# Integrity of the Lactotroph Axis and Antithyroid Antibodies in Patients with Hypopituitarism

Carolina Garcia Soares Leães
Caroline K. Kramer
Cristina Micheletto Dallago, MD
Miriam da Costa Oliveira, PhD

*Center of Neuroendocrinology, Santa Casa de Porto Alegre Hospital, Federal Faculty Foundation of Medical Sciences of Porto Alegre (FFFCMPA), Brazil*

**KEY WORDS:** prolactin, hypopituitarism, antithyroid antibodies, autoimmunity

## ABSTRACT

**Background:** Recent studies have suggested an immunology role in hypopituitarism not associated with pituitary tumors and have increased the knowledge about the interaction of prolactina with the immune response. This study aims to evaluate the presence of antithyroid antibodies and the lactotroph axis integrity in patients with hypopituitarism.

**Material and Methods:** Forty-three patients with hypopituitarism were divided into 2 groups. In Group I it was not associated with an intervention in the pituitary region (n=19) and in Group II it was always secondary to a sellar region procedure (n=24). Antithyroid antibodies, basal prolactina level, and prolactin level after thyrotropin-release hormone stimulation were evaluated in both groups.

**Results:** Antibodies were detected in 16% of the patients, with no significant difference between groups. Basal prolactin level median was significantly lower in group I (4 ng/mL vs 15 ng/mL; *P*=0.01), though the occurrence of hyperprolactinemia was similar between groups. Hypoprolactinemia was significantly more common in Group I (*P*=0.027). A low prolactin reserve was found in 84% of the patients with normal basal prolactin levels and in all patients with hypoprolactinemia. Antithyroid antibodies were positive in 15% of the patients with a diminished prolactin reserve.

**Conclusion:** Frequency of antithyroid antibodies in hypopituitarism was higher than in the normal population, especially in those with low prolactin reserve.

## INTRODUCTION

Recent studies have clarified the role of autoimmunity in the pathogenesis of pituitary disorders. Antipituitary antibodies were more frequently detected in patients with Sheehan's syndrome when compared with the control groups (respectively 63.1% and 14.2%).[1] A higher frequency of positivity for antipituitary antibodies was observed in adults with apparently idiopathic growth hormone (GH) deficiency when

compared to patients with GH deficiency secondary to surgical treatment of sellar and parasellar tumors (respectively 33% and 0%).[2] In addition, arginine vasopressin antibodies were found in one third of patients with a diagnosis of idiopathic diabetes insipidus.[3]

On the other hand, prolactin (PRL) plays a role as an immune-regulating hormone. PRL is produced by several hematopoietic cells and, acting through specific receptors expressed in the immune system cells, it exerts a cytokine-like activity. A positive correlation was demonstrated between hyperprolactinemia and autoimmune rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis,[4,5] Hashimoto's thyroiditis,[6,7] and rejection in heart transplantation.[8]

Experimental studies also showed impairment of immune activity in association with low levels of basal prolactin.[9] Thus, the role of PRL in the relationship between the endocrine system and the immune system has a biphasic character. At physiological levels, PRL is trophic for the lymphocytes; its insufficiency or hypersecretion appears to be immunosuppressive.[10]

This study was designed to extend the knowledge about the relationship between endocrine and autoimmune systems, assessing and relating the presence of antithyroid antibodies (TAb) and the integrity of the lactotroph axis in patients with hypopituitarism.

## PATIENTS AND METHODS

A total of 43 patients with a diagnosis of hypopituitarism were evaluated at a center of neuroendocrinology in the southern region of Brazil. The patients were divided in 2 groups according to hypopituitarism etiology: Group I, patients with hypopituitarism unrelated to surgery or radiotherapy in the sellar region (n=19), including 11 patients with Sheehan's syndrome and 8 patients with idiopathic hypopituitarism; and Group II, patients with hypopituitarism secondary to procedures in this region (n=24), surgery, and/or radiotherapy. Group I included 15 women and 4 men; Group II included 15 women and 9 men, with a mean age of 49.7 years (14 to 67) and 47.1 years (20 to 79), respectively. All of the patients were under adequate levothyroxine, estrogen/testosterone and glucocorticoid replacement, as needed.

Antibody antithyroperoxidase (TPOAb) was detected by chemoluminescence, with normal range values < 36 UI/mL. Antibody antithyroglobulin (TgAb) was detected by passive hemagluttination. Basal prolactin levels were measured by chemoluminescence and normal values were considered between 3 ng/dL and 30 ng/dL. Values above or below the limits of the reference range were respectively considered as basal hyperprolactinemia or hypoprolactinemia. In patients with normoprolactinemia or hyperprolactinemia, PRL reserve was analyzed through the thyrotropin-release hormone (TRH) stimulation test (PRL level between 30 and 60 minutes after stimulation with TRH intravenous, 200 mcg), performed at 8 a.m. fasting. The response to this test was considered adequate when there was at least a three-fold increase in the basal levels in women and a two-fold increase in men.[11]

Statistical analysis was performed through the Chi-square and Mann-Whitney tests, with a significance level of 5%.

This study was approved by the Committee of Ethics and Research of the institution where it was conducted.

## RESULTS

The frequency of positivity for one of the TAb in patients with hypopituitarism was 16% (n=7). Positivity for TPOAb was detected in 5 patients and positivity for TgAb was found in 4 patients. Two of

**Table 1.** Clinical, immunological, and hormonal features of patients with hypopituitarism.

| Patient | Etiology of hypopituitarism | Age (years) | Gender | TPOAb | TgAb | Basal PRL level (ng/dL) | Reserve PRL |
|---|---|---|---|---|---|---|---|
| 1 | Sheehan | 54 | F | | | 1 | □ |
| 2 | Sheehan | 56 | F | | | 6 | □ |
| 3 | Sheehan | 62 | F | | | 2 | □ |
| 4 | Sheehan | 44 | F | | | 1 | □ |
| 5 | Sheehan | 56 | F | + | | 4 | □ |
| 6 | Sheehan | 55 | F | | | 1 | □ |
| 7 | Sheehan | 67 | F | | | 2 | □ |
| 8 | Sheehan | 48 | F | | | 2 | □ |
| 9 | Sheehan | 64 | F | | | 3 | □ |
| 10 | Sheehan | 65 | F | | | 1 | □ |
| 11 | Sheehan | 37 | F | + | | 5 | □ |
| 12 | idiopathic | 31 | M | | | 51 | |
| 13 | idiopathic | 52 | F | | | 10 | □ |
| 14 | idiopathic | 48 | F | + | | 137 | |
| 15 | idiopathic | 47 | M | | | 2 | □ |
| 16 | idiopathic | 65 | F | | | 10 | □ |
| 17 | idiopathic | 14 | M | | | 24 | □ |
| 18 | idiopathic | 19 | F | | | 44 | |
| 19 | idiopathic | 61 | M | | | 10 | N |
| 20 | surgical | 60 | M | | | 16 | □ |
| 21 | surgical | 40 | F | | | 20 | |
| 22 | surgical | 43 | F | | | 2 | □ |
| 23 | surgical | 79 | M | | | 4388 | |
| 24 | surgical | 46 | F | | | 7 | □ |
| 25 | surgical | 39 | F | | | 15 | □ |
| 26 | surgical | 66 | M | | + | 10 | □ |
| 27 | surgical | 52 | M | | | 10,500 | |
| 28 | surgical | 29 | F | | | 38 | □ |
| 29 | surgical | 50 | F | | | 8 | N |
| 30 | surgical | 33 | F | | | 10 | □ |
| 31 | surgical | 47 | M | + | + | 129 | |
| 32 | surgical | 51 | F | | | 4 | □ |
| 33 | surgical | 48 | M | | | 2 | □ |
| 34 | surgical | 52 | F | | | 3 | □ |
| 35 | surgical | 49 | F | | | 31 | |
| 36 | surgical | 64 | M | | | 2000 | |
| 37 | surgical | 45 | F | | + | 29 | □ |
| 38 | surgical | 48 | F | | | 13 | □ |
| 39 | surgical | 34 | F | | | 19 | |
| 40 | surgical | 54 | F | | | 28 | |
| 41 | surgical | 20 | M | + | + | 13 | N |
| 42 | surgical | 20 | F | | | 44 | |
| 43 | surgical | 61 | M | | | 1 | □ |

TPOAb = antibody antithyroperoxidase
TgAb = antibody antithyroglobulin
PRL = prolactin
□ = diminished PRL reserve

these patients presented positive for both antibodies. There was no significant difference in the antibody frequency between groups. TAb were found in 3 (16%) patients of Group I (all women) and in 4 (16%) of Group II (3 men). TPOAb were present in 3 patients of Group I and in 2 of Group II (values ranging between 97 U/mL and 327 U/mL) and TgAb in 4 patients of Group II (titers ranging between 1/100 and 1/1600).

Hyperprolactinemia was detected in 10 patients and hypoprolactinemia in 11. In Group I, the basal serum PRL level ranged from 1 ng/mL to 137 ng/mL, while in Group II it ranged from 1 ng/mL to 10,500 ng/mL. The occurrence of hyperprolactinemia was similar in both groups; it was observed in 3 patients of Group I (16%) and in 7 patients of Group II (29%) ($P$=0.302). The frequency of hypoprolactinemia was significantly higher in Group I (8 cases; 42%) than in Group II (3 cases; 12%) ($P$=0.027). The basal PRL level median was significantly lower in Group I patients (4 ng/mL) when compared with that found in Group II (15 ng/mL) ($P$=0.01). From the 7 patients with hyperprolactinemia found in Group II, 4 were diagnosed with prolactinoma.

Regarding basal PRL levels, TAb positivity was detected in 23% of the patients with normal prolactinemia (5/22) and in 20% of those with hyperprolactinemia (2/10); no TAb positivity was found in patients with hypoprolactinemia ($P$=0.233).

Of 22 patients with hypopituitarism and normal basal PRL levels, 19 were submitted for a TRH stimulation test. Of those, 84% (n=16) presented with a low PRL reserve. There was no difference between groups (87% in Group I vs 82% in Group II; $P$=0.737). All patients with hypoprolactinemia were tested with no adequate result to TRH test. TAb positivity was found in 15% (4/27) of all patients with a low PRL reserve. Again, no difference between groups was found (2 from each group). Three patients presented with PRL levels at 60 minutes above the one measured at 30 minutes, with no consequences to the interpretation of the test.

## DISCUSSION

The observed frequency of TAb in patients with hypopituitarism was above that reported in the literature for the general population, in which the range is from 10% to 11%.[12] The frequency remained elevated considering the different etiologies of hypopituitarism. This finding suggests that the manifestation of thyroid autoimmunity is more related to the status of hypopituitarism and less to an autoimmunity factor involved in the genesis of hypopituitarism. The TAb did not prevail in the patients with hypopituitarism who had hyperprolactinemia, contrasting with literature evidence. Ferrari and colleagues evaluated 92 hyperprolactinemic patients and found that the prevalence of TgAb and antithyroid microssomal antibodies positivity was significantly higher than in controls, suggesting that autoimmune thyroid disorders, especially asymptomatic autoimmune thyroiditis, occurs in hyperprolactinemic women with a prevalence far exceeding that observed in the general population.[13]

Regarding the basal PRL level in patients with hypopituitarism, significantly higher levels were observed in patients with hypopituitarism secondary to a surgical procedure in the sellar region. This result might be associated with the permanence of functioning lactotrophs after intervention or with the presence of cell remnants of prolactinomas. On the other hand, hyperprolactinemia occurs in 44% of the cases of cranial/hypothalamic irradiation, with peak at 2 years and eventual decline to basal.[14] The higher frequency of

hypoprolactinemia in the group of patients with spontaneous hypopituitarism can be explained by the presence of women with Sheehan's syndrome, a situation where prolactin is usually the first pituitary hormone to be compromised. Noteworthy is the presence of positive antibodies in 31% of the patients with a diagnosis of low prolactin reserve. To the best of the authors' knowledge, there are no published studies about the prevalence of thyroid autoantibodies in hypoprolactinemic patients.

As an additional observation in this series, prolactin levels at 60 minutes did not influence the interpretation of the results of the TRH test, suggesting a reappraisal of the real necessity for determining the PRL level at this time as part of the test.

Finally, the results point to an increased prevalence of antithyroid antibodies in hypopituitarism, regardless of its etiology, particularly in cases where the reserve of prolactin is inadequate. Further investigation is necessary to verify whether thyroid autoimmunity is accompanied by pituitary autoimmunity and whether prolactin alterations mediate these processes.

## REFERENCES


1. Goswami R, Kochupilla N, Crock PA, et al. Pituitary autoimmunity in patients with Sheehan's syndrome. *J Clin Endocrinol Metab*. 2002;87:4137-4141.
2. DeBellis A, Bizzarro A, Conte M, et al. Antipituitary antibodies in adults with apparently idiopathic growth hormone deficiency and in adults with autoimmune endocrine diseases. *J Clin Endocrinol Metab*. 2003;88:650-654.
3. Pivonello R, DeBellis A, Faggiano A, et al. Central diabetes insipidus and autoimmunity: relationship between the occurrence of antibodies to arginine vasopressin-secreting cells and clinical, immunological and radiological features in a large cohort of patients with central diabetes insipidus of known and unknown etiology. *J Clin Endocrinol Metab*. 2003;88:1629-1636.
4. Jara LJ, Gomez-Sanchez C, Silveira LH, et al. Hyperprolactinemia in systemic lupus erythematosus: association with disease activity. *Am J Med Sci*. 1992;303:222-226.
5. Mateo L, Nolla J, Bonnin M, et al. High serum prolactin levels in men with rheumatoid arthritis. *J Rheumatol*. 1998;25:2077-2082.
6. Legakis I, Petroyianni V, Saramantis A, et al. Elevated prolactin to cortisol ratio and polyclonal autoimmune activation in Hashimoto's thyroiditis. *Horm Metab Res*. 2001;33:585-589.
7. Walker SE. Bromocriptine treatment of systemic lupus erythematosus. *Lupus*. 2001;10:762-768.
8. Carrier M, Wild J, Pelletier LC, et al. Bromocriptine as an adjuvant to cyclosporine immunosupression after heart transplantation. *Ann Thorac Surg*. 1990;49:129-132.
9. Yu-Lee L. Prolactin modulation of immune and inflammatory responses. *Recent Prog Horm Res*. 2002;57:435-455.
10. Reber PM. Prolactin and immunomodulation. *Am J Med*. 1993;95:637-644.
11. Cone RD, Low MJ, Elmquist JK, et al. Neuroendocrinology. In: Larsen PR, Kronenberg HM, Melmed S, et al, editors. *Williams Textbook of Endocrinology*. 13th ed. Philadelphia: WB Saunders; 2003:81-176.
12. Hollowell JG, Staehling NW, Flander D, et al. Serum TSH, T4 and thyroid antibodies in the United Sates population (1988-1994): National Health and Nutrition Examination Survey (NHANESIII). *J Clin Endocrinol Metab*. 2002;87:489-499.
13. Ferrari C, Boghen M, Paracchi A, et al. Thyroid autoimmunity in hyperprolactinaemic disorders. *Acta Endocrinol*. 1983;104:35-41.
14. Littley MD, Shalet SM, Beardwell CG, et al. Hypopituitarism following external radiotherapy for pituitary tumours in adults. *Q J Med*. 1989;70:145-160.