Case Report

SUCCESSFUL THERAPY FOR A MIXED THYROTROPIN- AND PROLACTIN-SECRETING PITUITARY MACROADENOMA WITH CABERGOLINE

James R. Mulinda, M.D., Stefan Hasinski, M.D., F.A.C.E., and Leslie I. Rose, M.D., F.A.C.E.

ABSTRACT

Objective: To describe the first case of a mixed thyrotropin (TSH)- and prolactin-secreting pituitary macroadenoma that responded to therapy with cabergoline.

Methods: We present a case report with clinical, laboratory, and radiologic details.

Results: An 84-year-old woman with central hyperthyroidism due to a mixed TSH- and prolactin-secreting pituitary macroadenoma was successfully treated with orally administered cabergoline, 0.25 mg twice per week. Serial assays of thyroid and pituitary hormones were done, and magnetic resonance imaging of the pituitary was performed before and 16 weeks after initiation of cabergoline therapy. The patient had complete resolution of the increased pituitary hormone indices within 6 weeks after implementation of therapy, and these results were sustained for more than 16 weeks. A magnetic resonance imaging scan showed no change in tumor size at 16 weeks of therapy.

Conclusion: When medical treatment of TSH-secreting tumors is considered, choices of efficacious drugs are limited. To our knowledge, this report describes the first case of a long-acting dopamine agonist used successfully to control hypersecretion of a mixed TSH- and prolactin-secreting macroadenoma. Oral administration of cabergoline twice a week was effective, convenient, and well tolerated. Further evaluation of cabergoline, when indicated as medical therapy for TSH-secreting tumors, is warranted. **(Endocr Pract. 1999;5:76-79)**

INTRODUCTION

Thyrotropin (thyroid-stimulating hormone [TSH])-secreting adenomas are rare, accounting for 2.8% of all pituitary adenomas (1,2). Current therapy for patients with TSH-secreting adenomas includes surgical excision, irradiation, long-acting somatostatin analogues, and dopamine receptor agonists. Short-acting dopamine receptor agonists have not been efficacious in managing TSH-secreting tumors; instead, long-acting somatostatin analogues have been the mainstay of medical management (2). We report the first case of a long-acting dopamine receptor agonist used successfully for sustained suppression of TSH and prolactin secretion by a pituitary macroadenoma.

CASE REPORT

An 84-year-old Caucasian woman with a 3-year history of hyperthyroidism was referred in June 1997 for evaluation of persistent fatigue, muscle weakness, and constipation. Her past medical history was significant for diabetes mellitus, breast cancer, and hypertension. Medications included levothyroxine (0.225 mg daily), atenolol (100 mg daily), insulin, hydrochlorothiazide-triamterene, and tamoxifen.

Physical examination revealed an elderly woman with a blood pressure of 176/70 mm Hg and a heart rate of 52 beats/min. She had no palpable thyroid tissue. Proximal muscle weakness was noted. The rest of the physical examination was unremarkable. Thyroid studies revealed a serum TSH of 4.4 mIU/L (normal, 0.3 to 4.5), a total thyroxine (T_4) of 19.4 µg/dL (normal, 5.5 to 11.5), and a triiodothyronine uptake ratio (T_3U) of 1.04 (normal, 0.8 to 1.2). Although the patient had hyperthyroxinemia, the serum TSH was not appropriately suppressed.

A review of the medical records showed normal results of thyroid studies in 1992. In November 1994, the patient had undergone assessment because of complaints of weakness and fatigue. Thyroid studies revealed a serum TSH of 1.86 mIU/L, T_4 of 17.3 µg/dL, and T_3U ratio of 1.13 (Table 1). No therapy was instituted at that time. In May 1995, thyroid studies showed a serum TSH of 1.5 mIU/L, T_4 of 16.8 µg/dL, and T_3U ratio of 1.26. A ^{123}I uptake study was then performed; the 6-hour uptake was 12.5% (normal, 6 to 16%), and the 24-hour uptake was 20% (normal, 10 to 35%). Again, no therapy was initiated. The patient's symptoms persisted, and results of multiple serum thyroid assays remained unchanged. In April 1996, the ^{123}I uptake study was repeated and revealed a normal 24-hour uptake of 26%. The patient was thought to

Submitted for publication March 5, 1998
Accepted for publication July 6, 1998
From the Allegheny University of the Health Sciences, Allegheny University Hospitals, Hahnemann Division, Division of Endocrinology and Metabolism, Philadelphia, Pennsylvania.
Address correspondence and reprint requests to Dr. L. I. Rose, Allegheny University of the Health Sciences, 230 North Broad Street, MS 426, Philadelphia, PA 19102.
© 1999 AACE.

have hyperthyroidism despite the normal 24-hour uptake, and 21 mCi of ^{131}I was administered. No thyroid scan reports were available for review. In August 1996, thyroid studies showed a serum TSH of 15.1 mIU/L and T_4 of 4.9 µg/dL. Levothyroxine replacement therapy was initiated. Increasing doses of levothyroxine were used in attempts to normalize her TSH. During levothyroxine treatment with 0.225 mg/day, the serum TSH was 4.4 mIU/L and T_4 was 19.4 µg/dL. Because her symptoms had not been alleviated, she was then referred for further evaluation.

A TSH-secreting adenoma was suspected on the basis of previous blood studies that showed persistently increased serum T_4 levels in the presence of detectable serum TSH levels before and after ^{131}I therapy. The dosage of levothyroxine was reduced to 0.175 mg daily, and the daily dose of atenolol was decreased to 50 mg. A magnetic resonance imaging (MRI) scan of the pituitary disclosed a macroadenoma (5.5 by 2.9 by 3.7 cm) invading the surrounding structures, including both cavernous sinuses and the sphenoid sinus, but sparing the optic chiasm and optic tracts. Pituitary studies revealed a serum prolactin level of 1,927 ng/mL and an alpha subunit level of 11 ng/mL (Table 2). Serum cortisol levels were normal in response to cosyntropin stimulation testing. Results of formal visual field testing were normal.

Different therapeutic modalities were discussed with the patient, and she agreed to begin medical therapy. Somatostatin analogues were considered, but this treatment was not initiated because the patient had diabetes and gastrointestinal symptoms. In August 1997, treatment was initiated with cabergoline, 0.25 mg orally twice per week. After 6 weeks of treatment with cabergoline, the serum prolactin, TSH, and alpha subunit levels decreased to 21.1 ng/mL, 1.1 mIU/L, and 0.8 ng/mL, respectively (Table 2). The dosage of levothyroxine was reduced to 0.125 mg daily. The atenolol therapy was subsequently discontinued. After 12 weeks of therapy, the serum prolactin, TSH, and alpha subunit levels had declined to 8.0 ng/mL, 1.2 mIU/L, and 0.4 ng/mL, respectively (Table 2). An MRI scan of the pituitary performed after 16 weeks of cabergoline therapy revealed no change in tumor size. The therapy was well tolerated, and the patient had no complications.

DISCUSSION

TSH-secreting pituitary adenomas are rare. They constitute 2.8% of all pituitary adenomas (2). Mixed pituitary adenomas that secrete both thyrotropin and prolactin are even less frequent, only 30 cases having been reported previously (2). These pituitary tumors manifest primarily in three clinical scenarios—hyperthyroidism, mass effects, or incidentally discovered. Up to a third of these patients have hyperthyroidism at assessment and may initially undergo thyroid ablation with radioactive iodine or thyroidectomy before the pituitary tumor is discovered (2-4). Central hyperthyroidism should be suspected in any patient with hyperthyroidism and a detectable serum TSH level. The differential diagnosis of a detectable serum TSH level in the presence of hyperthyroxinemia includes increased transport proteins, severe systemic illness, acute psychiatric illness, certain drug therapy, resistance to thyroid hormones, antithyroxine autoantibodies, TSH-producing pituitary adenomas, or excess thyrotropin-releasing hormone from a tumor or the hypothalamus. These entities can be diagnosed on the basis of the history and physical examination, evaluation of serum thyrotropin and thyroid hormone levels, evaluation of serum alpha subunit levels, and other appropriate laboratory and imaging studies. The presence of increased alpha subunit is suggestive of excessive production of thyrotropin.

The patient had increased thyroid hormone levels with inappropriately normal serum TSH levels for several months. She underwent radioactive iodine treatment for hyperthyroidism without resolution of her symptoms. The serum TSH was partially responsive to thyroid hormone replacement, which may have contributed to the delay in correct diagnosis. Patients may have mass effects such as visual field deficits in 50% of cases and headache in 17% (2). Although this patient had an invasive macroadenoma, she did not have any of these symptoms. When a pituitary tumor is suspected, pituitary hormonal studies should be performed. If any hormone level is inappropriate, the entire hormonal feedback axis should be evaluated. Imaging of the pituitary by computed tomographic scanning or, preferably, by MRI scanning should be done.

Table 1
Serial Results of Serum Thyroid Function Studies*

Study	Normal Range	Date							
		8/92	11/94	5/95	6/96	8/96	6/97	9/97	11/97
TSH (mIU/L)	0.3-4.5	1.77	1.86	1.5	2.2	15.1	4.4	1.1	1.2
Total T_4 (µg/dL)	5.5-11.5	10.8	17.3	16.8	14.2	4.9	19.4	11.0	10.9
T_3U ratio	0.8-1.2	1.12	1.13	1.26	1.12	0.81	1.04	0.96	0.81

*T_4 = total thyroxine; TSH = thyroid-stimulating hormone; T_3U = triiodothyronine uptake ratio.

Table 2
Serial Results of Serum Pituitary Hormone Studies*

Study	Normal range	Date 8/97	9/97	11/97
TSH (mIU/L)	0.3-4.5	4.4	1.1	1.2
Alpha subunit (ng/mL)	0.1-3.9	11	0.8	0.4
Prolactin (ng/mL)	0-24	1,927	21.1	8.0
ACTH (pg/mL)	0-70	19	…	…
FSH (IU/L)	39.3-120.6	4.9	…	…
LH (IU/L)	5.0-52.3	1.3	…	…
hGH (ng/mL)	0-14	2.92	…	…

*ACTH = adrenocorticotropic hormone (corticotropin); FSH = follicle-stimulating hormone; hGH = human growth hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone (thyrotropin).

Treatment of TSH-secreting macroadenomas is usually by surgical resection. Radiation therapy can be used if the tumor is large, if it recurs, or if surgical intervention is contraindicated. Antithyroid medications are used to restore a euthyroid state preoperatively. Medical therapy is reserved for tumors that are small or incompletely resected or for tumor recurrence. In addition, medical therapy can be used in patients who cannot tolerate irradiation or as an adjunctive measure to operative treatment. Long-acting somatostatin analogues such as octreotide and lanreotide are often the agents of choice (5-7). Both reduce serum TSH and alpha subunit levels in >90% of cases and are associated with TSH normalization in almost 80% of cases (2). These agents, however, are associated with euthyroidism in only 50 to 70% and tachyphylaxis in up to 22% of cases. Resistance to octreotide may occur in 4% of cases (1,2,5,8,9). Side effects to these agents include carbohydrate intolerance and gastrointestinal distress.

Dopamine agonists have traditionally been ineffective in TSH-secreting pituitary tumors partly because they are short acting. With the availability of long-acting dopamine agonists such as cabergoline, increasing numbers of pituitary tumors have been found to be responsive to dopamine agonists (10,11). In healthy subjects, cabergoline suppresses secretion of prolactin by the pituitary but has no effect on thyrotropin (12). To our knowledge, this is the first report of a patient with a mixed TSH- and prolactin-secreting pituitary tumor responsive to cabergoline, with return of hormonal levels to normal within 6 weeks after initiation of therapy. The response has been sustained for more than 16 weeks with use of the same dose of cabergoline. After 16 weeks of treatment, no change in tumor size was evident radiologically. The therapy seems to be well tolerated without major side effects.

CONCLUSION

Although ultrasensitive thyroid assays may assist in earlier diagnosis of TSH-secreting tumors, in many patients misdiagnosis delays surgical intervention. Herein we describe the first case of a thyrotropin- and prolactin-secreting pituitary macroadenoma treated with, and shown to have a sustained response to, cabergoline. On the basis of this experience, cabergoline warrants further clinical study in the management of TSH-secreting pituitary tumors, especially because it has a good side-effect profile, convenient dosing, and apparent efficacy.

REFERENCES

1. **Adriaanse R, Brabant G, Endert E, Bemelman FJ, Wiersinga WM.** Pulsatile thyrotropin and prolactin secretion in a patient with a mixed thyrotropin- and prolactin-secreting pituitary adenoma. *Eur J Endocrinol.* 1994;130:113-120.
2. **Beck-Peccoz P, Brucker-Davis F, Pesani L, Smallridge RC, Weintraub BD.** Thyrotropin-secreting pituitary tumors. *Endocr Rev.* 1996;17:610-638.
3. **Weintraub BD, Gershengorn MC, Kourides IA, Fein H.** Inappropriate secretion of thyroid-stimulating hormone. *Ann Intern Med.* 1981;95:339-351.
4. **Faglia G, Beck-Peccoz P, Piscitelli G, Medri G.** Inappropriate secretion of thyrotropin by the pituitary. *Horm Res.* 1987;26:79-99.
5. **Comi RJ, Gesundheit N, Murray L, Gorden P, Weintraub BD.** Response of thyrotropin-secreting pituitary adenomas to a long-acting somatostatin analogue. *N Engl J Med.* 1987;317:12-17.
6. **Beck-Peccoz P, Mariotti S, Guillausseau PJ, et al.** Treatment of hyperthyroidism due to inappropriate secretion of thyrotropin with the somatostatin analog SMS 201-995. *J Clin Endocrinol Metab.* 1989;68:208-214.

7. **Gancel A, Vuillermet P, Legrand A, Catus F, Thomas F, Kuhn JM.** Effects of a slow-release formulation of the new somatostatin analogue lanreotide in TSH-secreting pituitary adenomas. *Clin Endocrinol (Oxf).* 1994;40:421-428.
8. **Levy A, Eckland DJA, Gurney AM, Reubi JC, Doshi R, Lightman SL.** Somatostatin and thyrotropin-releasing hormone response and receptor status of a thyrotropin-secreting pituitary adenoma: clinical and "in vitro" studies. *J Neuroendocrinol.* 1989;1:321-326.
9. **Chanson P, Weintraub BD, Harris AG.** Octreotide therapy for thyroid-stimulating hormone-secreting pituitary adenomas: a follow-up of 52 patients. *Ann Intern Med.* 1993;119:236-240.
10. **Biller BM, Molitch ME, Vance ML, et al.** Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. *J Clin Endocrinol Metab.* 1996;81:2338-2343.
11. **Webster J, Piscitelli G, Polli A, et al. (European Multicentre Cabergoline Dose-Finding Study Group).** Dose-dependent suppression of serum prolactin by cabergoline in hyperprolactinaemia: a placebo controlled, double blind, multicentre study. *Clin Endocrinol (Oxf).* 1992;37:534-541.
12. **Pontiroli AE, Viberti GC, Mangili R, Cammelli L, Dubini A.** Selective and extremely long inhibition of prolactin release in man by 1-ethyl-3-(3′-dimethylaminopropyl)-3-(6′-allylergoline-8′-beta-carbonyl)-urea-diphosphate (FCE 21336). *Br J Clin Pharmacol.* 1987;23:433-438.