CASE REPORT

Cabergoline modulation of α-subunits and FSH secretion in a gonadotroph adenoma


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ABSTRACT. Most non-functioning pituitary adenomas respond poorly to medical therapy. We describe the case of a 62-year-old man who presented with clinical features of an invasive macroadeno­ma. Baseline hormonal evaluation revealed increased FSH and α-subunit (α-SU) levels. Trans­sphenoidal exeresis followed by radiotherapy (RT) was performed. Almost all neoplastic cells were intensely immunoreactive for α-SU. On PCR analysis, specific amplification products were observed for somatostatin 2, 3 and 5 receptors as well as for both short and long isoforms of the dopamine D2 receptor. In vitro, α-SU and FSH were released into the medium by adenoma cells and increased after TRH stimulation. After surgery, α-SU and FSH levels were still elevated. Short-term slow-release lanreotide treatment did not modify either α-SU or FSH levels. Cabergoline was started and a fast and long-lasting decrease in α-SU and, to a lesser ex­tent, in FSH was observed. The tumor remnant was unmodified on magnetic resonance imaging 3 years after surgery and RT. This case report shows that the in vitro expression of somatostatin receptors may not be directly associated to the in vivo response of α-SU and FSH to lanreotide, probably because of a functional uncoupling of the recep­tors. Cabergoline should be considered as an ef­fective therapy for hormonal, and perhaps prolifer­ative, control of gonadotroph adenoma remnants before the effects of RT are fully effective.

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INTRODUCTION

Non-functioning pituitary adenomas (NFPA) make up about one third of all pituitary tumors (1). Although gonadotroph cells give rise to these tumors, most se­crete gonadotrophins inefficiently, while their sub­units (SU) are often discordantly secreted. The clinical presentation of these tumors is often determined by their local mass effects, and, less frequently, by symp­toms of deficient hormone production (1). Neuro­surgery followed by adjuvant radiotherapy (RT) is the first line of treatment. NFPA respond poorly to me­dical therapy, showing only slight tumor shrinkage in response to dopamine and somatostatin agonists (1). We report a case of NFPA secreting FSH and α-SU in which clinical findings and hormonal markers were monitored for a long period during post-op­erative medical therapy. Cabergoline, but not slow­release lanreotide, decreased FSH and α-SU secre­tion by the tumor. To our knowledge, there is only one other report in literature of cabergoline use in an FSH-secreting tumor (2), while no clinical data are reported on lanreotide in NFPA, which seems to have an anti-proliferative effect in vitro (3).

CASE REPORT

A 62-year-old Caucasian man was admitted to the Neurosurgery Unit in March 1996 for right palpebral ptosis. Outstanding anamnestic findings were hyper­tension, benign prostatic hyperplasia and a 5-year loss of libido. Current medical therapy was indopa­mide (2.5 mg/die, per os) and alfuzosine (5.0 mg/die, per os). Physiological examination was unremarkable. Neurological examination showed a palsy of 3rd right
cranial nerve and a normal visual field. A macroadenoma invading the sphenoidal sinus, ethmoidal region and right cavernous sinus was detected on magnetic resonance imaging (MRI). In April 1996 the patient underwent transsphenoidal exeresis of the tumor, which remedied the palsy. On MRI, a tumor remnant was detected in the right part of the pituitary fossa and in the right cavernous sinus. In August 1996, RT was scheduled for a total dose of 6000 cGy.

**In vitro investigations**

Light microscopy of the tumor showed a diffuse architectural pattern with scattered pseudo-rosettes around vascular channels, pseudo-papillae and follicles. The tumor cell cytoplasm was mostly eosinophilic with focal oncocytic changes. Immunostaining was performed with specific antibodies and the avidin-biotin-peroxidase method. Intense α-SU immunoreactivity was found in almost all tumor cells, while occasional (<1%) cells reacted with LH, TSH and PRL antibodies. No immunoreactivity was found for FSH and ACTH. Only the central portion of the adenoma was used for the in vitro experiments. Tumor cells were cultured in vitro, to evaluate hormones released into the medium. Adenoma specimens, immediately frozen to -80°C, were subsequently analyzed for mRNA expression of the somatostatin (SSTR) and dopamine D2 receptors. Only α-SU (160 IU/l 24-h/200,000 cells) and FSH (>200 IU/l 24-h/200,000 cells) were released into cell medium: these increased after TRH (10⁻⁸ M) stimulation (data not reported). Specific amplification products were observed for SSTR 2, 3 and 5, as well as for both short and long isoforms of the D2 receptor (Fig. 1).

**In vivo investigations**

Pre-surgical evaluation revealed increased FSH (55.0 IU/l; normal range (n.r.) 5-15 IU/l) and α-SU (6.6 IU/l; n.r. <1 IU/l) levels associated to normal LH (2.3 IU/l; n.r. 2-15 IU/l), PRL (3.4 µg/l; n.r. 3-20 µg/l), testoste­rone (T; 21.7 nmol/l; n.r. 12-40 nmol/l) and thyroid function. Urine free-cortisol levels were in the normal range before and after neurosurgery and RT. One year after therapies, α-SU (3.1 IU/l) and FSH (24.2 IU/l) levels were still elevated, while LH (1.5 IU/l) and T (14.2 nmol/l) were slightly decreased; PRL levels were unchanged. A 30-day course of slow-release lanreotide treatment (30 mg im every 14 days) did not modify either α-SU (2.9 IU/l) or FSH (26.4 IU/l) levels. Cabergoline (2 mg/week per os) was subsequently started. A long-lasting decrease in PRL (median <1 µg/l), α-SU (median 0.4 IU/l) and, to a lesser extent, in FSH (median 13.2 IU/l) levels was observed. Two years after RT, clinical signs of secondary hypogonadism and hypothyroidism occurred. To exclude the possibility that the α-SU and FSH decreases were partially secondary to RT-induced pituitary damage, cabergoline was discontinued for a 2-month period. Before and after cabergoline discontinuation, α-SU and FSH secretion was evaluated following subsequent GnRH (50 µg iv) and TRH (200 µg iv) administration (Fig. 2). A significant increase in baseline α-SU (p=0.01) and FSH (p=0.001) levels was noted after cabergoline discontinuation. α-SU levels showed a slight response to GnRH and TRH stimulation before and after cabergoline discontinuation, while FSH levels were unresponsive to TRH and slightly responsive to GnRH (Fig. 2).

**Clinical course**

The tumor remnant was unmodified on MRI 3 years after surgery and RT. Visual field was normal and no objective findings were clinically observed. Cabergoline therapy is still in progress (November 1999: α-SU 0.6 IU/l, FSH 4.7 IU/l) without adverse events.

**DISCUSSION**

This report deals with a gonadotroph adenoma, well-defined in its in vitro and in vivo hormonal cha-