INVITED COMMENTARY

Unusual presentation of a TSH-secreting pituitary adenoma

Paolo Beck-Peccoz

Institute of Endocrine Sciences, University of Milan, Italy

The endocrinologist dedicated to the studies of pituitary adenomas is surprised when confronted by the highly variable biological appearance of pituitary tumours. By immunohistochemistry and in situ hybridization, pituitary tumours are frequently composed of cells able to co-secrete hormonal molecules with completely different biochemical and biological activities, such as GH/alpha-subunit, PRL/alpha-subunit or GH/TSH, together with normally differentiated cells. This phenomenon is particularly surprising taking into account the recent discovery that the great majority of pituitary tumours are monoclonal in origin. In addition, the frequent detection of allelic deletions of different chromosomes in sporadic pituitary adenomas suggests loss of tumour suppressor genes in these neoplasms. Recent findings also show mutations which result in the constitutive activation of GTP-binding proteins in subsets of pituitary adenomas and a pathogenetic role has been envisaged for gsp and ras oncogenes which are expressed in pituitary tumours with variable frequency.

The latest example of the above variability in pituitary tumour biology is the TSH-secreting adenoma (TSHoma), described by Karlsson et al. in the present issue of Acta Endocrinologica (pp. 291–5).

This tumour presents with the well-known finding of unbalanced hypersecretion of alpha-subunit, but also bears a very unusual repertoire of receptors and responses to agents usually unable to stimulate (TRH) or inhibit (thyroid hormones and their analogues, dopamine) tumoral TSH hypersecretion. In contrast with almost all the reported TSH-omas, it lacks membrane receptors for somatostatin and its analogue octreotide, and therefore the administration of these agents fails to inhibit TSH hypersecretion.

Previous thyroidectomy and the consequent reduction in the circulating levels of free thyroid hormones may have caused an additional alteration of feedback control mechanism. In fact, although TSHoma cells are in general unresponsive to stimulatory tests, they maintain some response to reduction of circulating thyroid hormone levels obtained by anti-thyroid drugs, surgery or irradiation.

The presence of functional receptors for inhibitory or stimulatory inputs may have had a crucial role in tumour formation and growth. Therefore, it is not surprising that the present adenoma is very aggressive, protruding into the sphenoidal bone and judged to be unremovable by neurosurgery. In keeping with this, a close relationship between previous thyroid ablation and the aggressivity of the TSH-secreting adenoma has been recorded in our series, where surgical failure was observed in 3 out of 15 patients. These three patients were the only ones who had previous thyroidectomy or 131I radiotherapy.

Therefore, the study of Karlsson et al. once again stresses the dramatic consequences of the misdiagnosis of these rare pituitary adenomas. In the past, TSH levels were not routinely measured in patients with hyperthyroidism and many patients with TSHoma were diagnosed as having Graves’ disease because of the presence of high levels of T4 and T3 along with goiter, tachycardia, and various signs and/or symptoms of hyperthyroidism. Today, ultrasensitive assays for TSH measurement are available and their use as first-line test for the evaluation of thyroid function will help to prevent the above-mentioned misdiagnoses since even low measurable TSH levels indicate an inappropriate secretion of TSH. The differential diagnosis between TSHomas and thyroid hormone resistance, the other form of inappropriate secretion of TSH, is nowadays easy owing to the high resolution of both computerized tomography and magnetic resonance in recognizing even very small pituitary adenomas (2 mm). If equivocal pituitary images are observed, the findings of normal levels of alpha-subunit and alpha-subunit/TSH molar ratio, as well as normal values of some parameters of peripheral thyroid hormone action, such as the sex hormone-binding globulin levels, are useful in ruling out the presence of a pituitary adenoma.

In summary, the article by Karlsson et al. suggests that there is an indication to try alternative treatments of TSHoma whenever an aggressive or a somatostatin unresponsive tumour is found. Such treatments include administration of dopaminergic drugs and thyroid hormone analogues. I would like to add that it is also important to treat the patient with pituitary irradiation, whenever possible. Finally, the real curiosity of the present paper is the inhibitory effect of D-T4 on tumour TSH secretion. Only future studies on the expression of the various thyroid hormone receptors, particularly the beta-2 and alpha-1 isoforms, and their ability to interact with the thyroid hormone response element (TRE) of the TSH subunit genes, will clarify the mechanism(s) responsible for such a rare behaviour of TSH-secreting pituitary adenomas.

Paolo Beck-Peccoz, Institute of Endocrine Sciences, University of Milan, Ospedale Maggiore IRCCS, Via F. Sforza, 35, 20122-Milan, Italy