Shrinkage of a primary thyrotropin-secreting pituitary adenoma treated with the long-acting somatostatin analogue octreotide (SMS 201-995)

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Abstract. The long-acting somatostatin agonist octreotide can control TSH hypersecretion from most thyrotropic adenomas. Octreotide therapy has even been shown to improve chiasmal dysfunction. We report another patient in whom octreotide therapy was associated with gradual suppression of TSH hypersecretion, which escaped partially, dramatic and very rapid and sustained improvement of chiasm compression, and dramatic and sustained shrinkage of an unresectable TSH-secreting pituitary tumour. Unusual and prolonged gastrointestinal adverse reactions eventually disappeared except for steatorrhea. In conclusion, octreotide may be considered as first line treatment in patients with unresectable thyrotropic adenomas.

Native somatostatin has been shown to suppress tumour secretion from some primary thyrotropic adenomas (1,2).

The long-acting somatostatin analogue octreotide (SMS 201-995) is effective in 70-80% of thyrotropinomas (3-7); moreover, as visual field defects have been reported to be improved in one patient (8), this suggests that some degree of tumour shrinkage may occur as in acromegalic patients (9-12).

We report a patient with an invasive thyrotropic macroadenoma where TSH hypersecretion was initially suppressed by octreotide. Subsequently, although TSH secretion escaped partially, this did not alter the dramatic improvement in visual field impairment nor the marked pituitary tumour size reduction. Some visual field data from this patient were reported elsewhere (13).

Patient and Methods

Case report

A 60-year-old man with tachycardia was treated with propranolol in 1977. Hyperthyroidism was diagnosed in 1982 (T₄ 319 nmol/l, T₃ 9.98 nmol/l, TSH 20 mU/l) and treated by radioiodine although TSH was high. However, this was not taken into consideration at that time. Thyroid hormones subsequently normalized. Two years after radioiodine treatment, visual disturbances began to occur and, in 1987, visual field defects led to the discovery of a large invasive pituitary adenoma in contrast to a slightly enlarged sella turcica. Sella size was the same as 27 years previously when the patient incidentally underwent a skull X-ray.

Hormone assays

Plasma hormones were measured in duplicate with commercial kits. TSH was measured using RIA Gnost kit (Hoechst-Behring, Rueil-Malmaison, France; normal range 0.1-4.5 mU/l; sensitivity 0.03 mU/l). Cross-reactivity of α-subunit was 1% (4). Free T₄ (FT4) and FT₃ were assayed with Amerlex kits (Amersham, Les Ulis, France; normal range 7.7-22.2 pmol/l and 3.1-8.6 pmol/l, respectively). Alpha-subunit was measured with purified hCGα and anti-hCGα polyclonal antiserum from UCB (Brussels, Belgium; normal range 0.25-1 mg/l). The molar
α-subunit/TSH ratio was calculated on the basis of the following molecular weight values: TSH 28 000 and α-subunit 13 600 (1 ng TSH corresponds to 5 μU).

Results are expressed as mean ± standard deviation.

Visual evaluation
Ophthalmological assessment included visual acuity measurements and visual field testing using the Goldmann perimeter. Patient cooperation was consistently excellent. Three different investigators were involved in these assessments, which were performed 3 times before initiation of octreotide in order to exclude that the improvement encountered during treatment could be due to patient adaptation.

Radiological evaluation
Magnetic resonance imaging (MRI) was performed with a 0.5 Tesla magnet taking 7-mm slices in sagittal and coronal planes. T1 and T2 weighted sequences were used for each examination. T2 weighted images allowed better tissue characterization and outlined a cystic portion of the upper part of the tumour (see below and Fig. 2, IA).

Octreotide treatment
During the first 7 days, octreotide was administered by continuous sc infusion at a dose of 100 μg daily for 5 days and thereafter by 3 sc injections of 100 μg each every 8 h. TSH and FT₃ were measured every hour for 11 h (from 08.00 to 1900 h) before and on day 2 and day 7 of octreotide therapy; visual assessment was made after 3 and 27 h of octreotide and repeated on day 4 and day 7.

Subsequently, octreotide was continued at a dose of 100 μg three times daily up to day 35, at which time the patient demanded that the number of injections was reduced to two daily administrations of 100 μg each for 15 days, increased to 200 μg each for a further 40 days. The dose was then reduced to 100 μg three times daily for 3 months and to 100 μg twice daily thereafter.

TSH, FT₄ and FT₃ determinations and ophthalmological assessments were performed at each dose change and every 2 months during the first 18 months of treatment.

MRI was performed before and after 3 and 15 months of octreotide therapy.

Gallbladder ultrasound imaging was performed before and after 6, 10, 16, and 23 months of therapy.

Results

Adenoma secretion
Before octreotide therapy TSH was very high, 40.7±4.6 mU/l (Fig. 1); α-subunit was high too, 9.9±0.1 μg/l, with an elevated molar ratio α/TSH = 2.5 (normal <1), whereas FT₄ and FT₃ was normal.

TSH secretion was not modified by TRH (200 μg iv) nor by bromocriptine (2.5 mg po).

During the first 7 days, TSH levels dropped markedly from 40.7±4.6 mU/l to 6.37±1.67 (on the 2nd day of continuous infusion of octreotide) and to 1.04±0.13 (on the 2nd day of thrice daily injections of octreotide) (Fig. 1). FT₃ dropped from 7.50±0.68 pmol/l to 4.8±0.46 and 3.38±0.57, respectively (Fig. 1). Alpha-subunit decreased from 9.9 to 0.9, with an elevation of α/TSH molar ratio to 8.8.

TSH levels were 1 mU/l on day 13, but rose to 5.9 mU/l on day 35 when the dose of octreotide was reduced to 100 μg twice daily on the patient’s request. TSH values remained between 6 and 11 mU/l irrespective of the octreotide doses administered subsequently, whereas FT₄ and FT₃ remained within normal limits.
**Other pituitary hormones**

Before treatment somatotropic function was subnormal, gonadotropic function borderline, and pituitary-adrenal function and prolactin were normal. During treatment none of them varied significantly.

**Visual improvement**

Before treatment, there was an asymmetric bitemporal hemianopsia for the central isopter especially on the left side with some reduction of visual acuity and optic-disk pallor.

During treatment visual field defects and left visual acuity already improved at the first evaluation performed 3 h after octreotide was started. Right visual field was normalized within 27 h. Maximum improvement was observed on the 45th day of therapy. Visual parameters remained stable thereafter.

**MRI data**

Before octreotide treatment, the adenoma had an irregular shape and extended mainly upwards to the left and in front of the fossa. The tumour surrounded the left carotid artery and reached the frontal lobe with a cystic subfrontal component (Fig. 2, IA). It filled the subfrontal subarachnoidal spaces and chiasmatic cistern (Fig. 2, IIA and IIIA), and the optic chiasm was not distinguishable (Fig. 2, IIA). There was no evidence of hematoma inside the adenoma. During treatment tumour shrinkage was noted on the first MRI after 3 months with reduction of the cystic part of the adenoma, which became more obvious on the next MRI performed after 15 months of therapy: the subfrontal cystic component had disappeared and the left carotid artery was set almost free (Fig. 2, IB), the optic chiasm became visible (Fig. 2, IIB), the subfrontal subarachnoidal and suprasellar spaces reappeared (Fig. 2, IIB and IIIIB). The intrasellar component produced heterogeneous signals suggesting structural alterations. There was no evidence of adenoma apoplexy. The tumour vertical, transversal and anteroposterior diameters were, respectively, 45, 30 and 40 mm before treatment and 32, 20 and 25 mm after 15 months of therapy. The estimated volume of the tumour, obtained by multiplying the product of the three diameters by \( \Pi/6 \) was \( 28.3 \times 10^{-3} \) and \( 8.4 \times 10^{-5} \), respectively, a shrinkage by 70 per cent.

**Tolerability**

Gastrointestinal discomfort and diarrhea disappeared only when meals were taken one hour after injections. Loose stools and steatorrhea (20 g/d) persisted. Plasma vitamin A and K, levels were unchanged.

Gallstones appeared after 6 months of treatment and disappeared within 4 months of combined therapy with ursodeoxycholic acid. Fasting blood glucose and glycosylated hemoglobin remained normal.

**Discussion**

This case report demonstrates the effectiveness of octreotide therapy of primary thyrotropinomas. The tumoral origin of TSH hypersecretion was obvious because of inappropriate elevation of TSH associated with hyperthyroidism before radiodine therapy and subsequent euthyroidism, TSH unresponsiveness to TRH and bromocriptine, \( \alpha \)-subunit elevation with \( \alpha/TSH \) molar ratio >1, and presence of a pituitary macroadenoma.

Surgical ablation seemed imperative despite the patient’s age, 60 years, the need for a transfrontal approach because of the tumour size and morphology, and the impossibility to remove the adenoma entirely. The brisk and spectacular response to octreotide enticed us to pursue this pharmacological therapy and postpone surgery.

TSH suppression by octreotide was dramatic but gradual and delayed. This seems to occur quite often in TSH-secreting adenomas (5), whereas GH hypersecretion is immediately suppressed in acromegaly (9,10,12). TSH bioactivity was also inhibited, since \( F_T \) levels dropped significantly in parallel with TSH reduction. This was also the case in other patients treated with octreotide (3-5), even when TSH was neither completely controlled (3) nor significantly reduced (3). Octreotide therapy might even cause transient hypothyroidism (3,4). Partial escape of TSH occurred after one month in our patient and was observed in 2 out of 6 patients treated with octreotide (4).

Visual improvement was dramatic and occurred rapidly in our patient. This is well established in prolactinoma patients treated with dopamine agonists. We have already observed this phenomenon in various types of pituitary macroadenomas (13), including another case of thyrotropic adenoma (8). In the latter case repeated CT scans did
Fig. 2.
MRI T1 weighted sagittal images 14 mm to the left (I), 7 mm to the left (II), and on the midline (III), before (to the left) and after (to the right) 15 months of treatment with octreotide. White circle: left carotid artery; open triangles delineate the cystic part of the adenoma; black circle: suprasellar portion of the adenoma; black arrow heads: optic chiasm; white rectangle: subfrontal subarachnoidal space; open white circle: suprasellar space. A 70% tumour shrinkage occurred within 15 months of treatment with octreotide.
not demonstrate any tumour shrinkage (5). However, visual improvement may precede tumour shrinkage as documented in patients with macroprolactinomas treated with bromocriptine (14). Indeed, in the current study, MRI showed pituitary tumour shrinkage after 3 months of octreotide therapy. Tumour size was further reduced one year later, although TSH secretion had partially escaped and that moderate doses of octreotide were used. This tumour shrinkage was certainly not due to apoplexy as no clinical, hormonal, or neuroradiological abnormalities suggestive of infarction could be found. Adverse reactions were more pronounced in our patient than in acromegalic patients. Asymptomatic cholelithiasis disappeared with combination of ursodeoxycholic acid.

In conclusion, this is the first report of undisputable shrinkage of a primary TSH-secreting pituitary adenoma by octreotide therapy. In our case as in most thyrotropinomas (15), the tumour was too large and invasive to expect surgery to be successful. In such cases where surgery has little chance of success, octreotide therapy can be considered as first line treatment.

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References