CLINICAL STUDY

Effect of 1-year treatment with interferon- β 1b on thyroid function and autoimmunity in patients with multiple sclerosis

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Abstract

Objective: Interferon- β (IFN- β) is a widely used therapy for multiple sclerosis (MS), a demyelinating disease of the central nervous system. This study has evaluated the effect on thyroid function and autoimmunity of a 1-year treatment with IFN- β 1b in patients with MS.

Patients: We studied 31 patients (age 34 ± 7 years, 21 women) with relapsing-remitting MS during IFN- β 1b treatment of 1 year duration. Systematic thyroid assessment and measurements of serum interleukin-6 (IL-6) levels were performed at baseline and every 3 months during treatment.

Results: Sixteen percent of the patients had autoimmune thyroiditis before IFN- β 1b, all positive for anti-peroxidase antibodies. The overall incidence of thyroid dysfunction was 33% over 1 year (10% hyperthyroidism, 23% hypothyroidism). Thyroid autoimmunity developed in 5/26 patients (19%), in one case without dysfunction. In addition to autoantibody positivity at baseline, female gender and the presence of an ultrasound thyroid pattern suggestive of thyroiditis were identified by multiple logistic regression as additional risk predictors for the development of thyroid dysfunction. During IFN- β 1b treatment, serum IL-6 levels rose in a consistent biphasic pattern; there was, however, no difference between patients with or without incident thyroid abnormalities.

Conclusions: We conclude that IFN- β 1b therapy can induce multiple alterations in thyroid function, some of which are unrelated to thyroid autoimmunity. IL-6 measurement is not useful to identify patients prone to develop thyroid abnormalities. Though thyroid dysfunction is generally subclinical and often transient, systematic thyroid assessment should be performed during IFN- β 1b treatment.

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Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that is associated with an aberrant immune response to myelin and, possibly, non-myelin self-antigens (1). Moreover, previous studies have shown a significant association between MS and several autoimmune disorders, including autoimmune thyroiditis (2, 3).

Recently, interferon- β (IFN- β) has been widely used to treat patients with relapsing-remitting MS (4). Since type I interferons modulate the immunoregulatory system, these cytokines may precipitate autoimmune disorders. In fact, thyroid disease, with clinical manifestations of hyper- or hypothyroidism, has been reported in 5–12% of patients treated with IFN- α for various diseases (5–7), especially in those with pre-existing autoimmunity (8–11). Apart from two case reports (12, 13), only one clinical study has investigated autoimmunity and thyroid function during IFN- β treatment (14). In that study, however, a thorough

evaluation of pretreatment thyroid autoimmunity and ultrasound features was not carried out.

The aim of the present study was to evaluate the effect on thyroid function and autoimmunity of a 1-year treatment with IFN- β 1b in patients with relapsing-remitting MS. The presence of pre-existing thyroid autoimmunity, or other possible risk factors for developing thyroid disease, was also evaluated.

Patients and methods

Patients

Thirty-one patients, 21 women and 10 men (mean age 34.4 years, range 23–49) attending the outpatient clinic of the Department of Neurosciences, were enrolled in this study after giving written informed consent. The study protocol was approved by the local Ethical Committee. Patients were affected by MS and classified as relapsing-remitting according to Lublin criteria (15).

Additional inclusion criteria were as follows: (i) patients with at least two acute exacerbations in the previous 2 years but clinically stable and off corticosteroid treatment for at least 30 days prior to the study; and (ii) patients whose rating score on the Kurtzke Expanded Disability Status Scale (16) ranged from 1 to 3.5.

Methods

IFN- β 1b was administered s.c. (8×10^6 IU every other day) for 12 months. Before interferon therapy was begun, all patients were submitted to a routine clinical work-up, and the presence of familial autoimmune history was recorded. Thyroid ultrasound examination with a 7.5 MHz real time transducer (Toshiba, Kawasaki, Japan) was carried out by the same operator (N C) at baseline and after 1 year of IFN- β 1b treatment. Blood samples were collected at baseline and every 3 months up to 1 year for evaluation of free thyroid hormone (triiodothyronine (FT₃) and thyroxine (FT₄)), thyrotropin (TSH), and serum thyroglobulin (Tg) levels. Anti-thyroglobulin (Tg-Ab), anti-thyroid peroxidase (TPO-Ab), anti-TSH receptor (TR-Ab) autoantibody, and interleukin-6 (IL-6) concentrations were also assessed basally and every 3 months. A ^{99m}Tc thyroid scan was performed in patients developing hyperthyroidism during IFN- β 1b treatment.

Serum FT₄, FT₃, Tg and TPO-Ab levels were measured by specific RIAs (Sorin Biomedica, Saluggia, Italy), Tg-Ab levels by a specific IRMA assay (ICN Pharmaceutical, Asse Relegem, Belgium) and TSH by an ultrasensitive IRMA method (Diasorin, Stillwater, MN, USA). Serum IL-6 levels were determined by ELISA (Biosource, Nirelles, Belgium), with a detection limit of 2 pg/ml. Normal ranges in our laboratory are as follows: FT₄: 7.2–19.3 pmol/l; FT₃: 3.7–8.6 pmol/l; Tg: <60 nmol/l; TSH: 0.3–3.6 mIU/l; TPO-Ab: <10 IU/ml; Tg-Ab: <50 IU/ml; TR-Ab: <16 IU/ml; IL-6: 3–8.5 pg/ml.

Statistical analysis

Unless otherwise stated, data are given as the mean $\pm$ s.e. Undetectable IL-6 levels were assigned an arbitrary value of 1 pg/ml, which equals one half of the detection limit (17). Mean values and percentages were compared by Student's *t*-test, ANOVA, Mann–Whitney U test and χ^2 test as appropriate. A multiple logistic regression model was used for the analysis of risk factors for the development of thyroid disease.

Results

All patients ($n = 31$) completed their 1-year IFN- β 1b treatment course. Among them five were affected by Hashimoto's thyroiditis at baseline, eight developed thyroid dysfunction and/or autoimmunity of various degrees during IFN- β 1b treatment, while 18 did not

Table 1 Clinical, ultrasound, functional and autoimmune features of the patients with MS submitted to IFN- β 1b therapy.

Patients ($n = 31$)	Sex	Ultrasound pattern	Familial autoimmunity	Onset of autoimmunity	Onset of dysfunction	Thyroid dysfunction
Staying euthyroid without autoimmunity ($n = 18$)	10 F/8 M	11 normal, 2 nodular goiter, 5 hypoechoic	yes = 9, no = 9	—	—	—
With thyroid dysfunction and autoimmunity ($n = 8$)	7 F/1 M	8 hypoechoic	yes = 7, no = 1	4 before IFN, 2 at 6 months, 2 at 12 months	1 before IFN, 4 at 3 months, 2 at 6 months, 1 at 9 months	5 subclinical hypo-, 2 subclinical hyper-, 1 overt hyper-
With thyroid autoimmunity only ($n = 2$)	1 F/1 M	1 hypoechoic, 1 with colloid areas	yes = 2	1 before IFN, 1 at 9 months	—	—
With thyroid dysfunction only ($n = 3$)	3 F	3 hypoechoic	yes = 1, no = 2	—	3 at 3 months	1 overt hypo-, 2 subclinical hypo-

Table 2 FT₄, FT₃, TSH, Tg, IL-6, Tg-Ab and TPO-Ab levels in the three patients with pretreatment Hashimoto's thyroiditis developing dysfunction during IFN- β 1b therapy.

Patient	Basal values							Values at onset of thyroid dysfunction							Onset/duration
	FT ₄ (pmol/l)	FT ₃ (pmol/l)	TSH (mIU/l)	Tg (pmol/l)	Tg-Ab (IU/ml)	TPO-Ab (IU/ml)	IL-6 (pg/ml)	FT ₄ (pmol/l)	FT ₃ (pmol/l)	TSH (mIU/l)	Tg (pmol/l)	Tg-Ab (IU/ml)	TPO-Ab (IU/ml)	IL-6 (pg/ml)	
BoG	10.8	5.3	2.06	18.3	4.0	259.0*	1.0	13.9	5.1	4.33*	18.3	7.0	419.0*	27.1*	3 months/transient
FA	11.1	5.4	1.14	169.8*	4.0	33.0*	12.3*	17.2	6.9	0.08*	164.5*	21.0	438.0*	2.7	6 months/transient
PR	7.7	3.7	2.61	163.6*	52.0*	187.0*	1.0	8.7	4.8	4.28*	153.9*	36.0	336.0*	5.2	3 months/permanent

* Pathological values.

Table 3 FT₄, FT₃, TSH, Tg, IL-6, Tg-Ab and TPO-Ab levels in the eight patients developing thyroid disease during IFN- β 1b therapy.

Patient	Basal values							Values at onset of thyroid dysfunction/autoimmunity							Onset/duration
	FT ₄ (pmol/l)	FT ₃ (pmol/l)	TSH (mIU/l)	Tg (pmol/l)	Tg-Ab (IU/ml)	TPO-Ab (IU/ml)	IL-6 (pg/ml)	FT ₄ (pmol/l)	FT ₃ (pmol/l)	TSH (mIU/l)	Tg (pmol/l)	Tg-Ab (IU/ml)	TPO-Ab (IU/ml)	IL-6 (pg/ml)	
PN*	12.6	5.2	3.34	38.2	1.0	2.0	16.5**	13.0	4.4*	4.01**	33.9	6.0	5.0	2.7	3 months/permanent
PC	9.1	4.4	1.02	112.5**	3.0	3.0	8.0	17.5	5.7	0.02**	118.3**	64.0**	4.0	30.5**	3 months/transient
VV ^o	14.8	5.8	0.58	50.4	1.0	8.0	8.6**	35.5**	13.2**	0.11**	346.2**	13.0	8.0	16.2**	3 months/transient
BG	18.6	4.9	2.65	45.3	4.0	3.0	4.8	9.5	4.8	4.25**	52.3	2.0	7.0	12.3**	3 months/transient
TT	8.1	4.6	1.85	38.1	1.0	6.0	7.3	9.3	4.8	3.74**	45.1	12.0	4.0	1.0	3 months/permanent
CR [^]	10.9	4.9	3.17	16.5	2.0	3.0	28.4**	10.3	5.4	3.00	13.5	3.0	15.0**	25.5**	9 months/permanent
TA	10.3	5.2	2.43	16.3	14.0	2.0	20.4**	11.4	5.8	3.88**	18.1	6.0	10.0**	1.0	6 months/transient
DM	10.9	6.4	1.18	31.9	6.0	3.0	16.5**	11.7	4.9	1.61	20.2	240.0**	4.0	23.2**	9 months/permanent

* At 12 months the patient developed overt hypothyroidism. ^o At 12 months the patient developed Tg-Ab antibodies (116 IU/ml). [^] At 12 months the patient developed subclinical hypothyroidism (TSH = 7.1 mIU/l). ** Pathological values.

develop any thyroid abnormality (Table 1). A significant TR-Ab titer was never observed during the study.

Among the five patients (three female and two male) with pretreatment Hashimoto's thyroiditis, four were positive for TPO-Ab and one for both Tg-Ab and TPO-Ab. As for their thyroid function one had subclinical hypothyroidism (FT₄: 8.9 pmol/l, FT₃: 5.2 pmol/l, TSH: 3.69 mIU/l) not worsening during treatment, while the other four were euthyroid. During the study period, one of them remained euthyroid but became positive also for Tg-Ab (64 IU/ml, at 3 months), while two developed subclinical hypothyroidism at the 3-month control, and one developed transient (lasting 6 weeks) subclinical hyperthyroidism at 6 months (Tables 1 and 2). This latter patient showed a diffuse reduction in thyroid uptake at ^{99m}Tc scintiscan (Fig. 1), and was effectively treated with propranolol only (60 mg daily) without interrupting IFN-β1b.

Among the remaining 26 patients, 8 (31%) developed thyroid disease during IFN-β1b treatment (Tables 1 and 3). All of them were female, and five had a positive family history of autoimmune diseases. In detail, one patient developed a positive Tg-Ab titer and remained euthyroid, while five (two with positive TPO-Ab titer,

and three without significant autoantibody levels) became hypothyroid (four subclinical and one overt). The last two patients became positive for Tg-Ab titer and developed transient hyperthyroidism (one subclinical, one overt) after 3 months of therapy. At baseline their thyroid ultrasound pattern was not homogeneous, mainly hypoechoic. At the onset of hyperthyroidism, the thyroid ultrasound echogenicity did not change in both patients, while a diffuse reduction in uptake was observed at ^{99m}Tc scintiscan (Fig. 1). Furthermore, the patient with overt hyperthyroidism showed a significant increase in serum Tg levels concomitant with the onset of hyperthyroidism. Both patients were effectively treated with propranolol (60 and 80 mg daily) without stopping IFN therapy. Hyperthyroidism was no longer evident 6 weeks later in both cases.

At baseline, mean serum IL-6 levels were 9.7 pg/ml (95% confidence interval (CI): 6.8–12.6). During IFN-β1b therapy, IL-6 values showed a biphasic behavior regardless of the presence of thyroid abnormalities (Fig. 2). In particular, serum IL-6 levels rose ~2-fold at 3 months (20.0 pg/ml, CI: 12.7–27.3, *P* < 0.005 vs basal levels), returned to baseline at 6 months (10.9 pg/ml, CI: 6.3–15.5), and then rose at 9 and 12

Figure 1 Reduced ^{99m}Tc thyroid uptake in a patient with hyperthyroidism during IFNβ-1b therapy (the thyroid scintiscan of the patient with overt hyperthyroidism is shown here).

Figure 2 Mean ($\pm$ S.E.M.) serum IL-6 concentrations in patients with MS at baseline and during treatment with IFN- β 1b. Open bars = patients without thyroid abnormalities; hatched bars = patients with thyroid abnormalities. * $P < 0.05$, ° $P < 0.02$ vs baseline.

months up to ~2-fold (14.9 pg/ml, CI: 10.3–19.5, and 21.7 pg/ml, CI: 11.5–31.8, $P = 0.02$, and $P < 0.01$ vs basal value respectively). No correlation between IL-6 value and thyroid hormone, TSH, Tg or thyroid auto-antibody level was found.

By ultrasonography, mean thyroid volume (as estimated by the ellipsoid formula, length $\times$ width $\times$ thickness $\times 0.52$) was 10.6 ml (range: 4.5–20.7). At 1 year, thyroid volume was significantly increased (13.0 ml, range 6.0–22.0, $P = 0.004$), with no difference between patients with or without incident thyroid abnormalities. Among patients not developing thyroid dysfunction, two had a single benign solid thyroid nodule, which remained unchanged cytologically and ultrasonographically after 1 year of IFN- β 1b therapy. Among the eight patients who developed thyroid dysfunction and/or autoimmunity during treatment, seven showed a diffuse hypoechoic pattern without changes at the 1-year ultrasound control (Table 1).

The development of thyroid dysfunction was significantly related to positive baseline TPO-Ab titer ($P = 0.01$). By multiple logistic regression, female gender ($P = 0.01$, odds ratio 55.4), and the presence of a diffuse hypoechoic thyroid pattern at ultrasound examination ($P = 0.04$, odds ratio 19.6) were additional risk factors. Familial autoimmunity, reported by 9/18 patients without development of thyroid disease, did not reach statistical significance ($P = 0.8$).

Discussion

Previous studies have reported an association between MS and autoimmune disorders (18), particularly thyroiditis, with a prevalence of ~16% (2, 3). In accord, we found 16% of patients with autoimmune thyroiditis before IFN- β 1b therapy, all of whom had a positive TPO-Ab titer. The development of thyroid disease, with clinical manifestations of hyper- or

hypothyroidism with or without evidence of autoimmunity, has been reported in 5–12% of patients treated with IFN- α for various diseases (5–7). A higher incidence has been observed in patients with HCV hepatitis undergoing long-term (12 months) IFN- α therapy: 20% hypothyroidism and 9% thyrotoxicosis (19).

In the present series, the overall incidence of thyroid dysfunction during IFN- β 1b therapy was 33%, with three cases of hyperthyroidism and seven of hypothyroidism. Moreover, thyroid autoimmunity developed in 5/26 patients (19%), in one case without organ dysfunction. These data only partially agree with a recent study (14) showing, during IFN- β treatment, thyroid autoimmunity in 5/17 (29%) MS patients and transient hyperthyroidism in one of these five (5.9%). In that study, however, pretreatment anti-thyroid antibodies were assessed only in three out of these five patients (two positive and one negative for thyroid autoimmunity), so the actual incidence of thyroid autoimmunity development was not available. Moreover, we observed an overall higher prevalence of dysthyroidism but overt thyroid dysfunction developed in only two patients (6.1%).

Pre-existing thyroid autoimmunity has been suggested as an important risk factor during IFN- α therapy, thyroid disease developing in up to 60% of patients with positive baseline TPO-Ab (8–11). Similarly, in our series 75% of the patients with elevated pre-treatment TPO-Ab levels developed thyroid dysfunction during IFN- β 1b therapy. Furthermore, we found that risk was higher in women and was significantly enhanced by an ultrasound thyroid pattern suggestive of thyroiditis (20).

Both IFN- α and IFN- β 1b administration promote autoimmune disease, but the mechanisms of this effect are not completely understood. IFN- α has been suggested to induce thyroid dysfunction by stimulating the production of thyroid-inhibitory cytokines and/or

activation of cytotoxic lymphocytes in the thyroid (21, 22). IFN- α is also known to suppress the expression of MHC class II antigens in thyroid cells (23). Thus, it seems likely that the expression of these antigens in thyrocytes is not necessary to induce thyroid autoimmunity in patients treated with IFN- α . Recently, Yamazaki *et al.* (24) demonstrated that *in vitro* IFN- α and IFN- β inhibited radioiodine (^{125}I) organification in human thyroid cells. Overall, these findings suggest a direct action of IFNs on thyroid function, possibly accompanied by autoimmunity and cytotoxicity.

Though the most likely explanation for the thyroid dysfunction occurring with IFN- β 1b therapy remains an autoimmune reaction, a direct inhibitory effect of IFN- β 1b on iodine organification may be presumed in those patients who developed hypothyroidism without thyroid autoimmunity. A similar mechanism may be involved in the thyroid volume increment observed in our study. Direct cytotoxicity may account, at least in part, for the development of transient hyperthyroidism, as suggested for IFN- α (10). This could explain the low $^{99\text{m}}\text{Tc}$ uptake and the absence of positive TR-Ab titer observed in our patients (although a significant increase of Tg was detected in the patient with overt hyperthyroidism only).

To test whether thyroid tissue damage may be involved in the development of transient thyroid dysfunction, we measured both IL-6 and Tg levels during IFN- β 1b treatment. In fact, similar to Tg, IL-6 has been regarded as a marker of thyroid destruction (17). In our patients, chronic IFN- β 1b treatment induced a significant increase of IL-6 secretion, which, however, was not associated with a concurrent increase in Tg levels. Although in most cases the appearance of thyroid abnormalities coincided with the first peak of IL-6 (3 months into therapy), no significant differences were observed between patients with or without thyroid dysfunction. Thus, IL-6 increments may reflect a systemic effect of IFN- β 1b on the immune system rather than a direct action on the thyroid gland (25). Moreover, in agreement with a previous study with IFN- α (26), IL-6 concentrations did not prove useful in identifying patients developing thyroid abnormalities.

In conclusion, IFN- β 1b therapy can induce multiple alterations in thyroid function, some of which are unrelated to thyroid autoimmunity. In addition to pre-existing thyroiditis, female gender and an hypoechoic thyroid pattern are reliable predictors of thyroid abnormalities. Though thyroid dysfunction is generally subclinical and often transient, systematic thyroid assessment should be performed before and during IFN- β 1b treatment.

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