Surgical Management and Outcomes in Patients with Cushing Disease with Negative Pituitary Magnetic Resonance Imaging

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Shozo Yamada[1,5], Noriaki Fukuhara[1], Hiroshi Nishioka[1,5], Akira Takeshita[2,5], Naoko Inoshita[3], Junko Ito[4,5], Yasuhiro Takeuchi[2,5]

Key words
- Cushing disease
- Long-term outcome
- Microadenoma
- Normal magnetic resonance imaging
- Transsphenoidal surgery

Abbreviations and Acronyms
3-T MRI: 3-Tesla MRI
ACTH: Adrenocorticotropic hormone
C/P ratio: Central-to-peripheral ACTH gradient
CD: Cushing disease
CRH: Corticotropin-releasing hormone
H&E: Hematoxylin and eosin
IPS:P: Inferior petrosal sinus-to-peripheral ACTH ratio
IPSS: Inferior petrosal sinus sampling
LH: Luteinizing hormone
MRI: Magnetic resonance imaging
PRL: Prolactin
SPGR: Spoiled gradient-recalled acquisition
TSS: Transsphenoidal surgery

From the Departments of [1]Hypothalamic & Pituitary Surgery, [2]Endocrinology, [3]Pathology, and [4]Pediatrics, Toranomon Hospital, Tokyo; and [5]Okinaka Memorial Institute for Medical Research, Tokyo, Japan

To whom correspondence should be addressed: Shozo Yamada, M.D., Ph.D. [E-mail: syamadays11@hotmail.com]

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OBJECTIVE: **To analyze our experience with transsphenoidal surgery (TSS) in patients with Cushing disease (CD) with no visible adenoma on magnetic resonance imaging (MRI).**

METHODS: **Between January 1988 and October 2010, 183 patients with CD underwent TSS at Toranomon Hospital. We retrospectively analyzed data in 18 patients without visible adenomas on MRI and compared them with 106 patients with microadenomas.**

RESULTS: **Of 106 patients with MRI-visible microadenomas, postoperative remission was achieved in 104 patients (98.1%) and recurrence of CD was observed in 4 patients (3.8%) during a mean follow-up of 5.2 years. Of the 18 patients with negative MRI, postoperative remission was achieved in 0 of the 3 patients with negative inferior petrosal sinus sampling (IPSS), in 50% of those with positive IPSS (7 of 14 patients), and in 1 patient with inconclusive IPSS. No disease recurrence has been observed during a mean follow-up of 3.3 years in the 8 patients with remission, and no tumor has emerged on MRI in 10 patients with failed surgery during a mean follow-up of 4.2 years. No major perioperative complications, including hypopituitarism, occurred in this series.**

CONCLUSIONS: **When the pituitary origin of adrenocorticotropic hormone secretion is established by IPSS in patients with normal MRI findings, we recommend TSS as the first-line treatment for CD, although chance of surgical cure (50% in this series) is lower than that of MRI-visible microadenomas. In contrast, other therapeutic options must be considered in patients with negative MRI and IPSS findings.**

INTRODUCTION

Cushing disease (CD) is a potentially life-threatening endocrinopathy and transsphenoidal pituitary microsurgery is the first-line treatment for these patients. It is therefore crucial to obtain accurate preoperative localization of the adrenocorticotropic hormone (ACTH)-producing adenoma and magnetic resonance imaging (MRI) has been considered the imaging method of choice for detection of these tumors for the past two decades. It was previously reported that ACTH-producing pituitary microadenomas were not visible on MRI in 36%–64% of patients (14), but various modifications of MRI techniques and widespread use of 3-tesla MRI (3-T MRI) have substantially improved the rate of tumor detection (2, 5, 18, 19). Bilateral inferior petrosal sinus sampling (IPSS) is the gold standard for establishing the pituitary origin of ACTH secretion in patients with negative MRI findings. However, it is still controversial whether surgical outcome in patients with negative MRI findings is less favorable compared with those with positive MRI findings (1, 3, 22-24). In addition, the optimal therapeutic approach in patients with normal MRI is also controversial (1, 23). This study evaluated the outcomes after a first-line surgical approach in patients with CD in whom adenoma was not detected by extensive MRI and these data were compared with patients with microadenoma detected on preoperative MRI.

MATERIALS AND METHODS

Patient Population

Between January 1988 and October 2010, 183 patients with CD underwent transsphenoidal surgery (TSS) performed by the same surgeon (S.Y.) at Toranomon Hospital. Eighteen patients fulfilled the criteria for the study: no detection of any tumor on extensive MRI studies and no previous surgery. During the same period, TSS was performed on 106 patients in whom microadenoma was detected (96 patients) or suspected (10 patients) on preoperative MRI, and

microadenoma was confirmed by histology after surgery. An additional 59 patients had surgery for macroadenoma during the same time period and were excluded from this study.

Preoperative Endocrine Examination

All patients had ACTH-dependent CD suggested by physical stigmata and endocrine examinations, including detectable basal serum ACTH and cortisol levels, loss of the circadian serum cortisol pattern, increased urinary free cortisol excretion, failure of low dose dexamethasone to suppress cortisol secretion, and peak serum ACTH level more than 1.5 times the basal level after a corticotropin-releasing hormone (CRH) stimulation test. The diagnosis of the 18 patients with negative MRI had been carefully distinguished from that of pseudo-Cushing syndrome and diagnosed as ACTH-dependent CD at our Endocrine Center based on their endocrine data before MRI examination.

MRI Procedures

All MRI scans were performed in a 1.5-T scanner (Magnetom Symphony syngo MR [Siemens, Erlangen, Germany]). Conventional T1-weighted spin echo and T2-weighted turbospin echo sequences were obtained in the coronal, sagittal, and axial planes with 2-mm-thick interleaved sections without a pregadolinium gap. After contrast enhancement, spoiled gradient-recalled acquisition (SPGR) with contiguous 1.5-mm-thick sections and/or dynamic study with contiguous 2-mm-thick sections, as well as T1-weighted coronal, sagittal, and axial MRI, were obtained. Additional MRI examinations with a 3-T scanner (Achieva, Philips Medical Systems; Best, the Netherlands) were performed since 2007 when no definite abnormal findings suggesting adenoma were detected on a 1.5-T scanner. Of the 18 patients with negative MRI, SPGR and 3-T MRI were performed in 14 and 11 patients, respectively. All imaging studies were independently reviewed by the radiologists, endocrinologists, and surgeons. MRI was strictly assessed as normal or negative when all reviewers judged the scan as normal based on absence of both direct signs (inhomogeneity in the pituitary, such as a less enhancing lesion) and indirect signs (deviation of the pituitary stalk, bulging or erosion of the sellar contour). Instances where MRI interpretation was ambiguous among the reviewers were classified arbitrarily as suspected microadenoma cases in the present study. Ten patients fulfilled this condition and underwent TSS after confirming the central origin of ACTH hypersecretion by IPSS. In addition, subsequent MRIs have been performed at least once a year to examine whether the tumor has become visible in patients in whom the tumor was not found during surgery and CD persisted after surgery.

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Simultaneous Bilateral IPSS

Bilateral IPSS was performed in all 18 patients with negative MRI scans to confirm the pituitary origin of ACTH. Serum ACTH concentrations were measured in blood samples obtained simultaneously from both inferior petrosal sinuses and peripheral blood drawn 0, 3, 5, and 10 minutes after the intravenous CRH (100 μg) administration. Inferior petrosal sinus-to-peripheral ACTH ratio (IPS:P) before and after CRH injection was calculated (6, 17, 26). In addition, prolactin (PRL) levels were also measured in 10 patients to obtain an IPS:P ratio of ACTH normalized to PRL, which has been considered a more reliable indicator than conventional ratios (6). Petrosal sinus-to-peripheral ACTH ratio more than 2.0 in the basal state, a peak ratio more than 3.0 after CRH administration, or a normalized IPS:P ratio more than 0.8 was considered to indicate CD. In addition, it was judged as positive for lateralization when the side-to-side ACTH ratio was more than 1.4 (15). No major adverse events occurred during these procedures.

Surgical Procedures

All patients were operated on by the same surgeon who had experience with more than 2000 pituitary surgeries. The same transsphenoidal surgical procedure was used to identify a tumor. The pituitary gland was widely exposed horizontally to both cavernous sinuses and vertically to both intercavernous sinuses. When a tumor was not visible in surface view after dural opening, the side of the pituitary gland ipsilateral to that suspected by IPSS findings was first sectioned vertically into three parts (each part is 1.5–2 mm thick) and existence of adenoma was meticulously searched. When no adenoma was seen at this step, the contralateral wing of the pituitary was sectioned in half, then the pituitary gland was cut horizontally to expose the entire anterior and posterior lobes. If no tumor was still identified, bilateral periglandular inspection with visualization of the medial wall of the cavernous sinus and the diaphragm was performed to detect an ectopic microadenoma located in the periglandular region. When a tumor was identified, selective adenomectomy was performed with removal of a rim of normal pituitary tissue surrounding the adenoma. When no reliable adenoma was detected with this procedure, hemihypophysectomy of the side suspected by IPSS was finally done. In this series, of three patients with negative IPSS findings, subtotal hypophysectomy (hemihypophysectomy + additional resection of small parts of tissues in the opposite lateral wing and median wedge of the remaining pituitary gland) was done in one patient and total hypophysectomy (removal of anterior pituitary gland except posterior gland) was performed in earlier patient. In addition, membranectomy of the sphenoidal sinus to avoid the possibility of a remaining adenoma in the sphenoid sinus was also performed in patients with negative sellar exploration.

Histologic and Immunocytochemical Studies

Intraoperative rapid histologic diagnosis was performed to confirm whether grossly tumor-suspected tissue under operative microscope was indeed a tumor before moving to the next surgical procedure during surgery. In addition, intraoperative rapid diagnosis was also used to confirm complete tumor removal by examining the tissue around a tumor. All the small pieces of tissue removed during surgery, as well as the sphenoidal membrane, were submitted to our pathologists for histologic examination. Pituitary specimens were fixed in buffered 10% formalin and embedded in paraffin wax. All specimens were initially evaluated using hematoxylin and eosin (H&E) staining to identify areas with loss of acinar organization. In addition, reticulin and periodic acid-Schiff stains were used to improve the accuracy of the histopathologic diagnosis. Adenoma tissue was usually identified on the basis of classic criteria: the presence of connective tissue, vascular

stroma, and neoplastic monomorphous epithelial cells arranged in a diffuse, papillary, or sinusoidal pattern. When a pituitary adenoma was not identified on the initial H&E-stained sections, a Cushing panel was ordered, consisting of 30 sequential 5-μm sections through the paraffin block with every slide stained with H&E. In sections that were suspicious for adenoma, the intervening unstained sections were stained for cytokeratin and anterior pituitary hormones, including ACTH, by immunohistochemistry. Immunocytochemical studies were performed as previously described (27).

Postoperative Biochemical Evaluation

No perioperative hydrocortisone was administered. Serum cortisol level was assayed the morning after surgery to judge the necessity for steroid replacement within days, and glucocorticoid replacement therapy was initiated at a dose of 20–30 mg of hydrocortisone daily. Postoperative biochemical investigations were performed 2 weeks after surgery. Patients were re-evaluated every 3 months for 2 years after surgery and thereafter at 6 months intervals. At each visit the fasting plasma cortisol concentration was measured after withdrawal of glucocorticoid substitution for 24 hours. In every patient in whom glucocorticoid substitution was started after surgery, we tried to reduce the dose of oral glucocorticoids and stopped glucocorticoid substitution when morning fasting plasma cortisol level became more than 336 nmol/L (12 μg/dL). Low dose dexamethasone suppression tests (1 mg overnight) were performed yearly (earlier when there was a clinical suspicion of recurrence of the hypercortisolism) in all patients after discontinuation of glucocorticoid administration.

The other basal anterior pituitary hormones (growth hormone, PRL, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone [LH]) and their target hormones (insulin-like growth factor 1, free tri-iodothyronine, thyroxine, testosterone, free testosterone, and estradiol) were measured preoperatively and postoperatively. In addition, to evaluate the other anterior pituitary hormones, pituitary stimulation tests were done preoperatively and postoperatively with a combination of thyrotropin-releasing hormone (500 mg) and LH-releasing hormone (100 mg). PRL, thyroid-stimulating hormone, LH, and follicle-stimulating hormone levels were measured in blood samples drawn 0, 15, 30, 60, 90, and 120 minutes after intravenous administration of thyrotropin-releasing hormone and LH-releasing hormone. Patients were then followed up closely in our outpatient department or by the referring endocrinologists.

Criteria for Remission and Recurrence

Patients were considered to be in initial postoperative remission if they had a basal plasma cortisol level of less than 140 nmol/L (5 μg/dL) or adequate suppression of plasma cortisol ($\leq$56 nmol/L) ($\leq$2 μg/dL) after the 1-mg dexamethasone test determined in the first month after surgery and disappearance of clinical signs and symptoms of hypercortisolism. In addition, patients were considered as being in long-term remission if they had a plasma cortisol of $\leq$84 nmol/L (3 μg/dL) after a 1-mg dexamethasone test at the last follow-up. In contrast, a recurrence was defined as an initial remission followed by recurrent hypercortisolism and development of inadequate suppression of plasma cortisol (>140 nmol/L) after the 1-mg dexamethasone test.

Statistical Analysis

The χ^2 test was used to compare postoperative outcomes between patients with normal MRI and those with abnormal MRI findings. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Surgical and Follow-Up Results of Patients with MRI-Visible Microadenoma

Of 183 patients with CD who underwent TSS at Toranomon Hospital, 106 (57.9%) had microadenomas demonstrated on preoperative MRI. Nineteen of 106 patients (17.9%) showed tumor invasion into the cavernous sinus. Selective adenomectomy was performed in all 106 patients and remission was achieved in 104 (98.1%), with the exception of 2 patients with cavernous sinus tumor invasion (1.9%). Local irradiation or medication was administered after surgery in these two unsuccessful patients who are now in complete or partial remission of their hypercortisolism. Recurrence of CD was observed at 3 years in three patients and at 6 years in one patient after initial successful surgery during a mean follow-up of 5.2 years (range 1–22 years). Therefore long-term remission rate after surgery was 100/106 (94.3%), and recurrence rate after successful surgery was 4/104 (3.8 %) in 106 patients with microadenoma detected on preoperative MRI.

In 10 of these 106 patients, tumor-like abnormal findings on MRI was found, but they were not typical for adenoma and were interpreted as ambiguous by the reviewers in this series. IPSS was then performed to clarify a central origin of ACTH hypersecretion and IPSS findings confirmed a central source of ACTH hypersecretion in these 10 patients. A distinct adenoma was found in all 10 patients, and complete remission was achieved as in the other patients with MRI-visible microadenoma. Regarding with the localization of the tumor, laterality of ACTH in IPSS was found in all patients, but a tumor was almost located in the central portion in one patient and in on the contralateral side to that predicted by IPSS in another patient.

Simultaneous Bilateral IPSS and Surgical Results in Patients with Negative MRI

Eighteen patients (13 women and 5 men; **Table 1**) undergoing TSS for CD had negative preoperative MRI. The details of MRI examinations performed in each of these 18 patients were summarized in **Table 1**. All patients with negative MRI findings underwent IPSS with CRH administration to decide on the origin of ACTH hypersecretion using the central-to-peripheral ACTH gradient (C/P ratio) (**Figure 1**).

Three patients (Nos. 1–3) did not show an ACTH C/P ratio of more than the cutoff level of >2 before and >3 after CRH administration, which was used to define a central source of ACTH hypersecretion (negative sampling), although the IPS:P ACTH ratio normalized to PRL was 0.94 (cutoff value for CD >0.8) in one patient (No. 3). This is considered consistent with a central origin of Cushing syndrome. However, no tumors were found in those three patients with negative MRI and IPSS findings during surgery. Total (No. 1), subtotal (No. 3), and hemihypophysectomy (No. 2) were accomplished in each of these patients.

In the remaining 14 patients (Nos. 4–17), the C/P ratio before and/or after CRH ad-

Table 1. Summary of Preoperative, Postoperative, and Outcome Data in All 18 Patients with CD and Normal MRI Findings Who Underwent TSS

Patient No.	Age (years)/Sex	MRI		IPSS					
				ACTH C/P Ratio					
		1.5 T	3 T	Basal	CRH	Peak ACTH/ Basal PRL	Laterality	Surgery	Surgical Outcome
1	57/F	Dy	NT	1.1	2.4	NT	—	Total hypophysectomy	NR
2	34/M	S · Dy	NT	1.0	3.0	NT	R>L	Hemihypophysectomy	NR
3	54/F	S	S	1.5	2.8	0.9	R>L	Subtotal hypophysectomy	NR
4	7/M	Dy	NT	6.9	17.3	NT	R.>L	Hemihypophysectomy	NR
5	51/F	S · Dy	NT	17.5	55.2	NT	R.>L	Hemihypophysectomy	NR
6	70/F	S · Dy	NT	3.0	15.3	3.6	R.>L	Hemihypophysectomy	NR
7	68/F	S · Dy	S · Dy	1.3	79.7	23.3	L>R	Hemihypophysectomy	NR
8	29/M	S · Dy	S · Dy	1.6	4.7	NT	L>R	Hemihypophysectomy	NR
9	61/F	S	S · Dy	2.8	35.2	1.7	L>R	Hemihypophysectomy	NR
10	58/F	S · Dy	S · Dy	2.2	7.2	0.8	R.>L	Hemihypophysectomy	NR
11	31/F	Dy	NT	6.9	17.3	NT	R.>L	Hemihypophysectomy	CR
12	33/F	Dy	Dy	30.8	69.3	NT	L>R	Adenomectomy	CR
13	30/F	S · Dy	NT	4.3	7.2	NT	R.>L	Adenomectomy	CR
14	40/F	S · Dy	Dy	218.0	279.0	279.0	L>R	Adenomectomy	CR
15	20/F	S	S · Dy	1.4	6.8	5.0	L>R	Adenomectomy	CR
16	58/F	S	S · Dy	49.0	131.7	48.4	L>R	Adenomectomy	CR
17	9/M	S	S · Dy	3.2	24.3	17.1	R.>L	Adenomectomy	CR
18	27/M	S · Dy	S · Dy	1.0	2.9	1.2	Inconclusive	Adenomectomy	CR

F, female; M, male; NT, not tested; R, right; L, left; —, no significant difference between both sides; NR, no remission; CR, complete remission; 1.5 T, 1.5 Tesla; 3 T, 3 Tesla; SPGR, spoiled gradient-recalled acquisition; MRI, magnetic resonance imaging; ACTH, adrenocorticotropic hormone; C/P ratio, central-to-peripheral ACTH gradient; IPSS, inferior petrosal sinus sampling; CRH, corticotropin-releasing hormone; PRL, prolactin; CD, Cushing disease; TSS, transsphenoidal surgery.

SPGR (S) and/or dynamic MRI (Dy) were performed on 1.5-T and/or 3-T MRI as well as conventional methods.

ministration fulfilled the criteria considered as CD (positive sampling), although the C/P ratio before CRH stimulation was less than 2 in three patients (Nos. 7, 8, 15). These C/P ratios were adjusted for simultaneously measured PRL levels in 8 of 14 patients and adjusted values were also greater than the cutoff value of 0.8. Among the 14 patients (Nos. 4–17) with positive sampling, adenomas ranging from 2–4 mm in diameter were found in six patients (Nos. 12–17), whereas adenomas were not detected in eight patients (Nos. 4–11). In the these six patients, a central wedge tumor was found in one patient (No. 17), and unilateral tumors on the side predicted preoperatively by IPSS data were found in the remaining five patients (Nos. 12–16), although a tumor was not localized in the pituitary, but in the inner wall of the left cavernous sinus in one patient (No. 14), indicating an extrapituitary origin of the tumor (12). Excision of tumor with surrounding normal pituitary tissue was performed in the former five patients and the tumor in the inner wall of the cavernous sinus was completely removed by opening the cavernous sinus in the latter one patient. In contrast, there was no postoperative improvement in the disease in seven of the eight patients (Nos. 4–11) in whom adenoma was not detected during surgery. Hemihypophysectomy was finally performed on the side predicted by IPSS after aggressive search in the entire pituitary gland in these eight patients and complete remission was obtained in one patient (No. 11), although adenoma was not found in the tissues examined by histology. All tissues obtained during surgery were submitted to pathologists and investigated by histology and immunohistochemistry. Neither tumor nor hyperplasia was observed in the eight patients in whom no tumor was found during surgery.

There was one patient (No. 18) in whom bilateral venous sampling was not completed due to failed catheterization of the left petrosal sinus. ACTH C/P ratios before and after CRH stimulation obtained on the right side were both less than the cutoff levels to define a central source of ACTH hypersecretion. A 4-mm diameter adenoma was found on the left side of the pituitary where catheterization failed.

With one exception (patient No. 1), there were no major perioperative complications and no postoperative hormonal replacement was necessary. This one patient (No. 1) had transient cerebrospinal fluid leakage

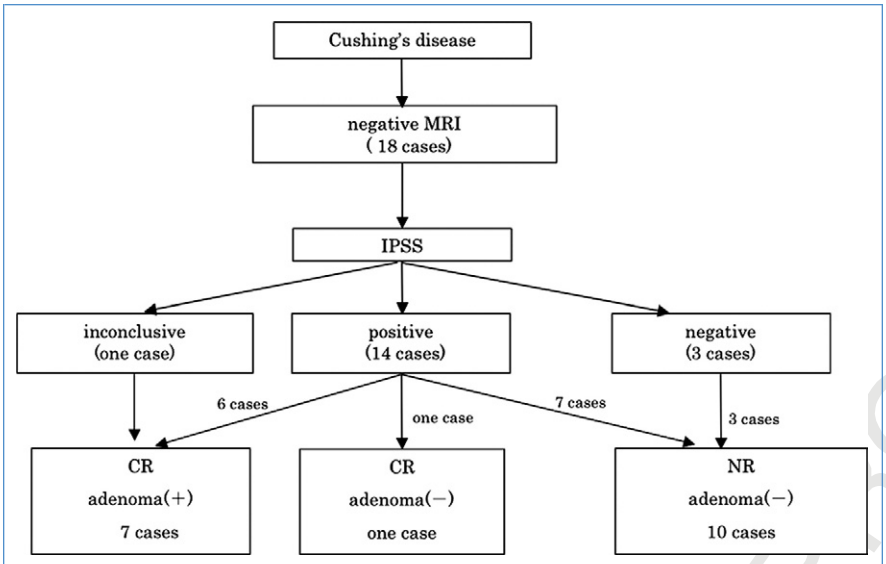

Figure 1. Flow diagram summarizing surgical outcomes correlating of inferior petrosal sinus sampling (IPSS) and intraoperative findings in 18 patients with no tumor on MRI. +, adenoma was found during surgery; −, adenoma was not found during surgery; CR, complete remission; NR, no remission.

with meningitis and thyroid hormone replacement was needed after total hypophysectomy (**Figure 1**, **Table 1**).

Postoperative Follow-Up Results in Patients with Negative MRI

There has been no endocrine recurrence of CD during a mean follow-up of 3.3 years in the eight patients who had complete remission after surgery (Nos. 11–18). In contrast, of the remaining 10 patients (Nos. 1–10) in whom no tumor was found and postoperative remission was not achieved, bilateral adrenalectomy was performed in two patients (Nos. 1 and 3) and medication was needed in the others. One of the two adrenalectomized patients passed away in a traffic accident 3 years after surgery. Hypercortisolism has been well controlled (Nos. 2, 4, 6, 7, 9, 10) or partially controlled (Nos. 5, 8) by metyrapone, mitotane, trilostane, or cabergoline in the remaining eight patients. In addition, tumor has not emerged in the pituitary on follow-up MRI in these 10 patients during a mean follow-up of 4.2 years.

Illustrative Cases

Case 1. This 20-year-old woman (No. 15) showed obesity with moon face since age 11 years and presented with amenorrhea at age 16 years. Endocrine examination suggested CD, but MRI failed to reveal any tumor in the pituitary and she was referred to our hospital for further examination. Extensive MRI studies including 3-T MRI could not demonstrate any findings suggesting tumor in the pituitary but IPSS suggested pituitary origin of her ACTH-dependent CD. TSS was chosen and performed after informed consent from the patient and her parents. A 3-mm diameter microadenoma was found on the left side of the pituitary as predicted by IPSS. Selective adenomectomy resulted in complete remission of the disease without tumor recurrence after 3 years of follow-up. No abnormal findings were found in preoperative MRI even after reviewing MRI scans retrospectively comparing them to postoperative MRI findings (**Figure 2**). F2

Case 2. A 29-year-old man (No. 8) noticed a recent 8-kg weight gain associated with moon face and muscle weakness. He was diagnosed with CD based on endocrine examination, but no adenoma was detected on MRI, and was then referred to us for further examination. IPSS suggested a pituitary tumor on the right side for his ACTH-dependent CD, although no adenoma was found even on 3-T MRI. He underwent TSS, but no adenoma was found during surgery and hemihypophysectomy was accomplished on the right side, which was pre-

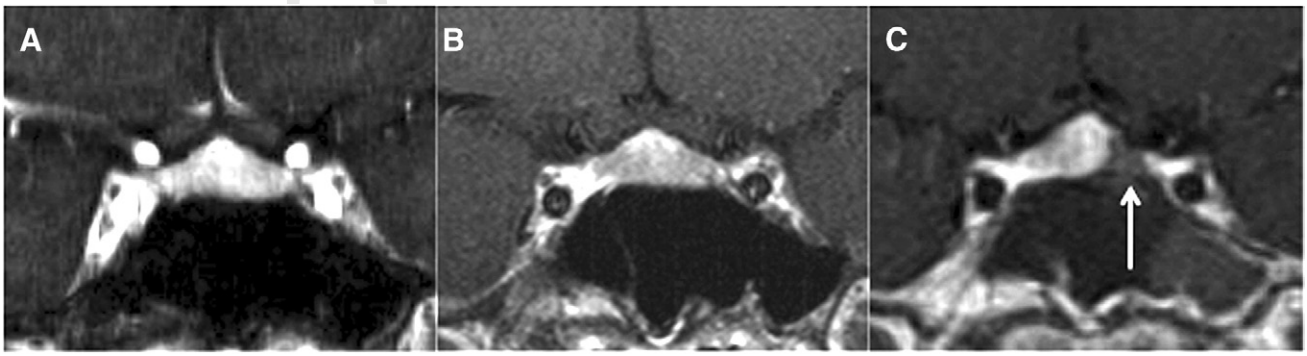

Figure 2. An adenoma was not visible on preoperative magnetic resonance imaging (MRI) (**A, B**) in this 20-year-old woman. (**A**) Preoperative coronal spoiled gradient-recalled acquisition enhanced 1.5-T MRI. (**B**) Preoperative coronal T1-weighted enhanced 3-T MRI. (**C**) A tiny (2 × 3 × 3 mm) microadenoma was found and resected on the left lateral wing of the pituitary depicted on postoperative coronal T1-weighted enhanced 1.5-T MRI (*arrow*). Abnormal findings suggesting the adenoma could still not be pointed out on retrospective reassessment of preoperative MRI (**A, B**) compared with postoperative MRI (**C**).

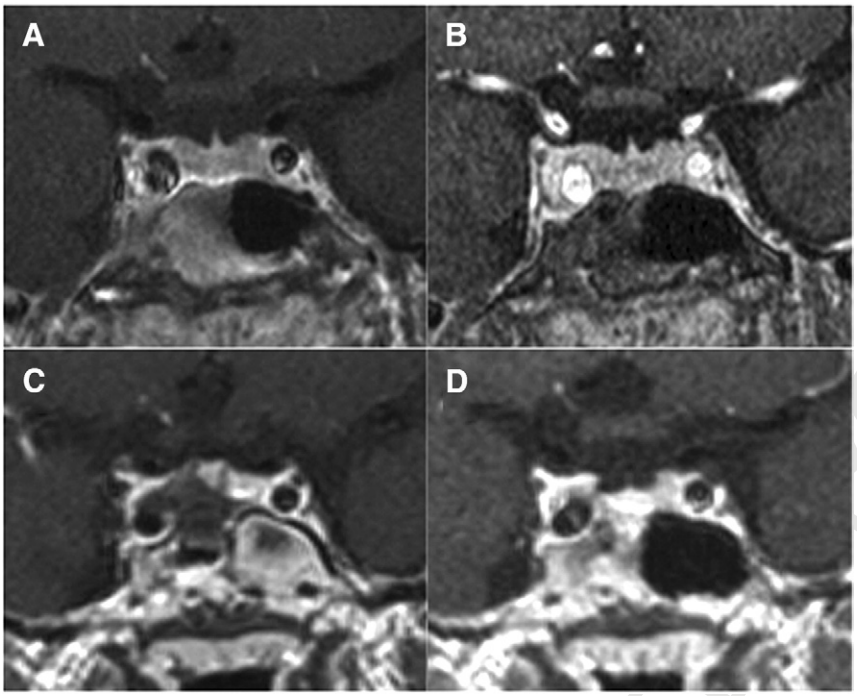

Figure 3. An adenoma was not visible on preoperative magnetic resonance imaging (MRI) in this 29-year-old man. (**A**) Preoperative coronal T1-weighted enhanced 3-T MRI; (**B**) preoperative coronal SPGR enhanced 3-T MRI. Hemihypophysectomy of the right side of the pituitary was performed after extensive exploration of the pituitary, which was confirmed on postoperative coronal T1-weighted enhanced 1.5-T MRI (**C**). No adenoma was visible on follow-up 1.5-T MRI (**D**), which was taken 3.5 years after surgery.

dicted to have an adenoma by IPSS. Postoperative hypercortisolism was not changed but he has been controlled partially by medication (metyrapone). He also has been followed up by MRI every year for 3.3 years, but no adenoma has emerged in the pituitary (**Figure 3**).

DISCUSSION

Appropriate diagnosis and management of CD is important because the mortality rate in patients with this disease is at least fourfold that in the general population matched for age and sex (21).

Preoperative MRI Examination

Once ACTH-dependent CD is confirmed or highly suspected by physical findings and thorough endocrine examination, MRI of the pituitary can be performed to detect a responsible pituitary adenoma. IPSS should then be done to clarify the cause of CD and to lateralize the microadenoma in patients without an adenoma on MRI (7, 9). Ludecke et al. (14) reported that the rate of negative MRI in microadenomas varied between 36% and 63%; and in their series of 51 microadenomas comprising the high rate (63%) not depicted by MRI, adenoma was primarily found during surgery in 96% of these 51 MRI-invisible adenomas. In addition, a recent report (8) that included a large number of patients (n = 426) described no tumor found in 49.3% of 270 MRIs. In contrast, 106 patients had microadenomas detected on MRI and only 18 (9.8%) had negative MRI among our 183 patients with CD who underwent TSS. The frequency of negative MRI was quite lower than those of other reports (17%–63%). In general, negative MRI can be the result of several variables, including field strength, technique (choice of pulse sequence), and method of analysis, in addition to the size and characteristics of the tumor. Lower rate of negative MRI in our series was therefore mainly due to our extensive MRI studies using high-field-strength MRI (1.5 and/or 3 T) with various methods including SPGR and/or dynamic study with 1.5- to 2.0-mm-thick sections, as well as conventional methods. It has been reported that the detection of tumors less than 3 mm in diameter was difficult by MRI with 2.5- to 3-mm-thick image sections (8). In contrast, SPGR involves acquiring thin image sections of 1–2 mm thickness using a spoiler gradient to shorten repetition time (18). Similarly, dynamic MRI and 3-T MRI also have been reported to increase the sensitivity of detecting ACTH-secreting microadenomas (2, 5, 19). The accuracy of MRI in the detection of very tiny pituitary microadenomas will increase with further improving technology and imaging techniques. In addition, MRIs were judged carefully and assessed strictly by several independent doctors, who we believed also improved the detection rate of adenomas in the present study. We retrospectively compared preoperative and postoperative MRIs in seven patients in whom adenoma was found during surgery. Interestingly, all seven adenomas were small, ranging from 2–4 mm in diameter, but no abnormal findings could be identified retrospectively on the preoperative MRIs (**Figure 2**). It may therefore be plausible that negative MRI is not only due to the small size of the tumor, but some specific characteristics of the tumor itself, which are unknown at present.

Preoperative Bilateral IPSS

Venous sampling is the method of choice to confirm CD when definitive tumor identification cannot be demonstrated on MRI. There are several techniques, but bilateral IPSS with CRH stimulation is the most widely used (13) and was also adopted in our patients. A C/P ratio of more than 2 before CRH stimulation or more than 3 after CRH infusion is exceedingly suggestive of CD (17). In the present study, no adenoma was found in the three patients who did not fulfill these criteria (negative IPSS sampling), whereas complete remission was achieved in seven (50%) of the 14 patients fulfilling the criteria of central origin of ACTH hypersecretion. IPSS is a very valuable tool, but the diagnostic accuracy of this procedure is now known not to be 100% as was originally thought (17), and both false-positive and false-negative samplings have been reported (10, 25). Simultaneous PRL measurement in the samples has been recommended to improve the diagnostic accu-

racy of IPSS (6, 16). However, it did not improve the sensitivity of sampling in this study. As to the localization of ACTH-secreting pituitary adenomas within the gland, Lad et al. (13) described in his review that the range of diagnostic accuracy for localization using IPSS was between 50% and 100% and a gradient of 1.4 or more across the two sides of the pituitary correctly predicted tumor location in 78% of cases. In the present study, adenoma was on the same side predicted by IPSS in 8 of 10 patients (80%) with ambiguous MRI findings, whereas adenoma was found on the side predicted by IPSS in only 5 of 14 patients (36%) with central origin of ACTH hypersecretion presented on IPSS.

Surgical Outcomes of Patients with MRI-Visible Microadenoma Versus Patients with Negative MRI

The preferred treatment for CD is selective transsphenoidal adenomectomy after accurate preoperative localization of the ACTH adenoma. Several large studies have reported remission rates of 59%–95% depending on factors including size of adenoma, cavernous invasion, experience of the surgeon, and the definition of remission. The best long-term remission rates, ranging from 86%–98%, were found in patients with noninvasive microadenomas, whereas lower remission rates were noted in patients with macroadenomas (range 31%–83%) or invasive adenomas (range 22%–65%) (11). In our series, long-term remission rate by surgery was 100/106 (94.3%), and recurrence rate after successful surgery was 4/104 (3.8%) with microadenoma detected on preoperative MRI. We believe that the extremely high remission rate and low recurrent rate accomplished in our 106 MRI-visible microadenomas were mainly due to our extensive tumor removal (complete tumor resection with surrounding pseudocapsule or rim of normal pituitary tissue surrounding the adenoma often with the help of intraoperative rapid histologic diagnosis). Two patients with unsuccessful surgery and four patients with recurrence had microadenomas associated with invasion of the cavernous sinus. In contrast, surgical results of 18 patients with negative MRI were significantly poorer ($P < 0.001$) than those of MRI-visible microadenoma, which is similar to other reports describing a lower success rate of pituitary neurosurgery in patients with normal MRI (1, 3, 4). We believe that such lower remission rate in patients with negative MRI was not a matter of poor surgical techniques, but a matter of tumor existence in the pituitary. This is logical in that if a tumor can be localized, there is a better chance of cure. Tumor was not visible in the pituitary on follow-up MRI in 10 patients with failed surgery during a mean follow-up of 4.2 years, suggesting the possibility of no tumor existence in the pituitary. However, several investigators claimed that remission rate was lower but not statistically significant between patients with MRI-visible microadenoma and those with negative MRI (8, 22-24).

Treatment Strategies for CD with Negative MRI Findings

The optimal therapeutic approach to patients with normal MRI is controversial. Some investigators have concluded that neurosurgical exploration is associated with more complications in these patients (23), and other researchers have even suggested that neurosurgical exploration is not indicated for CD with normal MRI (1).

In the present series, remission was not accomplished in all three patients with negative IPSS, indicating that there is no surgical indication of the pituitary for the patients with CD in whom tumor is not visible on extensive MRI studies and IPSS fails to show central origin of ACTH hypersecretion. In contrast, postoperative remission was achieved in half of the 14 patients in whom extensive MRI studies failed to depict adenoma in the pituitary but IPSS indicated a central origin of ACTH hypersecretion. We therefore recommend TSS as the first choice of treatment for these patients, although the possibility of remission is not very high (50% in the present series), especially when considering the poor prognosis of CD. If any responsible tumor cannot be found in the pituitary during surgery, ectopic pituitary adenoma or ACTH hyperplasia must be considered. In the present series, we observed one patient with ectopic pituitary microadenoma located in the medial wall of the cavernous sinus (12), but no cases with focal or diffuse ACTH hyperplasia of the pituitary. Therefore, bilateral periglandular inspection should be performed to detect an ectopic microadenoma when no tumor is identified after exploration of the pituitary. However, it is still controversial what we shall do during surgery when tumor still cannot be found after extensive exploration of the pituitary and periglandular regions. We believe that total hypophysectomy should be avoided in this situation when taking into account considerably higher complication rates and no ensuring of postoperative remission after total hypophysectomy (8, 11, 20, 22). We recommend hemihypophysectomy on the side of suspected tumor localization based on IPSS or partial hypophysectomy in patients without lateralization on IPSS in the hope that an undetected tiny adenoma will be removed, although the possibility of remission may be not so high. In the present series, remission was accomplished in only one patient after hemihypophysectomy among eight patients in whom adenoma was not detected after extensive exploration of the pituitary. The lateralization of IPSS was not so useful to predict the localization of the tumor and tumor existed in the same side predicted by IPSS in only 5 of 14 patients in the present series, but we believe that it would provide us with a clue as to where to explore in the pituitary when a tumor is not visible on surface view after dural opening of the sellar floor or which side should be excised (partial or hemihypophysectomy) when a tumor is not found after extensive exploration of the pituitary.

CONCLUSIONS

The remission rate of CD with MRI-invisible tumor was significantly lower than that of patients with MRI-visible microadenoma (8/18, 44.4% vs. 100/106, 94.3%, respectively). In addition, remission was achieved in 7 of 14 patients (50%) with positive IPSS, whereas remission was not achieved in any of three patients with negative IPSS. Thus, if the pituitary origin of ACTH secretion is established by IPSS in patients with normal MRI findings, we recommend pituitary neurosurgery as the first-line treatment for CD, although chance of surgical cure is obviously lower than in patients with MRI-visible microadenoma. In contrast, other therapeutic options must be considered in patients with negative MRI and IPSS findings. An approach based on selective adenomectomy when an adenoma is found during surgery, and partial or hemihypophysectomy offers an acceptable risk-benefit ratio when no adenoma is found.

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