkey.

CONCLUSION

According to our study, TD secondary to interferon therapy may develop in a substantial frequency (21.5%) in patients with CHB-C. Independent risk factors in TD development were found to be female gender and age (over 40 years). TD commonly develops in the first 6-months and is in the sub-clinic form, not requiring treatment. Prospective multi-center studies are needed on this issue in our country on larger patient samples.

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Table 1: Some demographic, clinical and laboratory characteristics of the patients and their comparison

Feature	TD (+) (N=20)	TD(-) (N=73)	P value	All (N=93)
Age (mean-SD), years	49.7±11.5	44.6±13.5	$p^1 > 0.05$	44.8±13.7
Gender (male/female)	5/15	50/23	$p^2 < 0.05$	55/38
Viral hepatitis type (CHB / CHC)	11/9	35/38	$p^2 > 0.05$	46/47
Presence of thyroid auto-antibodies (yes / no)	5/15	4/69	$p^2 < 0.05$	9/84
Response to IFN treatment (response / recurrence / no response)	10/8/2	45/15/13	$p^2 > 0.05$	55/23/15
CHB (genotype)	11 (-)	35 (-)	-	46 (-)
CHC (genotype 1b / other genotypes)	9 (9/0)	38 (35/3)	-	47 (44/3)

N: Patient number; TD: Thyroid gland dysfunction; SD: Standard deviation; p^1: according to the independent t test; p^2: according to the chi - square test; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C

Table 2: Evaluation of risk factors that may be associated with thyroid dysfunction with multiple regression analysis

Variable	OR	95% CI	P value
Age[1]	7.25	1.46-35.80	0.015
Gender (female)	5.83	1.31-25.76	0.020
Viral type	0.0345	0.09-1.27	0.111
Thyroid auto-antibodies	2.24	0.41-12.01	0.345
Response to treatment [2]	1.41	0.36-5.45	0.614

OR: Odds Ratio; Age[1]: < 40 and ≥40 years; Response to treatment [2]: yes or no