ORIGINAL

The Prevalence of Thyroid Autoimmunity in Patients with Prolactinoma

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Abstract

Prolactin (PRL) is a hormone characterized by its immunomodulatory properties. The aim of this study was to evaluate the prevalence of thyroid autoimmunity in patients with prolactinoma. Seventy-seven patients and 56 healthy individuals in the control group, sex and age matched, had their serum PRL, free tetraiodothyronine, thyroid-stimulating hormone and anti-thyroid peroxidase (anti-TPO) levels measured. The prevalence of anti-TPO for patients was 13% and 8.9% for control group (p = 0.58). The analysis of subgroups of patients, divided in accordance with tumor size at diagnosis, showed no significant difference in the frequency of anti-TPO. However, when they were divided in accordance with the prolactin levels at the moment of the study, 18.8% with valid hyperprolactinemia and 3.4% without hyperprolactinemia had positive autoantibody (p = 0.07). In conclusion, there was no greater prevalence of thyroid autoimmunity in patients with prolactinoma. Nevertheless, those with valid hyperprolactinemia showed a greater tendency for positive autoantibody anti-TPO.

Keywords: autoimmune thyroid diseases, autoimmunity, hyperprolactinemia, prolactin.

INTRODUCTION

Human prolactin (PRL) is a polypeptide hormone composed of 19 amino acids, produced and secreted by lactotrope cells in the anterior pituitary and in other cells and tissues[1].

The main cause for pathological hyperprolactinemia, after excluding the use of drugs, is prolactinoma, a pituitary adenoma PRL producer, and its therapeutic option is based on tumor size, gonadal function and the desire for fertility[2].

PRL is associated with reproductive function, the development of the mammary glands and lactation; however, other functions have been recognized, such as its immunomodulatory property[3]. As a result, the clinical consequences of hyperprolactinemia may be more complex than what has been postulated thus far.

In the immune system, PRL may work as autocrine, paracrine and hormonal[3]. The PRL production by the human immune cells was originally mentioned by Pellegrini et al., who demonstrated that the peripheral blood mononuclear cells constitutively expressed the hormone[4]. Afterwards, it was observed that other cells of the lympho-hematopoietic system (thymocytes, cells of the bone marrow stroma, hamopoietic progenitors and macrophage differentiation) also produced prolactin[5]. On the other hand, the prolactin receptor was found in various immune cells, such as monocytes, T lymphocytes, B lymphocytes and natural killer cells[6].

Although the exact role of PRL in immunoregulation is not recognized, studies in vitro and with animals have been associated with the proliferation and survival of lymphocytes, production of cytokine, antibodies secretion and with the differentiation antigen-presenting cells[7]. PRL´s function in the immune system is confirmed by studies relating PRL to the autoimmune diseases in animals[8] and humans.

Notwithstanding data concerning the frequency of autoimmunity, mainly thyroid autoimmunity (TAI), with prevalence between 1 - 10% in adults and 13% in women after 35 years old, on a population in Rio de Janeiro, Brazil,10 data on prolactinoma are scarce in the literature.

Thus, this study aimed at assessing whether the probability of thyroid autoimmunity was greater in individuals with prolactinoma.

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PATIENTS AND METHODS

Seventy-seven patients were selected from the Endocrinology Service of the HUCFF/UFRJ, in the period of April 2005 to October 2006. This selection included men and women, above 18 years old, diagnosed with prolactinoma, confirmed as either: 1) a microprolactinoma (MIC) symptomatic patient with initial serum PRL levels ≥ 100 ng/ml, minimum of two doses, and pituitary tumor ≤ 10mm, as to computerized tomography (CT) or magnetic resonance imaging (MRI) image testing of the sella turcica, or; 2) a macroprolactinoma (MAC) symptomatic patient with initial serum PRL levels of ≥ 200 ng/ml, minimum of two doses, and pituitary tumor > 10mm as to CT or MRI image test.

Exclusion criteria included current or previous use of drugs that interfere on thyroid function, personal history of hepatitis C, family history of autoimmune diseases in first-degree relatives, pregnancy or breastfeeding and use of illegal drugs.

The control group consisted of 56 healthy volunteers with normal serum PRL levels, sex and age matched with the patients group. The exclusion criteria for both were the same. The project was approved by the Research Ethics Committee of the Medical School and HUCFF – UFRJ, under number 191/06.

After inclusion in the study, records were revised for the collection of data related to: 1) prolactinoma, as to initial PRL, tumor size at diagnosis (through CT or MRI) and current or previous treatment for the tumor (use of dopamine agonist (DA), transsphenoidal and/or transcranial surgery, and/or radiotherapy; 2) type of thyroid disease, previous history of dysfunction (hypothyroidism or hyperthyroidism) and their treatments (levothyroxine, anti-thyroid drugs, radiotherapy or thyroidectomy).

Determinations of serum PRL and anti-TPO levels were performed. For those with no previous diagnosis of dysfunction, the same sample of serum for dosages of thyroid-stimulating hormone (TSH) and free tetraiodothyronine (FT4) was used. For patients with previous diagnosis of dysfunction, the measures of TSH and FT4 were considered at the time of the diagnosis. Patients with TSH levels above reference values and normal FT4 had another sample taken with a 4-week minimum interval so that results could be confirmed.

All the tests were carried out in the hormone and immunology laboratories of HUCFF/UFRJ. The PRL dosage was conducted by solid-phase chemiluminescent immunometric assay with IMMULITE 2000® analyzer, by Diagnostic Products Corporation (DPC) Ltd.; the coefficients of variation intra- and inter-assay were 2.3 - 5.9% for concentration of 22 ng/ml and 2.3 - 7.9% for concentration of 164 ng/ml, respectively; and the reference range was 1.9 - 25.0 ng/ml for women and 1.9 - 17.0 ng/ml for men. The anti-TPO dosage was measured by IMMULITE 2000® analyzer, DPC Ltd, with coefficients of variation intra and inter-assay 4.3 - 5.6% and 7.8 - 10.5%, respectively; and the reference value was ≤ 35 UI/ml. The TSH was measured by the third-generation chemiluminescent immunometric assay, with IMMULITE 2000®, DPC Ltd; with coefficients of variation intra-assay 3.8 - 12.5% and inter-assay, 4.6 - 12.5%, the reference values were 0.4 to 4.0 mUI/L. Finally, the FT4 dosage was measured by the chemiluminescent immunoenzymatic assay, with IMMULITE 2000® analyzer, DPC Ltd; with coefficients of variations intra-assay 4.4 - 7.5% and inter-assay, 4.8 - 9.0%, the reference range was 0.8 to 1.9 ng/dL.

For the purpose of data analysis, the patient group was subjected to subdivisions according to: tumor size and initial PRL levels in MIC and MAC patients, by previously mentioned criteria; current PRL levels in patients without hyperprolactinemia (individuals in treatment or previously treated with PRL levels within the normality range) and with hyperprolactinemia (in or without treatment, with PRL levels above reference range of the applied method).

The patients and individuals in the control group having anti-TPO above reference values of the kit used were classified as positive for this antibody and with TAI.

The patients and individuals in the control group were classified based on TSH and FT4 dosages or on the data obtained in the medical records.

STATISTICAL ANALYSIS

Data were evaluated by SPSS (Statistical Package for the Social Science, version 11.0) program. The proportions were determined by Fisher's Exact Test. The comparison between the continuous variables by Student's T-Test (parametric variables) or was performed by Mann-Whitney (non-parametric variables). For all analyses, bicaudate ratio tests were used. Considered statistically significant for all analyses was a $p \leq 0.05$, both in univariate and multivariate analysis.

RESULTS

Out of 77 patients with prolactinoma, 13 were men (16.9%) and 64 were women (83.1%). The mean age, in years, for men was 42.7 ± 13 and 40.3 ± 12.2 for women, with the mean rate for the group at 40.92 ± 12.25. Fifty--six individuals from the control group were included, 14 men (25%) and 42 women (75%), with mean age of 45.9 ± 11.9 and 45.9 ± 11.9 years old, respectively. The mean age for the group was 42.6 ± 12.6 years old. There was no statistical difference between patients and the control group when taking age and sex into account.

Difference was noticed in the PRL levels of the patients [median: 34.5 ng/mL (maximum value: 1376.0 ng/mL and minimum: 1.4 ng/mL)] x the control group [median: 8.7 ng/mL (maximum value: 24.0; and minimum: 2.1); $p < 0.0001$].

Seventy-three patients, at some point in their treatment, had already used DA (the first option for prolactinoma treatment), bromocriptine (BRC) or cabergoline (CAB). Three of them were new to treatment and one female patient with microprolactinoma had undergone transsphenoidal surgery and was cured.

During the study, 23 patients (29.8%) were not receiving medication for at least one month. They were therefore considered not users of DA. Only 7 out of the 23 patients showed normal serum PRL levels.

Eighteen patients (23.4%) had surgical treatment. Seventeen had preference for transsphenoidal access and two preferred transcranial access. One patient was submitted to both. Conventional radiotherapy was a complementary treatment for two patients (2.6%) with MAC.

In the subdivision of the 77 patients, selected by tumor size, 50.6% had MIC (6 women and 3 men). For the remaining 38 patients, 49.4%, with MAC, 10 were males and 28 were females. Thus, out of the 13 men, 76.9% had MAC and 23.1%, MIC. The frequency of MAC among women was 43.8% and of MIC, 56.2%. This difference was statistically significant (OR=4.2; p=0.036) (Table 1).

Hyperprolactinemia was observed in 48 patients (62.3%) and normoprolactinemia, in 29 (37.7%) (Table 2).

FREQUENCY OF INCREASED LEVELS OF ANTI-TPO ANTIBODY

High levels of anti-TPO were noticed in 13% of the individuals with prolactinoma (10/77), all cases in women, with prevalence of 15.6% (10/64 women). As for the control group, the frequency observed of positive anti-TPO was 8.9% (5/56), for one man and four women. There was no significant statistical difference between the two groups (p = 0.58).

Out of 38 patients with MAC, three had positive anti-TPO (7.9%), while out of 39 with MIC, seven had positive antibody (17.9%). There was no statistical difference between those groups (p = 0.31).

The analysis of the frequency of anti-TPO in the subgroups of patients with and without hyperprolactinemia showed that nine out of the ten cases with positive anti--TPO were in the subgroup with hyperprolactinemia. On the other hand, only one patient with positive anti-TPO belonged to the subgroup with normoprolactinemia. The difference between those two subgroups shows tendency for statistical significance (p = 0.07).

For those on DA, the prevalence of positive anti--TPO was 11.1% (6/54) and in the subgroup of patients not using DA, the frequency was 17.4% (4/23). There was no significant difference in the frequency of anti-TPO among those subgroups (p = 0.47).

THYROID DYSFUNCTION

In total, the frequency of thyroid dysfunction for the patients group was 13% (10/77), of which seven had primary hypothyroidism (four had manifested hypothyroidism and three had subclinical hypothyroidism), one had hyperthyroidism caused by Graves' disease (GD) and two had secondary hypothyroidism. Considering only the cases of primary thyroid dysfunction (primary hypothyroidism and GD), the frequency for the patients with prolactinoma was 10.7% (8/75). The cases of primary dysfunction were greater in women and in MIC patients (except the patient with GD). The frequencies for those subgroups were 12.5% (8/64 women) and 17.9% (7/39 microprolactinomas), respectively. On the contrary, the two cases of secondary thyroid dysfunction were noticed in men (2/13; 15.4%)

Table 1. Comparison between patients with micro and macroprolactinoma.

	Macroprolactinoma (n=39)	Microprolactinoma (n=38)	p
Age (years) [average value; standard deviation]	42.2 ± 11.1	39.5 ± 13.3	0.32
Initial PRL (ng/mL) [median; maximum and minimum values]	126.0 (310-100)	710.9 (17.000-200)	< 0.0001
Current PRL (ng/mL) [median; maximum and minimum values]	30.0 (264-1.4)	46.8 (1376-1.6)	0.43

n: number of patients; PRL: prolactin.

Table 2. Comparison between the patients with and without hyperprolactinemia at the time of the antithyroid peroxidase antibody dosage.

	With Hyperprolactinemia (n=48)	No Hyperprolactinemia (n=29)	*p*
M/W	7/41	6/23	0.53
Age (years) [average value; standard deviation]	37.5 ±11.9	46.4 ± 10.8	< 0.017
DA** (n)	32	22	0.45
Initial PRL (ng/mL) [median; maximum and minimum values]	226.5 (17,000.0-100.0)	193.5 (7.000.0-100)	0.70
Current PRL (ng/mL) [median; maximum and minimum values]	72.6 (1.376.0-19.5)	10.7 (22.7-1.4)	<0.0001

n: number of patients; M: men; W: women; DA**: use of dopamine agonist for at least 30 days; PRL: prolactin.

and in MAC patients (2/38; 5.3%). The major prevalence of secondary hypothyroidism in patients with macroprolactinoma was statically significant ($p = 0.02$).

The four patients with prolactinoma and primary manifested hypothyroidism had positive anti-TPO and two of them were diagnosed with hyperprolactinoma in the initial investigation. The PRL levels remained high even after the TSH levels reached normality. The PRL values were 102 ng/ml and 154 ng/ml, which led the investigation to continue, confirming pituitary microadenoma. The other two had diagnosis of thyroid dysfunction during the course of treatment for MIC; one was diagnosed before being included in our study.

The three patients with subclinical hypothyroidism (TSH levels above reference values in at least two dosages with a 4-week minimum interval and FT4 within the limits of reference values) had their results confirmed by a second sample. Two of them had the diagnosis established when they were included in the study and one during follow-up visits. Two of them presented positive anti-TPO in the dosage.

The patient with hyperthyroidism caused by GD was diagnosed on the third year of the use of DA for treatment of MAC, when she was 23 years old. The serum PRL level at that time was 23.7 ng/ml. She was treated with methimazole varying from 40 to 60 mg/per day for five months, without compensation from the clinical and laboratorial symptoms of hyperthyroidism. She was subjected to Iodine 131 (11.5 mCi) and one year later she (thyroidectomized) still had hyperthyroidism. Throughout the course of hyperthyroidism, she did not take DA and the maximum PRL level was 35.5 ng/ml. The MRI through sella turcica (carried out after resolution of thyroid dysfunction) confirmed sella partially empty. The PRL, while she was included in the study, was 32.2 ng/ml, being asymptomatic and not on DA for three years. The anti-TPO was negative while having the hyperthyroidism and three years later (period after the inclusion in the study).

In the control group, three patients presented TSH above reference values and normal levels of FT4 in the first assessment. One of them did not have subclinical hypothyroidism confirmed in the second dosage of TSH, though two of them had subclinical hypothyroidism diagnosis confirmed. The number of anti-TPO for both was high. As a conclusion, the frequency of primary thyroid dysfunction for the control group was 2/56 (3.57%) and no case of secondary hypothyroidism was observed. There was no statistically significant difference in the prevalence of primary thyroid dysfunction between both groups ($p = 0.18$).

DISCUSSION

We have known for a long time that one of the causes of hyperprolactinemia may be primary hypothyroidism[11,12]. Various mechanisms may be involved: 1) more PRL release, through the increase in the production and secretion of TRH (TSH-releasing hormone found in the hypothalamus), and greater sensitivity to this factor, which is secondary to the increase of expression of the TRH receptor in the lactotrophs; 2) increase in the expression of the PRL gene, by reduction of the inhibitory effect of the T3 and increase in the fraction free of estradiol; 3) lower PRL purification[13].

Nevertheless, it is not yet established that the thyroid autoimmunity triggers hyperprolactinemia. Studies in the field are scarce in the literature.

The determination of the frequency of anti-TPO in all 77 patients with prolactinoma did not prove greater prevalence of this antibody when compared to the control group (13% x 8.9%, respectively). All 10 cases of positive anti-TPO happened with women, with frequency of 15.6%. This difference related to sex is in accordance with the literature[14-18]. In a study with Brazilian population, conducted by Sichieri et al.[10], and applying the same methodology for the anti-TPO dosage, the prevalence for positive anti-TPO in 1220 women, above 35 years old, was 13.1%, with 11 - 15% variation (depending on the ethnic group).

Those findings go against the study of Ishibashi et al.[19], who found prevalence of positive anti-thyroid antibodies, antimicrosomal antibodies (anti-Ms) and anti-thyroglobulin (anti-Tg) (20.2%) significantly higher for the patients with prolactinoma than for the individuals in the control group (17.9% x 7.0% and 20.2% x 3.5%, respectively; $p < 0.05$ and $p < 0.01$). According to this study, all 84 patients with prolactinoma presented high PRL levels and all women presented clinical manifestations of hyperprolactinemia. These differences in the samples may justify the divergent findings.

This is verified by the tendency revealed for greater prevalence of positive anti-TPO in the subgroup of patients with current hyperprolactinemia, when compared to the ones without hyperprolactinemia. These subgroups did not present differences in the frequency of male/female sexes or the use of DA at the time of the study, which could be an explanation for that fact. Furthermore, the literature establishes that the prevalence of the autoimmune thyroid disease increases with age[12,13]. In this sample, individuals having hyperprolactinemia were younger and still showed tendency for thyroid autoimmunity. Maybe, if there was an increase in the cases selected for study, the statistical significance could have been noticed.

Greater prevalence of TAI with high serum PRL levels was reported by Ferrari et al[20]. They assessed the presence of anti-Ms and anti-Tg antibodies in 92 patients (10 men and 82 women) with hyperprolactinemia from different etiologies. They observed prevalence of anti-thyroglobulin and anti-microsome of 19.5% and 12.2%, respectively, but could not find anything in the individuals from the control group.

The importance of the state of hyperprolactinemia for the activation of auto-reactive B-lymphocytes and for the production of thyroid autoantibodies is confirmed by the study of Kramer et al[21]. They assessed the presence of antithyroid antibodies (anti-Tg, anti-MIC, anti-TPO) in different groups: 26 with systemic lupus erythematosus; 20 with rheumatoid arthritis, 24 with hyperprolactinemia and 28 individuals from the control group without rheumatologic disease or thyroid diseases. Despite the greater frequency of antibodies in all groups, compared to the control group, only the group with hyperprolactinemia showed significant statistical difference. However, when subdivided in patients with hyperprolactinemia without treatment (average PRL levels of 14.1 ng/ml), only the first subgroup presented greater prevalence of TAI.

In the study of Giusti et al.[22], the greatest frequency of antithyroid antibodies and thyroid echographic alterations in the patients from different etiologies with hyperprolactinoma, and already in treatment, was not subjected to the initial PRL levels and the duration of the hyperprolactinemia. The average PRL level for this sample was 17.9 ± 2.1 ng/ml. The frequency of echographic alterations was 30.8% for the patients group and 15.5% for the control group. Concerning the positive antithyroid autoantibodies, anti-TPO and/or anti-Tg, the prevalence for the control group was 14.3% (9/63) while, for the patients, it was 29.6% (29/98).

Aiming at assessing the influence of the initial PRL levels and once the direct relation between the tumor size and the intensity of the hyperprolactinemia is established; we compared the differences in frequency of anti-TPO between patients with MAC and MIC[23] but could not find any significant difference in its prevalence. As a result, the initial PRL levels did not influence the prevalence of TAI.

The ideal model for assessing the importance of hyperprolactinemia, caused by prolactinoma through the induction of autoimmunity, would be long-term follow--up, observing the clinical and serum parameters of autoimmunity. This, however, is not possible due to the hyperprolactinemia morbidity and the local effect of the tumor on the macroprolactinoma.

CONCLUSION

In the present study, we evaluate that patients with prolactinoma did not present greater prevalence of thyroid autoimmunity and primary thyroid dysfunction.

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