TABLE 3: Preoperative factors influencing surgical outcome: results of univariate analysis*

Factor	Successful Surgery (n = 76)	Unsuccessful Surgery (n = 14)	p Value
age in yrs			0.3938
median	42	41	
IQR	33–57	30–51	
sex (female/male)			0.3254
female	38	9	
male	38	5	
date of surgery			0.5094
2005 & earlier	11	3	
2006 & later	65	11	
cosecretion of GH			0.0235
present	9	5	
absent	67	9	
hyperprolactinemia			0.7976
present	9	2	
absent	67	12	
serum TSH in μIU/ml			0.382
median	3.22	2.30	
IQR	1.94–4.65	1.49–3.08	
serum FT3 in pg/ml			0.4569
median	5.81	5.91	
IQR	4.85–7.74	4.73–7.89	
serum FT4 in ng/dl			0.3242
median	2.13	1.94	
IQR	1.73–2.76	1.55–2.74	
visual disturbance			0.0033
present	7	6	
absent	58	8	
max tumor diameter in mm			<0.0001
median	15	32	
IQR	10–20	23–40	
Knosp grade			<0.0001
0	34	2	
1	24	0	
2	12	2	
3	6	2	
4	0	8	
tumor consistency			0.1063
soft	17	6	
hard	59	8	
CSI			<0.0001
present	8	13	
absent	68	1	

* Surgery was defined as successful if the tumor was completely resected and complete endocrinological remission was achieved.

TABLE 4: Preoperative factors influencing surgical outcome: results of multivariate analysis

Factor	Category	RR (95% CI)	p Value
CSI	+/–	72.4 (10.5–1546.6)	<0.0001
max diameter (mm)	per 1-mm rise	1.1 (1.0–1.3)	0.0043

es at Toranomon Hospital may be partially due to this institution's establishment of a pituitary center in 2005, the first such center to be established in Japan.

The prevalence of microadenomas is progressively increasing due to improved thyroid function testing and awareness among endocrinologists and general practitioners. Although microadenomas accounted for fewer than 15% of cases before 1996,[32] Beck-Peccoz and Persani reported that 8 (62%) of 13 TSH-secreting tumors were microadenomas in cases diagnosed after 1996.[3] In our study, the overall frequency of microadenomas was 18%, but it was significantly higher in the more recently diagnosed cases (12 of 45 cases) than in the earlier group (4 of 45 cases) (p = 0.0274). In approximately 30% of cases, TSH-secreting adenoma is misdiagnosed as primary hyperthyroidism and the patients undergo thyroid ablative treatment such as administration of antithyroid medication, thyroidectomy, or radioactive iodine thyroid ablation prior to discovery of the pituitary lesion.[4,7,32] However, only 6 of our patients had undergone inappropriate treatment. TSH-secreting adenomas have been reported in patients ranging from 8 to 84 years of age (most are in the 5th or 6th decade of life), with equal frequency in men and women,[3] which agrees with our findings. Similar to other reports,[21,34] one case was associated with previous Hashimoto's thyroiditis and hypothyroidism and one case was associated with multiple endocrine neoplasia Type 1.

Patients with TSH-secreting adenomas present signs and symptoms of hyperthyroidism, but they are usually mild or clinically silent. Seven of our patients did not show signs or symptoms of thyrotoxicosis, even though they had supranormal FT4 concentrations. TSH-secreting adenomas are often plurihormonal, and testing demonstrated plurihormonal immunostaining in 75 (83%) of 90 cases. Hypersecretion of GH and/or prolactin (PRL), resulting in acromegaly and/or amenorrhea/galactorrhea syndrome, respectively, are most common and are present in about 30% of patients with TSH-secreting adenomaa.[3,30] We similarly found cosecretion of GH and/or PRL in 22% of 90 patients. However, we did not find any associations with LH/FSH or ACTH hypersecretion in our series, possibly because GH and PRL cells share common transcription factors, such as Prop-1 and Pit-1, with TSH cells.[15]

Differential Diagnosis

Elevated thyroid hormone concentrations in the presence of normal or supranormal TSH levels is termed "inappropriate TSH secretion" and is the biochemical characteristic of central hyperthyroidism. Along with measurement of serum TSH and thyroid hormone concentrations, serum α-subunit measurement and both T3 suppression and TRH

TABLE 5: Review of studies describing surgical results in patients with TSH-secreting adenoma*

Authors & Year	No. of Cases	Microadenoma	Surgical Remission	Recurrence	Criteria of Remission
Mindermann & Wilson, 1993	19	0 (0)	ND	ND	ND
Bertholon-Grégoire et al., 1999	12	2 (17)	4/8 (50)	ND	ND
Brucker-Davis et al., 1999	25	2 (8)	8/23 (35)	ND	a, c, d, e
Losa et al., 1999	24	6 (25)	12/24 (50)	0/12 (0)	a, c, e
Sanno et al., 2000	16	2 (13)	10/16 (63)	2/10 (20)	a, c, d†, e
Socin et al., 2003	43	9 (21)	21/36 (58)	2/21 (10)	a, b, c, d†, e
Ness-Abramof et al., 2007	11	1 (9)	0/9 (0)	none	ND
Clarke et al., 2008	14	2 (14)	7/12 (58)	none	a, c, e
Macchia et al., 2009	26	15 (63)	12/22 (55)	none	a, c, d†, e
Elston & Conaglen, 2010	6	1 (17)	1/5 (20)	none	a, b, c, e
Zhao et al., 2012	8	3 (38)	3/7 (43)	none	a, c, e
van Varsseveld et al., 2014	14	3 (21)	2/14 (14)	3/14 (21)	a, c, e
current series	90	16 (18)	76/90 (84)	none	a, b, c, e

* Values represent numbers of patients (%). a = euthyroidism; b = normalization of α, GH, or prolactin hypersecretion; c = series with long-term follow-up; d = T3 suppression test; e = no residual tumor on postoperative MRI; ND = not defined.
† In a few selected cases.

tests are recommended to increase the specificity and sensitivity of diagnosis.[1,4] We found elevated serum α-subunit levels in 76% of patients and a blunted TSH response (less than two times the basal value) to a pituitary stimulation test in 87% of patients examined in our study. In general, these additional data did not help us in further diagnosing TSH-secreting adenomas, although the T3 suppression test was not performed in most patients. Furthermore, TRH is no longer available in the US,[7] and α-subunit assay is neither covered by medical insurance nor performed in Japan. In contrast, all but 3 patients (with a history of long-term antithyroid drug treatment, radioactive I[131] thyroid ablation, or previous pituitary surgery) showed SITSH when first diagnosed at Toranomon Hospital. SITSH and identification of a definite pituitary adenoma on MRI are key factors for diagnosis of a TSH-secreting adenoma. Losa et al.[18] also concluded that unsuppressed TSH levels in conjunction with clinical and biochemical hyperthyroidism should prompt a neuroimaging study to document the presence of a pituitary mass. Differentiating true SITSH from pseudo-SITSH and subsequently distinguishing between TSH-secreting adenoma and thyroid hormone resistance are essential for an accurate diagnosis. Pseudo-SITSH may be caused by acute elevation of FT4 or FT3 levels in the early phase of destructive thyroiditis or recurrence of primary hyperthyroidism, levothyroxine sodium hydrate treatment for hypothyroidism, methodological interferences, or familial dysalbuminemic hyperthyroxinemia.[3,4] Repeat measurement of TSH, FT4, and FT3 using different assay methods may help identify true SITSH when the diagnosis is uncertain.[3,4] Thyroid hormone resistance should be considered, and the *thyroid hormone receptor, beta (THRB)* gene should be examined first when a patient has an uncertain diagnosis of adenoma on MRI, a neurodevelopmental disorder and/or impaired bone growth, or a first-degree relative with similar biochemical characteristics.[28]

Surgical Treatment

The first-line therapy for patients with TSH-secreting adenomas, which was applied in the majority of our cases, is a transsphenoidal resection of the tumor to remove neoplastic tissues and restore normal pituitary/thyroid function. Although previous studies have shown the surgical outcome to be poor[7,9,23,34,35,38] (Table 5), we were able to achieve complete remission for 76 (84%) of the 90 patients in our study, including all 16 of the patients with microadenomas, 60 (81%) of the 74 with macroadenomas, and 8 (38%) of the 21 with cavernous sinus invasion. The different results may be partially explained by different criteria of remission and the small number of patients who received thyroid-targeted treatments among the studies. Aggressive and invasive macroadenomas are more frequently found in patients with previous thyroid ablation.[1] Our approaches of aggressively attacking the tumors with cavernous sinus invasion and using extended transsphenoidal sugery or a simultaneous combined approach for the giant adenomas may have also improved our surgical removal rate.[25]

Poor surgical outcome may be related to fibrosis, cavernous sinus invasion, or large tumor size. However, the frequencies of macroadenoma (82%) and cavernous sinus invasion (23%) in our study were similar to previous reports (macroadenoma, 45%–100%; cavernous sinus invasion, 25%–28%).[4,7,32] TSH-secreting adenomas are more often fibrotic than other types of pituitary tumors,[4,29,32] and fibrotic characteristics were present in 74% of our cases. Fibrosis may worsen surgical results in TSH-secreting adenomas.[4,32,35] For example, Socin et al. showed that while 60% of the tumors have a soft consistency that allows them to be gently removed or aspirated, the remaining tumors have fibrotic characteristics and are difficult to excise.[32]

The prognostic factors for surgical treatment of TSH-secreting adenomas have not been identified because

these tumors are relatively rare and most surgical studies investigate a small number of cases.[19] Our study was the first to investigate preoperative factors that predict surgical outcome in a large number of cases at a single center. We confirmed that cavernous sinus invasion and tumor size, but not tumor consistency, were significant predictors of unsuccessful surgery. Our ability to successfully remove hard fibrous tumor may be one reason why we had a relatively high remission rate (84%) compared to other studies. Fibrous hard tumors do not always cause poor surgical outcomes and may be easier to remove completely. Exposing a smooth line of cleavage between the pituitary and/or the inner wall of the cavernous sinus and reducing the tumor size using tumor forceps and microscissors or an ultrasonic aspirator allows further dissection of the hard thick capsule from the surrounding structure. Thus, the surgeon can excise the remaining tumor en bloc (Fig. 1). This microsurgical removal technique, similar to that used for meningiomas, may be preferable to conventional methods used for ordinary soft adenomas, such as a suction and curette. Most neurosurgeons believe that fibrous adenoma is difficult or impossible to remove completely. Changing the term for a firm elastic or hard pituitary adenoma from "fibrous adenoma" to "meningioma-like adenoma" may therefore change neurosurgeons' approach for tumor removal, as they may be less likely to remove a meningioma-like tumor by suction and curette. Further studies should investigate why fibrotic changes occur more frequently in TSH-secreting adenomas than in other types of adenomas, although overexpression of basic fibroblast growth factor may be involved in the development of fibrosis in these tumors.[10]

Preoperative Medical Treatment

Medical treatment of TSH-secreting adenoma has been significantly improved by the use of somatostatin analogs. The efficacy of this treatment in the present series is similar to that in previous reports.[3,4,11,13,31,32] Preoperative octreotide administration led to FT4 normalization in 40 (83%) of 48 cases and tumor shrinkage in 24 (55%) of 44 cases in this study. These results are similar to those of Beck-Peccoz and Persani, who report that octreotide reduces TSH levels in more than 90% of cases, restores a euthyroid state in the majority of patients, and decreases tumor size as assessed by imaging in nearly half of patients.[2] Therefore administration of octreotide, rather than antithyroid drugs and/or an iodine compound, can help not only by restoring euthyroidism preoperatively in patients with SITSH, decreasing the risk of perioperative thyroid storm, but also by reducing tumor size, which may improve surgical outcome.

It has been reported in the literature that surgical cure rates for patients with TSH-secreting adenomas are low (0%–63%, Table 5), tumors seem refractory to irradiation, and the majority of patients are still in need of medical therapy after unsuccessful surgery. Given the high efficacy of somatostatin analogs (normalization of thyroid hormone levels in 95% and tumor shrinkage in 40% of the patients[4]), van Varsseveld et al. concluded that primary medical therapy may be considered in virtually all patients with TSH adenomas, except in those with op-

tic chiasm compression.[35] However, when we take into account the fact that somatostatin analogs are expensive and treatment must be continued over a long period of time once started, surgery should be the first choice of treatment in patients with TSH-secreting adenomas as in patients with acromegaly or Cushing's disease if we can achieve surgical cure rates in the range of 60%–85%, which is almost similar to those of other types of functioning pituitary adenomas. Our current study can clearly demonstrate that a high surgical cure rate (84%) can be achieved by earlier proper diagnosis of TSH-secreting adenomas and aggressive tumor removal with adequate surgical approaches for various types of tumors. However, as in the treatment of acromegaly, primary medical therapy may be recommended when there is a low probability of a surgical cure (for example, in cases of tumors with cavernous sinus invasion lateral to the carotid artery or large extrasellar tumors with no evidence of central compressive effects), the risk of surgery is quite high, or patients do not want to undergo surgery.[2]

Surgical and Follow-Up Results

Residual tumor was confirmed by postoperative MRI in 13 of the 14 patients with an unsuccessful surgical outcome. Only 4 patients exhibited SITSH after surgery, whereas subnormal TSH levels with euthyroidism were found in the remaining 10 patients. Therefore, low TSH levels in the early postoperative period may not predict the success of the surgery. Cosecretion of GH, which was one of the unfavorable factors affecting surgical outcome in our study, was found in 5 of 14 unsuccessful cases. Endocrine data did not meet the criteria for remission in four patients, whereas one fulfilled the criteria for cure of acromegaly despite the presence of residual tumor in the left cavernous sinus. Some tumors may secrete hormones inefficiently, allowing for biochemical normalization despite tumor residual. Such discrepancy has been reported and highlights the lack of imaging criteria for characterizing remission of GH adenomas.[12,26] Laws et al. reported that 9 patients with macroadenoma undergoing surgery for TSH-secreting adenoma had postoperative remnants, and all experienced a relapse of hyperthyroidism despite initial biochemical stabilization in 2 cases.[17] In contrast, 9 of the 11 patients who underwent postoperative medical and/or radiation treatment in our study had good control of hypersecretion of hormones and residual tumor during the follow-up period. This suggests that these adjuvant therapies normalized TSH-FT4 levels and/or prevented tumor regrowth and should be administered in patients in whom surgery has not been successful. None of the remaining 76 patients who had a successful surgery experienced relapse during the follow-up period.

Few reports describe postoperative thyroid hormone replacement after surgery. Most of the patients in our study with a successful surgery experienced slight or mild postoperative hypothyroidism for several months. However, temporary thyroid hormone replacement was needed in only 11 patients (14%), suggesting that thyroid hormone replacement is unnecessary in most patients even after successful surgery.

Surgical Complications and Histology

Major complications occurred in 4 cases (6%). One patient developed malignant hyperthermia syndrome and 3 had postoperative CSF leaks. Similar to previous findings,[33] various degrees of pituitary dysfunction developed in 15 patients (17%), and delayed hyponatremia was found in 9. No patient experienced perioperative thyroid storm in our study, possibly due to our preoperative procedures for correcting hyperthyroidism.

The proliferation marker Ki-67 is often used to evaluate invasiveness and recurrence of a tumor.[25] However, the Ki-67 labeling index was not significantly different between successful and unsuccessful surgeries (p = 0.257) or noninvasive and invasive tumors (p = 0.460) in this study, supporting other reports indicating that the prognosis cannot be predicted based on the Ki-67 labeling index alone.[8]

Conclusions

Although this is a retrospective case series and there may be some limitations of retrospective analysis, including selection bias for patient referral, changes in treatment modalities over time, or potential inaccuracy of various objective measures, we were able to make the following conclusions on the basis of in this study. We found that TSH adenomas have increased in frequency over the past 5 years and are more commonly found at the microadenoma stage. The improved success rate of surgery in this series is due to earlier diagnosis and smaller tumors. In addition, our surgical strategies, including extracapsular removal of hard or solid adenomas, aggressive attack of tumors with cavernous sinus invasion, and extended transsphenoidal surgery or simultaneous combined approach for large/giant multilobulated adenomas, may contribute to our superior results (higher rate of success combined with acceptable complication rate) in comparison with previous reports.

Disclosure

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Bromocriptine, a Dopamine Agonist, Increases Growth Hormone Secretion in a Patient with Acromegaly

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Bromocriptine, a potent D2-dopamine agonist, suppresses growth hormone (GH) secretion in most patients with acromegaly and has been approved for the treatment of acromegaly. Here we report a patient with acromegaly who showed increased GH secretion after administration of bromocriptine. A 70-year-old man with acromegalic manifestation was admitted to our hospital because of a pituitary tumor invading to the right cavernous sinus detected by brain magnetic resonance imaging. Serum GH and insulin-like growth factor-I (IGF-I) levels were elevated in several occasions (GH: 15.0-51.7 ng/mL, reference range: < 2.47 ng/mL; and IGF-I: 776-856 ng/mL, reference range: 57-175 ng/mL). Effect of bromocriptine on serum GH levels was then studied because pre-operative treatment with a D2-dopamine agonist was planned in order to reduce the tumor size and serum GH levels before surgery. After oral administration of 2.5 mg of bromocriptine, serum GH levels were unexpectedly increased from 30.7 ng/mL to 189 ng/mL, despite the fact that the levels of prolactin (PRL) were decreased from 4.2 ng/mL to 0.6 ng/mL. By contrast, serum GH levels were decreased by a somatostatin analogue, octreotide. Transsphenoidal surgery of the pituitary tumor was performed after treatment of octreotide. Histological analysis and immunohistochemistry revealed a GH-producing pituitary adenoma positive for D2-dopamine receptor. This case of acromegaly suggests that the preliminary test with a single administration of a short-acting D2-dopamine agonist, bromocriptine, is mandatory before the long-term therapy with a D2-dopamine agonist in patients with GH-secreting pituitary tumors.

Introduction

Acromegaly is a chronic disease caused by hypersecretion of growth hormone (GH) and insulin-like growth factor-I (IGF-I), mostly due to the GH-secreting pituitary adenomas, and is known to have higher rate of mortality (Melmed 2006; Holdaway et al. 2008). Surgical removal of the tumor is the first-line treatment. Medical treatment, however, is commonly done for the patients who do not wish the surgery or who have not been cured by the surgery (Melmed et al. 2009). Medical treatment is also carried out before the surgery in order to shrink the tumor size (Bush and Vance 2008). Dopamine agonists, also known as stimulators of GH secretion in healthy subjects (Eddy et al. 1971), act as suppressors of GH secretion in patients with

acromegaly and have been used for the medical therapy of acromegaly as well as prolactinoma (Thorner et al. 1975). Somatostatin receptor agonists (somatostatin analogues), such as octreotide and lanreotide, have been widely used to treat acromegaly during the past two decades, and dopamine agonists are not as effective as somatostatin receptor agonists (Melmed et al. 2009). However, dopamine agonists still play an important role for the medical therapy of acromegaly because of its less expensiveness and easier administration. Moreover, the role of dopamine agonists is being improved by the combination therapy with somatostatin analogue for patients who failed to normalize GH/IGF-I by the somatostatin analogue monotherapy (Fløgstad et al. 1994).

Bromocriptine, a dopamine agonist, decreases serum

GH levels in most patients with acromegaly (Thorner et al. 1975). However, to the best of our knowledge, only one case report is available on a patient with acromegaly, in which serum GH levels were increased by bromocriptine (Shimatsu et al. 2000). Here, we report a patient with acromegaly who demonstrated a marked rise of serum GH levels in response to bromocriptine.

Methods

Endocrine tests

Hormone assays were performed by using following kits; serum GH was measured by immunoradiometric assay using GH "Daiichi" kit (TFB Inc., Tokyo, Japan), serum IGF-I by immunoradiometric assay using IGF-I IRMA "Daiichi" kit (TFB Inc.), and serum prolactin (PRL) by 2-site immunochemiluminescent assay using Chemilumi ACS-Prolactin kit (ADVIA Centaur, Tokyo, Japan).

Dynamic hormone tests were performed after overnight fasting. An indwelling catheter was inserted in a forearm vein at 8:00, and blood samples were collected before and after the injection of following stimulators: thyrotropin-releasing hormone (TRH) (TRH injection 0.5 mg "Tanabe," Mitsubishi Tanabe Pharma Co., Osaka, Japan), luteinizing hormone-releasing hormone (LHRH) (LHRH injection 0.5 mg "Tanabe," Mitsubishi Tanabe Pharma Co.), corticotropin-releasing hormone (CRH) (hCRH injection 100 μg "Tanabe," Mitsubishi Tanabe Pharma Co.), and metoclopramide, a D2-dopamine antagonist [intravenous injection (i.v.) of primperan 10 mg, Astellas, Tokyo, Japan]. Octreotide test and bromocriptine test were performed as follows. After basal blood samples were collected, octreotide [subcutaneous (s.c.) injection of sandostatin 50 μg, Novartis pharma Co., Tokyo, Japan] or bromocriptine (Parlodel Tablet 2.5 mg, Novartis pharma Co.) was administered, and blood samples were then collected at indicated times.

Histological analysis

Transsphenoidal surgery was performed at the Department of Hypothalamic and Pituitary surgery, Toranomon Hospital. Pathological diagnosis and immunohistochemistry of GH, adrenocorticotropic hormone (ACTH), PRL, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotropin (TSH), Ki-67 (MIB-1) (a cell

proliferation marker), cytokeratin (CAM5.2) (a marker for epithelial cells), Pit-1 (a pituitary specific transcription factor involved in the specification of the lactotrope, somatotrope, and thyrotrope phenotypes), somatostatin receptor 2 and 5 (SSTR2, SSTR5) and dopamine D2 receptor (D2R) were performed at the Department of Pathology, Toranomon hospital in Tokyo, Japan. Expression of SSTR2 and SSTR5 was studied because these two somatostatin receptor subtypes mediate the inhibitory action of somatostatin analogues on GH secretion (Shimon et al. 1997). D2R expression was studied because it is the predominant dopamine receptor subtype that mediates the action of dopamine agonists including bromocriptine on GH secretion (Ren et al. 2003; Neto et al. 2009).

The pituitary tumor was fixed in formalin. Paraffin-embedded sections were stained for hematoxylin and eosin (H.E.). Sections were also immunostained for pituitary hormones, Ki-67, CAM5.2, Pit-1 and cell membrane receptors by the avidin-biotin-peroxidase complex (ABC) technique. Automated immunohistochemistry was performed by BenchMark GX (Ventana) with the following panel of antibodies: cytokeratin (CAM5.2; Becton Dickinson Bioscience, San Jose, CA, USA), ACTH (02A3; Dako, Carpinteria, CA, USA), FSH (C10; BioGenex, San Ramon, CA, USA), GH (54/9 2A2; BioGenex), LH (C93; Dako), PRL (polyclonal; Dako), and TSH (0042; Dako), Ki-67 (MIB-1; Dako), Pit-1 (BD Bioscience), SSTR2 (SS-800, Gramsch Lab., Germany), SSTR5 (SS-838, Gramsch Lab., Germany) and D2R (GTX-71745, Gene-Tex Inc., Irvine, CA, USA).

Informed consent was obtained from the patient concerning all the studies related to his case. This study was approved by the ethics committees of Sendai Medical Center and Toranomon hospital.

Case Presentation

A 70-year-old man was admitted to the Sendai Medical Center because of a pituitary tumor detected by brain magnetic resonance imaging (MRI), which was performed to examine the cause of forgetfulness. The pituitary adenoma was 15 mm in diameter and suspected to invade right cavernous sinus (Fig. 1). The patient was treated for diabetes mellitus with oral anti-hyperglycemic agents for several years. His height and body weight were 163.7 cm and 65.1 kg, respectively. Moreover, he showed typical acromegalic
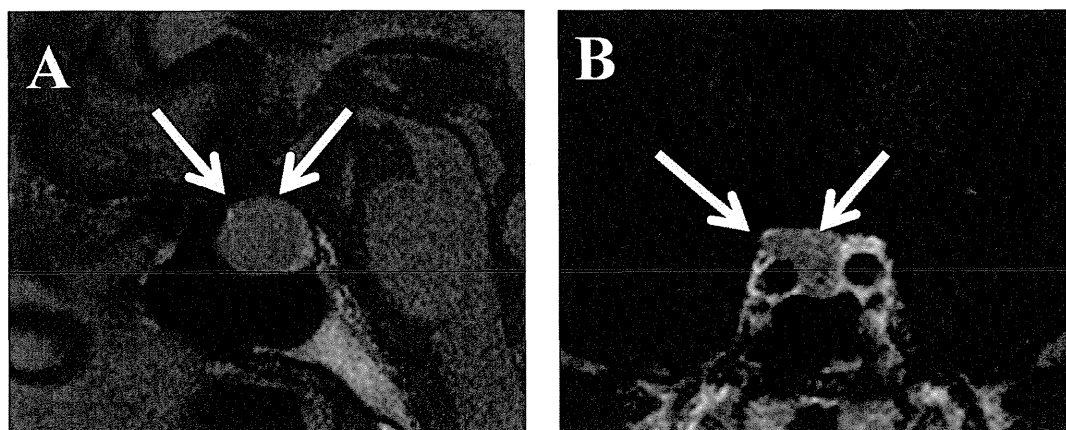

Fig. 1. Brain magnetic resonance imaging (MRI) of the patient.
Shown are the sagittal section of T1 weighted image (A) and the coronal section of enhancing image (B). A less enhancing lesion 2.5 cm in diameter suggesting a pituitary adenoma (indicating by arrows) was observed in the right wing on T1-weighted enhancing MRI (B).

disfigurement, such as countenance with forehead protrusion, enlarged tongue, thickened fingers and so on. Both serum GH and IGF-I levels were measured repeatedly and were greatly elevated (GH: 15.0-51.7 ng/mL, reference range: < 2.47 ng/mL; and IGF-I: 776-856 ng/mL, reference range: 57-175 ng/mL, respectively). Serum PRL level was 4.2 ng/mL. Other pituitary hormones and their peripheral hormones were within normal ranges: TSH 1.216 μIU/mL, free triiodothyronine (T3) 3.07 pg/mL, free thyroxine (T4) 1.63 ng/dL, ACTH 56.6 pg/mL, cortisol 6.7 μg/dL, LH 2.34 mIU/mL, FSH 5.80 mIU/mL, and testosterone 305.4 ng/mL.

TRH test caused the increase in serum GH from 15.0 to 37.4 ng/mL, and serum PRL from 2.7 to 10.3 ng/mL, respectively (Fig. 2A). Serum GH levels were elevated by LHRH test (from 31.1 to 55.0 ng/mL) and CRH test (from 27.0 to 59.9 ng/mL), respectively (data not shown). Serum GH levels were decreased by octreotide test at least up to 6 hours after injection (51.7 ng/mL before the test, and 6.42 ng/mL at nadir after 4 hours) (Fig. 2B).

Serum GH levels were greatly elevated by bromocriptine from 30.7 ng/mL to 145 ng/mL after 1 hour. After a transient decrease at 4 hours (38.8 ng/mL), serum GH levels continued to be higher than 100 ng/mL at least up to 24 hours (Fig. 2C). Serum PRL levels were decreased by bromocriptine from 4.2 ng/mL to the lower levels (below 1 ng/mL from 4 hours to 24 hours with the minimum value of 0.6 ng/mL found after 12 hours) (Fig. 2C). Serum GH and PRL levels were increased from 26.1 ng/mL to 36.7 ng/mL and from 4.2 ng/mL to 15.9 ng/mL to metoclopramide, respectively (Fig. 2D).

Octreotide was administrated in order to shrink the tumor. The patient was treated with octreotide (s.c. 50 μg) three times a day for initial three days and with octreotide (s.c. 100 μg) three times a day for next four days, followed by intramuscular injection (i.m.) of octreotide LAR (20 mg) two times for every four weeks. He then underwent surgical treatment of the pituitary tumor. Soft and white tumor tissue was completely removed by transsphenoidal surgery. Both serum IGF-I and GH levels were restored to normal. Serum GH level was decreased to 0.13 ng/mL by 75 g oral glucose tolerance test (OGTT) after the surgery, indicating that the pituitary tumor was successfully removed.

Histopathological examinations using H.E. staining demonstrated an eosinophilic adenoma (Fig. 3A). Immunohistochemistry demonstrated diffuse, strongly positive immunostaining for GH (Fig. 3B) and negative immunostaining for PRL (Fig. 3C), TSH, ACTH, LH and FSHmono (data not shown). MIB-1/Ki-67 labeling index was 0.3 %, and CAM5.2 staining showed a characteristic perinuclear dot-like pattern (data not shown). Pit-1 transcription factor was positive (data not shown). Immunostaining of membrane receptors showed positive for SSTR2 (Fig. 3D), SSTR5 (Fig. 3E) and D2R in tumor cells (Fig. 3F).

Discussion

The present case of acromegaly showed great increases of serum GH levels by bromocriptine. After the initial rise at one hour, sustained elevated levels of serum GH over 100 ng/mL were observed from 6 hours, and at least up to 24 hours after bromocriptine administration. By contrast, the elevation of serum GH levels over 100 ng/mL was not observed in other GH stimulating tests, including TRH, CRH and LHRH tests. The rise of serum GH after bromocriptine was, therefore, unlikely to be a non-specific reaction or an accidental phenomenon.

Dopamine agonists inhibit the release of GH from human fetal pituitary cells and from most GH adenoma cells in vitro (Ren et al. 2003). The D2R belongs to the Gi/o-coupled family of receptors and inhibits pituitary cell proliferation, transformation, and hormone production (Missale et al. 1998). The inhibition of PRL secretion mediated by D2R leads to major therapeutic application in the treatment of hyperprolactinemia caused by PRL-secreting tumors (Missale et al. 1998). D2R is the predominant dopamine receptor subtype that is expressed in both normal pituitaries and somatotropinomas (Neto et al. 2009). Moreover, D2R and somatostatin receptor subtypes interact physically through hetero-oligomerization to create a novel receptor with enhanced functional activity (Rocheville et al. 2000; Ren et al. 2003). Ren et al. (2003) showed a functional interaction between D2R and SSTR2 for regulating GH and PRL secretion on pituitary cells including adenoma cells, and D2R appeared to have a dominant role over SSTR2 in regulating their secretion.

In contrast to the inhibition of the GH secretion by dopamine agonists in most acromegalic patients in vivo, dopamine agonists evoked GH secretion from normal subjects via central mechanism, possibly due to growth hormone-releasing hormone (GHRH) and/or somatostatin. GH secretion in the pituitary is mainly regulated by GHRH and somatostatin, both of which are derived from the neurosecretory nuclei of the hypothalamus and are controlled by dopamine (Tannenbaum and Ling 1984; Arce et al. 1991; Müller et al. 1999). García-Tornadú et al. (2006) showed that a loss of dopamine signaling via the hypothalamic D2R caused the reduced release of GHRH from hypophysiotropic neurons in D2R knockout mice, suggesting that hypothalamic D2R plays an important role in GHRH secretion. It was reported that endogenous GHRH was required for the GH response to pharmacologic stimuli, such as L-dopa, in healthy subjects (Jaffe et al. 1996). In patients with acromegaly, the hypothalamic GHRH is suppressed by negative feedback due to hypersecretion of GH and IGF-I (Abe et al. 1983; Jaffe et al. 1998). Therefore, D2R agonists might be a therapeutic application in patients with acromegaly.

In the present case, metoclopramide, a D2-dopamine antagonist caused only a modest increase in serum GH levels (less than a 1.5 fold increase compared to the basal level), whereas bromocriptine, a D2-dopamine agonist,
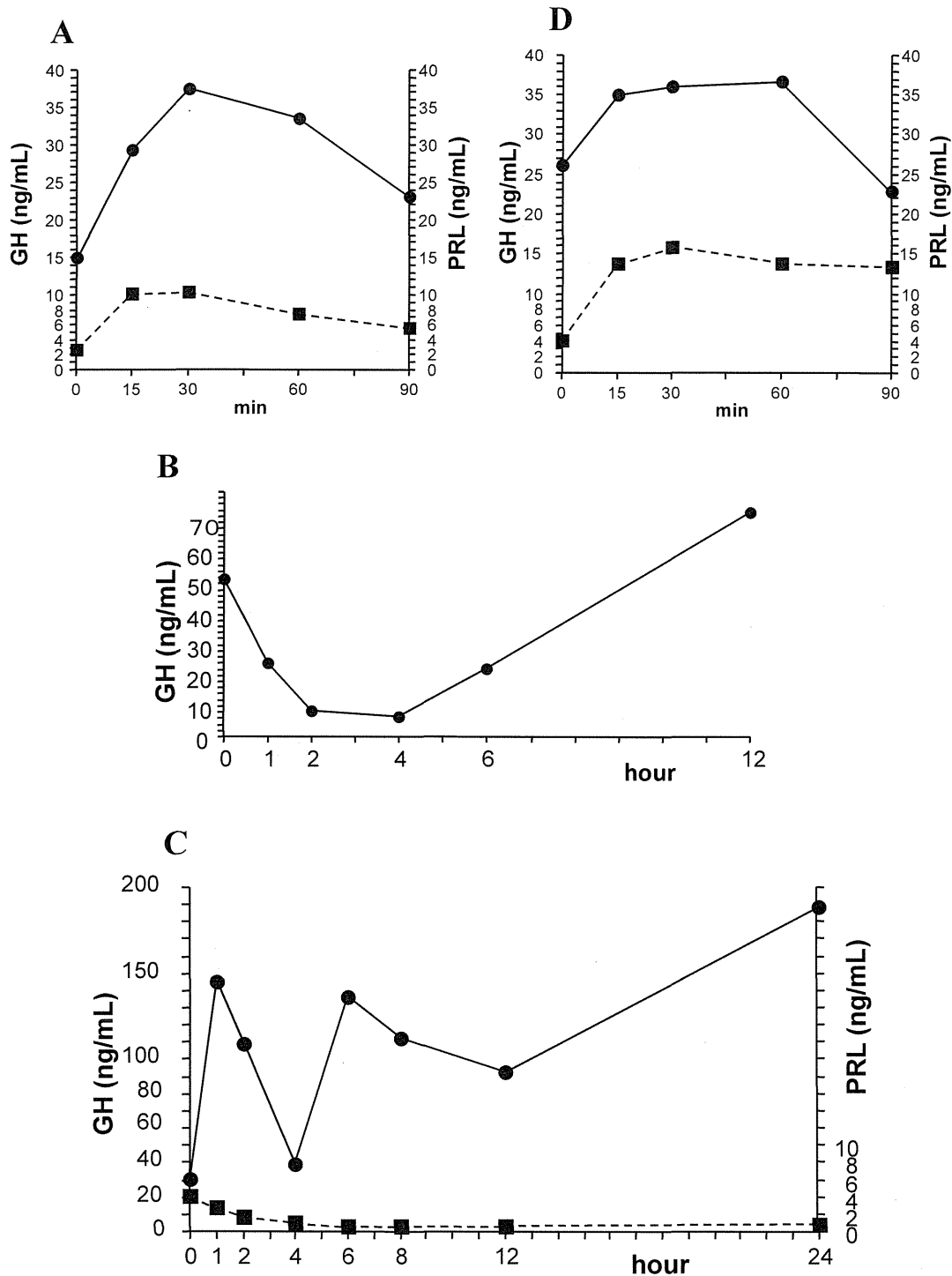
Fig. 2. Results in dynamic endocrine tests.
   Changes in serum growth hormone (GH) and prolactin (PRL) levels in thyrotropin-releasing hormone (TRH) test (A),
   octreotide test (B) and bromocriptine test (C) and metoclopramide test (D). Blood samples were collected at indicated
   times before and after the administration of TRH (0.5 mg, i.v.), octreotide (50 μg, s.c.), bromocriptine (2.5 mg, per os)
   or metoclopramide (10 mg, i.v.), and serum GH and PRL levels were measured. Closed circle and solid line: GH;
   closed square and dotted line: PRL.

increased serum GH levels greatly. Arce et al. (1991)
showed that blockade of the central dopaminergic pathway
by metoclopramide in 10 normal human subjects increased
GHRH-induced GH secretion, possibly by inhibiting the

hypothalamic release of somatostatin. The modest increase
in serum GH by metoclopramide in the present case may be
caused by the blockade of the central dopaminergic path-
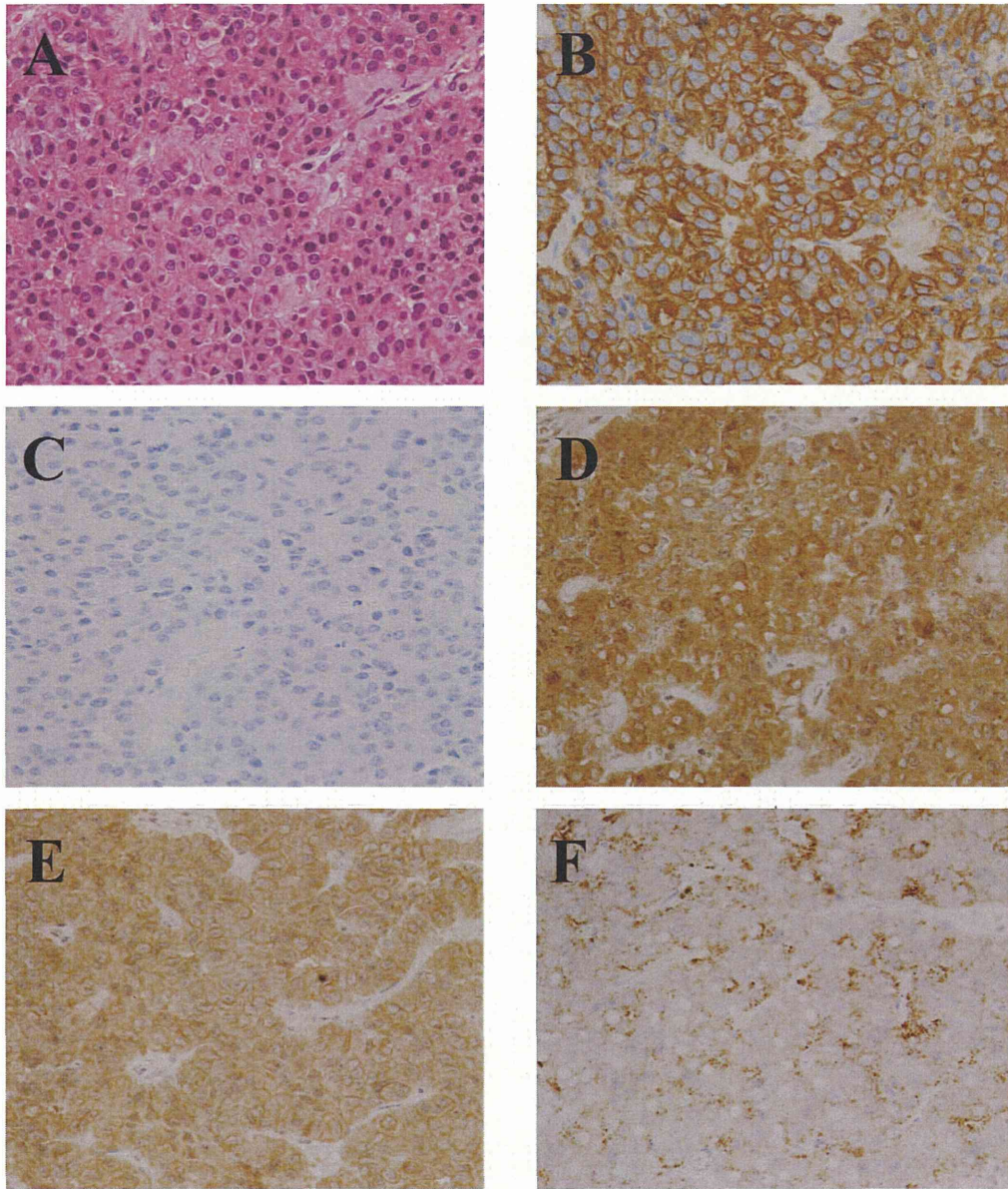way as well as its antagonistic action on D2R in the pitu-

Fig. 3. Immunohistochemistry of anterior pituitary hormones and cell membrane receptors in the adenoma.
Hematoxylin and eosin (H.E.) staining (A) and immunohistochemistry of GH (B), PRL (C), somatostatin receptor 2 (SSTR2) (D), somatostatin receptor 5 (SSTR5) (E), and dopamine D2 receptor (D2R) (F). Expression of SSTR2 and SSTR5 was studied because these two somatostatin receptor subtypes mediate the inhibitory action of somatostatin analogues on GH secretion. Expression of D2R was studied because it mediates the action of dopamine agonists including bromocriptine on GH secretion. Immunohistochemistry showed positive immunostaining for GH (B), negative for PRL (C), positive for SSTR2 (D), positive for SSTR5 (E) and positive for D2R (F).

itary adenoma.

One possible explanation for serum GH response to bromocriptine is the presence of pituitary hyperplasia either due to hypothalamic or to ectopic hypersecretion of GHRH. The findings of MRI scan of the pituitary and the pathological examination of the surgical specimen, however, did not support this possibility in this case. Moreover, the presence of an ectopic GHRH producing tumor was not observed in the whole body scan of computed tomography (CT) (data not shown).

Immunohistochemistry revealed positive immunos-

taining for SSTR2, SSTR5 and D2R in the tumor tissue of pituitary adenoma, similarly to ordinary somatotroph adenomas. The presence of altered intracellular signaling may explain for the serum GH response to bromocriptine in the present case. Vallar et al. (1987) found a profoundly altered Gs protein in a group of human GH-secreting pituitary adenomas, characterized by high secretory activity and intracellular cyclic AMP levels, and suggested that the alteration of Gs could be the direct cause of the high secretory activity of the adenomas. Moreover, Ballaré et al. (1997) showed a low expression of proteins of the Gi subfamily in human