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Original Article

Immunohistochemical expression of somatostatin receptor subtypes 2 and 5 in thyrotropin-secreting pituitary adenomas: a consecutive case series of pituitary adenomas

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Abstract: Thyrotropin-secreting pituitary adenomas (TSHomas) are a rare cause of hyperthyroidism. Somatostatin analogue has proved to be effective for inhibiting pituitary hormones secretion, working via interactions with somatostatin receptors (SSTRs). We therefore determined the relative predominance of SSTR2 and SSTR5 subtypes among the different types of adenomas, especially TSHoma, investigated the relationship between efficacy of short-term octreotide (OCT) treatment and SSTR expression. Patients were enrolled at Beijing Tiantan Hospital between 2009 and 2015. Serum hormone determinations and histological findings in resected tissue resulted in five diagnoses: 16 TSHomas, eight acromegaly, three prolactinomas, three corticotropinomas, and four clinically nonfunctioning adenomas (NFPAs), and four normal pituitary specimens. IHC was performed on formalin fixed and paraffin embedded tissue in tissue microarrays. IHC of SSTR subtypes in the different cohorts showed that SSTR2 staining intensity scores higher than SSTR5 in TSHoma, acromegaly and prolactinoma, whereas in corticotropinoma and NFPA, the expression of SSTR5 was stronger than SSTR2. SSTR2 and SSTR5 expression were significantly higher in TSHoma than in other pituitary adenomas. OCT treatment for a median of 8.4 days (range: 3-18 days) and with a total median dose of 1.9 mg (range: 0.9-4.2 mg) witnessed significant decrease of all patients' thyroid hormone levels (TSH [μIU/ml]: 4.95 ± 3.59 to 0.92 ± 1.55 [t = 4.721, P = 0.000]; FT3 [Pmol/L]: 11.77 ± 8.69 to 4.17 ± 0.88 [t = 3.507, P = 0.003]; FT4 [Pmol/L] 29.56 ± 8.51 to 16.72 ± 4.13 [t = 6.662, P<0.01]) respectively. Patients with low SSTR5 expression presented a significantly higher TSH suppression rate (*P values <0.05*). The present data confirm that somatostatin analogs should be considered as a medical alternative to surgical treatment, especially in patients with TSHoma, and short-term response to OCT therapy may be related to the expression of SSTR5.

Keywords: Pituitary adenoma, TSH-secreting pituitary adenoma, somatostatin receptor, expression, immunohistochemistry

Introduction

Discovered in 1973, somatostatin (SS) is a native inhibitory peptide hormone distributed throughout the central nervous system and peripheral tissues of the body [1]. Medical treatment of endocrine pituitary tumors with somatostatin analogs depends on somatostatin receptor (SSTR) expression [2, 3]. SSTR expressed in both normal and neoplastic human pituitary cells, SSTR2 and SSTR5 predominate [4, 5], but the characteristic expression pattern of SSTR subtypes in pituitary adenomas is species-specific, tissue-specific, and subtype-specific [6].

The therapeutic effects on pituitary adenomas of somatostatin analogues like octreotide and lanreotide depends on the expression of specific somatostatin receptors on the target cells [7, 8]. And their effectiveness is limited by the development of tumor resistance. Possible mechanisms of resistance include impairment or heterogeneity of SSTR expression, SSTR gene mutations, and decreased sensitivity of SSTRs owing to uncoupling of signaling

pathways [9]. The most accepted hypothesis is the absence or reduced density of specific SSTRs in the tumors, especially SSTR2 and SSTR5. Therefore, it would be helpful to know the expression profile of SSTR subtypes in pituitary adenomas.

Thyrotropin (TSH)-secreting pituitary adenomas (TSHomas) are rare, accounting for 0.5 to 3% of all functioning pituitary adenomas [10]. Studies indicate that somatostatin analogs may control TSH secretion by interacting with SSTR2, and restrain cell proliferation by interacting with SSTR5 [10-12]. To the best of our knowledge, the expression of SSTR2 and SSTR5 in TSHoma has been demonstrated by IHC in only a few patients [13]. Highly specific antibodies can confirm the expression of SSTR subtype proteins, but heterogeneity of tumors and the use of different detection methods often lead to inconsistency in the reported expression of SSTR subtypes in different types of pituitary tumors [6, 13-18]. As it is clinically meaningful to identify the expression profiles of SSTR subtypes in pituitary adenomas, we investigated the expression of SSTR2 and SSTR5 in a series of patients with TSHoma and other pituitary adenomas, and the association of SSTRs expression with efficacy of short-term OCT treatment.

Materials and methods

Patients

TSHoma patients enrolled were those who were newly diagnosed and previously untreated, while those with primary hyperthyroidism or resistance to thyroid hormone syndrome were excluded. All patients had undergone surgery at Beijing Tiantan Hospital, Capital Medical University between January 2009 and June 2015. The diagnosis was based on a combination of clinical manifestations, biochemical assessments of pituitary function, findings of pituitary imaging, and pathological evaluation. On such basis, sixteen patients with TSHoma were identified and enrolled in the study. Those with acromegaly, corticotropinoma, prolactinoma, or nonfunctioning pituitary adenomas (NFPA) were randomly sampled. and four normal pituitary specimens collected from the donor's head. The gender, age at diagnosis, pathological diagnosis, tumor size, and date of the last follow-up of each participant were collected from their medical records. The informed consent was obtained from all the participants.

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

Octreotide used in this investigation came from Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA). Each patient received an initial dose of 100 μg, injected subcutaneously at 8:00 am. If the patient showed no obvious side effects (such as nausea, vomiting, stomach ache and diarrhea), their dosages were increased to 100 μg two or three times/day. Serum TSH, FT3, FT4, TT3 and TT4 concentrations were measured by chemiluminescent enzyme assays using commercially available kits. TSH suppression rate (%) = [(before treatment TSH value-after treatment TSH value)/before treatment TSH value]×100.

Pathological diagnosis of pituitary adenoma

All tissue specimens of the patients were obtained during pituitary surgery, fixed in 4% paraformaldehyde overnight, routinely processed, and embedded in paraffin. For adenoma classification, the specimens were 4-μm sectioned and stained with hematoxylin and eosin and the periodic acid Schiff (PAS) staining protocol. ICH staining with monoclonal antibodies against the specific pituitary hormones including TSH, growth hormone (GH), prolactin (PRL), ACTH (adrenocorticotropic hormone), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and were also carried out on the tumor tissues. The pathological diagnoses were verified by experienced pathologists following the 2004 World Health Organization classification [19].

Immunohistochemical staining of SSTR subtypes

Fixed in formalin, the slides were prepared in unstained 3 μm-sections, and 48-dot cores (diameter 2.0 mm) matrix chip template. Immunohistochemical staining was performed with a Leica BOND-III, automatic IHC and ISH stainer (Leica Biosystems, Nussloch, Germany), which is an automatic and continuous access slide-staining system that simultaneously processes IHC protocols, with a 10-minute heat-induced epitope retrieval and a 15-minute antibody incubation. The primary SSTR2 antibody was ab13120 (1:100), and the primary SSTR5

Table 1. Patient demographics in the five cohorts

Case	Sex	Age (years)	SSTR2		SSTR5		Tumor size (mm)
			Staining intensity	Percent positivity (%)	Staining intensity	Percent positivity (%)	
T 1	M	24	3	90	1	75	30×20×30
T 2	M	40	3	90	2	95	8×6×6
T 3	M	25	3	90	2	85	48×44×29
T 4	F	40	3	90	2	30	5×7×8
T 5	M	33	3	90	1	50	17×12×13
T 6	M	24	3	90	1	90	24×13×34
T 7	F	27	3	90	2	80	16×15×20
T 8	M	26	3	60	2	50	24×14×31
T 9	M	31	3	90	2	70	9×6×8
T 10	M	52	3	90	2	90	11×12×10
T 11	M	33	3	90	2	90	32×28×25
T 12	M	51	3	90	2	90	16×14×18
T 13	F	45	3	90	2	90	21×16×33
T 14	F	25	3	90	1	55	15×21×17
T 15	M	17	3	90	1	80	24×36×53
T16	F	39	3	90	1	50	41×25×38
S1	M	39	3	90	1	60	32×36×17
S2	M	39	3	90	1	40	14×13×15
S3	M	12	3	90	1	50	64×39×39
S4	F	26	3	90	1	80	24×27×14
S5	M	29	1	90	2	80	36×25×26
S6	F	32	1	50	1	70	6×8×7
S7	F	44	3	90	2	60	16×10×9
S8	F	43	3	90	2	80	17×24×17
C1	F	53	0	100	2	70	8×5×6
C2	F	38	3	80	1	60	12×12×16
C3	F	61	0	100	1	80	22×22×32
P1	F	64	1	60	1	35	27×35×22
P2	F	46	1	80	1	70	38×28×22
P3	F	31	3	90	2	90	15×16×19
N1	M	61	0	100	1	40	19×20×28
N2	M	39	0	100	1	60	29×28×41
N3	F	31	0	100	1	60	10×12×14
N4	M	65	0	100	2	60	30×35×29

Note: F = female, M = man, T = thyrotropinoma, S = somatotrophinoma, C = corticotropinoma, P = prolactinoma, N = nonfunctioning pituitary adenoma.

antibody was ab13121 (1:100; Abcam, Cambridge, UK). The preparation and evaluation of the tissues were performed at the Department of Neuropathology, Beijing Tiantan Hospital, Capital Medical University.

Quantification of immunostaining

The sections were assessed independently by two experienced pathologists who were blinded to both the clinical and the pathology data. The scoring of each section was determined by consensus and followed the immunoreactive score (IRS) method described by Remmele et al. [20]. The IRS was calculated by multiplying the staining intensity (0 = no staining, 1 = weak staining, 2 = moderate staining, 3 = strong staining) by the percentage of positively stained cells (0 = 0%, 1 = 1% to 33%, 2 = 33% to 66%, and 3≥66%). The resulting IRS scores ranged from 0 (no staining) to 9 (maximum staining). IRS scores of 0 were negative, 1-2 were low, 3-4 were intermediate, 5-7 were high-intermediate, and 8-9 were high.

Statistical analysis

The data were statistically analyzed using SPSS software version 20.0 for Windows (SPSS, Chicago, IL). Data of normal distribution were reported as means ± standard error (SE). Otherwise, the data were reported as medians and ranges (minimum-maximum). Multiple linear regression was used for analyzing factors for efficacy of short-term preoperative OCT treatment. Wilcoxon rank sum test was used to compare the two groups. $P<0.05$ was considered significantly different.

Results

Patient characteristics

As shown in **Table 1**, in addition to the 16 patients with TSHoma, 8 with acromegaly, 3

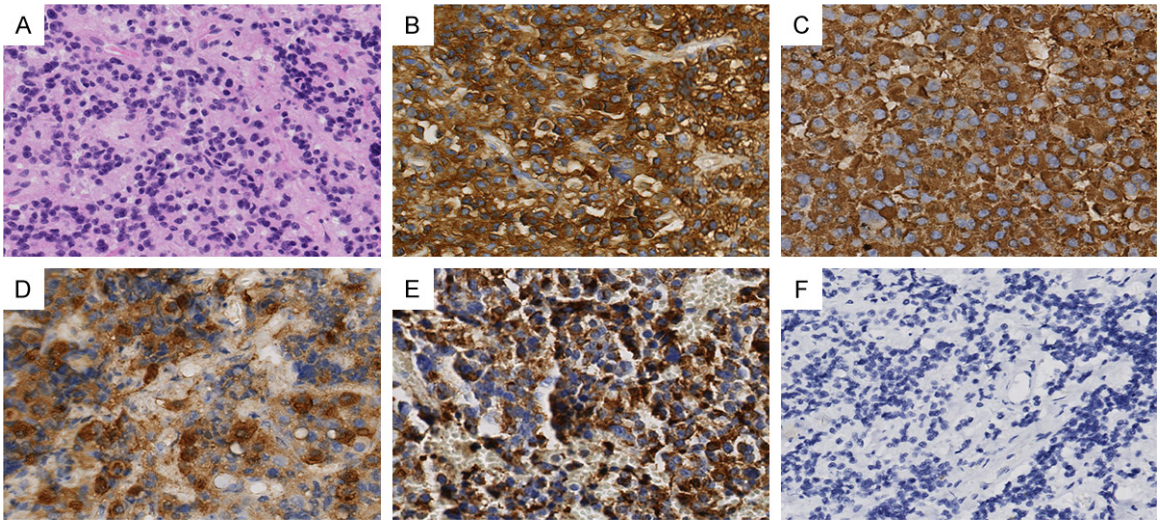

Figure 1. Immunohistochemistry of pituitary adenoma tissue. Immunohistochemical staining among the tumor cells. A. Histopathology findings of TSHoma (hematoxylin-eosin staining); B. Strong TSH staining of TSHoma; C. Growth hormone-producing cells; D. Prolactin-producing cells; E. Adrenocorticotrophic-producing cells; F. Nonfunctioning pituitary adenomas. (Magnification×200).

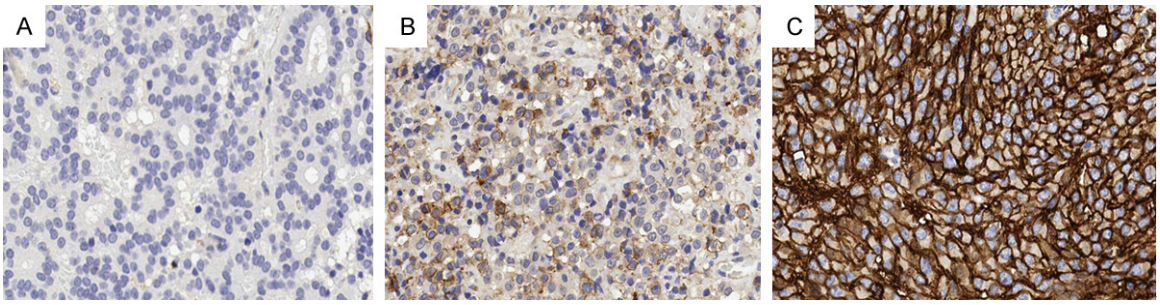

Figure 2. Heterogeneous immunohistochemical expression of SSTR2 in TSHoma. Representative examples of SSTR2 expression. A: Negative (IRS 0); B: High-intermediate (IRS 5-7); C: High (IRS 8-9) (Magnification 200×).

with prolactinoma, 3 with corticotropinoma, and 4 with clinically NFPA were included as well. Characteristics of the 34 patients included in our study are as shown in **Table 1**. Tumors over 10 mm were defined as macroadenomas, and those smaller than 10 mm as microadenomas. We identified 16 TSHoma patients (11 men and five women) with a mean age of 33 years (range: 17-51 years). Three TSHomas were microadenomas and 13 were macroadenomas. Eight were acromegalic patients (four men and four women) with a mean of 33 years (range: 12-39 years); one with microadenoma and seven with macroadenomas. Three patients had Cushing disease, who were all women and a mean age of 45 years (range: 38-53 years); one had a microadenoma and two had macroadenomas. Three patients had prolactinomas, who were all women with a mean age of 47 years (range: 31-64 years), and all had macroadenomas. Four patients had NFPAs (three men and one woman) with a mean age of 45 years (range: 31-65 years), all having macroadenomas. The diagnosis of functional pituitary adenoma was based on clinical manifestations, hormone levels, imaging results, and confirmed by pathological evidences (**Figure 1**).

Expression of SSTR2 and SSTR5 protein in pituitary tumor tissue

The immunohistochemistry of SSTR2 and SSTR5 was positive in the cytoplasm, as shown in **Figures 2** and **3**. The immunostaining pattern in TSHoma SSTR2>SSTR5, with 15 of 16 specimens (93.7%) having high SSTR2 IRC scores and only one specimen having a high-intermediate score. The SSTR5 IRS scores were high-

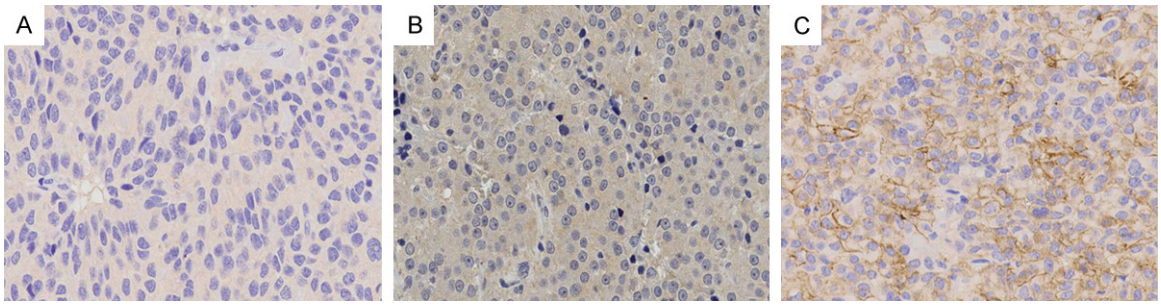

Figure 3. Heterogeneous immunohistochemical expression of SSTR5 in TSHoma. Representative examples of SSTR5 expression. A: Low (IRS 1-2); B: Intermediate (IRS 3-4); C: High-intermediate (IRS 5-7) (magnification 200×).

intermediate in eight specimens (50%), intermediate in four (25%), and low in four (25%). SSTR2 and SSTR5 expression were higher in TSHomas than in other pituitary adenomas.

IHC staining (**Table 2**) demonstrated that in acromegaly, SSTR2 expression was more frequent and stronger than SSTR5 expression. High IRC scores were seen for SSTR2 in six of the eight acromegaly specimens (75%), with low and intermediate intensity staining in the remaining two specimens (12.5% each). High-intermediate SSTR5 staining intensity was seen in two of the eight acromegaly specimens (25%); while low and intermediate staining intensity was found in three of the eight (37.5% each). The three prolactinoma specimens had different SSTR2 (low, intermediate, and high-intermediate) and SSTR5 (low, intermediate, and high) staining intensities. High-intermediate SSTR2 staining intensity was seen in one of the three corticotropinoma specimens, while the remaining two were negative. SSTR5 staining was also found different in each of the corticotropinoma specimens (low, intermediate, and high-intermediate). All the four NFPA specimens were negative for SSTR2 expression; high-intermediate SSTR5 staining was observed in one (25.0%) and the remaining three were negative. In normal pituitary tissues, SSTR2 expression was high-intermediate in two of the four samples tested and intermediate in two. Two of the specimens had high-intermediate SSTR5 expression, and the other two were negative.

Efficacy of short-term OCT treatment

Short-term preoperative OCT administration was highly effective in normalizing excessive hormone concentrations, with tolerable side effects as well. Due to incomplete date, 1 TSHoma patient was excluded. Following OCT treatments for a median of 8.4 days (range: 3-18 days) and with a total median dose of 1.9 mg (range: 0.9-4.2 mg), all patients presented significant decrease of TSH and thyroid hormone levels (TSH [μIU/ml]: 4.95 ± 3.59 to 0.92 ± 1.55 [t = 4.721, P = 0.000]; FT3 [Pmol/L]: 11.77 ± 8.69 to 4.17 ± 0.88 [t = 3.507, P = 0.003]; FT4 [Pmol/L] 29.56 ± 8.51 to 16.72 ± 4.13 [t = 6.662, P<0.01]; As show in **Table 3**). Reference ranges are TSH: 0.35-4.94 μIU/ml; FT3: 2.63-5.7 Pmol/L; FT4: 9.00-19.04 Pmol/L. Safety of treatment with SST analogs was proven; no patients discontinued treatment due to unbearable side effects.

Relationship between TSH suppression rate and SSTR5 expression

Linear regression analysis found no statistical significance between the TSH suppression rate and general characteristics (age or gender), tumor size (micro-or macro adenoma), and SSTRs expression (**Table 4**). With IRS scores categorized as low expression (0-4) and high expression (5-9), we analyzed the relationship between TSH suppression rate and SSTR5 expression with two independent sample Wilcoxon rank sum test. The results showed *P* value = 0.002, which prove statistically significant, prompting that SSTR5 expression may be related to the efficacy of short-term OCT therapy.

Discussion

Quantitative real-time polymerase chain reaction (RT-PCR) and western blot assays were used to describe the expression profiles of SSTR subtypes in pituitary adenomas [14, 15].

Table 2. Expression of SSTR2 and SSTR5 as determined by immunohistochemistry (n = 38)

Tumor type	Anti-SSTR2 staining					Anti-SSTR5 staining				
	Negative	Low	Inter mediate	High-intermediate	High	Negative	Low	Inter mediate	High-intermediate	High
TSHoma (n = 16)	0 (0%)	0 (0%)	0 (0%)	1 (6.3%)	15 (93.7%)	0 (0%)	4 (25%)	4 (25%)	8 (50%)	0 (0%)
Acromegaly (n = 8)	0 (0%)	1 (12.5%)	1 (12.5%)	0 (0%)	6 (75%)	0 (0%)	3 (37.5%)	3 (37.5%)	2 (25%)	0 (0%)
Prolactinoma (n = 3)	0 (0%)	1 (33.3%)	1 (33.3%)	0 (0%)	1 (33.3%)	0 (0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0%)
Corticotropinoma (n=3)	2 (66.7%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0%)
NFPA (n = 4)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (75%)	1 (25%)	0 (0%)	0 (0%)
Normal pituitary specimen (n = 4)	0 (0%)	0 (0%)	2 (50%)	2 (50%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)

Note: negative (IRS = 0), low (IRS = 1-2), intermediate (IRS = 3-4), high-intermediate (IRS = 5-7), and high (IRS = 8-9).

Table 3. Thyroid function before and after short-term octreotide treatment

	Before	After	T	*P*
TT3 (nmol/l)	3.50 ± 1.35	1.36 ± 0.32	6.112	*P = 0.000*
TT4 (nmol/l)	193.85 ± 50.23	109.80 ± 31.10	7.848	*P = 0.000*
FT3 (Pmol/L)	11.77 ± 8.69	4.17 ± 0.88	3.507	*P = 0.003*
FT4 (Pmol/L)	29.56 ± 8.51	16.72 ± 4.13	6.662	*P = 0.000*
TSH (ulu/ml)	4.95 ± 3.59	0.92 ± 1.55	4.721	*P = 0.000*

Quantitative RT-PCR might overestimate the actual percentage of tumors expressing SSTR subtypes because immune, stromal and normal tissue cells as well as blood vessels that are present in or surrounding the tumors might also express SSTR subtypes. Most reports publicly available focused on tumor types other than growth hormone-secreting adenomas, especially TSHoma, and many of which are case reports, or limited to assays of RNA expression.

Somatostatin peptides bind to the SSTRs expressed on the cells of the target tissues, exerting a series of biological effects. In the central nervous system, somatostatin acts as a neuromodulator and neurotransmitter [21]. The immunohistochemical method performed on surgically removed tumor tissue reveals the expression of receptor proteins and demonstrates their cellular localization [18]. Although immunohistochemical methods can detect receptor proteins and show the subcellular localization of the receptors, they are rarely used to study the expression of SSTR subtypes because of a lack of well-characterized SSTR subtype-specific antibodies. Schmid et al. [22, 23] have developed a series of mouse monoclonal antibodies with high specificity for the five SSTR subtypes and no cross reactivity of IHC staining. Few of such studies called into play IHC. In this study however, we assessed the expression profiles of SSTR2 and SSTR5 in pituitary adenomas by IHC technique, and found significant differences in the expression and distribution of SSTR subtypes in various adenomas. This finding could prove helpful in the selection of treatment strategies.

Previous studies enrolled patient cohorts with compositions different from ours, which might have resulted in different SSTR subtype expression profiles. Our immunohistochemical results differ from findings of previous molecular studies. For example, Pisarek et al. [24] found that the pattern of SSTR immunostaining in acromegaly was SSTR 5>SSTR 1>SSTR 2A = SSTR 3>SSTR 2B. Thodou et al. [25] used immunohistochemistry to study the expression of SSTR subtypes in TMAs and qPCR to compare absolute mRNA copy numbers for all five SSTR isoforms in 23 somatotropinomas, and found that expression was SSTR5>SSTR2A>SSTR2B. Taboada et al. [16] found that in somatotropinomas, expression of subtype SSTR5 mRNA was the highest followed by SSTR2>SSTR3>>SSTR1>>>SSTR4.

Some previous IHC studies also found high SSTR2 and low SSTR5 immunoreactivity in Cushing's disease [11, 26]; others have reported low expression of SSTR2 mRNA in patients with Cushing's disease [27-29]. Low expression of SSTR2 and SSTR5 mRNA was reported in a sample of 19 NFPAs, while SSTR3 expression was high and predominant in more than half of the tumors [15]. Some studies have also reported high expression of both SSTR3 and SSTR2 mRNA in NFPAs [17, 30]. Tateno et al. [17] found that SSTR3 had the highest expression level followed by SSTR2 in a series of 15 NFPAs, and Pisarek et al. [14, 24] reported an expression pattern of SSTR2B>SSTR2A>SSTR5 in a group of 22 NFPAs. Because most prolactinomas are responsive to treatment with dopamine agonists, specimens are hardly available. Pisarek et al. [14] reported an IHC staining pattern of SSTR 2B = SSTR 3 = SSTR 5>SSTR 1 = SSTR 2A in prolactinomas. Among the three prolactin secreting adenomas in our series, expression of SSTR2 was stronger than that of SSTR5.

TSHoma is a very rare disease, with few reports of the relative expression of SSTR subtypes. Horiguchi et al. [11] reported an mRNA expression pattern of SSTR2A>SSTR1>SSTR5>SSTR3 in a series of TSH-secreting adenomas compared with expression in normal pituitary tissue. No expression of SSTR2B or SSTR4 mRNA was observed in the TSHoma tissue. Overall, the results of this study are not completely consistent with existing research findings. Possible explanations include the small sample size, and population-related differences, as all the patients in our study were Chinese, while data of other studies were obtained from Caucasian patients.

Table 4. Relationship between the expression levels of SSTR and TSH suppression rate (n = 15)

Case	Sex	Age	Dose (mg)	Time days		TSH 0.35-4.94 μIU/mL	FT3 2.63-5.7 pmol/L	FT4 9.00-19.04 pmol/L	Tumor size (mm)	SSTR2 IRS	SSTR5 IRS	TSH suppression rate (%)
1	M	24	2.1	7	Before	1.586	15.47	40.83	Macro	High	Low	98.99
					After	0.016	3.32	15.02				
2	M	40	1.4	5	Before	15.4	18.15	26.65	micro	High	High	84.94
					After	2.319	4.17	18.44				
3	M	25	0.9	3	Before	6.609	40.96	52.27	Macro	High	High	89.12
					After	0.719	5.66	24.16				
4	F	40	0.9	3	Before	10.106	5.89	16.91	micro	High	Low	89.77
					After	1.034	4.34	14.31				
5	M	33	2.8	14	Before	2.53	8.64	30.22	Macro	High	Low	99.29
					After	0.018	5.46	11.26				
6	F	27	3.6	18	Before	3.797	8.36	27.15	Macro	High	High	97.00
					After	0.114	4.03	15.79				
7	M	26	1.2	6	Before	2.882	9.34	25.09	Macro	High	Low	97.71
					After	0.066	3.35	14.06				
8	M	31	4.2	16	Before	4.316	8.43	25	Micro	High	High	86.68
					After	0.575	3.63	16.02				
9	M	52	1.2	6	Before	4.523	10.23	25.72	Macro	High	High	82.98
					After	0.77	4.52	17.3				
10	M	33	1.9	8	Before	6.84	5.93	21.69	Macro	High	High	11.07
					After	6.083	4.82	21.94				
11	M	51	2.2	11	Before	1.756	8.22	28.12	Macro	High	High	67.37
					After	0.573	2.28	12.12				
12	F	45	1.1	11	Before	4.487	7.7	23.87	Macro	High	High	74.88
					After	1.127	4.64	20.06				
13	M	17	1.2	4	Before	4.641	9.53	24.37	Macro	High	Low	96.44
					After	0.165	3.34	9.81				
14	M	25	1.8	6	Before	2.964	11.16	36.95	Macro	High	Low	91.62
					After	0.278	4.37	20.52				
15	F	39	2.4	8	Before	3.107	6.85	26.65	Macro	High	Low	97.62
					After	0.074	4.62	18.44				

Note: F = female, M = man; high (IRS score, 0-4); low (IRS score, 5-9); TSH suppression rate (%) = [(before treatment TSH value-after treatment TSH value)/before treatment TSH value]×100.

Most (80%) of TSHoma patients have macroadenomas, with microadenomas thus being exceptional [31]. TSHomas are often large and invasive lesions and highly fibrous, which hampers complete removal. As for medical therapy, somatostatin analogues are reported to inhibit TSH secretion in addition to tumor growth in combination with the surgical or radiological therapy [12]. Our study found short-term preoperative OCT can control TSH and thyroid hormone levels.

But the relationship between the response to OCT and expression of subtype-specific SSTRs in tumor tissues has yet to be clarified. TSH secretion are mediated via interactions with SSTR2 and tumor size reduction via interactions with SSTR5 [11, 12]. In our study, low SSTR5 expression show a higher TSH suppression rate. First, SSTR2 expression alone might be suppress TSH secretion in short term. Second, SSTR 5 expression might be lost during the therapy. Short-term response to OCT therapy may be related to the expression of SSTR5. However, additional studies with larger numbers of cases are necessary to establish the SSTR5 expression spectrum in pituitary adenoma and the role of SSTRs in OCT therapy for TSHoma.

Limitations

Limitations of this study are as follows. The low incidence of TSHoma makes it difficult to col-

lect more cases. Even in studies of pituitary tumors that are of certain size, the number of TSHomas patients is relatively small (N<40) as well. In addition, the number of non-TSH-secreting adenomas patients may be too small to avoid bias if any. A larger number of patients is required to demonstrate widely applicable findings given that this study used a unique ethnic population, exhibited differences from previous findings, and analyzed a relatively large series of TSH-secreting adenomas.

Conclusion

TSH-secreting pituitary adenomas preferentially express SSTR2, with higher SSTR2 IHC staining intensity scores as compared to SSTR5. In addition the patients with TSHoma had stronger expression of SSTR2 and a higher prevalence of SSTR5 expression as compared to patients with the other types of pituitary adenomas. SSTR2 and SSTR5-preferring octreotide and lanreotide may represent a useful treatment approach, especially in TSHoma or somatotropinoma patients. Therefore, immunohistochemical staining for detection of SSTR subtypes is recommended for all surgical specimens.

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Disclosure of conflict of interest

None.

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