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Central hypothyroidism in patients with chronic hepatitis C and relation with interferon-alpha treatment

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Objective. Since some authors referred to panhypopituitarism or central hypothyroidism during the treatment of chronic hepatitis C virus (HCV) infection using interferon-α, it is intended to evaluate the prevalence of central hypothyroidism (CH) in HCV patients before and during interferon-α therapy.

Patients and Methods. We evaluated 308 HCV patients treated with standard interferon-α (IFN) and/or pegylated-interferon-α (PEG-IFN) associated with ribavirin. Free thyroxine (FT4) and thyrotropin (TSH) levels were measured before, during and after treatment. CH was diagnosed when the level of FT4 was lower than normal values with concomitant normal or lower TSH as verified at least in two consecutive measures.

Results. Before treatment, 18 (5.8 %) patients presented CH Twelve patients maintained laboratory changes during the treatment and 17 new patients developed central hypothyroidism. Among the 29 patients (9.4 %) with CH, 11 used IFN, six used PEG-IFN and 12 patients used two or more therapeutic schedules. The differences in gender, age, cirrhosis, viral genotype, duration of treatment and the type of interferon used were not statistically significant. The absence of sustained virologic response was associated with central hypothyroidism (OR=3.83).

Conclusion. HCV patients may develop CH due to viral infection or during the interferon treatment. These patients presented 3.83 times more chance of not obtaining sustained virologic response.

Keywords: central hypothyroidism, hepatits C, interferon-alpha

Thyroid function disorders are known as complications resulting from the treatment of chronic hepatitis C virus (HCV) with **i**nterferon-α (IFN). Clinical and subclinical forms of hypothyroidism and hyperthyroidism are described in the literature. Furthermore, the occurrence of autoimmune thyroiditis is not rare (Carella et al. 2001; Prummel and Lauberg 2003).

Sakane et al (1995) published the first description of the patient who developed panhypopituitarism two weeks after beginning the IFN treatment and recovered the pituitary function after medication withdrawal. Similarly, other authors reported patients presenting panhypopituitarism or central hypothyroidism during IFN treatment (Kato et al. 1996; Mabe et al. 1997; Ridruejo et al. 2006; Tebben et al. 2007).

The aim of the present study was to evaluate the prevalence of central hypothyroidism in HCV patients before, during and after IFN therapy.

Patients and Methods

Patients. We prospectively studied 308 euthyroid patients diagnosed with chronic hepatitis C virus infection, assigned to treatment with IFN plus ribavirin

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(RBV) followed at the Infection Diseases Service during the 2002-2008 period. Other causes of chronic hepatitis were excluded and no patient was diagnosed with virus B hepatitis or AIDS.

The thyroid function was evaluated before the beginning of treatment and then every three months during treatment as well as at least three and six months after the withdrawal of therapy. Patients who manifested thyroid dysfunction (TD) either before or during the treatment were excluded.

The patients were from the city of Campinas and region, Sao Paulo, Brazil which is known as iodine-sufficient area. This study was approved by the local Research Ethics Commission.

Therapeutic schedule. The patients underwent 1-3 treatments. They were treated for 24 weeks against viral genotype 2 or 3, and for 48 weeks against type 1 or 4 genotypes. The standard dose of IFN was 3 MUI administered subcutaneously three times per week. The dose of pegylated IFN (PEG) was 180 μg subcutaneously, once weekly to Pegasys® and 1.5 μg/kg/week to PegIntron®. The dose of ribavirin ranged from 1000 to 1250 mg/day. The sustained virologic response was obtained 24 weeks after the treatment withdrawal.

Table 1

Central hypothyroidism in patients with virus C chronic hepatitis before treatment with interferon-α

Number of the patient	Central hypothyroidism before treatment# (n=18)	
	fT4*	TSH**
	0.9-1.8 ng/100 ml	0.41-4.15 μIU/ml
1	0.78	3.61
2	0.68	3.28
3	0.88	1.26
4	0.88	3.43
5	0.89	1.71
6	0.80	1.87
7	0.75	0.49
8	0.86	0.42
9	0.74	1.75
10	0.83	2.28
11	0.42	2.15
12	0.88	2.89
13	0.89	1.10
14	0.82	3.54
15	0.74	2.46
16	0.88	1.80
17	0.79	2.20
18	0.87	3.26

Reference Values: *fT4 **TSH
#FT4 and TSH verified at least by two consecutive examinations

Laboratory tests. The chronic hepatitis C virus was diagnosed by the presence of anti-HCV antibodies, HCV-RNA (HCV-PCR quality, Amplicor 2.0; Roche) and virus genotyping. The liver injury was evaluated with the aid of quantitative accelerated life test (qALT) (e.g. ALT of the patient/ALT maximum value of reference; reference values, RV <1) and liver biopsy according to the recommendations of the Brazilian Society of Pathology.

We evaluated the thyroid function by serum free thyroxine levels (FT4, RV = 0.9-1.8 ng/ 100ml serum) and serum thyrotropin levels (TSH, RV = 0.41-4.15 μIU/ml) with the aid of enzyme immunoassay (GenBio, San Diego, USA).

Central hypothyroidism was diagnosed in patients who presented decreased serum level of FT4 as well as either decreased or normal range level of TSH as verified at least by two consecutive examinations. The changes were considered transient when normalized, or definite when remained after drug withdrawal.

The therapeutic schedule to hepatitis C infection was not changed in the patients who developed thyroid disease.

Statistical evaluation. The description of the sample profile was carried out using frequency tables of categorical variables (gender, age, qALT, C virus genotype, presence of cirrhosis, liver biopsy characteristics, therapeutic schedule, type of interferon used, total treatment duration, sustained virologic response), showing the values of absolute frequency (n) and percentage (%), in addition to the descriptive statistical analysis (measures of dispersion and position – mean, standard deviation, a minimum, maximum, median and quartiles) of continuous variables (age, qALT, FT4, TSH, duration of treatment).

The comparison of categorical variables between patients with normal thyroid function and patients who developed central hypothyroidism was performed using the chi-square test or Fisher's exact test. The Mann-Whitney test was used to compare numeric variables among patients with and without central hypothyroidism. The statistical significance level was 5 % ($p < 0.05$).

The Statistical Analysis System (SAS System for Windows, version 9.1.3., SAS Institute Inc., 2002-2003, Cary, NC, USA) and Statistical Package for the Social Sciences (SPSS for Windows, version 10.0.7.; SPSS Inc.,

1989-1999, Chicago, IL, USA) were used for statistical analysis.

Results

A total of 308 patients were evaluated, with mean age of 43.9±9.2 years (72.7 % were men; 87.0 % were Caucasoid). Eighteen patients (5.8 %) presented central hypothyroidism (11 men, 7 women) before treatment, with a mean of FT4 = 0.80 ± 0.11 ng/100 ml serum (0.42-0.89; median = 0.83) and of TSH = 2.19 ± 1.00 μIU/ml (0.42-3.61; median = 2.18) as demonstrated in Table 1. During the treatment, laboratory findings remained unchanged in 12 patients, while three became euthyroid (two women; one man, patients number 7, 11 and 12) and three women developed primary hypothyroidism (patients number 1, 2 and 4). During the treatment, 17 new patients (12 men; 5 women; patients number 19 to 35) corresponding to 5.5 % of total, developed central hypothyroidism (Table 2). Among 29 patients (9.4 %; 22 men, 7 women) with central hypothyroidism, 11 used IFN and 6 used PEG. Twelve patients used two or more therapeutic schedules and 71.4 % did not reach sustained virologic response. Virus C genotype 1 was found in 63 % of them.

Comparative analysis of patients who presented central hypothyroidism prior to the hepatitis C treatment did not show any significant differences between euthyroid and central hypothyroid in relation to gender (p= 0.285), age (p= 0.826), qALT (p= 0.728), presence of cirrhosis (p= 0.336), viral genotype (p= 0.469), duration of treatment (p= 0.431), type of interferon used (p= 0.849) and sustained virologic response (p= 0.642). Table 3 shows the comparative analysis of continuous variables between patients before IFN treatment.

Among the patients who remained euthyroid and the patients who developed or maintained central hypothyroidism during the treatment, the comparative analysis showed that gender, age, cirrhosis, viral genotype, duration of treatment and the type of interferon used were not statistically significant. The absence of sustained virologic response was associated with the presence of central hypothyroidism (p= 0.015; OR= 3.83; CI 95 %= 1.21-12.12). Table 4 shows the comparative analysis of continuous variables between patients during IFN treatment.

Table 2

Central hypothyroidism in patients with virus C chronic hepatitis using interferon-α

Number of the patient	Central hypothyroidism during treatment# (n=29)	
	fT4*	TSH**
	0.9-1.8 ng/100 ml	0.41-4.15 μIU/ml
3	0.84	1.04
5	0.72	1.83
6	0.87	2.06
8	0.75	1.79
9	0.78	2.05
10	0.75	2.36
13	0.78	1.01
14	0.68	3.85
15	0.81	2.03
16	0.79	0.93
17	0.73	1.94
18	0.78	2.33
19	0.86	0.68
20	0.86	0.67
21	0.84	2.50
22	0.83	0.94
23	0.81	0.87
24	0.84	2.51
25	0.86	1.30
26	0.86	2.29
27	0.82	3.03
28	0.86	1.75
29	0.81	1.44
30	0.85	2.35
31	0.86	1.70
32	0.88	2.31
33	0.79	1.34
34	0.82	1.26
35	0.87	1.00

Reference Values: *fT4 **TSH
#FT4 and TSH verified at least by two consecutive examinations
##Patients 19 to 35: euthyroid before IFN use

Discussion

Several reports confirmed a higher prevalence of autoimmune thyroid disease and primary hypothyroidism in patients with chronic C hepatitis infection (Pateron et al. 1993; Antonelli et al. 2006); nevertheless, there is a little information in the literature about the development of central hypothyroidism in these patients.

Hypophysitis can occur, resulting in a partial or total gland dysfunction, due to a definitive etiological agent leading to an inflammatory reaction, such as sarcoidosis, Wegner's granulomatosis and Langerhans cell histiocytosis. Additionally, in several cases the etiological agent cannot be identified, being referred as

Table 3

Patients with hepatitis C before IFN treatment

	Euthyroid	Central hypothyroid	p-value
Age (years)	43.95 ± 9.15 (18.00-71.00) 43.00	42.24± 8.31 (22.00-53.00) 42.00	0.673
FT4 (ng/100ml serum)	1.28 ± 0.70 (0.02-8.10) 1.17	0.91± 0.27 (0.42-1.70) 0.85	<0.001
TSH (μIU/ml)	1.94 ± 1.09 (0.06-6.14) 1.64	1.66±0.86 (0.42- 3.54) 1.70	0.448
QALT	2.53 ± 1.82 (0.30-13.70) 2.00	2.69±1.47 (0.40-5.40) 2.60	0.447

Mean ± SD (minimun-maximum) median
Mann-Whitney test

Table 4

Patients with hepatitis C during IFN treatment

	Euthyroid	Central hypothyroid	p-value
Age (years)	43.86 ± 9.18 43.00	44.22± 10.95 40.50	0.786
FT4 (ng/100ml serum)	1.18 ± 0.18 1.15	0.93± 0.13 0.87	<0.001
TSH (μIU/ml)	1.87 ± 0.90 1.73	1.81±1.13 1.55	0.490
QALT	2.55 ± 1.75 2.10	2.67±2.74 1.80	0.765

Mean ± SD median
Mann-Whitney test

lymphocytic hypophysitis (Cheung et al. 2001; Caturegli et al. 2005). The finding that 5.8 % of our patients presented hypothyroxinemia associated with normal or lower levels of TSH which means the values compatible with central hypothyroidism, suggests that the chronic HCV infection could involve some impairment of the hypothalamus and/or pituitary gland. Perhaps, the hepatitis C virus may act directly or trigger an inflammatory process in the pituitary or hypothalamus.

In patients under HCV treatment using interferon-α, the prevalence of primary hypothyroidism ranged between 3.9 % and 11.8 % (Dalgard et al. 2002; Bini and Mehandru 2004; Doi et al. 2005; Moncoucy et al. 2005). However, in some reports this kind of treatment has been directly related to central hypothyroidism (Sakane et al. 1995; Ridruejo et al. 2006; Tebben et al. 2007). In our study, the total prevalence of central hypothyroidism verified under interferon-α use was remarkable (9.4 %) and related to lower chance of sustained viral response. It is important to highlight that approximately 40 % of patients presented some disturbances before the treatment and, in addition, 60 % of them developed during the use of interferon-α thus suggesting the action of this drug in the hypothalamus or pituitary gland. Moreover, approximately 30 % of the patients presenting central hypothyroidism before the treatment became euthyroid or developed primary hypothyroidism under interferon-α use.

In conclusion, this study suggests that HCV patients may develop central hypothyroidism due to viral infection, since the diagnosis was made before the treatment in some cases. In accordance with the literature, the treatment with interferon-α probably triggered central hypothyroidism in these patients. Additionally, in this study, these patients presented 3.83 times more chance of not obtaining sustained virologic response.

Central hypothyroidism could be included as possible effect of hepatitis C virus and/or adverse effect of interferon-α treatment. Surely, panhypopituitarism should be investigated for the proper hormone replacement, and further studies should be carried out to confirm these results.

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