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# Recurrent goiter and amenorrhea-galactorrhea syndrome in a patient with a thyrotropin (TSH) and prolactin (PRL) producing pituitary adenoma

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The pathophysiological mechanisms of the simultaneous hypersecretion of TSH and PRL due to a pituitary adenoma are discussed on the basis of one very unusual patient.

## CASE HISTORY

In 1968 the female patient suffered from rapid goitral growth and clinical signs of hyperthyroidism. In 1969 the first resection of the goiter was performed, mainly because of tracheal compression. Two years later, she complained of recurrent goiter with stridor and dyspnea. Therefore, in 1971 thyroid surgery with plastic reconstruction of the trachea had to be performed. In 1972, at the age of 20 years, she was admitted to hospital because of a third period of goitral growth despite prophylactic thyroid hormone therapy. At this time amenorrhea and galactorrhea became apparent.

## RESULTS AND DISCUSSION

On admission the levels of T4 (10.8  $\mu\text{g}\%$ ), of T3 (189  $\text{ng}\%$ ) and of the  $\text{RT}_3\text{U}$  (43%) were slightly elevated (normal ranges: T4 = 4.5-10.0  $\mu\text{g}\%$ ; T3 = 80-150  $\text{ng}\%$ ;  $\text{RT}_3\text{U}$  = 32-42%). The basal TSH level was elevated (23  $\mu\text{U}/\text{ml}$ ; normal range: 0.4-3.8  $\mu\text{U}/\text{ml}$ ). The basal PRL level was grossly increased up to 4800  $\mu\text{U}/\text{ml}$ , corresponding to 240 ng VLS Standard/ml (normal range in females: 150-650  $\mu\text{U}$  RSA 71/222/ml).

The history and the findings indicated a hormonally active anterior pituitary tumor. The sella turcica was enlarged, but visual fields were normal. Other pituitary functions were not impaired, as shown by a normal rise of growth hormone and cortisol during the insulin hypoglycemia test and of LH and FSH after application of 25  $\mu\text{g}$  LRF.

In healthy subjects TSH and PRL increase after TRH stimulation (normal ranges after 200  $\mu\text{g}$  TRH i.v.;  $\Delta$  TSH 30 min: 2.7-23.6  $\mu\text{U}/\text{ml}$ ;  $\Delta$  PRL 20 min: 500-1700  $\mu\text{U}/\text{ml}$ ). The TSH and PRL responses to TRH are suppressed (TSH) or diminished (PRL) in hyperthyroidism, but increased in hypothyroidism. In this patient, the rise of the elevated basal TSH and PRL levels after TRH stimulation were inadequate ( $\Delta$  TSH 30 min: 0.5  $\mu\text{U}/\text{ml}$ ;  $\Delta$  PRL 20 min: 605  $\mu\text{U}/\text{ml}$ ). Such impaired responsiveness of PRL to TRH has been demonstrated in patients with a prolactin-producing pituitary adenoma (Von Werder, 1975). The non-suppressibility of TSH and PRL could be demonstrated by the application of thyroid hormones up to 150  $\mu\text{g}$  T4 plus 30  $\mu\text{g}$  T3 which raised the T4 to 16.2  $\mu\text{g}\%$  and the T3 uptake to 52%. A disturbance of peripheral conversion of T4 to T3 could be excluded, since the T3 level increased to 392  $\text{ng}\%$  (T4: 19.1  $\mu\text{g}\%$ ) after administration of 300  $\mu\text{g}$  T4 per day. However, both TSH and PRL levels remained elevated, fluctuating between 13.6 and 25.6  $\mu\text{U}/\text{ml}$  (TSH), and between 3100 and 6600  $\mu\text{U}/\text{ml}$  (PRL). This indicated that TSH and PRL could not be physiologically regulated by TRH and thyroid hormones.

Pharmacological studies showed that both TSH and PRL levels could be lowered by

500 mg L-dopa with a nadir after 120 min. TSH decreased from 26.0  $\mu\text{U/ml}$  to 19.0  $\mu\text{U/ml}$  and PRL from 4400  $\mu\text{U/ml}$  to 1800  $\mu\text{U/ml}$ . As expected, 5 mg of bromocriptine decreased the PRL levels from 3100 to 740  $\mu\text{U/ml}$  and in parallel decreased the TSH levels from 11.9 to 6.4  $\mu\text{U/ml}$  with a nadir after 180 min.

The unknown proliferative potency of TSH and PRL producing tumors prompted us to have this hormonally active tumor removed by transsphenoidal hypophysectomy and cryoresection of possible remnants of tumor tissue. This decreased TSH and PRL levels in parallel to unmeasurable values (Fig. 1). Today, the patient has panhypopituitarism, but she is fully active as a nurse under replacement therapy with cortisol, thyroxine and gonadal steroids.

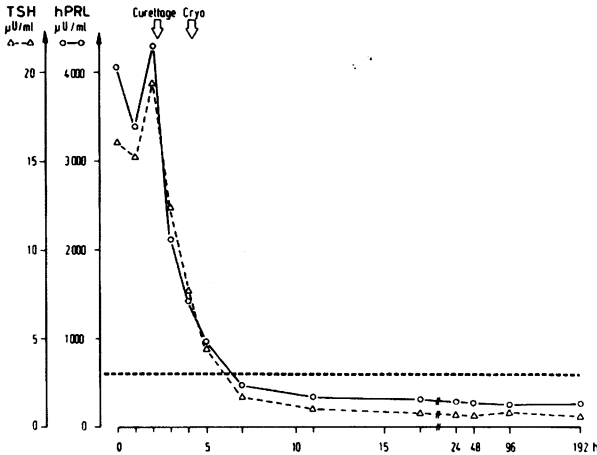


FIG. 1. Parallel decline of PRL and TSH during and after transsphenoidal surgery.

Several possible pathophysiological mechanisms may explain the simultaneous hypersecretion of TSH and PRL:

1. Concomitant hypersecretion of PRL with TSH. In primary hypothyroidism, the elevated TSH and PRL can be normalized by thyroid hormone therapy; this was not so in our patient. The development of TSH-producing tumors in rats can result from chronic hypothyroidism. Analogous pituitary tumors in humans can occur in areas with severe iodine deficiency and cretinism (König, 1968). However, this explanation is not applicable to our patient, since hypothyroidism was never experienced.
2. PRL hypersecretion due to a suprasellar extension of the TSH-producing tumor resulting in PIF inhibition. Our patient had no ophthalmological, laboratory or pneumencephalographic signs of suprasellar extension.
3. Autonomous TSH and PRL hypersecretion by the pituitary tumor. The inadequate increase of both TSH and PRL after TRH stimulation and the lack of suppression by thyroid hormones indicated an autonomous hormone secretion. In addition electron-microscopic and immunofluorescent findings revealed no signs of a diffuse hyperplasia of the pituitary gland, but instead two closely associated cell types were found throughout the adenoma, of which one was identified as lactotroph and the other thyrotroph.
4. Primary TRH hypersecretion leading to a hyperplasiogenic TSH and PRL producing pituitary adenoma. This is excludable only by measuring TRH in the portal vessels, something not feasible in humans. The results of long-term oral treatment with TRH argue against an endogenous TRH excess causing hyperthyroidism. Daily application of 40 mg TRH orally over a period of 4 weeks diminished the TSH response after 200  $\mu\text{g}$  TRH i.v., while the T4 and T3 levels were not increased (Table 1), whereas transitory increases of the thyroid hormone levels within the normal range after each oral application of TRH occur more acutely (unpublished data). This indicates that the suppressive effect of thyroid hormones on TSH release overrules the stimulatory effect of TRH as

TABLE 1 Effect of oral TRH application to healthy subjects (N = 12; 40 mg per day over a period of 4 weeks)

		Before TRH	After TRH
		40 mg per day	
Serum TSH ( $\mu$ U/ml)	Basal	2.0 $\pm$ 0.8	1.0 $\pm$ 0.5*
	$\Delta$ TSH 30 min	8.1 $\pm$ 3.0	3.0 $\pm$ 1.9*
Serum T4 ( $\mu$ g/100 ml)		6.2 $\pm$ 1.9	6.5 $\pm$ 1.8
Serum T3 (ng/100 ml)		112 $\pm$ 22	109 $\pm$ 32

\*  $p < 0.005$

shown by repetitive i.v. administration of TRH (Snyder and Utiger, 1973). Thus endogenous TRH excess is unlikely to cause the hypersecretion of TSH and PRL, resulting in a toxic goiter and amenorrhea-galactorrhea syndrome, as observed in this patient.

In conclusion, the patient studied is the first presenting a pituitary adenoma with autonomous TSH and PRL hypersecretion.

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