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Short-term preoperative octreotide treatment for TSH-secreting pituitary adenoma

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Abstract. Preoperative control of hyperthyroidism in patients with TSH-secreting pituitary adenomas (TSHoma) may avoid perioperative thyroid storm. Perioperative administration of octreotide may control hyperthyroidism, as well as shrink tumor size. The effects of preoperative octreotide treatment were assessed in a large number of patients with TSHomas. Of 81 patients who underwent surgery for TSHoma at Toranomon Hospital between January 2001 and May 2013, 44 received preoperative short-term octreotide. After excluding one patient because of side effects, 19 received octreotide as a subcutaneous injection, and 24 as a long-acting release (LAR) injection. Median duration between initiation of octreotide treatment and surgery was 33.5 days. Octreotide normalized free T4 in 36 of 43 patients (84%) and shrank tumors in 23 of 38 (61%). Length of octreotide treatment did not differ significantly in patients with and without hormonal normalization ($p = 0.09$) and with and without tumor shrinkage ($p = 0.84$). Serum TSH and free T4 concentrations, duration of treatment, incidence of growth hormone (GH) co-secretion, results of octreotide loading tests, form of administration (subcutaneous injection or LAR), tumor volume, and tumor consistency did not differ significantly in patients with and without hormonal normalization and with and without tumor shrinkage. Short-term preoperative octreotide administration was highly effective for TSHoma shrinkage and normalization of excess hormone concentrations, with tolerable side effects.

Key words: TSH-secreting pituitary adenoma, Octreotide, Preoperative treatment, Outcome

TSH-SECRETING PITUITARY ADENOMAS (TSHoma) are rare tumors, accounting for only about 2% of pituitary adenomas [1, 2]. These tumors may cause hyperthyroidism through a condition called syndrome of inappropriate secretion of TSH (SITSH). Patients with thyrotoxicosis such as uncontrolled Grave's disease who experience stress can develop thyroid crisis, indicating that hyperthyroidism should be adequately controlled prior to surgery. As with Grave's disease, TSHoma can also cause perioperative thyroid storm [3], indicating the need to preoperatively control the thyroid hormone levels in these patients.

Although antithyroid agents such as thiamazole can control hyperthyroidism in patients with TSHomas, long-term administration of these agents may induce TSHoma enlargement by a negative feedback mechanism that follows a decrease in thyroid hormone concentrations [1, 2]. In contrast, somatostatin analogues have been reported to be effective in the hormonal control of TSHomas as well as GH-secreting adenomas [2, 4, 5]. Because of the rarity of TSHomas, however, most previous reports assessing the efficacy of preoperative treatment with somatostatin analogues involved only small numbers of patients with TSHoma. We have therefore assessed the outcomes of short-term preoperative octreotide treatment in a larger cohort of patients with TSHoma who were treated at Toranomon Hospital, Tokyo.

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Materials and Methods

Between January 2001 and May 2013, a total of 81 patients underwent surgery at Toranomon Hospital for TSHoma. Of these, 50 patients received octreotide

treatment. Six of these 50 patients had been treated for a long period, and the other 44 received short-term preoperative octreotide treatment for preoperative hormonal control. The first six patients were excluded because pre-treatment data were lacking and durations of octreotide treatment were unknown. In addition, one of the latter 44 patients was excluded from the study because of side effects (headache, nausea, bradycardia). This study therefore included 43 patients (25 men and 18 women) who received preoperative octreotide for TSHoma.

Serum TSH, free T3, and free T4 concentrations were measured by chemiluminescent enzyme assays using commercially available kits (Lumipulse TSH, Lumipulse FT3, and Lumipulse FT4, Fujirebio Inc., Tokyo, Japan). Reference ranges were 0.54–4.30 mIU/L for TSH, 2.29–4.17 pg/mL for free T3, and 0.72–1.52 ng/dL for free T4. These reference ranges differed in four patients, however, because their TSH, free T3 and free T4 before octreotide treatment were measured at other hospitals, from which these patients had been referred. Values and reference ranges of TSH, free T3, and free T4 in those four patients are listed in Table 1.

Of the 43 patients, eight had microadenomas and 35 had macroadenomas, with Knosp classification of grades 0, 1, 2, 3, and 4 in 19, 6, 10, 3, and 5 patients, respectively. All patients presented with SITSH, and TSH immunoreactivity was confirmed on pathologic examinations. Eleven of these 43 TSHomas showed co-secretion of growth hormone (GH), with all 11 patients presenting with clinically overt acromegaly. Prolactin (PRL) was elevated in three of the 43 patients, with all adenomas immunopositive for PRL. One patient showed hypersecretion of GH, PRL, and TSH.

MRIs before and after octreotide treatment to evaluate tumor shrinkage were available for 31 patients. Approximate tumor volume was calculated as 0.5 × width × length × height [6]. Tumor shrinkage was defined as a >20% reduction in tumor volume. Additionally, data on tumor shrinkage were obtained in another seven patients from medical records, although their exact percentage of volume reduction was not available. TSHomas have been reported to be hard in consistency because of fibrosis [7]. In all 43 patients, tumor consistencies were evaluated from intraoperative findings. Octreotide loading tests were performed in 37 patients by subcutaneously injecting octreotide 100 mg and sampling blood 0, 2, 4, and 6 hr later.

Table 1 TSH, free T3 and free T4 concentrations before octreotide treatment in four patients measured at other hospitals

Patient	TSH, mIU/L	Free T3, pg/mL	Free T4, ng/dL
1	4.98 (0.48–0.58)	4.85 (2.37–3.91)	2.19 (0.95–1.57)
2	1.31 (0.5–5.0)	4.90 (2.3–4.0)	2.57 (0.9–1.7)
3	1.26 (0.35–4.94)	5.38 (1.71–3.71)	1.77 (0.70–1.48)
4	3.58 (0.27–1.2)	13.30 (2.3–4.0)	4.10 (1.0–1.8)

( ): reference range

Octreotide was administered as a daily intermittent subcutaneous injection (2 or 3 times/day) in 17 patients, as a continuous subcutaneous injection in two patients, and as a long-acting release (LAR) in 24 patients. Subcutaneous injection was continued until the day before surgery. Octreotide LAR 20 mg was administered every four weeks, with the last administration about four weeks before surgery. Clinicopathological characteristics of the 43 patients evaluated are also summarized in Table 2.

Primary outcomes included normalization of free T4 levels and tumor shrinkage. The relationships between outcomes of octreotide treatment and TSH and free T4 concentrations, GH co-secretion, results of octreotide loading tests, form of octreotide administration, tumor volumes, and tumor consistency were evaluated. Additionally surgical outcomes were compared between patients who did and did not receive preoperative octreotide. Surgical outcome was defined as total removal of the tumor on MRI, and improvement of hyperthyroidism without medication.

Continuous variables were expressed as median, range, and interquartile range (IQR). Categorical variables were expressed as number and percentages. Median values were compared using Mann-Whitney U-test, and categorical variables were compared using the χ^2 test or Fisher's exact test. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 21.0.

Octreotide has not been approved for treatment of TSHoma in Japan. Thus, preoperative octreotide treatment was introduced after obtaining informed consent from each patient with TSHoma in the present study. Due to the retrospective nature of the study, approval for octreotide treatment in TSHomas was not obtained from the ethical committee of our institute.

Table 2 Characteristics of the 43 patients with TSHoma preoperatively treated with octreotide

Patient (total)	43
Sex	
Male	25 (58%)
Female	18 (42%)
Age (median, IQR), year	11–73 (44.5, 33–59)
TSH (median, IQR), mIU/L	0.80–14.77 (2.28, 1.46–3.60)
Free T3 (median, IQR), pg/mL	3.58–23.28 (5.89, 4.98–8.17)
Free T4 (median, IQR), ng/dL	1.53–5.85 (2.19, 1.80–2.96)
Co-secretion of other pituitary hormones	
GH-TSH	10 (23%)
PRL-TSH	2 (5%)
GH-PRL-TSH	1 (2%)
Tumor volume (median, IQR), cm^3 * (n = 31)	0.048–14 (1.9, 0.36–4.5)
Tumor consistency	
Hard	34 (79%)
Soft	9 (21%)
Octreotide loading test (n = 37) **	
Suppressed	27 (73%)
Mildly suppressed	10 (27%)
Form of octreotide	
Intermittent subcutaneous injection	17 (40%)
Continuous subcutaneous injection	2 (5%)
Octreotide LAR	24 (56%)
Duration from initiation of octreotide treatment to surgery (median, IQR), days (n = 42)	5–91 (33.5, 23–51)

* Calculated as 0.5*height*width*depth.
** Suppression on octreotide loading test defined as TSH <1/2 of baseline concentration.

Results

Administration of octreotide resulted in the normalization of free T4 concentrations in 36 of 43 patients (84%), with normalization of thyroid function detected after a median 20 days (range, 1–75 days; IQR, 5–30 days). Two patients required thyroid hormone replacement because their free T4 concentrations were below the reference range. Tumor shrinkage was observed in 23 of 38 patients (61%) at a median 37 days (range, 7–80 days; IQR, 29–55 days) after initiating octreotide treatment. Median time between the initiation of octreotide treatment and surgery was 33.5 days (range 5–91 days; IQR 23–51 days). The duration could not be determined accurately in one patient who received a single dose of octreotide LAR one month before operation. Duration of octreotide treatment did not differ significantly in patients who did (median 31 days; range, 2–89 days; IQR, 18–43 days) and did not (median 5.5 days; range, 3–45 days; IQR, 3–38 days) achieve hormonal normalization ($p = 0.09$). Similarly, days from initiation of octreotide treatment to MRI did not differ significantly in patients with (median 37 days; range, 7–87 days; IQR, 29–57 days) and without (median 37 days; range, 22–67 days; IQR, 30–46 days) tumor shrinkage ($p = 0.84$). There were no significant differences in rates of tumor shrinkage ($p = 0.42$), even after dividing patients into three groups by days from initiation of octreotide treatment to MRI (Table 3). In addition, normalization of thyroid hormone did not correlate with tumor shrinkage ($p = 0.35$).

Table 3 Rates of tumor shrinkage by days from initiation of octreotide treatment to MRI

Days	– 30	31 – 45	46 –
Shrinkage	6	6	6
No shrinkage	5	4	4
Rate	55%	60%	60%

The percentage of tumors showing shrinkage was unrelated to duration of treatment.

Of the seven patients who did not achieve normalization of free T4 concentration after octreotide treatment, five attained free T4 concentrations just above the normal range, with four of these five patients receiving octreotide for a shorter period of time (3–6

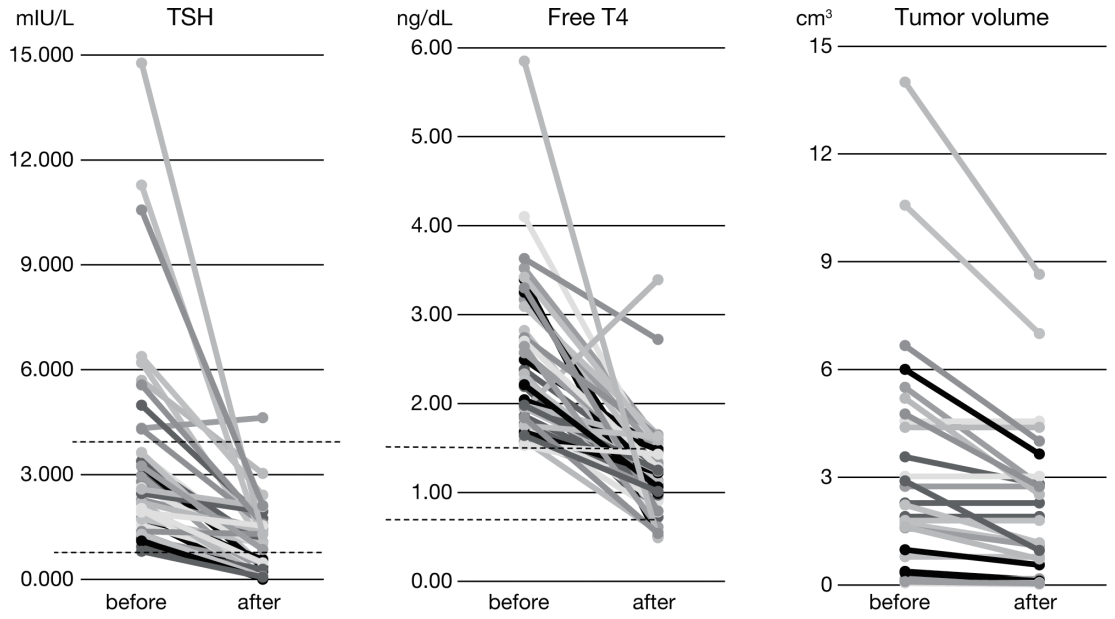

Fig. 1 TSH and free T4 concentrations and tumor volume before and after octreotide treatment
Tumor volume was measured in 31 patients who underwent MRIs before and after octreotide treatment. Dotted lines for TSH and free T4 indicate the upper and lower limits of their reference ranges.

days) than the other patients. The other two patients showed no change in thyroid hormone concentrations, despite octreotide administration for a sufficient period of time. These two patients had pituitary adenomas co-secreting GH and TSH. One of these two patients with octreotide resistant tumors was treated with thiamazole before surgery. However, the other patient underwent surgery without additional treatment for hyperthyroidism. Five patients who showed reductions in T4 near the normal range also did not receive additional treatment before surgery. The patient who had to discontinue preoperative octreotide treatment due to side effects was also treated with thiamazole before surgery. Changes in TSH and free T4 concentrations before and after octreotide treatment are shown in Fig. 1.

TSH concentrations before octreotide treatment did not differ significantly in patient groups that did and did not achieve hormonal normalization (p = 0.86), and in groups with and without tumor shrinkage (p = 0.22). Similarly free T4 concentrations before octreotide treatment were similar in patients with and without hormonal normalization (p = 0.25), and in groups with and without tumor shrinkage (p = 0.10). Thus, TSH and free T4 levels before octreotide treatment were predictive of neither thyroid hormone normalization nor tumor shrinkage.

As mentioned above, hormone levels did not normalize and tumor shrinkage did not occur in two patients with adenomas co-secreting GH and TSH, despite octreotide treatment for a sufficient period of time. A comparison of outcomes in TSHoma patients with and without GH co-hypersecretion showed thyroid hormone normalization in eight of 11 (72.7%) and 26 of 30 (86.7%), respectively (p = 0.29), and tumor shrinkage in seven of 10 (70.0%) and 15 of 26 (57.7%) patients, respectively (p = 0.50). After treatment with octreotide, IGF-1 concentrations were reduced in nine out of 11 patients with adenomas co-secreting GH, and IGF-1 was normalized in two patients. In contrast, octreotide normalized PRL in all patients with adenomas co-secreting PRL.

Octreotide loading tests suppressed TSH to less than half of baseline in 27 out of 37 patients (73%). Of the 27 patients, 25 (93%) achieved normalization of thyroid hormone, with 14 of these 25 (56%) showing tumor shrinkage. Of the 10 patients who showed mild TSH suppression, which was not less than half of baseline on octreotide loading tests, seven (70%) showed normalization of thyroid hormone, and five out of nine (56%) showed tumor shrinkage. Rates of hormonal normalization (p = 0.07) and tumor shrinkage (p = 0.98) did not differ significantly in these two groups.

Table 4 Effects of preoperative octreotide on thyroid hormone normalization and tumor shrinkage in patients with TSHoma

	Thyroid hormone normalization		Tumor shrinkage	
Period of Oct treatment	Normalized	median 31 days	Shrinkage	median 37 days
	Non-normalized	median 5.5 days	Non-shrinkage	median 37 days
TSH	Normalized	median 2.51 mIU/L	Shrinkage	median 1.94 mIU/L
	Non-normalized	median 2.20 mIU/L	Non-shrinkage	median 2.97 mIU/L
Free T4	Normalized	median 2.19 ng/dL	Shrinkage	median 1.98 ng/dL
	Non-normalized	median 2.74 ng/dL	Non-shrinkage	median 2.70 ng/dL
GH co-secretion	With GH secretion	Normalized 73%	With GH secretion	Shrinkage 70%
	Without GH secretion	Non-normalized 87%	Without GH secretion	Shrinkage 58%
Oct loading test result*	Suppressed	Normalized 93%	Suppressed	Shrinkage 56%
	Mild-suppressed	Non-normalized 70%	Mild-suppressed	Shrinkage 56%
Cumulative dose of Oct	Subcutaneous injection	Normalized 74%	Subcutaneous injection	Shrinkage 47%
	LAR	Non-normalized 92%	LAR	Shrinkage 70%
Drug form of Oct	Normalized	median 20 mg	Shrinkage	median 20 mg
	Non-normalized	median 20 mg	Non-shrinkage	median 20 mg
Tumor volume	Normalized	median 2.1 cm^3	Shrinkage	median 2.8 cm^3
	Non-normalized	median 1.5 cm^3	Non-shrinkage	median 1.6 cm^3
Tumor consistency	Hard	Normalized 82%	Hard	Shrinkage 57%
	Soft	Non-normalized 89%	Soft	Shrinkage 75%

Oct: octreotide.
*Suppression on the octreotide loading test was defined as TSH <1/2 of baseline concentration after subcutaneous injection of octreotide 100 μg.

Of the 19 patients treated with intermittent or continuous subcutaneous octreotide injection (subcutaneous group), 14 (74%) showed normalization of thyroid hormone, and 7 out of 15 (47%) showed tumor shrinkage. In the 24 patients treated with octreotide LAR (LAR group), 22 (92%) showed normalization of thyroid hormone levels, and 16 out of 23 (70%) showed tumor shrinkage. The percentages of patients achieving hormonal normalization ($p = 0.11$) and tumor shrinkage ($p = 0.16$) did not differ in the subcutaneous and LAR groups. The median times from initiation of octreotide to nadir of free T4 concentration were 13.5 days (range, 2–48 days; IQR, 5–24 days) in the subcutaneous group and 35 days (range, 8–89 days; IQR, 28.5–44.5 days) in the LAR group, and the median periods from initiation of octreotide to MRI were 29.5 days (range, 7–46 days; IQR, 24.5–38.5 days) and 42.0 days (range, 20–80 days; IQR, 32–60 days), respectively. Thus, the time required to attain hormonal normalization ($p < 0.001$) and tumor shrinkage ($p = 0.03$) were significantly shorter in the subcutaneous than in the LAR group, despite the absence of significant differences in the percentages of these groups achieving hormonal normalization and tumor shrinkage. Median calculated cumulative doses of octreotide were 7.5 mg (range, 1.5–24.0 mg; IQR, 2.1–13.5 mg) in the subcutaneous group and 20 mg (range, 20–60 mg; IQR, 20–40 mg) in the LAR group ($p < 0.001$). However, calculated cumulative doses did not differ significantly between patients with and without hormonal normalization ($p = 0.91$) and with and without tumor shrinkage ($p = 0.75$).

Median calculated tumor volume before octreotide treatment in all 31 patients in whom tumor volume was calculated was 1.9 cm^3 (range 0.048–14 cm^3; IQR 0.36–4.5 cm^3), and was similar in patients with and without hormonal normalization ($p = 0.36$) and with and without tumor shrinkage ($p = 0.42$). Changes in tumor volume before and after octreotide treatment are shown in Fig. 1.

Of the 43 tumors, 34 (79%) were intraoperatively determined to be hard and nine (21%) were soft. Hormonal normalization was attained in eight out of nine patients (89%) with soft tumors and 28 out of 34 (82%) with hard tumors ($p = 0.64$), with tumor shrinkage attained in six of eight (75%) soft and 17 out of 30 (57%) hard tumors ($p = 0.35$). The results of octreotide treatment are summarized in Table 4.

Three patients required thyroid hormone replacement before surgery because octreotide treatment resulted in thyroid hormone concentrations below normal range. Two patients had painless thyroiditis after initial admin-

istration of octreotide. In these patients, serum TSH levels were low but serum free T3 and free T4 levels remained high after initiation of octreotide LAR. As octreotide treatment continued, painless thyroiditis improved, enabling these patients to undergo surgery. Side effects of octreotide treatment included transient mild diarrhea in five patients, constipation in one, transient nausea in one, and mild elevation of total bilirubin in one. Of the 31 patients who did not receive preoperative octreotide treatment, only one received iodine the day before surgery for control of hyperthyroidism. One of these 31 patients experienced painless thyroiditis soon after surgery, which caused no symptoms and was spontaneously resolved. None of the 81 patients experienced a thyroid crisis irrespective of use of preoperative octreotide. In addition, surgical cure rate did not differ significantly between the 43 patients with (36/43, 83.7%) and the 31 patients without (28/31, 90.3%) preoperative octreotide treatment ($p = 0.41$).

Discussion

Normalizing thyroid function before pituitary surgery in patients with TSHomas associated with hyperthyroidism is important to avoid the risk of perioperative thyroid crisis [3]. Similar to GH-producing adenomas, treatment with somatostatin analogues is effective for hormonal control and tumor shrinkage in TSHomas, since these tumors also express somatostatin receptors [8-11]. Short- and long-term octreotide treatment of patients with TSHoma had been reported to result in normalization of thyroid hormone levels in 72% and 95% of patients, respectively, with tumor shrinkage in 45–52% [2, 4]. In the present series, we confirmed that short-term octreotide treatment normalized thyroid hormone levels in 84% and shrank tumors in 61% of patients with TSHomas. Even if thyroid hormone levels were not normalized, they were reduced close to the normal range after octreotide administration for several days, suggesting that longer use may have resulted in thyroid hormone normalization in these patients. The results presented here suggest that octreotide treatment requires a relatively short time to normalize thyroid hormone concentrations.

Indications of octreotide treatment for acromegaly are generally determined by the results of octreotide loading tests. Octreotide is usually more effective for the control of GH levels and tumor shrinkage in patients who achieved GH reduction on octreotide loading tests [12]. We found that thyroid hormone normalization was more frequently achieved in patients with TSH suppression to less than half of baseline than mild TSH suppression on octreotide loading tests. However, 70% of the latter showed hormonal normalization after preoperative octreotide administration and 56% showed tumor shrinkage. These findings indicate that preoperative octreotide treatments are effective, regardless of the results of octreotide loading tests, in most patients with TSHoma.

We found that subcutaneously infused and LAR octreotide were equally effective in achieving hormonal normalization and tumor shrinkage. Hormonal control was attained in a shorter period of time in the subcutaneous group than in the LAR group, presumably because thyroid hormone concentrations were assessed one month after octreotide administration in most of the latter group. Thyroid hormone concentrations may normalize within one to two weeks, even in the LAR group. Thus when selecting the form of octreotide administration the choice may depend on the time between initiation of octreotide to surgery, although octreotide LAR may be suitable for long-term treatment. Moreover, hormone levels cannot be evaluated immediately after surgery in the LAR group because several months are required for washout of the effects of octreotide LAR.

TSH and free T4 concentrations, GH co-secretion, and tumor volume were not predictive factors for hormonal normalization and tumor shrinkage. These findings, however, suggest that octreotide treatment should be considered for all patients with TSHoma presenting with hyperthyroidism. In addition, the rates of hormonal normalization and tumor shrinkage were similar in patients with hard and soft tumors, indicating that tumor consistency cannot be predicted by the results of octreotide treatment.

In the present study, only one patient (2%) experienced adverse events severe enough to interrupt octreotide treatment. Octreotide has been reported to be safe in most patients with TSHoma, with side effect rates nearly 7% [2]. However, three patients required thyroid hormonal replacement before surgery because octreotide reduced their free T4 concentrations below the normal range. However, it is easier to control hypothyroidism than hyperthyroidism, and none of these three patients had any symptoms of hypothyroidism.

Because surgical outcomes were not associated with preoperative octreotide administration, the significance of preoperative short-term octreotide treatment would

only be to achieve thyroid hormone control. Moreover, in our series, patients who did not receive preoperative octreotide had fewer perioperative problems related to hyperthyroidism. Thyroid crisis in patients with TSHoma is especially rare, and to date has only been reported in two studies [3, 13]. Our results, however, confirm that short-term administration of octreotide resulted in thyroid hormone control in most patients and tumor shrinkage in more than half. Preoperative octreotide treatment should be recommended for patients with TSHoma due to its tolerability and effectiveness, as well as its low risk.

Conclusion

Preoperative short-term octreotide treatment of patients with TSHoma was highly tolerable and effective, resulting in tumor shrinkage and normalization of hormone excess in most patients. Preoperative octreotide treatment should be recommended to patients with TSHoma to prevent problems associated with hyperthyroidism, especially thyroid crisis.

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Disclosure

None of the authors has any potential conflicts of interest associated with this research.

References

1. Beck-Peccoz P, Persani L, Mannavola D, Campi I (2009) Pituitary tumours: TSH-secreting adenomas. *Best Pract Res Clin Endocrinol Metab* 23: 597-606.
2. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD (1996) Thyrotropin-secreting pituitary tumors. *Endocr Rev* 17: 610-638.
3. Page KA, Roehmholdt BF, Jablonski M, Mayerson AB (2008) Development of thyroid storm after surgical resection of a thyrotropin-secreting pituitary adenoma. *Endocr Pract* 14: 732-737.
4. Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, et al. (2003) The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. *Eur J Endocrinol* 148: 433-442.
5. Shimatsu A, Murabe H, Kamoi K, Suzuki Y, Nakao K (1999) Treatment of thyrotropin-secreting pituitary adenomas with octreotide. *Endocr J* 46: 113-123.
6. Lundin P, Pedersen F (1992) Volume of pituitary macroadenomas: assessment by MRI. *J Comput Assist Tomogr* 16: 519-528.
7. Ezzat S, Smyth HS, Ramyar L, Asa SL (1995) Heterogenous in vivo and in vitro expression of basic fibroblast growth factor by human pituitary adenomas. *J Clin Endocrinol Metab* 80: 878-884.
8. Gatto F, Barbieri F, Castelletti L, Arvigo M, Pattarozzi A, et al. (2011) In vivo and in vitro response to octreotide LAR in a TSH-secreting adenoma: characterization of somatostatin receptor expression and role of subtype 5. *Pituitary* 14: 141-147.
9. Horiguchi K, Yamada M, Umezawa R, Satoh T, Hashimoto K, et al. (2007) Somatostatin receptor subtypes mRNA in TSH-secreting pituitary adenomas: a case showing a dramatic reduction in tumor size during short octreotide treatment. *Endocr J* 54: 371-378.
10. Yoshihara A, Isozaki O, Hizuka N, Nozoe Y, Harada C, et al. (2007) Expression of type 5 somatostatin receptor in TSH-secreting pituitary adenomas: a possible marker for predicting long-term response to octreotide therapy. *Endocr J* 54: 133-138.
11. Filopanti M, Ballare E, Lania AG, Bondioni S, Verga U, et al. (2004) Loss of heterozygosity at the SS receptor type 5 locus in human GH- and TSH-secreting pituitary adenomas. *J Endocrinol Invest* 27: 937-942.
12. Colao A, Ferone D, Lastoria S, Marzullo P, Cerbone G, et al. (1996) Prediction of efficacy of octreotide therapy in patients with acromegaly. *J Clin Endocrinol Metab* 81: 2356-2362.
13. Fujio S, Ashari, Habu M, Yamahata H, Moinuddin FM, et al. (2014) Thyroid storm induced by TSH-secreting pituitary adenoma: a case report. *Endocr J* 61: 1131-1136.