EFFECT OF OCTREOTIDE ACETATE ON THYROTROPIN-SECRETING ADENOMA: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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Objective. To present two cases with thyrotropin-secreting adenoma and the effectiveness of octreotide acetate treatment on their tumor size as well as on thyroid stimulating hormone (TSH) and thyroid hormone levels.

Case reports. The first case presented with tremor, palpitations and sweeting as suggestive of hyperthyroidism, but the other one presented with predominantly headache, while the other symptoms such as palpitation and nervousness were less prominent and he also did not have any thyroid enlargement at physical examination. Thyroid hormone levels in both cases were increased. However, TSH levels were not suppressed thus indicating an inappropriate secretion of TSH. Moreover, TSH levels did not change after T3 and TRH administration, which also contributed to the assumption of an inappropriate TSH secretion. One case had no increase in the TSH alpha subunit level, while this was increased in the other one. Both magnetic resonance imaging and somatostatin receptor scintigraphy revealed that there was a microadenoma (the first case; 6x7 mm in diameter) and a macroadenoma (the second case; 14X18 mm in diameter). Both patients were placed on a therapy with somatostatin analog octreotide (Sandostatin, Sandoz). Octreotide was initially given at a dose of 300 μg daily and then increased gradually up to 600 μg per day. There was some decrease in the levels of TSH and thyroid hormones at first. However, such decreases did not persist with ongoing therapy for 6 months. In addition, there was no change in the tumor size with this therapy at the end.

Conclusions. We conclude that the treatment by somatostatin analogue octreotide may not be an effective means of reducing the pituitary tumor size, though it may be used to reduce TSH and thyroid hormones temporarily.

Key words: TSH secreting adenoma – Octreotide treatment – Case reports – Minireview

An inappropriate secretion of thyroid stimulating hormone (TSH) should be considered if serum levels of TSH are not decreased or not suppressed in the presence of an increased levels of thyroid hormones. As this condition can be seen in the states of resistance to thyroid hormone, it may also be seen in cases of pituitary thyrotropin-secreting adenomas (TSHomas). These adenomas are rarely encountered, and, up to date, approximately 200 cases were reported (Girod et al. 1986; Magner 1993; Refetoff et al. 1993). TSHomas commonly present with symptoms due to intracranial mass effects, such as headache and visual disturbance. A number of measurements, including serum level of TSH alpha subunit, molar ratio of α-subunit of TSH/TSH, thyrotropin releasing hormone (TRH) stimulation test, T3 suppression test, as well as several indicators of peripheral effects of thyroid hormones, such as sex hormone binding globulin (SHBG), serum angiotensin converting enzyme, carboxyterminal telopeptide of type I collagen, and ferritin are suggested for the differential diagnosis (Persani et al. 1997). Therapeutic options available for the other types of pituitary tumours may also be valid for the treatment of TSHomas. A somatostatin analog, octreotide acetate, has also been used for the treatment of many endocrino-

Table 1: Baseline findings of the two cases

	Case 1	Case 2
Age (years)	32	21
Sex (M/F)	M	M
Free T_3 (pg/ml)	13.4	8.3
Free T_4 (ng/ml)	5.3	2.7
TSH (mIU/L)	3.4	4.2
α-SU (μg/L)	0.10	5.3
α -SU/TSH	0.29	1.26
Antithyroidal antibodies	Negative	Negative
SHBG (nmol/L)	146.5	108.4
Ferritin (μg/L)	42.4	189.6
After Werner's test		
T_3	14.2	8.6
T_4	5.5	2.4
TSH (mIU/L)	8.0	6.8
SHBG	130.2	134.2
Ferritin (μg/L)	45.0	234.4
Peak TSH response to TRH (mIU/L)	13.6	11.9
Pituitary MRI	Mass sized 6x7 mm	Mass sized 14x18 mm
Octreotide scintigraphy	Positive imaging	Positive imaging

logic diseases in addition to being a very helpful tool in the diagnosis some of them. Many studies reported that octreotide is an effective drug in reducing both TSH and thyroid hormone levels as well as reducing tumor size in pituitary TSHomas (Lee et al. 1994; Beckers et al. 1991; Kamio 1993). In this article we presented the effects of octreotide acetate therapy on the TSHomas, within two cases.

REPORT OF CASES

Case 1

The first case who will be presented here was a thirty-four year old male patient, who has been followed up as a case of multinodular goitre for 6 years. During this period, the patient complained about palpitation, tremor, nervousness, insomnia, and excess sweating, but no treatment was given to the patient until 1990, when we firstly saw him. When we examined him in 1990, he had nodular thyroid enlargement of grade II degree, which was later also confirmed by the imaging techniques, thyroid ultrasonography and ^{99m}technetium pertecnatate scintigraphy. The patient had both an increased thyroid hormone levels and thyroid stimulating hormone, suggesting an inappropriate secretion of TSH. There was no increase in the serum levels of antithyroid antibodies, such as antimicrosomal antibody and anti-thyroid peroxidase antibody. The other pituitary hormones of the case were in normal limits. Sex hormone binding globulin (SHBG), an index of peripheral effects of the thyroid hormones, was higher than normal whereas serum ferritin level was normal (Table 1). A pituitary tumor, sized 6-mm, was identified on pituitary computerised tomography in 1991. The patient had no visual computerized defect on the perimetric examination. There was no malignancy, but increased cellularity, on the fine needle aspiration biopsy of the thyroid gland. All these findings suggested the TSH increase was in neoplastic origin. The patient was given bromocriptin, its

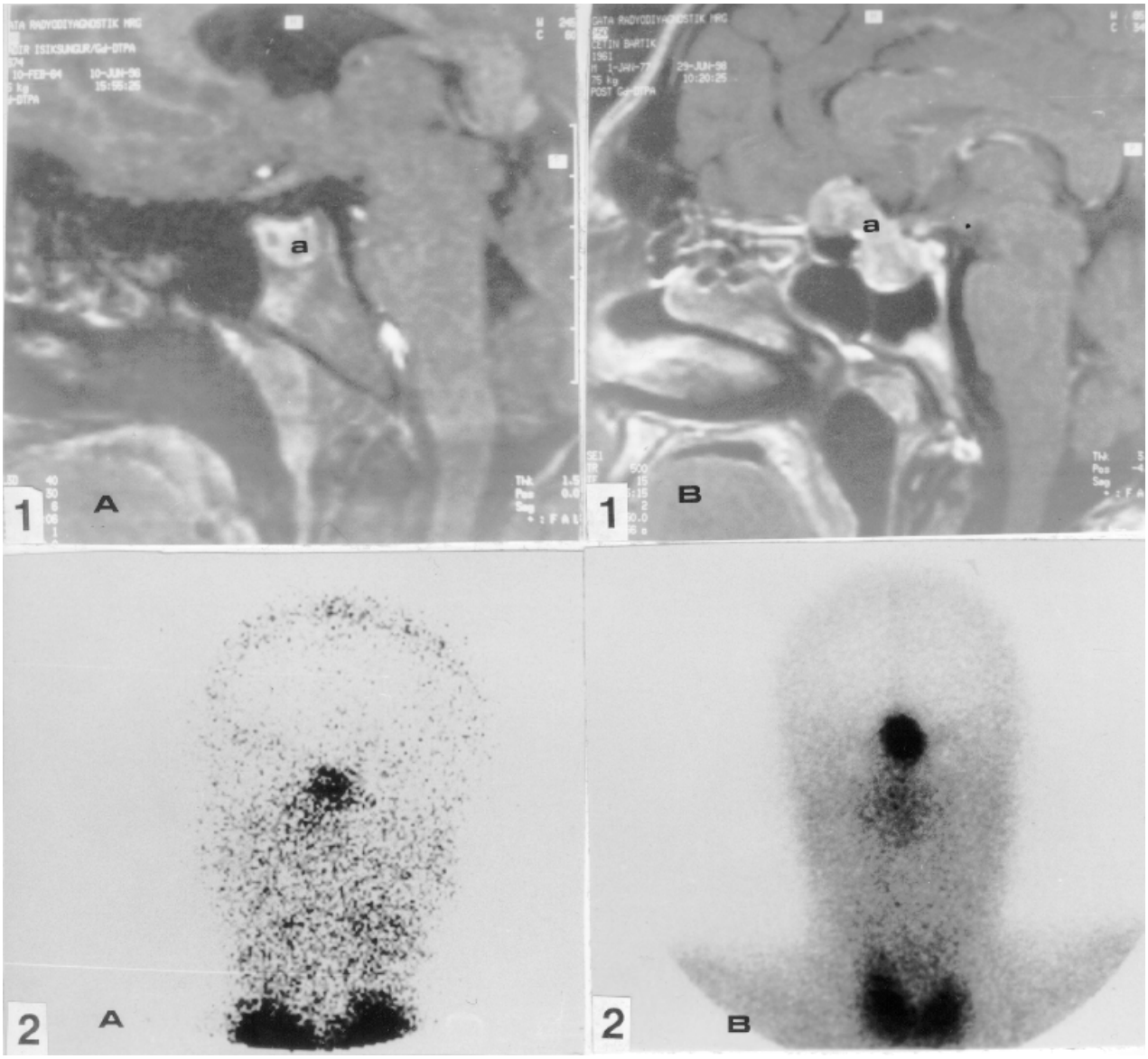

Figure 1: Baseline MRI's of the pituitary of the cases 1(A) and 2(B). A: adenoma
Figure 2: Baseline octreotide scintigraphy of pituitary of the case 1 (A) and the case 2 (B).

dose gradually increased up to 20 mgr per day, but the drug showed no effect on both laboratory and clinical parameters after 3 month's therapy. Then, the patient was only followed up, without any treatment, until the beginning of 1995. During this period, it was observed that the increases of thyroid hormones and TSH persisted on repeating measurements. At the beginning of 1995, the patient was reevaluated in more detail, with TRH stimulation test, measurement of α-subunit, and Werner's test (their results were shown on the Table 1), and pituitary magnetic resonance imaging (Fig. 1A). In brief. Werner's test was performed as follows: baseline serum levels of T_4, TSH, SHBG and ferritin were determined and then T_3 (200 μg daily) was administered perorally for 8 days. After that the same parameters were measured. After these tests, which strongly suggested a neoplastic TSH increase in origin, we performed somatostatin receptor scintigraphy with 3 mCi ^{111}In-DTPA-octreotide. This technique showed well that the pituitary tumor was somatosta-

Table 2: The effects of octreotide acetate treatment on the serum TSH, T_3, T_4 levels and the pituitary tumor size

	Case 1			Case 2		
	Baseline	3rd month	~ 6th month	Baseline	3rd month	6th month
FT_3 (pg/ml)	13.4	8.6	9.4	8.3	5.8	6.2
FT_4 (ng/ml)	5.3	3.4	4.5	2.7	2.9	3.0
TSH (mIU/ml)	3.4	3.2	4.6	4.2	3.6	4.1
Tumor size (mm)	6x7	-	5x7	14x18	-	13x16

tin-receptor positive (Fig. 2A). Based on this somatostatin receptor positivity of the tumor, we planned a therapy with octreotide acetate, which was repeatedly suggested as an effective therapeutic agent in the treatment of pituitary tumors. We applied this agent in a dose of 100 μg three times a day, subcutaneously. After 3 months, the dose was increased to 200 μg three times a day, because we did not observe any satisfactory response. At the sixth month of therapy with octreotide acetate, we decided to stop the therapy because there was a little decrease in the levels of serum TSH and thyroid hormones and no change in pituitary tumor size. We thought that octreotide acetate therapy in this patient was not effective, for this reason, the patient was offered a surgical intervention but he refused this offer. Later, he did not come to control visits, therefore, we were not able to hear of his fate.

Case 2

The second case who will be presented here was 21 year-old male patient. The most important one of his complaints was headache, although he also had a number of minor symptoms, such as palpitations, nervousness, and faintness. The patient was given a number of analgesic drugs for 2 months, but there was no improvement of his complaint of headache. For this reason, a computerized tomography was obtained to find out any intracranial pathology. With this imaging technique, a mass lesion in the pituitary gland was shown, then, the patient was referred to our endocrinology department for further evaluation and treatment.

Except very mild tremor in the fingers and the heart rate of 96 per minute, there was no apparent abnormality on the physical examination, including thyroid region, when he came to our hospital in 1998. On the perimetric examination there was no visual field defect. Routine biochemical investigations, such as whole blood count, urinalysis, erythrocyte sedimentation rate, fasting blood glucose, urea, creatinine, uric acid, transaminases, alkaline phosphatase, total cholesterol, triglyceride, albumin, and serum electrolytes were in normal limits. We obtained ultrasonography and Tc-99m pertechnatate scintigraphy of the thyroid gland of the patient, revealing minimal thyroid enlargement and diffuse homogenous appearance. Serum free T_3 and T_4 levels were high, inconsistent with this result, serum level of TSH was also high. Thyroid autoantibodies, such as antithyroglobulin and anti-thyroid peroxidase antibody, were in normal ranges. The other pituitary hormones were in normal limits. X-ray showed an enlarged sella. Magnetic resonance imaging of the pituitary revealed a macroadenoma, sized 14 X 18 mm, with central heterogeneity (Fig. 1B). Werner's test was applied to the patient (its result was shown on the Table 1). ^{111}Indium-octreotide scintigraphy showed a well-circumscribed, oval, and homogenous uptake within the pituitary gland, suggesting a macroadenoma (Fig. 2B). Serum α-subunit level of TSH was higher than normal.

Based on these findings, the patient was diagnosed as a case of pituitary TSHoma and was offered to have been operated on. But, the patient did not accept the suggestion at the beginning, therefore, we started a medical therapy with a somatostatin analog, octreotide acetate, in doses as described in our first case. We observed the case with respects to changes in the thyroid size, serum levels of thyroid hormones and TSH, pituitary tumor size, and side effects of the drug for 6 months. During this period, the patient did not have any adverse effects related

to the drug. After this treatment, tumor size changed only from 14 X 18 mm to 13 X 16 mm. Also, serum levels of T_3, T_4, and TSH changed only minimally. Therefore, we stopped the drug therapy and offered him again surgical intervention. The patient accepted surgery, and he was operated on with a transsphenoidal surgery. At the 2nd month of the surgery, serum levels of thyroid hormones and TSH were in normal limits, clinically free of symptoms, and there was no abnormality in the other pituitary hormones.

Discussion

Although rarely encountered tumors in the past, thyrotropin-secreting adenomas have been diagnosed in a gradually increasing rate owing to the application of newer and more sensitive measurement techniques of TSH (Kamio 1993). In these tumors there is an increase in the level of thyroid hormones, but TSH level is inappropiately also high or not suppressed (Kamio 1993). However, a few conditions that may result in similar clinical tables, such as pituitary TSH hyperplasia and thyroid hormone resistance, also should be kept in mind when interpreting these states. A number of measurements, including serum level of TSH α-subunit, molar ratio of TSH α-subunit/TSH, thyrotropin releasing hormone (TRH) stimulation test, T_3 suppression test, as well as several indicators of peripheral effects of thyroid hormones, such as sex hormone binding globulin (SHBG), serum angiotensin converting enzyme, carboxyterminal telopeptide of type I collagen, and ferritin should be performed to make a differential diagnosis (Persani et al. 1997). A molar ratio of α-subunit to TSH may be suggested as to be the most useful of these options. However, some studies reported that there might be no increase in this ratio in some TSHomas (Korn et al. 1994; Smallridge 1994). One of our cases, but not the other, had an increased ratio of α-subunit/TSH, being consistent with the literature findings.

Somatostatin analogs have been used to treat pituitary tumors as well as imaging of them. With the use of this technique we visualised well the pituitary TSHomas in our two cases, proving with the concept some TSHomas may have somatostatin receptor.

As in the other pituitary tumors, no treatment approach alone can be effective in the treatment of TSHomas. For example, pituitary surgery alone in these tumors have been found as curative only in 30-38% of cases (McCuthean et al. 1990; Gancel 1994). Other therapeutic approaches have been tried to treat these tumors, consequently, somatostatin analog treatment has been introduced in to use. A study by Lee and coworkers showed that octreotide therapy was effective in reducing both tumor size and serum levels of TSH and thyroid hormones in 55 patients with TSHoma (Lee et al. 1994). Another studies by Gancel et al. (1994) and Mayinger et al. (1999) showed that there were significant decreases in the levels of both thyroid hormones and TSH, using a long-acting somatostatin analog, lanreotide, in 4 patients with TSHoma. But these studies did not evaluate the changes in the tumor size. In another study, it was shown that octreotide treatment reduced both the tumor size and the hormone levels in patients with mixed TSHoma and gonadotropinoma (Sy et al. 1992). Although our octreotide therapy, up to doses of 600 μg/day, reduced the thyroid hormone and TSH levels slightly, this decrease did not persist with ongoing therapy later. More importantly, with octreotide acetate therapy, we did not observe any significant decrease in the tumor size in neither of the cases. In addition to our present study, when the other studies about this subject in the literature are considered, it is evident that the data is not sufficient to do such a certain conclusion on the efficacy of octreotide acetate in the treatment of TSHomas. Consequently, we need to have more studies to clarify this matter.

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