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Treatment of Thyrotropin-Secreting Pituitary Adenomas with Octreotide

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Abstract. Five hyperthyroid patients with TSH-secreting pituitary adenoma were treated with octreotide. Acute administration of octreotide decreased plasma TSH levels in all patients (mean decrease, 50.6 ± 14%). Treatment with octreotide (25–300 μg/day) for 2–360 weeks resulted in reductions in plasma TSH and α-subunit levels in three patients, and serum free thyroxine levels were normalized with concomitant clinical improvements such as disappearance of excessive sweating, tachycardia and finger tremors. In two patients, plasma TSH and free thyroxine levels were initially decreased, but tachyphylaxis occurred 3 and 10 weeks after the initiation of therapy. Mild to marked shrinkage of the tumor was observed 2–50 weeks later in four patients. Shrinkage of the tumor seems to be reversible in one case. Frequent bowel movements and epigastric discomfort occurred in two patient. Somatostatin receptor subtype 2 (sst_2) mRNAs were detected in two adenoma tissues studied by RT-PCR. Long-term treatment with octreotide is effective in controlling hyperthyroidism and tumor growth in patients with TSH-secreting pituitary adenoma.

Key words: Thyrotropin-secreting pituitary adenoma, α-Subunit, Octreotide, Tumor shrinkage, Hyperthyroidism, Tachyphylaxis

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TSH-secreting pituitary adenomas are rare, but are now recognized with increased frequency due to the development of more sensitive and specific TSH assays [1]. Generally they present as macroadenomas with symptoms related to mass effect and hyperthyroidism. Surgical resection can be curative for microadenomas, whereas incomplete resection is common for large tumors [2]. Medical treatment such as dopamine agonists has not usually been successful in controlling tumor growth and hormonal hypersecretion except in a few cases [3, 4]. Long acting somatostatin (SRIF) analogs, which have proved effective in the management of acromegaly and pituitary gigantism [5, 6], are potentially useful agents in patients with hyperthyroidism due to TSH-secreting pituitary adenoma [7, 8]. Until now more than seventy cases treated with octreotide have been described in the literature [1]. We report here five additional patients on long-term treatment with octreotide. Four of them had a reduction in the tumor size during octreotide treatment.

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Subjects and Methods

Case reports

Case 1: A 29-year-old male was referred to the Kyoto University Hospital for the evaluation of hyperthyroidism. He had a history of tachycardia for seven years and noted excessive sweating and finger tremors. Magnetic resonance imaging (MRI) showed a cystic pituitary macroadenoma. Treatment with octreotide was initiated after obtaining informed consent. Sixteen weeks later, the patient underwent transsphenoidal surgery. He was still mildly thyrotoxic with high serum free thyroid hormones four weeks after the surgery.

Case 2: A 54-year-old female was admitted to the Nagaoka Red Cross Hospital for recurrent hyperthyroidism. She has complained of loss of appetite and body weight, and excessive perspiration. She had a history of hyperthyroidism due to a TSH-secreting pituitary adenoma, which was treated by surgery and subsequently followed by Graves' disease [9]. On admission, the slightly enlarged thyroid gland was palpable. MRI showed residual pituitary adenoma invading the left cavernous sinus. Since the patient refused the surgery, treatment with octreotide was started after obtaining informed consent.

Case 3: A 48-year-old female was referred to the Kyoto University Hospital with a twelve-month history of palpitation and increased perspiration [10]. She has noted gradual enlargement of acral and facial features for more than fourteen years. She also had a history of amenorrhea of eight years' duration. Physical examination showed a female with acromegalic features, tachycardia, slightly enlarged thyroid gland and finger tremors. Plasma GH levels were persistently high and not suppressed by oral glucose loading. Plasma IGF-I and PRL levels were also high. MRI showed a large invasive macroadenoma with infra-, supra- and para-sellar extension. Treatment with octreotide was initiated after obtaining informed consent. The pituitary tumor was subtotally removed by transsphenoidal surgery. Immunostaining of the tumor showed different cell populations reacting with anti-TSH, -GH or -PRL antibody. Since hyperthyroidism persisted with high levels of plasma TSH, GH and PRL after surgery, bromocriptine therapy was started.

Case 4: A 25-year-old male was referred to the Hamamatsu Medical University Hospital for recurrent pituitary adenoma and hyperthyroidism [11]. He has complained of right visual disturbance for ten years and hyperthyroidism that had been poorly controlled by antithyroid drugs for seven years. He had received transsphenoidal surgery twice and craniotomy twice for the recurrence of pituitary adenoma. He suffered from agranulocytosis caused by methimazole, and total thyroidectomy was performed to control his severe thyrotoxicosis. Plasma TSH levels were very high despite the sufficient replacement dose of thyroxine. Plasma GH and IGF-I levels were also high with the stigmata of acromegaly. MRI showed a large macroadenoma with noticeable suprasellar extension. Treatment with octreotide was started after obtaining informed consent.

Case 5: A 41-year-old man was referred to the Kyoto University Hospital with an eight-month history of visual disturbances. Before admission, he had experienced severe headache and nausea, and CT scan showed a large pituitary adenoma with suprasellar extension complicated with obstructive hydrocephalus. Physical examination showed bilateral hemianopsia, moist skin, tachycardia and enlarged thyroid gland without evidence of clinical acromegaly. Plasma TSH levels were within the reference range and accompanied by high concentrations of thyroid hormones. VP shunting was performed followed by transcranial adenomectomy. The adenoma cells immunostained positively for TSH, GH and PRL. Since a significant residual tumoral mass remained and mild hyperthyroidism persisted, octreotide treatment was started after obtaining informed consent.

The pertinent clinical and endocrinological data of these five patients are summarized in Table l.

Endocrine studies

The stimulatory effects of 500 μg TRH, iv, on TSH and α-subunit secretion were studied in all patients. The responses of TSH and α-subunit to dopamine infusion (2 μg/kg/min for 120 min) were studied in four patients (cases 1, 3, 4 and 5). The

Table 1. Pertinent clinical and endocrinological data of the patients with TSH-secreting pituitary adenoma treated with octreotide

Patient No.		1	2	3	4	5	Reference intervals
Age (yr) /Sex		29/M	54/F	48/F	25/M	41/M	
Clinical symptoms							
Hyperthyroidism		+	+	+	+	+	
Acromegaly				+	+		
Amenorrhea					+		
Visual disturbance					+	+	
TT_4	(nmol/L)	232	ND	251	344	191	51–142
TT_3	(nmol/L)	4.9	ND	3.7	5.2	3.3	1.2–2.4
Free T_4	(pmol/L)	52.5	51.5	44.3	88.8	39.0	12–23
TSH	(mU/L)	19.2	1.34	0.50	2.2	4.0	0.30–4.0
α-subunit	(μg/L)	1.8	5.3	1.3	15.7	23.5	<1.2[b],<5[c]
GH	(μg/L)	2.5	0.7	41.0	17.1	0.6	<5
PRL	(μg/L)	4.3	3.7	32.4	4.0	5.1	<15
TSH/α-subunit response (%[a]) to							
TRH		+99/+100	+3/0	+103/0	+27/+17	+15/+14	
Dopamine		-42/-21	ND/ND	-70/-11	-25/0	+15/+14	
Bromocriptine		-63/ND	-35/ND	-68/0	-35/-18	+8/ND	
Octreotide		-63/-22	-56/-46	-63/-20	-35/-18	-36/0	

ND: not determined. [a]: percent increase(+) or decrease (-) from baseline value. [b]: reference value for men and premenopausal women. [c]: reference value for postmenopausal women.

acute responses of TSH and α-subunit to 50 or 100 μg octreotide, sc, were also studied.

Plasma TSH levels were measured with an immunoradiometric assay (IRMA) kit provided by Hoechest Japan Ltd. (Tokyo, Japan) with a sensitivity of 0.03 mU/L. Plasma α-subunit levels were measured by RIA as previously described [12]. Serum total and free thyroid hormones and plasma levels of GH, PRL, gonadotropins and IGF-I were also measured with commercial RIA and IRMA kits, as previously described [13].

Octreotide treatment

The patients were treated with octreotide (Sandostatin™) over a period of 16 weeks (case 1), 56 weeks (case 2), 4 and 3 weeks (case 3), 2, 36 and 360 weeks (case 4), and 18 and 118 weeks (case 5). The initial daily dose was two 50 μg doses, sc and was increased to three 50 μg doses given to one patient (case 1), three 100 μg doses and was changed to 22.5 μg administered every 2 h by means of a portable intermittent sc infusion pump to one patient (case 3), 300 μg initially by pump and decreased to 90 μg to one patient (case 2), 300 μg initially by pump and decreased to 90 μg and after interruption 30 μg given twice daily to one patient (case 4), and 50 μg two doses and decreased to a once daily 50–25 μg dose to one patient (case 5). Follow-up was performed by measuring pituitary and thyroid hormones. Tumor size was evaluated by MRI and CT scan before and during the treatment.

Reverse transcriptase-PCR (RT-PCR) of somatostatin receptor (sst)

Total RNAs were extracted by the acid guanidinium thiocyanate-phenol-chloroform method with ISOGEN™ (Nippon Gene, Toyama, Japan) from pituitary adenoma tissues (cases 3 and 5), and treated with Deoxyribonuclease I (Amplification Grade: GIBCO BRL, Gaithersburg, MD). First strand complementary DNA (cDNA)s were synthesized by using oligo (dT) primer and reverse transcriptase (SuperScript Preamplification System for First Strand cDNA Synthesis™; GIBCO BRL). The same reaction mixtures without reverse

transcriptase served as negative controls.

First strand cDNA products derived from 50 ng of total RNA were used as templates for PCR amplification in a 30-μL reaction mixture containing 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.5 mM $MgCl_2$, 1 U of Taq DNA polymerase and 1mM oligonucleotide primers specific for each somatostatin receptor (sst) subtype [14]. The forward and reverse primers of sst subtype were as follows; 5'-AAATGCGTCCCAGAACGGGA-3' and 5'-ACAACGTGGAGGTGACTAGG-3' for sst_1, 5'-GTCATGACTGTGGATGGCAT-3' and 5'-TGT ACCAAGCCCCAGATTCA-3' for sst_2, 5'-CGACCT CAGAACCTGAGAAT-3' and 5'-TTGATGCCAT CCACCGCCAT-3' for sst_3, 5'-CATGGTCGCTATC CAGTGCA-3' and 5'-AGCACGGTGAGACAGAA GAC-3' for sst_4 and 5'-TGCTGTACCTGCTGG TGTGT-3' and 5'-GTAGCGGTCCACGCTCATGA-3' for sst_5, respectively. As an internal control, forward and reverse primers corresponding to β-actin, 5'-TCATGAAGTGTGACGTGGAC-3' and 5'-ACCGACTGCTGTCACCTTCA-3', were used. The PCR mixtures were denatured for 5 min at 94 °C and followed by 40 cycles of PCR (94 °C, 60 sec; 65 °C, 60 sec; 72 °C, 90 sec), with a final 5-min extension at 72 °C. PCR products were separated by electrophoresis on 2% agarose gels and stained with ethidium bromide.

Results

Clinical and endocrinological data (Table l)

Hyperthyroidism was confirmed in all patients by means of high total or free thyroid hormone levels. Plasma TSH levels varied between 0.50 and 19.2 mU/L. Plasma α-subunit levels were high in four and upper normal in one patient. TRH provoked a rise in the plasma TSH level in two patients (cases 1 and 3). α-Subunit secretion was also stimulated by TRH in one patient (case 1). Significant TSH inhibition was obtained after dopamine infusion in one patient (case 3). Concomitantly increased plasma GH and IGF-I concentrations were found in two patients (cases 3 and 4). A high PRL level was observed in one patient (case 3). Pituitary-adrenal and pituitary-gonadal axes were normal in four patients but not in case 5.

Octreotide treatment

After acute administration of octreotide, plasma TSH levels were decreased in all patients (mean decrease, 50.6 ± 14%), with the nadir being obtained between the third and twelfth hours after the injection. Plasma α-subunit levels also decreased in four out of five patients (mean decrease, 26.5 ± 13%), as shown in Fig. 1. In one patient (case 3), plasma GH and PRL levels also normalized with the injection.

Long-term treatment with octreotide (25–300 μg/day) for 2–360 weeks resulted in noticeable reductions in plasma TSH and α-subunit levels in two patients (cases 3 and 4), as shown in Table 2. Serum free thyroxine levels were normalized with concomitant clinical improvements such as the disappearance of excessive sweating, tachycardia and finger tremors. When octreotide treatment was temporarily interrupted, plasma TSH and thyroid hormone levels returned to those before therapy (cases 3, 4 and 5). In two patients (cases 1 and 2), plasma TSH and free thyroxine levels were at first decreased, but tachyphylaxis occurred 3 and 10 weeks after the start of therapy, as shown in Fig. 2. Concomitant administration of methimazole with octreotide could control their mildly thyrotoxic state.

MRI and/or CT scan performed after 2–50 weeks showed mild to marked shrinkage of the tumor size in four patients (Fig. 3). In one patient (case 3), withdrawal of octreotide for 4 weeks reversed the shrinkage of the tumor (Fig. 3G) and reinstallation of octreotide again promptly decreased the size of the tumor (Fig. 3H). Frequent bowel movements and epigastric discomfort occurred in two patient. No other adverse effect including impaired glucose tolerance or cholelithiasis has been observed in these patients.

RT-PCR of sst mRNAs

Fig. 4 shows a representative result of RT-PCR of sst subtypes in case 3, in which sst_1, sst_2 and sst_5 were clearly expressed. No PCR product was detected when the reverse transcriptase was omitted from the reaction, indicating that the products were not due to amplification of contaminating genomic DNA. In case 5, sst_1 and sst_2 were detected by RT-PCR. Neither sst_3 nor sst_4 was expressed in these adenomas.

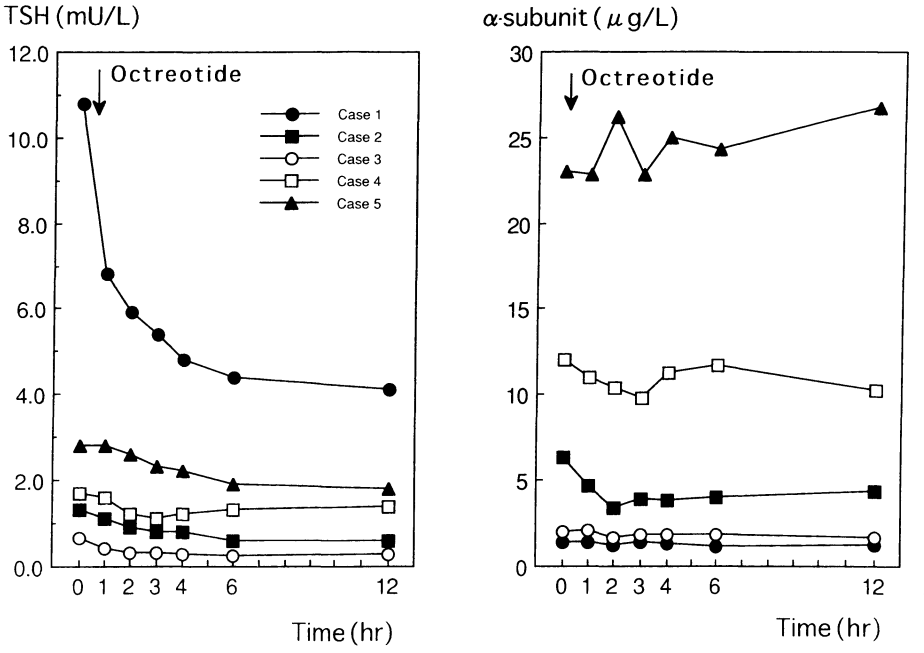

Fig. 1. Responses of plasma TSH and α-subunit levels to octreotide administration (50–100 μg, sc) in patients with TSH-secreting pituitary adenoma. Cases 1 (●), 2 (■), 3 (○), 4 (□) and 5 (▲) are shown.

Discussion

Hyperthyroidism due to inappropriate secretion of TSH is rarely encountered and may result from either a TSH-secreting pituitary tumor or selective pituitary resistance to thyroid hormone action [1]. The plasma α-subunit levels and/or the α-subunit/TSH molar ratio are commonly used to differentiate TSH-secreting pituitary adenomas from other forms of inappropriate TSH secretion. But some TSH-secreting adenomas do not accompany α-subunit hypersecretion, as in the present case 1, resulting in a α-subunit/TSH molar ratio below unity [15–17]. A blunted TSH response to TRH and the absence of TSH suppression by T_3 were suggestive of a tumor [1]. TSH response to TRH, however, could not exclude the presence of an adenoma, as in cases 1 and 3. Laboratory studies and dynamic tests alone may not provide results discriminating between tumorous and nontumorous TSH hypersecretion. Careful examination of the pituitary by MRI or CT scan is indicated in all patients with inappropriate secretion of TSH.

The optimal treatment of TSH-secreting pituitary adenoma is as yet undetermined. About two-thirds of TSH-secreting adenomas are under control with pituitary surgery and/or irradiation [1]. The remaining patients require alternative pharmacological therapy. Specific ^{125}I-SRIF binding sites have been demonstrated in TSH-secreting pituitary adenomas [18–20]. There was a good correlation between ^{125}I-SRIF binding capacity and the magnitude of SRIF inhibition of adenylyl cyclase in these tumors [20]. SRIF analog octreotide is therefore a promising medical method for the treatment of TSH-secreting pituitary adenomas [7, 8, 21].

The present study demonstrated that a single injection of octreotide (50–100 μg) reduced TSH and α-subunit levels in all five and four out of five adenomas, respectively, and the suppression of TSH lasted at least 12 hours in four patients. The suppressive effect of octreotide appears to be longer lasting in TSH-secreting pituitary adenomas [22], when compared to the suppression of GH (average; 6–8 h) in acromegaly [6, 23]. From our experience, a regimen of twice daily (or even once daily) injection of octreotide might be sufficient to achieve suppression of TSH and thyroid hormones in most cases.

Normalization of thyroid hormone levels and

Table 2. Plasma TSH, free T_4 and α-subunit levels in patients with TSH-secreting pituitary adenoma during octreotide therapy

Patient no.		Before therapy	On therapy		
			4 weeks	16 weeks	52 weeks
Case 1	TSH	9.8	2.1	2.6	– (mU/L)
	Free T_4	74.6	30.5	40.2	– (pmol/L)
	α-subunit	2.1	0.6	ND	– (μg/L)
Case 2	TSH	1.34	0.70	0.58	0.89
	Free T_4	51.5	24.5	29.6	20.6[a]
	α-subunit	6.3	2.0	3.7	3.5
Case 3	TSH	0.58	< 0.03	–	–
	Free T_4	51.2	24.3	–	–
	α-subunit	1.7	0.8	–	–
Case 4	TSH	30.3	0.4	0.6	–
	Free T_4	15.4[b]	18.0[b]	24.4[b]	–
	α-subunit	2.9	0.7	1.2	–
	TSH[c]	20.0	3.7	1.8	1.8
	Free T_4[c]	11.6[b]	21.8[b]	19.3[b]	20.6[b]
Case 5	TSH	7.1	1.4	2.8	–
	Free T_4	30.1	25.8	19.1	–
	TSH[c]	3.6	2.1	2.6	2.9
	Free T_4[c]	26.5	16.3	18.1	11.6
	α-subunit[c]	23.0	13.7	ND	ND

[a] under MMI therapy, [b] under thyroxine replacement after total thyroidectomy.
[c] octreotide therapy was temporarily interrupted and reinstituted. ND: not determined.

TSH levels was achieved in 78% and 72%, respectively, of 33 patients treated with octreotide for up to 2 weeks [8]. All patients exhibited a reduction in thyroid hormone levels. Despite an initial response to octreotide therapy, thyroid hormone levels continued to rise after 3 and 10 weeks of therapy in our two patients with TSH-secreting adenoma. Such tachyphylaxis occurred in 22% of patients and usually responded to increasing octreotide doses, whereas long term studies demonstrated true escape from the inhibitory effects in only about 10% of cases [1]. Tachyphylaxis and escape phenomenon were both observed in pure TSH-secreting adenomas and mixed TSH/GH-secreting adenomas [8, 16, 18, 24–27], but these observations are in sharp contrast to the case of acromegaly in which the escape phenomenon is seldom documented [28–30]. Whether these are due to the fundamental differences between GH- and TSH-secreting pituitary adenomas in biological behavior must await further studies.

The escape phenomenon during octreotide therapy is also observed in the case of gut neuroendocrine tumors [31, 32]. The underlying cellular mechanism leading to the escape phenomenon is now under investigation. It could be due to the disappearance of sensitive receptors or the presence of different cell clones with different sensitivity to inhibition by SRIF. In one patient escape from therapy occurred with high thyroid hormone levels. The treatment was stopped and reinstituted 6 months later with recovered sensitivity, arguing in favor of a desensitization process [24]. Agonist-mediated receptor reduction could explain the desensitization, and is associated with receptor phosphorylation, uncoupling of the receptor from G proteins, receptor internalization and receptor degradation [33, 34]. On the other hand, some of the ssts are increased by prolonged agonist treatment [33]. There seems to be difference between the regulation of ssts in normal tissues and in tumors, and underlying molecular signals remain to be identified.

The striking finding in our cases was the reduction in tumor size during octreotide therapy,

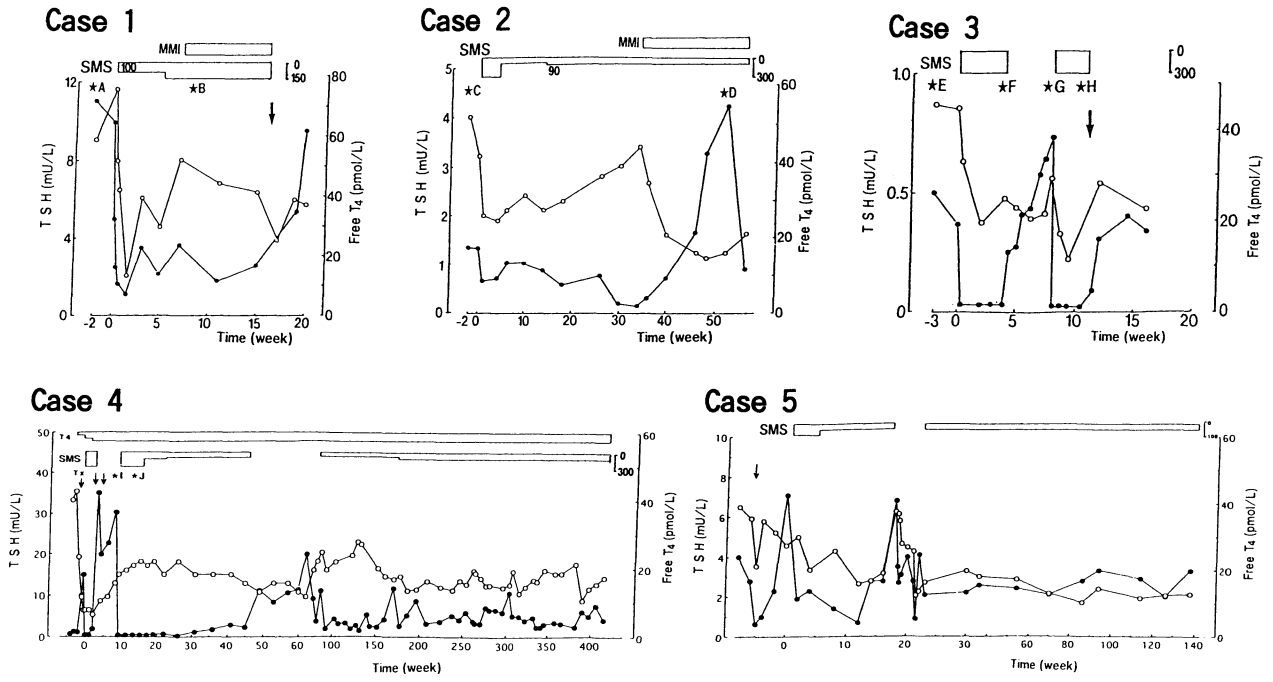

Fig. 2. Clinical courses of the patients with TSH-secreting pituitary adenoma showing changes in plasma TSH (●) and free T_4 (○) levels during octreotide treatment. MMI, methimazol; SMS, octreotide; Tx, total thyroidectomy; T_4: thyroxine replacement. Arrows indicate the time of transsphenoidal or transcranial surgery, and *A-*J represent the time of MRI or CT scan (see figure legend to Fig. 3).

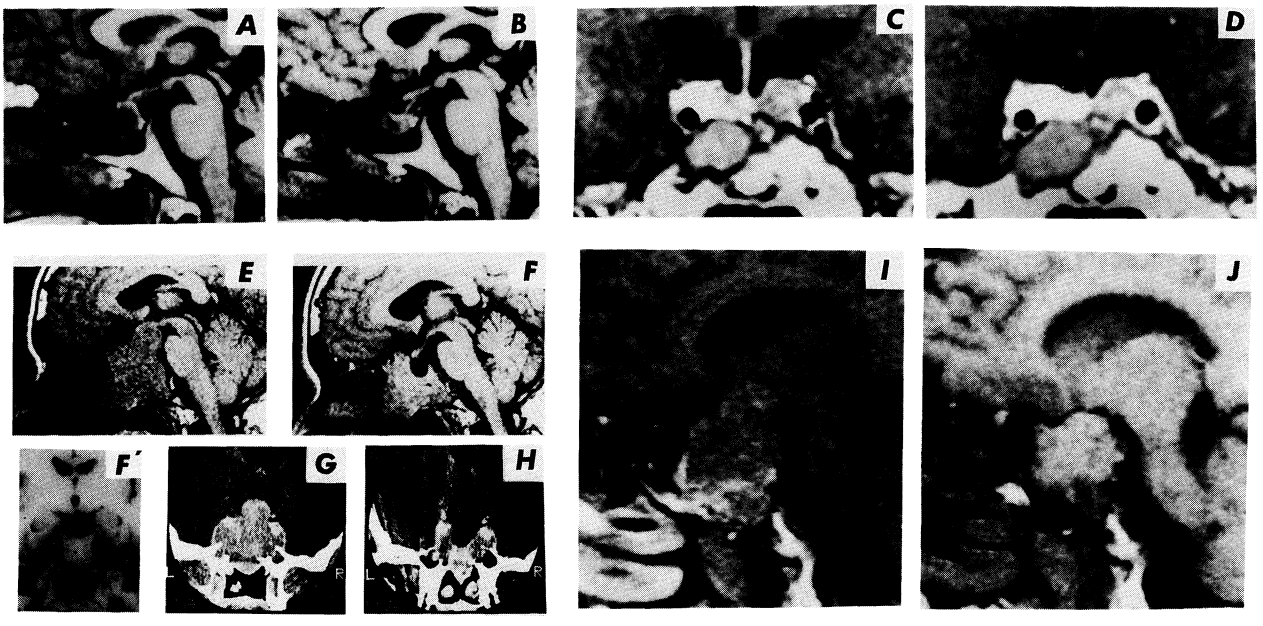

Fig. 3. MRI and CT scans of TSH-secreting pituitary adenomas before and during treatment with octreotide. MRI before (A) and after (B) treatment for 8 weeks in case 1; MRI before (C) and after (D) treatment for 50 weeks in case 2; MRI before (E) and after (F) treatment for 4 weeks in case 3; CT scan after withdrawal of octreotide treatment for 4 weeks (G) and 2 weeks after reinstallation of octreotide (H) in case 3; MRI before (I) and after (J) treatment for 4 weeks in case 4.

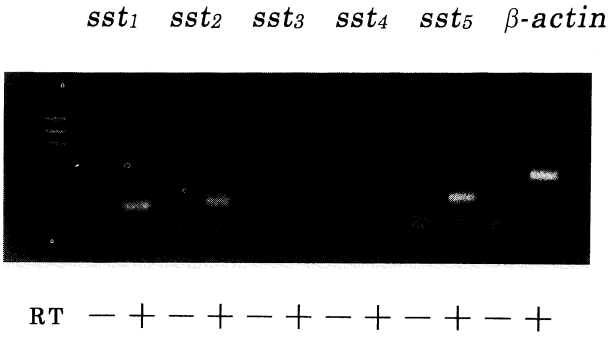

Fig. 4. Representative result of RT-PCR of sst subtypes in a TSH-secreting pituitary adenoma (case 3). RT– was the control in which reverse transcriptase was omitted while constructing the cDNAs. Sst_1, sst_2 and sst_5 mRNAs were detected and the possibility of contamination by genomic DNAs was excluded. The DNA size marker was Hae III digest of øX174. RT: reverse transcription.

but initially few reports were published [16, 26, 35, 36]. 52% patients receiving long-term therapy with octreotide had a clear shrinkage of the tumor mass [1], regardless of whether they had a pure TSH-secreting adenoma or a mixed adenoma with concomitant hypersecretion of other anterior pituitary hormones. The reduction in tumor size was similar to that seen in acromegalic patients who received octreotide therapy [37]. Tumor shrinkage, however, was not as dramatic as that seen in patients with prolactinoma who received bromocriptine therapy. The mechanism through which octreotide induces a shrinkage has not yet been established. Although no striking morphological changes in GH-secreting adenomas are associated with octreotide treatment [38], cell shrinkage secondary to reduced cytoplasmic volume might occur [39]. There is no evidence of a direct tumoricidal effect of octreotide, and the process of cell shrinkage seems to be reversible at least within 4 weeks of octrotide treatment judging from our observations. Recent studies have shown that SRIF analog inhibits cell proliferation through stimulation of tyrosine phosphatase and the inositol phospholipid/calcium pathway [41] and also regulates cell growth in the G_2 phase to induce apoptosis [42].

Among the five cloned human sst subtypes, octreotide binds with a high and relative high affinity to sst_2 and sst_5, respectively, with low affinity to sst_3, and has no affinity with sst_1 and sst_4 [43, 44]. In the present study, sst_2 mRNA were detected in two TSH-secreting adenomas examined. Sst_5 mRNA was detected in one adenoma which showed marked shrinkage of the tumor during octreotide therapy, but a recent report did not support the significance of ssts in tumor shrinkage caused by octreotide, since *in vivo* sst scintigraphy with ^{111}In-pentetreotide did not predict the shrinkage of GH-secreting or nonfunctioning adenomas [45]. Although sst_2 and sst_5 are mediated in regulating TSH and GH secretion from the human fetal pituitary [46], their role in controlling tumor growth remains to be determined.

Preoperative use of octreotide has been reported to improve the surgical remission in acromegaly [47–49], but our cases did not result in clinical cure by surgery. Controlled trials employing large numbers of patients may address the question whether preoperative use of octreotide would improve the surgical outcome. We observed mild gastrointestinal complaints in two patients. No serious side effect such as impaired glucose tolerance or cholelithiasis has been observed. The present study has shown that octreotide is effective in controlling hyperthyroidism and growth of TSH-secreting adenoma, but several practical problems should be solved before establishing octreotide as the therapeutic method for the control of TSH-secreting adenoma. The benefits of treatment must be weighed against the risk of adverse effects associated with long-term treatment. The high cost of treatment should also be considered. Octreotide has to be administered sc two or three times daily, but the recent long-acting depot preparations, octreotide-LAR and lanreotide-SR, would make therapy much easier and of better compliance [50]. We recommend the use of octreotide for long-term treatment of TSH-secreting pituitary adenoma after unsuccessful surgery.

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