apresentação de casos

Persistence of Hyperprolactinemia After Treatment of Primary Hypothyroidism and Withdrawal of Long Term Use of Estrogen. Are the Tuberoinfundibular Dopaminergic Neurons Permanently Lesioned?

Luiz Augusto Casulari
Fábio Celotti
Luciana A. Naves
Lucília Domingues
Carla Papadia

Unidade de Neurocirurgia, Hospital de Base do Distrito Federal - Escola Superior em Ciências da Saúde, SES-DF, Brasília, DF (LAC); Istituto di Endocrinologia, Università degli Studi di Milano, Itália (FC); Serviços de Endocrinologia (LAN,CP) e de Ginecologia (LD), Universidade de Brasília, DF

Recebido em 02/08/04
Revisado em 18/10/04 e 06/12/04
Aceito em 29/04/05

ABSTRACT

Long term use of high doses of estrogen and the presence of chronic hyperprolactinemia may, at least in the rat, provoke lesions in the tuberoinfundibular dopaminergic (TIDA) neurons responsible for the control of prolactin (Prl) secretion. This occurrence, which is not yet well documented in humans, may have taken place in a patient on chronic oral hormonal contraceptive (OC) treatment who was seen for primary hypothyroidism, hyperprolactinemia and a pituitary mass. After thyroid hormone replacement, OC withdrawn and bromocriptine treatment, this patient could not maintain normal Prl levels, unless continuously treated with a dopaminergic agonist even when MRI was indicative of a normal situation. Function of TIDA neurons was investigated by TRH test (200µg IV) performed before and after treatment with 25mg carbidopa plus 250mg L-dopa every 4 hours for one day. Basal TSH was normal (3.9µU/mL) whereas basal Prl was high (67.5 ng/mL); both TSH and Prl levels appropriately increased after TRH: peaks 31.8µU/mL and 157.8 ng/mL, respectively. After treatment with carbidopa/L-dopa, basal TSH (1.6µU/mL) and Prl (34ng/mL) decreased and the response to TRH was partially blocked (10.3µU/mL and 61ng/mL, respectively). In spite of a normal response, we discuss the possibility that the persistence of hyperprolactinemia is due to lesion of the TIDA neurons produced by the long term use of high doses of estrogens and by the presence of chronic hyperprolactinemia. **(Arq Bras Endocrinol Metab 2005;49/3:468-472)**

Keywords: Hypothyroidism; Hyperprolactinemia; Estrogen; Dopamine; Pituitary.

RESUMO

Persistência de Hiperprolactinemia Após Tratamento de Hipotiroidismo Primário e Suspensão do Uso Prolongado de Estrogênio: os Neurônios Dopaminérgicos Túberoinfundibulares São Permanentemente Lesados?
Uso prolongado de altas doses de estrogênio e a presença de hiperprolactinemia crônica pode, pelo menos no rato, provocar lesão nos neurônios dopaminérgicos tuberoinfundibulares (TIDA) responsáveis pelo controle da secreção de prolactina (Prl). Essa ocorrência, ainda não bem documentada em humanos, pode ter ocorrido em uma paciente em tratamento crônico com contraceptivo oral (OC), que veio para consulta por hipotiroidismo primário, hiperprolactinemia e uma massa hipofisária. Após reposição de hormônio tiroidiano, suspensão do tratamento com o OC e a bromocriptina, essa paciente não manteve níveis normais de Prl, necessitando tratamento contínuo com agonista dopaminérgico, mesmo quando a RM da região selar indicava uma situação normal. A função dos neurônios TIDA foi investigada pelo teste do TRH (200µg IV), realizado antes e após 25mg de carbidopa e 250mg de L-dopa a cada 4 horas por um dia. TSH basal (3,9µU/mL) era normal, enquanto Prl (67,5 ng/mL) estava alta; ambos aumentaram apropriadamente após o estímulo com TRH, com picos de 31,8µU/mL (TSH) e 157,8ng/mL (Prl). Após tratamento com carbidopa/L-dopa, os níveis de

TSH (1,6µU/mL) e Prl (34ng/mL) diminuíram e a resposta ao TRH foi parcialmente bloqueada (10,3µU/mL e 61ng/mL, respectivamente). Apesar da resposta normal, discutimos a possibilidade que a persistência da hiperprolactinemia é devida a uma lesão dos neurônios TIDA, produzida pelo longo uso de altas doses de estrogênios e pela presença de hiperprolactinemia crônica. **(Arq Bras Endocrinol Metab 2005;49/3:468-472)**

Descritores: Hipotiroidismo; Hiperprolactinemia; Estrogênio; Dopamina; Hipófise

PROLACTIN SECRETION IS REGULATED by dopamine (DA) produced in the hypothalamus. DA is synthesized by the tuberoinfundibular dopaminergic (TIDA) neurons which have their cell bodies in the arcuate and periventricular nuclei of the hypothalamus and axon terminals in the median eminence (1).

Several studies in the rat have demonstrated the inhibitory effects of long term treatment with estradiol on the function of TIDA neurons, in contrast with the stimulatory effects caused by a short term treatment (see (2) for references). The inhibition of TIDA neurons contributes to hyperprolactinemia associated with the use of hormonal oral contraceptives (OC) and estrogen replacement therapy in post-menopause. Moreover, estrogens are responsible for lactotrope hyperplasia and prolactin (Prl) hypersecretion occurring during gestation (1).

Frequently, primary hypothyroidism is associated with hyperprolactinemia which almost never exceeds 80ng/mL (3). Several mechanisms are possibly involved in this occurrence: reduced secretion of some Prl inhibitory factors, increased secretion of TRH and enhanced pituitary sensitivity to tonic TRH secretion (1). Long lasting primary hypothyroidism can induce hyperplasia of TSH and Prl producing cells, causing a radiological image suggestive of a pituitary tumor (4-8).

In this report, we evaluated a patient with primary hypothyroidism on OC for 13 years who developed a pituitary pseudo-tumor associated with greatly increased TSH and Prl secretion. After L-thyroxine (L-T4) replacement, bromocriptine treatment and OC withdrawn, TSH and Prl levels normalized, as well as the radiological pituitary image. However, to maintain normal circulating Prl levels it was necessary to treat the patient chronically with bromocriptine, even after seven years from the beginning of the L-T4 treatment. In an attempt to evaluate TIDA neurons function, a TRH test was performed, both before and after previous L-dopa plus carbidopa treatment.

We discussed the possibility that the chronic use of OC and the long lasting hyperprolactinemia might have produced an irreversible damage to the TIDA neurons, perpetuating the hyperprolactinemia syndrome in the patient.

CASE REPORT

A 35 year-old white woman, came initially to our observation for amenorrhoea, galactorrhea, headache, cold intolerance, sleepiness and intestinal constipation. Physical exam revealed a very dry yellowish skin, dry and brittle hair, brittle fingernails and pre-tibial edema. Thyroid was not palpable. Heart frequency was 64 bpm and blood pressure 100x70mmHg. Her symptoms have started one year earlier when OC therapy (ethinylestradiol 0.05mg + cyproterone acetate 2mg), continuously used for the last 13 years, was interrupted. The patient reported menarche when she was 13, followed by regular 28±3 day cycles and a normal pregnancy with vaginal delivery. Her mother was affected by hypothyroidism, systemic arterial hypertension and hepatic cirrhosis.

Laboratory results at the initial observation were: Prl = 243ng/mL (NR <25ng/mL); TSH = 827µU/mL (NR 0.35-4.5µU/mL); thyroxine (T4) = 1.68µg/dL (NR 4.5-12µg/dL); triiodothyronine (T3) = 35ng/dL (NR 80-210ng/dL); free T4 = 0.5ng/dL (NR 0.8-1.8ng/dL); antithyreoglobulin <1:100 and antimicrosomal 1/25,600 antibodies; FSH = 2.8mUI/mL (NR 4-13mUI/mL, follicular phase; microparticles enzymatic immunoassay); LH = 0.77mUI/mL (NR 1-18mUI/mL, follicular phase); total cholesterol = 238mg/dL (NR <200mg/dL); triglyceride = 162mg/dL (NR <150mg/dL); HDL = 62mg/dL (NR >40mg/dL). Prl and LH were measured by immunoluminescence assay; TSH, T4, T3, and free T4 by immunofluorimetric assays.

Computerized sellar tomography (CT) showed a 1.1cm pituitary mass, with suprasellar extension (figure 1).

Initial replacement therapy with 25µg/day of L-T4 was followed by a progressive increase up to 100µg/day, together with bromocriptine (1.25mg twice a day). After 6mo of treatment, menses resumed, and galactorrhea, headache, and hair fall improved; TSH (2.6µU/mL) and Prl (12.5ng/mL) normalized. Pituitary CT scans did not show the presence of any pituitary mass. Seven years after the beginning of treatment, sellar MRI discloses a normal pituitary image (figure 2) with normal TSH levels (from 0.8 to

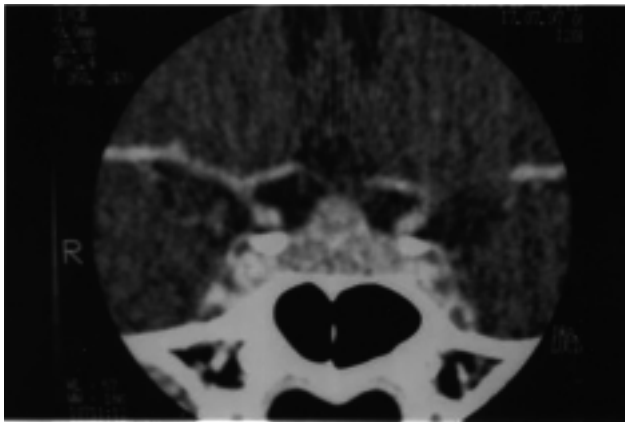

Figure 1. Computerized sellar tomography showing pituitary hyperplasia with suprasellar extension.

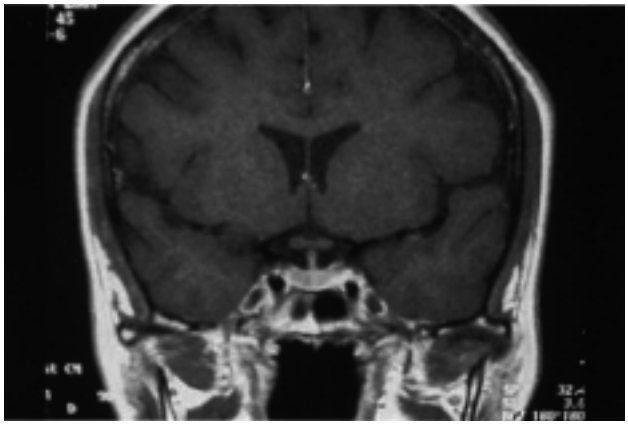

Figure 2. Magnetic resonance imaging seven years after the beginning of treatment discloses a normal pituitary image.

Table 1. Prolactin and TSH responses to TRH (200µg IV) before and 24 hours after treatment with 250mg L-dopa and 25mg carbidopa.

Hormone / time (min)	-10	0	20	40	60	80
Prolactin (ng/mL)						
Before	68.5	67.5	158	150	104	126
After	64	34	61	59	50	43
TSH (µU/mL)						
Before	4.0	3.9	34.5	31.8	17.5	24.4
After	1.6	1.6	10.3	9.2	6.8	5.0

4.0µU / mL). However, Prl levels, almost normal while on bromocriptine, increases as soon as treatment is interrupted (from 33.9 to 77.0ng / mL). Assessment of macroprolactin was negative.

Due to persistence of hyperprolactinemia, we investigated the tuberoinfundibular dopaminergic function by TRH test, performed before and after one day treatment with L-dopa+carbidopa (see discussion for the rationale of the test). While maintained on 100µg of L-T4 replacement, the patient was submitted to consecutive (one day apart) TRH tests (200 µg IV), one before and one after the administration of 25mg carbidopa plus 250mg L-dopa (MSD, São Paulo) every 4 hours for 24 hours. Blood samples were collected at -10, 0, and 20, 40, 60 and 80min after injection. Blood was immediately centrifuged (3000rpm, for 10min) and the serum obtained frozen at -20°C, until TSH and Prl were assayed.

As seen in Table 1, basal TSH levels (-10 and 0) were normal whereas basal Prl was high; both TSH and Prl levels increased appropriately after TRH stimulation. After carbidopa / L-dopa treatment, basal TSH levels (-10 and 0) decreased and its response to TRH was partially blocked. Prl level at -10min was similar to that observed before treatment, but the level at time 0 was lower. Prl response to TRH was partially blocked by previous treatment with carbidopa / L-dopa.

DISCUSSION

It is well known that long term primary hypothyroidism may increase TSH and Prl levels (8-11) and produce pituitary enlargement, documented by neuroradiologic imaging (4-8). These alterations are mainly produced by the high levels of TRH induced by the decreased negative feedback of thyroid hormones at the hypothalamic / pituitary level (9). TRH stimulates the secretion of both TSH and Prl producing hypertrophy and hyperplasia of TSH and Prl secreting cells. In primary hypothyroidism the number and sensitivity of TRH receptors increases in the thyrotrope and the lactotrope. TSH and Prl responses to TRH are also increased (9). After thyroid hormone replacement, normalization of TSH secretion might be delayed for months after normalization of T3 and T4 levels (6).

This delay probably represents the time needed for the thyrotrope mass to regress (5). Recovery of the thyroid axis function (basal TSH levels and its response to TRH) occurs earlier than that of Prl (6,9).

Primary hypothyroidism is associated with a modest increase of Prl levels in 40% of the patients, whereas levels higher than 25ng / mL are reached only in 10% of subjects (11). The patient described in this study had very high Prl levels (243 ng / mL), a concentration never observed in patients with primary hypothyroidism (11). Moreover, she was persistently hyperprolactinemic, in spite of the fact that she was euthyroid in the last 7 years after adequate L-T4 replacement.

The possibility that our patient has developed a Prl-secreting microadenoma due to long term use of OC is unlikely because: 1) the initial CT (figure 1) showed only a homogeneous hyperplasia of the pituitary, and further control images showed a normal pituitary, even when the use of dopamine agonists were interrupted with resultant increase in Prl levels; 2) it has not yet been proved that the use of OC may cause a prolactinoma (see 1 for discussion and references).

We suggest that the use of ethinylestradiol plus cyproterone acetate for 13 years might have contributed to produce the hyperprolactinemic syndrome in our patient. It is known that the use of an OC, or the estrogen replacement therapy for menopause, increases 1.5 to 2-fold the circulating Prl levels (12). Estrogens stimulate the synthesis of Prl DNA, mRNA, of Prl itself and the proliferation of lactotropes (see 1 for references). Moreover, estrogens enhance the response of Prl to TRH, increasing the number of TRH receptors in the lactotrope. It has also been demonstrated in long term estrogen-treated mice the presence of an irreversible lesion of TIDA neurons (see 1 for review). Also, in Fischer 344 rats, prolonged exposure to estradiol 17-beta (E2) has been shown to decrease dopamine synthesis and release from TIDA neurons (13); these lesions appear to persist even after E2 removal (14). Since bromocriptine prevents the tuberoinfundibular neuronal release of dopamine after removal of chronic estrogen treatment, it is possible that the decline in TIDA neuronal release of dopamine induced by chronic E2 treatment is at least in part exerted via the marked hyperprolactinemia in the mouse (15,16).

We have tried to evaluate the integrity of the TIDA system in our patient using the TRH test before and after a L-dopa / carbidopa treatment. The rationale for this test relies on the fact that the administration of L-dopa, when given alone, increases the amount of dopamine reaching the lactotrope directly in the pituitary or via TIDA pathways, since dopa-decarboxylase, the enzyme that transforms dopamine into L-dopa, is present both at the pituitary and at the hypothalamic level (17). If the compound is administered together with carbidopa, a dopa-decarboxylase inhibitor, the enzyme is blocked only at pituitary level, because carbidopa cannot cross the blood-brain barrier. Hence, the treatment with L-dopa / carbidopa increases only the pool of dopamine reaching the pituitary cells from TIDA pathways. In subjects with normal TIDA pathways, the degree of Prl inhibition after L-dopa alone or after carbidopa treatment is similar (17).

As can be observed in table 1, basal TSH levels and its response to TRH were normal in our patient; TSH peak after TRH in an euthyroid subject is 5 to 10 times higher than the basal TSH serum concentration (18). This demonstrates that the patient was adequately L-T4 replaced and that her high Prl levels were not due to the presence of primary hypothyroidism. After L-dopa / carbidopa treatment, both baseline TSH levels and its response to TRH were decreased. This is compatible with a normal TIDA neuronal function in controlling TSH secretion since dopamine inhibits basal and TRH-stimulated TSH secretion in normal subjects (19).

The data of the Prl response to TRH before and after treatment with L-dopa / carbidopa are also shown in table 1. Before treatment, baseline Prl levels were increased. After treatment with L-dopa / carbidopa, Prl levels at time -10 was equal to that observed before treatment but decreased at time 0. It is possible that the high Prl level observed at time –10 was due to stress caused by the patient arriving to the hospital in order to perform the test. The Prl increase induced by stress is usually short-lasting and it is not mediated by dopaminergic pathways (20).

The 44% decrease observed in baseline Prl levels after L-dopa / carbidopa is similar to that reported in normal women (21). Before treatment, the TRH stimulus produced a 134% increase over basal levels; a Prl response to TRH higher than 100% over baseline is considered normal (1). After treatment with L-dopa / carbidopa, Prl response to TRH decreased to 79% of baseline, a result similar to that observed in normal subjects (22).

In conclusion, the results obtained in our patient did not allowed to identify the level at which the hormonal dysregulation takes place. The patient's morphologically normal pituitary gland produces normal responses to exogenous TRH in terms of both TSH and Prl secretion, suggesting a hypothalamic

involvement. However, the TRH test with L-dopa/carbidopa does not appear to support the hypothesis of a lesion in the TIDA neurons, produced by the long term use of estrogen/hyperprolactinemia. It is possible that inhibition of peripheral dopa-decarboxylase by carbidopa was not complete and that even modestly increased plasma dopamine levels could have been sufficient to inhibit Prl stimulation by TRH (22) making the L-dopa/carbidopa pretreatment unable to prove a central lesion of the TIDA system.

ACKNOWLEDGMENT

We are indebted to Luiz Gustavo Domingues Casulari da Motta for technical assistance.

REFERENCES

1. Molitch ME. Prolactinoma. In: Melmed S, editor. **The pituitary**. Blackwell Science:Cambridge, **1995**. p.443-77.
2. Arita J, Kimura F. Direct inhibitory effect of long term estradiol treatment on dopamine synthesis in tuberoinfundibular dopaminergic neurons: In vitro studies using hypothalamic slices. **Endocrinology 1987**;121:692-8.
3. Motta LDC, Gandulfo V, Simões P, Zaconeta A, Silva NC, Motta LACR. Hiperprolactinemia. Avaliação etiológica, clínica e laboratorial. **Rev Bras Ginec Obstet 1997**;19:573-86.
4. Yamada T, Tsukui T, Ikejiri K, Yukimura Y, Kotani M. Volume of sella turcica in normal subjects and in patients with primary hypothyroidism and hyperthyroidism. **J Clin Endocrinol Metab 1976**;42:817-22.
5. Jawadi MH, Ballonoff LB, Stears JC, Katz FH. Primary hypothyroidism and pituitary enlargement: Radiological evidence of pituitary regression. **Arch Intern Med 1978**;138:1555-7.
6. Smallridge RC. Thyrotropin-secreting pituitary tumors. **Endocrinol Metab Clin N Amer 1987**;16:765-92.
7. Dadachanji MC, Bharucha NE, Jhankaria BG. Pituitary hyperplasia mimicking pituitary tumor. **Surg Neurol 1994**;42:397-99.
8. Betônico CR, Rodrigues R, Mendonça SCL, Jorge PT. Hipotiroidismo primário simulando volumoso macroadenoma hipofisário. **Arq Bras Endocrinol Metab 2004**;48:423-6.
9. Snyder PJ, Jacob LS, Utiger RD, Daughaday WH. Thyroid hormone inhibition of the prolactin response to thyrotropin-releasing hormone. **J Clin Invest 1973**;52:2324-9.
10. Onishi T, Miyai K, Aono T, Shioji T, Yamamoto T. Primary hypothyroidism and galactorrhea. **Am J Med 1977**;63:373-8.
11. Honbo KS, Herle AJV, Kellett KA. Serum prolactin levels in untreated primary hypothyroidism. **Am J Med 1978**;64:782-7.
12. Abu-Fadil S, DeVane G, Siler TM, Yen SS. Effects of oral contraceptive steroids on pituitary prolactin secretion. **Contraception 1976**;13:79-85.
13. Gottschall PE, Meites J. Evidence for a permanent decline in tuberoinfundibular dopaminergic neuronal function after chronic estrogen treatment is terminated in Fischer 344 rats. **Neuroendocrinology 1986**;44:211-6.
14. Gottschall PE, Sarkar DK, Meites J. Persistence of low hypothalamic dopaminergic activity after removal of chronic estrogen treatment. **Proc Soc Exp Biol Med 1986**;181:78-86.
15. Sarkar DK, Gottschall PE, Meites J. Decline of tuberoinfundibular dopaminergic function resulting from chronic hyperprolactinemia in rats. **Endocrinology 1984**; 115:1269.
16. Gottschall PE, Meites J. Bromocryptine prevents the decline in tuberoinfundibular neuronal release of dopamine after removal of chronic estrogen treatment. **Proc Soc Exp Biol Med 1987**;186:150-6.
17. Fine SA, Frohman LA. Loss of central nervous system component of dopaminergic inhibition of prolactin secretion in patients with prolactin-secreting pituitary tumors. **J Clin Invest 1978**;61:973-80.
18. Hershman JM, Pittman JA Jr. Response to synthetic thyrotropin-releasing hormone in man. **J Clin Endocrinol Metab 1970**;31:457-460.
19. Scanlon MF, Weightman DR, Shale DJ, Mora B, Heath M, Snow MH, et al. Dopamine is a physiological regulator of thyrotrophin (TSH) secretion in normal man. **Clin Endocrinol 1979**;10:7-15.
20. Gala RR. The physiology and mechanism of the stress induced changes in prolactin secretion in the rat. **Life Sci 1990**;46:1407-20.
21. Rao A, Scommegna A, Frohman LA. Integrity of central dopaminergic system in women with postpartum hyperprolactinemia. **Am J Obstet Gynecol 1982**;143:883-7.
22. Carlson HE. Carbidopa plus L-dopa pretreatment inhibits the prolactin (PRL) response to thyrotropin-releasing hormone and thus cannot distinguish central from pituitary sites of prolactin stimulation. **J Clin Endocrinol Metab 1986**;63:249-51.

Address for correspondence:

Luiz Augusto Casulari
CLINEN - Ed. América Office Tower, salas 1105/06
SCN, quadra 1, bloco F
70710-500 Brasília, DF Brazil
E-mail: lacasulari@unb.br