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# Recurrent Goiter, Hyperthyroidism, Galactorrhea and Amenorrhea due to a Thyrotropin and Prolactin-Producing Pituitary Tumor

K. HORN,\* F. ERHARDT,\* R. FAHLBUSCH,\*\* C. R. PICKARDT,\*  
K. v. WERDER,\* AND P. C. SCRIBA\*

II. Medizinische Klinik\* and Neurochirurgische Klinik,\*\* University of Munich, Munich, Germany

**ABSTRACT.** A 22-year-old woman with recurrent goiter, hyperthyroidism, galactorrhea, and amenorrhea due to a pituitary tumor is described. She had been treated surgically twice for recurrent goiter with tracheal compression. Despite clinical signs of hyperthyroidism and slightly elevated plasma thyroid hormone levels ( $T_3$ : 11  $\mu\text{g}/\text{dl}$ ;  $T_4$ : 189  $\text{ng}/\text{dl}$ ), without thyroid hormone replacement therapy the basal TSH level was elevated up to 23  $\mu\text{U}/\text{ml}$  and could not be suppressed by exogenous thyroid hormones: even when the serum thyroid hormone levels were raised into the thyrotoxic range ( $T_4$ : 16.2  $\mu\text{g}/\text{dl}$   $T_3$ : 392  $\text{ng}/\text{dl}$ ), the basal TSH fluctuated between 12 and 29  $\mu\text{U}/\text{ml}$ . The basal PRL level was elevated up to

6000  $\mu\text{U}/\text{ml}$ . The administration of TRH (200  $\mu\text{g}$  iv) led only to small increments of TSH and PRL levels. Bromocriptin (5 mg p.o.) or L-dopa (0.5 g p.o.) suppressed TSH and PRL values significantly. After transsphenoidal hypophysectomy, TSH and PRL were below normal and the patient developed panhypopituitarism. The adenoma showed two cell types which could be identified as lactotrophs and thyrotrophs by electronmicroscopy and immunofluorescence. From these data we conclude that the patient had a pituitary tumor with an overproduction of thyrotropin and prolactin. (*J Clin Endocrinol Metab* 43: 137, 1976)

**H**YPERTHYROIDISM due to a thyrotropin-producing pituitary adenoma is extremely rare. To our knowledge, there are only a few well documented cases in the literature (1,2,3). In contrast, female patients with prolactin-producing tumors and with amenorrhea and galactorrhea have been described frequently during recent years (4,5). We have now observed a patient with recurrent proliferation of the thyroid gland, hyperthyroidism, galactorrhea, and amenorrhea due to the simultaneous hypersecretion of TSH and PRL.

## Materials and Methods

TSH (6), PRL (7), GH, LH, and FSH (8) were measured by double-antibody radioimmunoassay techniques. The reagents for the TSH and PRL radioimmunoassay were obtained from the National Pituitary Agency, National Institutes of

Health Bethesda, Maryland, USA, and the National Institute for Medical Research, (MRC), London. Thyrotropin and PRL were expressed in  $\mu\text{U}/\text{ml}$ . Twenty  $\mu\text{U}$  of the hPRL research standard A-71/222 were equivalent to 1 ng VLS-hPRL (7,8). Human growth hormone and LH were measured, as described previously (8), using our own antisera and GH (2 IU/mg) from Kabi Comp., Sweden and pituitary LH (2135 IU of 2nd IRP-hMG/mg) as standard and tracer preparation. The FSH preparation had a biological activity of 3500 IU 2nd IRP/mg and a radioimmunological activity of 2330 IU 68/39 MRC and was obtained together with a specific FSH antiserum from CEA/Gif-sur-Yvette, France. After extraction from the serum by means of chromatography on sephadex columns in automatized procedures, as described previously,  $T_3$  was determined by radioimmunoassay (9), and  $T_4$  (9) and cortisol (9,10) by competitive protein-binding analysis. The  $T_3$ -uptake test was performed by dextran gel filtration (10).

The normal ranges were:  $T_3$ : 80–150  $\text{ng}/\text{dl}$ ;  $T_4$ : 4.5–10  $\mu\text{g}/\text{dl}$ ;  $T_3$ -uptake test: 32–42%; Basal TSH: <1.0–3.8  $\mu\text{U}/\text{ml}$ ; Basal PRL: 150–650  $\mu\text{U}/\text{ml}$  (women).

## Endocrine stimulation and suppression tests

TRH stimulation test: 200  $\mu\text{g}$  TRH (Hoechst, Frankfurt, FRG) was injected iv. L-Dopa suppres-

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Reprint requests to: Dr. Med. Klaus Horn, II. Med. Klinik der Universitaet, 8 Muenchen 2, Ziemssenstrasse 1, FRG.

sion test: 500 mg L-dopa (Hoffmann-La Roche AG, Grenzach, FRG) was given orally. Bromocriptin (CB-154) suppression test: 5 mg CB-154 (Sandoz, Basel, Switzerland) was given orally. Blood samples were taken at different times before and after the administration of these agents, as indicated in Fig. 1–3. The  $T_3$ -suppression test was performed with 100  $\mu\text{g}$   $T_3$  (Thybon<sup>®</sup>, Hoechst, Frankfurt, FRG) per day orally over a period of 4 weeks. LHRH stimulation test: LH and FSH levels were determined before and 30 min after the injection of 25  $\mu\text{g}$  LHRH intravenously (Hoechst, Frankfurt, FRG). Insulin hypoglycemia test: regular insulin (0.15 U/kg body-weight) was injected iv, and blood was drawn before and 30, 45, 60, and 90 min after the insulin injection. The nadir of blood glucose was 35 mg/dl 45 min after the insulin injection.

#### Case report

In 1968 a 16-year-old girl noticed a rapid growth of a goiter with dyspnea and stridor. In addition, she complained of weight loss and hyperphagia, muscle weakness, heat intolerance, and nervousness without ophthalmopathy. Since the patient was admitted to a surgical ward of a small hospital no more detailed clinical records and no thyroid hormone levels of that period are available. A subtotal resection of her goiter was performed in 1969, mainly because of tracheal compression. Postoperatively, 60  $\mu\text{g}$   $T_3$  daily was given, but two years later hyperthyroidism and goiter recurred. Again, tracheal compression led to a second thyroid resection, this time combined with a plastic surgical reconstruction of a part of the trachea because of tracheomalacia.

After the second operation, therapy with 100  $\mu\text{g}$   $T_4$  and 20  $\mu\text{g}$   $T_3$  per day did not prevent the recurrence of the goiter. Therefore, the patient was admitted to our hospital in 1973 for the first time.

On admission, she had no complaints concerning her thyroid, but she reported that three years ago her periods had become irregular and that one year later she observed amenorrhea. Since that time, she had also observed galactorrhea from both breasts.

The physical examination revealed a diffusely enlarged thyroid gland. Each lobe had a size of about  $4 \times 3$  cm. There were no signs of tracheal compression by clinical and X-ray examination. She had no clinical signs of Graves' disease.

There were no visual field defects. After the withdrawal of thyroid hormone therapy for four weeks,  $T_4$  (11.0  $\mu\text{g}/\text{dl}$ ),  $T_3$  (189 ng/dl), and  $T_3$  resin uptake (41.5%) were slightly elevated. Surprisingly, the basal TSH was 23  $\mu\text{U}/\text{ml}$ , but could not be further elevated by TRH. The basal PRL level was 4800  $\mu\text{U}/\text{ml}$  and only rose to 5400  $\mu\text{U}/\text{ml}$  30 min after TRH.

## Results

### *Effect of thyroid hormone administration on serum TSH levels*

After four weeks of therapy with 100  $\mu\text{g}$   $T_4$  and 20  $\mu\text{g}$   $T_3$  per day, the  $T_4$  level was 10.2  $\mu\text{g}/\text{dl}$ . The basal TSH level was still elevated and showed only a small increase from 18  $\mu\text{U}/\text{ml}$  to only 23  $\mu\text{U}/\text{ml}$  30 min after TRH injection. Raising the daily dosage of thyroid hormones to 150  $\mu\text{g}$   $T_4$  and 30  $\mu\text{g}$   $T_3$  for a period of 24 days led to an increase in the serum  $T_4$  level up to 16.2  $\mu\text{g}/\text{dl}$ , but the basal TSH level was persistently elevated and resistant to TRH stimulation (22.9 and 23.2  $\mu\text{U}/\text{ml}$ , respectively).

In order to exclude a disturbance of the peripheral conversion of  $T_4$  to  $T_3$ , the patient was treated with 300  $\mu\text{g}$   $T_4$  per day over a period of 4 weeks. During this period, the  $T_4$  level increased to 17.5  $\mu\text{g}/\text{dl}$  and the  $T_3$  uptake test to 63.7%. The basal TSH level was still significantly elevated (13.6  $\mu\text{U}/\text{ml}$ ) although the conversion of  $T_4$  to  $T_3$  was documented by an increase in the  $T_3$  level up to 392 ng/dl. Furthermore, following therapy with 100  $\mu\text{g}$   $T_3$  per day over a period of four weeks, the basal TSH level remained elevated (25.6  $\mu\text{U}/\text{ml}$ ). The basal PRL level was clearly elevated throughout all these observations and ranged from 4000 to 6000  $\mu\text{U}/\text{ml}$ .

### *TSH and PRL levels after TRH stimulation*

The TRH stimulation test was performed twice, first after a period of four weeks without exogenous thyroid hormones, and second during therapy with thyroid hormones (100  $\mu\text{g}$   $T_4$  and 20  $\mu\text{g}$   $T_3$  p.o. daily).

Under both conditions, the TSH and PRL levels showed no significant increase after TRH injection (Fig. 1).

#### *TSH and PRL levels after L-dopa suppression*

L-Dopa and bromocriptin suppression tests were done without thyroid hormone therapy.

Both hormones decreased from elevated levels to a nadir 120 min after the L-dopa administration (Fig. 2). When 200  $\mu\text{g}$  TRH was injected 60 min after L-dopa was given, no increase, but a further decline in TSH and PRL levels was observed, reaching the lowest values 120 min after L-dopa (Fig. 2).

#### *TSH and PRL levels after bromocriptin (CB-154)*

Following 5 mg bromocriptin, PRL and TSH levels fell in a parallel fashion. However, normal values could not be reached after this single oral dose (Fig. 3).

#### *Immunologic characterization of TSH and PRL*

In order to prove the immunological identity of the circulating TSH and PRL with the respective standard preparations, TSH and PRL were estimated in different serum dilutions. The resulting displacement curves were parallel with the standard curves (not shown).

#### *Additional clinical studies*

Insulin hypoglycemia induced a rise in cortisol from a normal basal value of 14  $\mu\text{g}/\text{dl}$  to 31  $\mu\text{g}/\text{dl}$ , and a rise in GH from 2.0 ng/ml to 9 ng/ml 90 min after insulin injection. After LHRH stimulation, LH rose from 3.9 to 10.1 ng/ml and FSH from 3.4 to 8.0 ng/ml. The sella turcica was enlarged; pneumoencephalography revealed a cisterna optochiasmatica of normal size interpreted as an intrasellar growth of the tumor without suprasellar extension. The visual fields were normal.

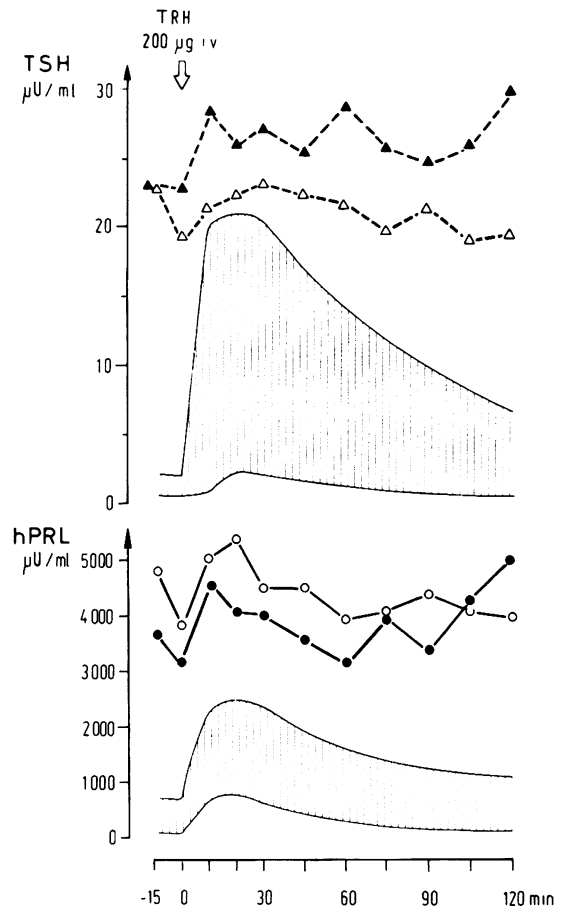


FIG. 1. Plasma TSH and PRL levels before and after TRH stimulation without (closed symbols) and with thyroid replacement therapy (open symbols). The two tests were performed with an interval of four weeks. The shadowed area represents the response of TSH and PRL in normal controls (mean  $\pm$  2 SD).

#### *Clinical course*

On April 22, 1974, a transsphenoidal hypophysectomy was performed by curettage combined with a cryoresection of the pituitary tumor. As shown in Fig. 4, both TSH and PRL levels declined in parallel fashion after the removal of the tumor. Six hours after the operation, both hormone levels were within the normal range. Post-operatively, the patient had no radioimmunoassayable TSH and very low PRL levels in her serum. At present, the patient receives replacement therapy with

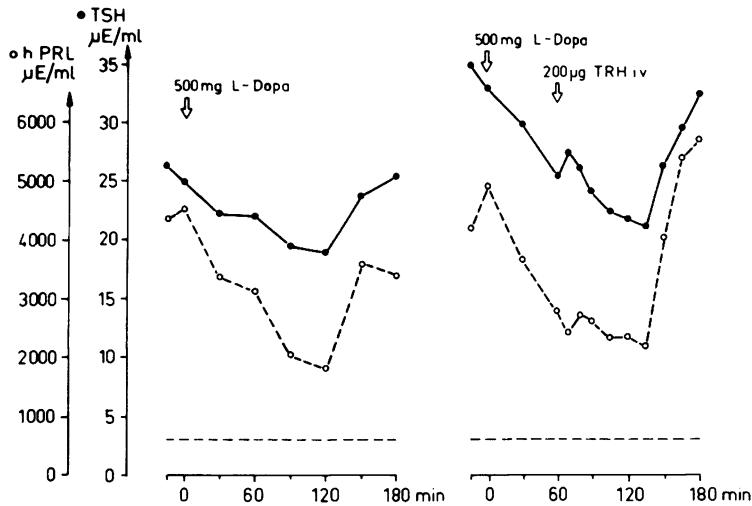


FIG. 2. Plasma TSH and PRL responses due to L-dopa alone (left panel) and to L-dopa and subsequent TRH injection (right panel). The broken lines represent the upper limit of the normal range of the basal values for both hormones.

ADH, cortisol, thyroid hormones, and gonadal steroids. She has no thyroid enlargement, has ceased to lactate and is without complaints and fully active as a nurse.

#### *Histology of the pituitary tumor*

The light microscopic investigations<sup>1</sup> revealed a pituitary adenoma with both acidophilic and chromophobe cell elements. In the electronmicroscopic picture two cell types were found. One showed indented nuclei and dense nucleoli, the cytoplasm was rich in rough endoplasmic reticulum. These cells were indistinguishable from the lactotrophic cells seen in pregnancy and in lactotrophic pituitary tumors. The other cell type, with long cell bodies, frequently showed secretory phenomena at the cell membrane. The granules of these cells, with a diameter of 90 to 200 nm, were smaller than those in the lactotrophic cells. These cells reacted with an antihuman TSH serum by an immunoperoxidase sandwich technique.<sup>2</sup> Therefore, it seems likely that these cells are TSH-producing adenoma cells.

<sup>1</sup> We are indebted for these results to Prof. Dr. O. Stochdorph, Abt. für Neuropathologie, Patholog. Institut, University of Munich.

<sup>2</sup> We are indebted for these results to Prof. Dr. U. Hachmeister, Zentrum für Pathologie, University of Giessen, FRG.

#### Discussion

The present study is, to our knowledge, the first report of a patient with a pituitary adenoma with simultaneous hypersecretion of thyrotropin and prolactin. To explain this hypersecretion of TSH and PRL, one has to consider the possible pathophysiological mechanisms (11–13):

a. The concomitant hypersecretion of prolactin and TSH was due to primary hypothyroidism.

b. The pituitary adenoma produced only TSH and inhibited by suprasellar extension the production and/or the portal vessel transport of the hypothalamic prolactin-inhibiting factor (PIF).

c. The patient had enhanced hypothalamic TRH secretion, which led to a pituitary adenomatous hyperplasia of the thyrotrophic and lactotrophic cells.

d. Both hormones, TSH and PRL, were produced by an "autonomous" pituitary adenoma, which was not suppressed by thyroid hormones and was not stimulated by TRH.

The first theoretical possibility can be eliminated, since our patient was never hypothyroid. In addition, the PRL levels in hypothyroidism are only slightly higher and decrease towards normal, parallel with the fall of TSH levels during thyroid hormone replacement therapy (14). In our patient,

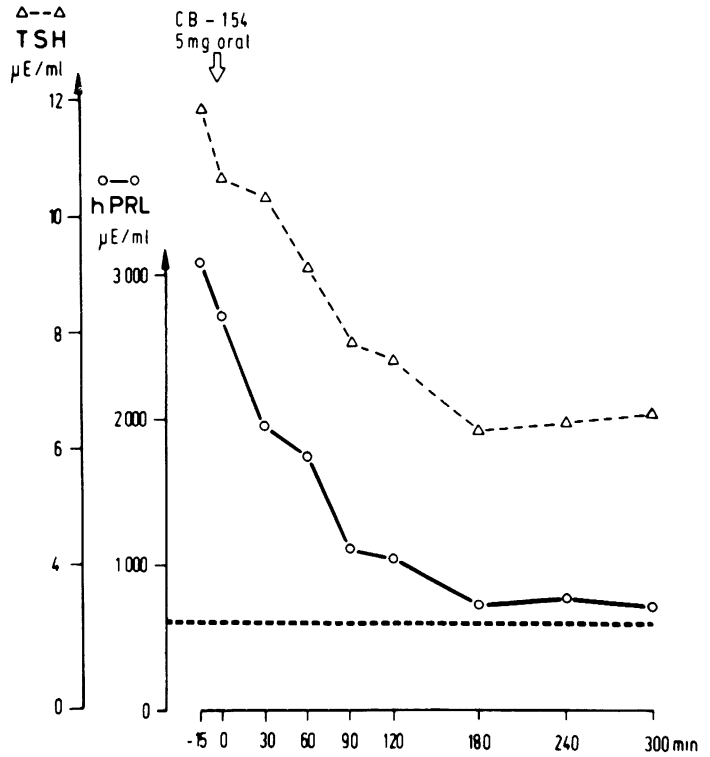


FIG. 3. Plasma TSH and PRL levels before and after the administration of 5 mg CB-154 (bromocriptin). The broken line represents the upper limit of the normal basal values of both hormones.

neither her TSH levels nor the PRL levels were lowered to normal by thyroid hormones, even when the peripheral thyroid hormone levels were elevated. The development of TSH producing tumors as a conse-

quence of long-standing hypothyroidism occurs in the rat (15). Analogous pituitary adenomas in humans are observed in areas with severe iodine deficiency and endemic cretinism (16).

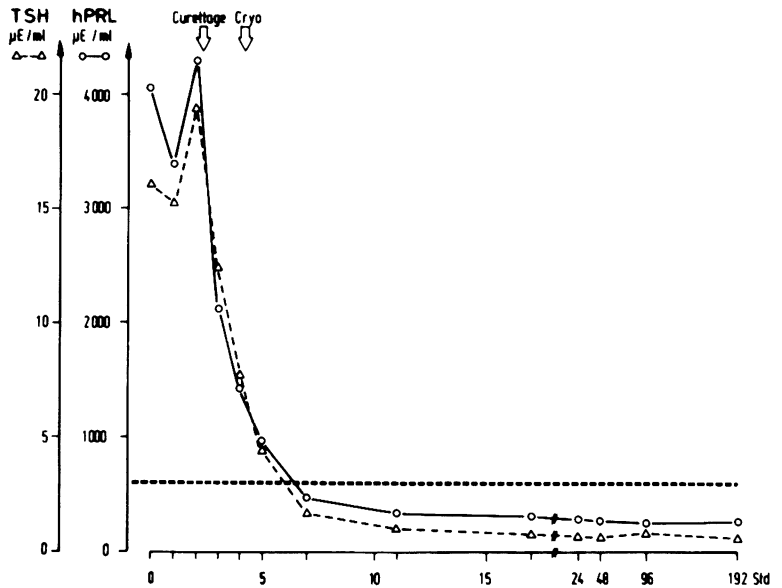


FIG. 4. Plasma TSH and PRL levels before, during neurosurgery, and after transsphenoidal resection of the pituitary (curettage) and cryohypophysectomy (cryo). The broken line represents the upper limit of the normal basal values of both hormones. The time in hours is shown on the abscissa.

It is difficult to differentiate diffuse hyperplasia from an adenoma on histological grounds. The pituitary tumor of our patient showed two closely associated cell types, of which one could be identified as a lactotroph, the other as a TSH-producing cell. Since these two different cell types were evenly distributed in the adenomatous tissue, it is unlikely that a TSH-producing tumor induced the hyperprolactinemia in this case by PIF inhibition. In addition, this tumor did not show any suprasellar extension, and insulin hypoglycemia induced a normal rise of cortisol and hGH in our patient, indicating an intact hypothalamic-pituitary axis. This does not favor the theory of any disturbances in the hypothalamus or in the pituitary stalk.

The results of the endocrine tests in our patient do not exclude an adenoma due to endogenous TRH hypersecretion. However, the elevated basal levels of TSH and PRL could not be stimulated normally with synthetic TRH. Furthermore, the lack of suppression of TSH and PRL by thyroid hormones suggests an autonomous production of both hormones by a pituitary adenoma.

The pharmacologic suppressors for prolactin, L-dopa and bromocriptin caused a parallel fall in both hormones. The inhibition of elevated prolactin levels by bromocriptin occurs at the pituitary level (4). Evidence has been accumulated that this inhibition is not specific for the lactotrophic cells, since it has been shown that both the elevated TSH levels in primary hypothyroidism (17) and the elevated GH levels in patients with acromegaly can be inhibited by bromocriptin (18). We now demonstrate that the hypersecretion of TSH by a pituitary tumor can also be inhibited by this drug. The inhibition of prolactin secretion by L-dopa is in part due to the stimulation of the hypothalamic PIF (12). An additional direct effect of L-dopa on pituitary prolactin secretion has also been postulated (19). The inhibition of TSH by L-dopa occurs probably at the pituitary

level, since L-dopa inhibits the normal TSH response induced by TRH (4,20). Furthermore, a hypothalamic inhibitor for TSH release is not known. Finally, the parallel decrease in both PRL and TSH in our patient suggests that the inhibitory effect of these drugs occurs at the pituitary level for both hormones. Thus, the results of the pharmacologic studies support the concept of an autonomous pituitary adenoma. However, the endocrine studies alone cannot rule out hypothalamic TRH hypersecretion as a possible cause for a pituitary adenoma. For this to be excluded with absolute certainty, TRH levels would have to be measured in the portal vessels, which is not feasible in humans.

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