ORIGINAL ARTICLE

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

R Harman[1], E Sahin[2]

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 identify possible influencing factors.*

Methods: *A total of 93 CHB-C patients treated with interferon were included in this study. Tests of thyroid functions (thyroid-stimulating hormone (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 six months after initiation of interferon therapy. In 18.3% of these patients, the condition was temporary, while 3.2% of patients required treatment for TD. The most frequently seen condition was the subclinical types. Age (over 40 years) (OR: 7.25 95% CI: 1.46, 35.80,* p *= 0.015) and sex (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 proportion of cases, most of these cases are temporary and do not require TD treatment. Independent risk factors in TD development were found to be sex and age.*

Keywords: Chronic viral hepatitis, interferon, thyroid gland dysfunction

INTRODUCTION

Chronic viral hepatitis consists of 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 haematologic changes (anaemia, 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 thyroid gland dysfunction (TD) between 3 and 35% (4–7).

Although the TD 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 to patients with chronic hepatitis B (CHB), which suggested that causes of viral origin may be effective in the development of TD (8).

In various research studies, sex presence of thyroid auto-antibodies, and ethnic factors were shown to be

From: [1]Department of Infectious Diseases, Mersin Toros State Hospital, Mersin, Turkey and [2]Department of Nuclear Medicine, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.

Correspondence: Dr Rezan Harman, Department of Infectious Diseases, Sani Konukoglu (SANKO) University Hospital, Gaziantep, Turkey. Email: drrezanharman@yahoo.com

associated with TD developing due to interferon (IFN) (7–11).

CHB-C is a frequently encountered health problem in our country and similar to global practice, 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.

SUBJECTS AND METHODS

Patients

Patient file records of individuals diagnosed with CHB-C, and who were treated and followed-up between 2010 and 2015 in a 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 four 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 the 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-hepatitis C [HCV]) were measured from patient peripheral blood samples by microparticle ELISA method (Abbott-Architec i2000sr, Malvern, Pennsylvania, USA), measurement of levels of HBV-DNA, HCV-RNA and HCV genotyping were done with real-time polymerase chain reaction device.

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

Group 1

A total of 46 patients with a diagnosis of CHB were designated as group 1, 22 were females and 24 were males, with an age range of 20–61 years (mean 37.4 ± 10.3 years). In patients with CHB, pegylated 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) for a period of 48 weeks.

Group 2

A total of 47 patients with a diagnosis of CHC were designated as group 2. Of these, 16 patients were females and 31 were males, with an age range of 18–71 years (mean 52.6 ± 12.5 years), 44 patients (93.6%) were of the genotype1b, while the other 3 patients had genotypes 2, 3 and 4 subtypes.

In patients with CHC, pegylated 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 triiodothyronine (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, and TSH measurements were done by ultra-sensitive immune chemoluminescence non-competitive assay (ICMA) (Immmulite 2500 DPC, Siemens, Erlangen, Germany).

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, the 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, and anti-TG were measured. These patients were followed-up at more frequent (every 6weeks) 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 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 to determine the normal distribution of the data. Inter-group comparisons for categorical data were done with chi-square test, and student *t*-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) who met the inclusion criteria were included in this study. Thirty-eight of them were females (F), fifty-five were males (M), aged between 18 and 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 among females in group 2 and in the whole of the group (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 was 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 ($p = 0.06, 0.09, 0.07$).

Thyroid gland dysfunction (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 the 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.

Before IFN therapy, thyroid autoantibodies (anti-TPO and/or anti-TG) were elevated in 9 of 93 patients (7 with CHC and 2 with CHB). Among the 20 patients who developed TD, thyroid autoantibodies were initially elevated in 5 patients (3 with CHC and 2 with CHB), and this difference was statistically significant ($p = 0.008$). Of the 3 patients with permanent-type TD (2 F, 1 M), one patient with CHB had overt hypothyroidism, while the other two patients (male with CHB and female with CHC) had subclinical hyperthyroidism.

Genotyping of patients with CHC was done and 44 (93.6%) were found to have genotype 1b while 3 patients had a 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.

Table 1: Demographic, clinical and laboratory characteristics of the patients and a 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	> 0.05[a]	44.8 ± 13.7
Sex (male/female)	5/15	50/23	< 0.05[b]	55/38
Viral hepatitis type (CHB/CHC)	11/9	35/38	> 0.05[b]	46/47
Presence of thyroid auto-antibodies (yes/no)	5/15	4/69	< 0.05[b]	9/84
Response to IFN treatment (response/ recurrence/no response)	10/8/2	45/15/13	> 0.05[b]	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; CHB = chronic hepatitis B; CHC = chronic hepatitis C.
[a] = According to the independent *t*-test.
[b] = According to the chi-square test.

All of 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 sex, age (below 40 years and above 40 years), thyroid auto-antibodies (present or absent), viral type, and response to hepatitis treatment with the development of TD. Among these, age and sex were statistically significant variables and age, over 40 years, (OR: 7.25 95% CI: 1.46, 35.80, $p = 0.015$) and female sex (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 that could be associated with thyroid dysfunction with multiple regression analysis are presented in Table 2.

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

Variable	OR	95% CI	*p* value
Age[a]	7.25	1.46–35.80	0.015
Sex (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[b]	1.41	0.36–5.45	0.614

OR = odds ratio.
[a]: < 40 and ≥ 40 years.
[b]: Yes or no.

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 wide range, such as 3%–35%. These different results may be related to 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 *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 autoimmunity, independently from IFN therapy (14, 15). On the other hand, TD was observed to develop more frequently, albeit not statistically significant, 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 sex and age, which are associated with 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 IFN therapy, while this proportion 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 in the 6th month to be 55%. While this is a lower rate than that found by Yan *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 six months.

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 *et al*. (18).

Patients in whom TD had developed were followed up for 24 months after IFN treatment was completed. At the end of the 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 9th 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 whom TD persisted at the end of 24 hours, one had overt hypothyroidism and the other two had subclinical hyperthyroidism, and their appropriate treatment and controls were continuing.

If we summarise 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, sex and age are among the factors that are effective in TD development. Especially in terms of sex, the 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 sex 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 was 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 *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 and 30% in patients with CHC, and the presence of anti-TPO or anti-TG antibodies 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. Considering the studies reporting the prevalence of thyroid autoantibodies between 20% and 30% in CHC patients, the rate of 14.9% found for the CHC group 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 *et al*. (27), a significant association was found between TD development and response to IFN therapy.

The main limitations of our study were it being a retrospective and uni-centre 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. Our study also contributes to the literature, both globally and in Turkey.

CONCLUSION

According to our study, TD secondary to IFN 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 sex and age (over 40 years). TD commonly develops in the first six

months and in the sub-clinic form, not requiring treatment. Prospective, multi-centre studies are needed on this issue in our country on larger patient samples.

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