Partial Reconstitution of the Hypothalamo-Pituitary Axes After Pituitary Stalk Sectioning and Specific Magnetic Resonance Imaging Findings

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■ BACKGROUND: **Pituitary stalk sectioning is only essential in cases of craniopharyngioma originating from the stalk or metastatic tumor to the stalk. Some patients can discontinue postoperative antidiuretic hormone (ADH) supplementation with special conditions.**

■ METHODS: **Sixty-three patients with craniopharyngiomas who were treated by surgery with pituitary stalk sectioning were included in this study. Great care was taken to preserve the fine arteries running along the lateral walls of the third ventricle. Removal rates, change of endocrinologic status, and magnetic resonance imaging (MRI) findings were investigated.**

■ RESULTS: **Total removal was achieved in 52 of 54 patients in initial surgery (96.3%), and in 5 of 9 patients in retreatment (55.6%). ADH supplementation was required in all patients from the day of surgery, but was discontinued in 29 of 54 patients among the initial surgery group (53.7%) and in 2 of 9 patients among the retreatment group (22.2%). Preservation of thyroid hormone secretion was observed in 24 of 31 patients who could discontinue ADH (77.4%), but only in 12 of 32 patients who could not discontinue ADH (37.5%). Recovery from diabetes insipidus (DI) was significantly associated with preservation of thyroid function ($P < 0.01$). Postoperative MRI showed that part of the hypothalamus was enhanced in patients with recovery from DI.**

■ CONCLUSIONS: **Total removal was achieved in 91% of all cases. Half of the patients could discontinue ADH supplementation, which was associated with preservation of thyroid function. The findings of hypothalamic enhancement on postoperative MRI may be associated with recovery from DI.**

INTRODUCTION

Pituitary stalk sectioning is only essential in the rare cases of craniopharyngioma originating from the stalk or metastatic tumor to the stalk.[1-8] Unfortunately, the inevitable consequence is hyposecretion of the pituitary hormones including glucocorticoid and antidiuretic hormone (ADH) because of disconnection of the hormonal networks, and recovery is thought to be unlikely. Subsequent central diabetes insipidus (DI) easily leads to dehydration, which could be life-threatening; therefore, the risk of morbidity and mortality is higher, including greater incidence of serious infections.[9-11]

However, necessary postoperative ADH supplementation can be discontinued with special care and conditions, as first reported in experimental sectioning of pituitary stalk in bovines.[12] Similar improvement has been observed in clinical cases.[13,14] The most important factor is thought to be avoidance of nucleic disturbance of the hypothalamus,[15] but no supporting imaging findings are known.

We present chronologic magnetic resonance (MR) imaging findings after surgery for craniopharyngioma with pituitary stalk sectioning in patients who could subsequently discontinue ADH supplementation. Presumptive mechanisms of recovery and implications for surgery are discussed.

Key words
- Diabetes insipidus
- Hypothalamus
- Magnetic resonance imaging
- Pituitary stalk sectioning
- Reconstitution
- Recovery

Abbreviations and Acronyms
ADH: Antidiuretic hormone
DDAVP: Desmopressin acetate
DI: Diabetes insipidus
GH: Growth hormone
MR: Magnetic resonance

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MATERIALS AND METHODS

This retrospective review identified 63 patients (33 men and 30 women; age, 3–80 years; mean, 43.5 years) with craniopharyngiomas who were treated by surgery through the extended transsphenoidal approach with pituitary stalk sectioning from April 2006 to August 2018 at Kohnan Hospital. Another 29 patients treated through the extended transsphenoidal approach with preservation of the pituitary stalk during the same period were included as a control group. All tumors were located from the sella turcica up to the suprasellar cistern, which corresponded to the Kassam classification type 2 in 11 cases, type 3a in 31 cases, and type 3b in 21 cases.[16] Initial surgery was performed in 54 patients, and salvage surgery was performed for tumor regrowth after craniotomy in 9 patients. Surgery was intended to achieve maximum tumor removal without causing neurologic deficits. Dissection and removal of the tumor were performed as much as possible from the surface of the optic chiasm and/or mammillary bodies. On the contrary, the dissection plane was not traced at the surface of the third ventricle floor, and these structures were removed en bloc together with the tumor to avoid possible interdigitation of tumor tissue in these structures. Great care was taken to preserve the fine arteries running along the surface of the optic chiasm, lateral walls of the third ventricle, and the arachnoid sheath around the optic chiasm. If the tumor bed involved the pituitary stalk, the posterior lobe of the pituitary gland, and/or the third ventricle floor, incision of the pituitary stalk was made just at the transition to the posterior lobe of the pituitary gland, and the third ventricle floor was incised 1.5 mm anterior from the mammillary bodies.

The morning serum concentrations of luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, free T3, free T4, growth hormone (GH), insulin-like growth factor-1, prolactin, adrenocorticotropic hormone, and cortisol were measured in addition to urinary free cortisol, both preoperatively and 11 days after the operation. Follow-up hormonal examination was performed 3 and 6 months after the operation in the outpatient department. If hyposecretion was suspected, stimulation tests were added to assess the need for supplemental glucocorticoid and/or levothyroxine administration. If DI was detected, continuous injection of vasopressin was administered until 2 days after the operation, followed by intermittent desmopressin acetate (DDAPV) medication. The indication of DDAVP use was based on urinary volume and specific gravity in the hospitalization period, and was defined both as more than 250 mL/h urinary volume and less than 1.005 specific gravity. Daily body weight evaluation and micturition frequency at night were continued thereafter, and reconfirmed by measurement of serum electrolyte concentrations and osmolarity at the outpatient department. Diagnosis of disturbance of the GH–insulin-like growth factor-1 axis and indications for supplemental GH depended on the opinions of the attending endocrinologists and pediatricians without randomization.

All patients underwent 3-dimensional T1-weighted, with and without contrast medium, and T2-weighted MR imaging (1.5T system, MAGNETOM [Siemens AG, Erlangen, Germany] and Signa Horizon [General Electric, Milwaukee, Wisconsin, USA]) preoperatively, within a few days postoperatively, and 3 months postoperatively. Follow-up MR imaging was performed at 6-month intervals after the operation. Gross total removal was defined as absence of visible tumor bulk both as intraoperative findings and on postoperative MR imaging. Progression was defined as newly observed tumor bulk and/or any enlargement of the tumor remnants. If recurrence or regrowth of the tumor was detected, follow-up MR imaging was discontinued, and radiation therapy, gamma knife surgery, or reoperation was performed. The follow-up period ranged from 3 to 108 months.

The surgical policy was explained preoperatively to the patients, and written informed consent was obtained. The clinical characteristics of the recovery group and nonrecovery group were examined and compared. Statistical comparisons used Statmate 5 software (ATMS Co., Ltd., Tokyo, Japan), and $P < 0.05$ was regarded as significant. Overall, study design was approved by the ethical committee of the institute in 2018.

RESULTS

Gross total removal was achieved in 57 of 63 patients (90.5%), and all patients were discharged without severe hypothalamic disturbances such as autonomic and/or thermal disturbances. Initial surgery achieved gross total removal in 52 of 54 patients (96.3%). Tumor remnants were identified with tight adhesion to the optic chiasm with arachnoid sheath disruption in one patient, who was additionally treated with fractionated irradiation. Another patient had tight adhesion to the medial wall of the cavernous sinus, which required salvage surgery 1 year after the initial operation. No patient in this group with gross total removal suffered tumor recurrence thereafter. Retreatment achieved gross total removal in 5 of 9 patients (55.6%), but tumor remnants were found in the remaining 4 patients. Tumor remnants were identified with tight adhesion to the lenticulostriate arteries from the A1 portion of the anterior cerebral artery in 1 patient and the thalamotuberal arteries in 2 patients. The tumor had no evident cleavage from the mammillary bodies in one patient and extremely tight adhesion to the optic chiasm in another patient. Two patients required postoperative irradiation (fractionated irradiation in 1 patient and gamma knife surgery in 1 patient), and 2 patients required retreatment through craniotomy.

ADH supplementation was required in all patients from the day of surgery, but was discontinued in 31 of 63 patients (49.2%) in the follow-up period. No patient in the initial surgery group had preoperative DI, and ADH supplementation was discontinued in 29 of 54 patients in the follow-up period (53.7%). Seven patients in the retreatment group had preoperative DI, and none of the patients in this group could discontinue ADH supplementation in the follow-up period. Two patients in the retreatment group without preoperative DI could discontinue ADH administration in the follow-up period. Glucocorticoid administration could not be discontinued in any patients except for one case of usage as needed. The period of DDAVP usage before discontinuation ranged from 3 days to 136 weeks, which was reconfirmed by evaluations at the outpatient department. Therefore, 60% of the patients could discontinue ADH supplementation within 10 weeks and 80% of the patients could discontinue ADH supplementation within 30 weeks (mean, 28.7 weeks)

(Figure 1). In comparison, 10 of 29 patients with preservation of pituitary stalk did not require ADH supplementation, but the remaining 19 patients required ADH supplementation. Eight of the 19 patients could discontinue ADH supplementation during the follow-up period, but all 8 patients had no preoperative DI, whereas none of the 11 patients with preoperative DI could discontinue ADH supplementation.

Preservation of thyroid hormone secretion was achieved in 24 of 31 patients (77.4%) who could discontinue DDAVP usage, but in only 12 of 32 patients (37.5%) who could not discontinue DDAVP usage. Recovery from DI was significantly associated with preservation of thyroid function (χ^2 test, $P < 0.01$). However, recovery and nonrecovery from DI showed no significant relationship with patient age, postoperative prolactin value, preoperative tumor volume, and preoperative tumor transverse diameter (Table 1). Postoperative complications related to glucocorticoid usage occurred in the recovery group from DI as diabetes mellitus in 2 patients, hypercholesterolemia in 4 patients, and hyperphagia in 1 patient. Postoperative complications related to glucocorticoid usage occurred in the nonrecovery group from DI as diabetes mellitus in 2 patients and influenza encephalitis in 1 patient, who was successfully treated with oseltamivir and plasma apheresis. Other complications were hypercholesterolemia in 4 patients, deep venous thrombosis in 1 patient, and hyperphagia in 2 patients. Mild dementia persisted in 4 patients with preoperative disturbed consciousness (some patients had multiple complications).

MR imaging showed that part of the hypothalamus had become faintly enhanced in 30 patients in the follow-up period; of these patients, 27 had discontinued ADH supplementation. Among the patients, hypothalamic enhancement was found in the follow-up period in 26 of 31 patients who could discontinue ADH supplementation. Postoperative hypothalamic enhancement was thought to correlate with recovery from DI based on a Pearson correlation coefficient of 0.731 and contribution rate of 0.534 ($P < 0.001$) (Figure 2).

Representative Case 1

The patient was a 17-year-old young adult had suffered from psychomotor retardation since infancy. Suprasellar tumor was incidentally discovered on admission to a pediatric department for seizure, but observation was recommended. Two years later, the tumor had enlarged and the patient had decreased appetite and body weight, and he was referred to our institute. MR imaging revealed a large sellar tumor extending to the suprasellar cistern and the optic chiasm, and upward displacement of the floor of the third ventricle (Figure 3). Pituitary stalk was not evident; therefore, the tumor was speculated to originate from the stalk. Extended transsphenoidal surgery was performed with pituitary stalk sectioning at the transition to the posterior lobe of the pituitary gland, and gross total removal was achieved (Figure 4A and B). From the day of surgery, hormonal supplementation was required with glucocorticoid and ADH. However, thyroid hormone secretion was preserved, and he was discharged with medication of dexamethasone 0.5 mg and DDAVP. Around 12 months later, DDAVP usage was sometimes discontinued because of a decrease of urinary volume and edema in the lower legs, and was finally

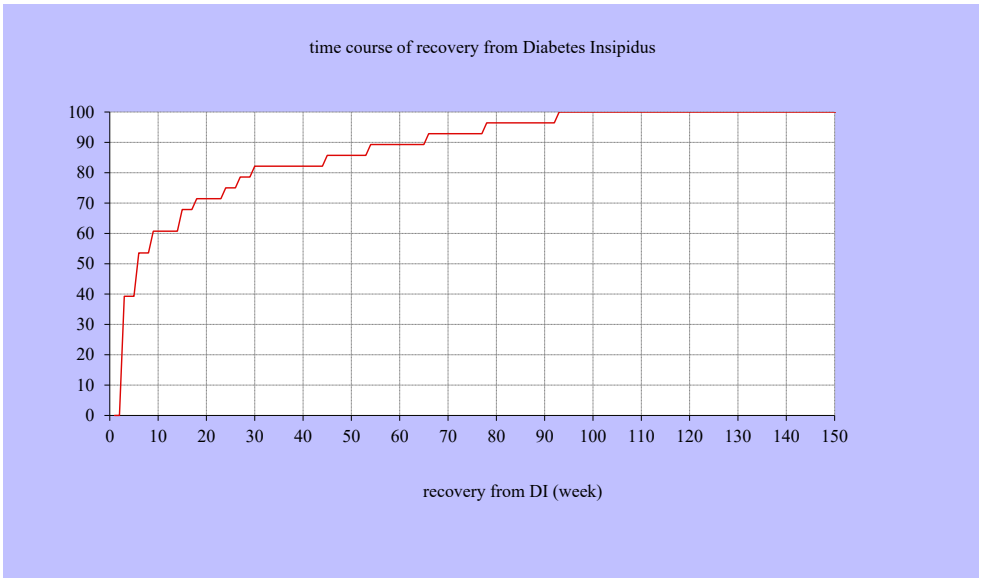

Figure 1. Kaplan-Meier curve demonstrating that 60% of the patients could discontinue antidiuretic hormone (ADH) supplementation within 10 weeks and 80% of the patients could discontinue ADH supplementation within 30 weeks (mean, 28.7 weeks). DI, diabetes insipidus.

Table 1. Comparison of Patients with Resolved and Nonresolved Diabetes Insipidus

	Patients with Resolved DI (n = 31)	Patients without Resolved DI (n = 32)	*P* Value
Patient age (years)	45.9	41.2	0.514*
Sex (men/women)	16/15	17/15	0.904†
Histology (adamantinomatous/papillary)	19/11	21/10	0.717†
Recovery from glucocorticoid supplementation	1/31	0/32	0.306†
Type of glucocorticoid (dexamethasone/other)	11/19	14/18	0.569†
Preoperative thyroid function (euthyroid/hypothyroid)	31/0	10/22	0.001†
Preserved thyroid function	24/31	12/32	0.001†
Preoperative prolactin value (ng/mL)	31.7	34.2	0.484*
Postoperative prolactin value (ng/mL)	28.2	24.1	0.429*
Preoperative tumor volume (mL)	5.38	5.46	0.907*
Preoperative tumor transverse diameter (mm)	20.1	20.6	0.928*
Postoperative hyperlipidemia	4	4	0.961†
Postoperative diabetes mellitus	1	1	0.981†
Postoperative hyperphagia	1	2	0.573†

Ciliated and goblet cell craniopharyngiomas were involved in 1 case in the resolved group and 1 case in the nonresolved group, respectively. One patient recovered and could take glucocorticoid as needed in the resolved group.
DI, diabetes insipidus.
*Mann-Whitney *U* test.
†Chi-square test.

discontinued at 18 months after the operation. MR imaging showed that part of the hypothalamus had become faintly enhanced at 12 months after the operation, and became evident at 18 months postoperatively (Figure 4C–F).

Representative Case 2

The patient was a 50-year-old man had suffered from typical bitemporal hemianopsia and was introduced to our institute from the ophthalmologic department. MR imaging revealed a large multicystic sellar tumor extending to the suprasellar cistern and the optic chiasm, and upward compression of the floor of the third ventricle (Figure 5). Pituitary stalk was barely identified at the proximal portion near to the hypothalamus, and the tumor was speculated to originate from the stalk. Extended transsphenoidal surgery was performed with pituitary stalk sectioning at the transition to the posterior lobe of the pituitary gland, and gross total removal was achieved (Figure 6A and B). From the day of surgery, hormonal supplementation was started with glucocorticoid and ADH. Thyroid hormone secretion was preserved. On postoperative day 5, abnormal body weight gain was detected with hyponatremia because of hemodilution, and DDAVP was discontinued. MR imaging on postoperative day 4 revealed that part of the hypothalamus was evidently enhanced; however, the resection stump of the pituitary stalk had lost enhancement. Three months after the operation, the pituitary stalk had become atrophied, whereas enhancement of the hypothalamus was maintained (Figure 6C).

DISCUSSION

Possible recovery from DI was first identified by investigation of the postoperative endocrinologic status after craniopharyngioma surgery without pituitary stalk preservation.[13] Pituitary stalk disturbances at the proximal portion near the hypothalamus were associated with more severe postoperative DI compared with disturbances at the distal portion near the posterior lobe of the pituitary gland. Therefore, proximal disturbance including hypothalamic nucleic damage can lead to the most severe DI even if the pituitary stalk is morphologically preserved as a result of intraoperative traction to the hypothalamus.[3,13,14] Consequently, refraining from traction stress to the hypothalamus during intentional sectioning of the pituitary stalk at the distal portion could lead to milder endocrinologic deficits than adherence to morphologic preservation of the pituitary stalk if the tumor originated from the stalk or was metastatic to the stalk.[14,17] Our finding that postoperative enhancement of the hypothalamus correlated with recovery from DI suggests preservation of vascularity to the lateral walls of the third ventricle, which may imply some production enhancement and reconstitution of the hypothalamic function.

The hypothalamus is thought to contain various neuropeptide fibers, which connect the autonomic nervous systems. However, some functional localization of nuclei is also thought to exist.[2,4,18,19] Recovery from DI and preservation of thyroid function involve the simultaneous status of hypothalamic hormones such as ADH and thyroid-releasing hormone, which are mainly secreted in the same

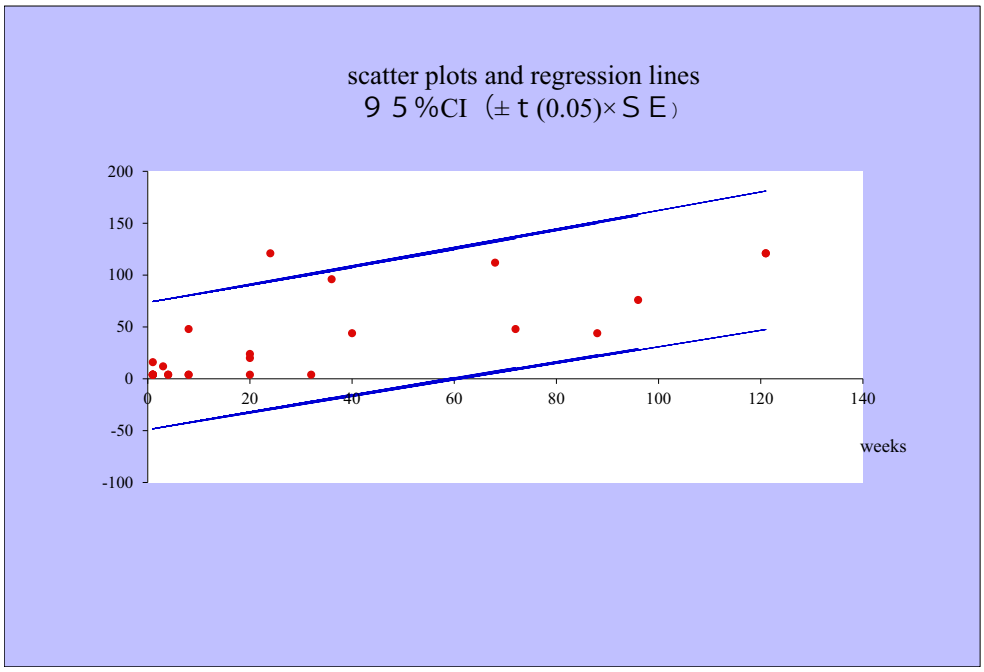

Figure 2. Correlation of postoperative hypothalamic enhancement and recovery from diabetes insipidus with Pearson coefficient of 0.731 and contribution rate of 0.534 ($P < 0.001$). CI, confidence interval.

paraventricular and/or supraoptic nucleus.[20-22] Therefore, the present findings may indicate evidence of the actual mechanistic link between inappropriate secretion of ADH and hypothyroidism. The present investigation found a relationship between recovery from DI and preservation of thyroid function, which supports the theory of functional localization in the human hypothalamus.

The findings of functional localization of hypothalamic nuclei could help to establish the link between higher tumor removal rate and amelioration of severe endocrinologic deficits. The most important nuclei of the hypothalamus are located beneath the lateral walls of the third ventricle.[2,15,18] In contrast, the floor of the third ventricle has no distinct function except for the mammillary bodies, which are located at the posterior pole of the floor.[23] Therefore, delicate attention and precise manipulation are necessary to preserve the lateral walls of the third ventricle and its feeding arteries. This suggestion is compatible with the

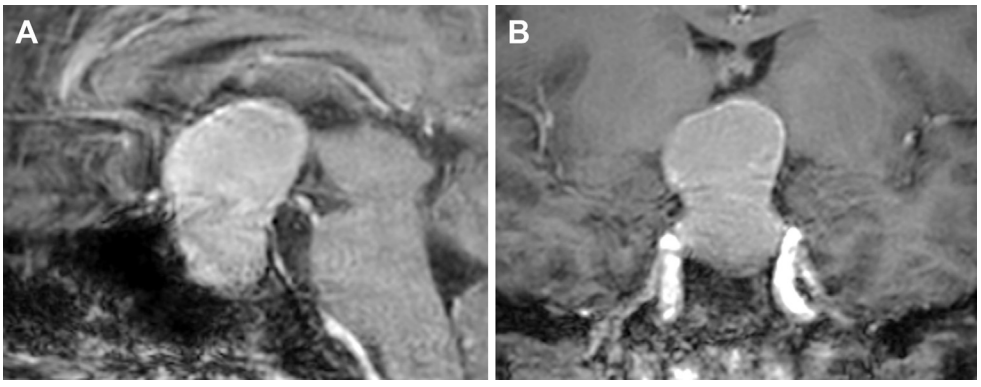

Figure 3. Case 1: coronal (**B**) and sagittal (**A**) magnetic resonance images showing a large tumor in the sellar region extending up to the suprasellar cistern. Both the optic chiasm and third ventricle floor were significantly displaced upward. The pituitary stalk was not detected, suggesting the tumor originated from the stalk. The tumor was significantly enhanced with contrast medium.

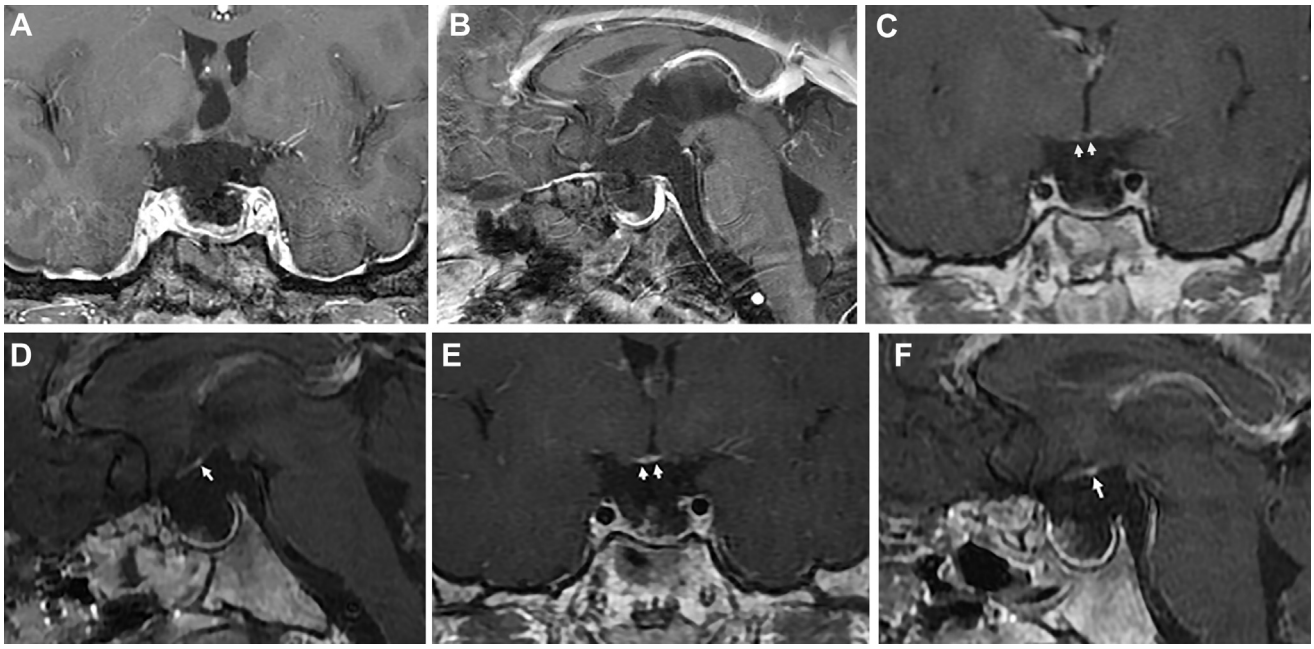

Figure 4. Case 1: postoperative magnetic resonance images showing total removal of the tumor (**A**: coronal image, **B**: sagittal image). Twelve months after the operation, part of the hypothalamus was slightly enhanced (*arrows*) (**C**: coronal image, **D**: sagittal image), and the enhancement had become evident at 18 months after the operation (*arrows*) (**E**: coronal image, **F**: sagittal image).

outcomes of our patients with preservation of the pituitary stalk because all the patients without preoperative DI could discontinue ADH supplementation in the follow-up period. However, if the tumor bed is involved in the anterior and/or mid-portion of the third ventricle floor, en bloc removal of the tumor together with the third ventricle floor and pituitary stalk could lead to better outcome.

Finally, there are some limitations in this investigation. First, this is a single-center experience and the number of patients was rather small. Second, not all but selected patients were evaluated by stimulation tests for possible hyposecretion. However, compatibility of lower tumor recurrence rate with milder endocrinologic deficits could be pursued with preservation of hypothalamic function.

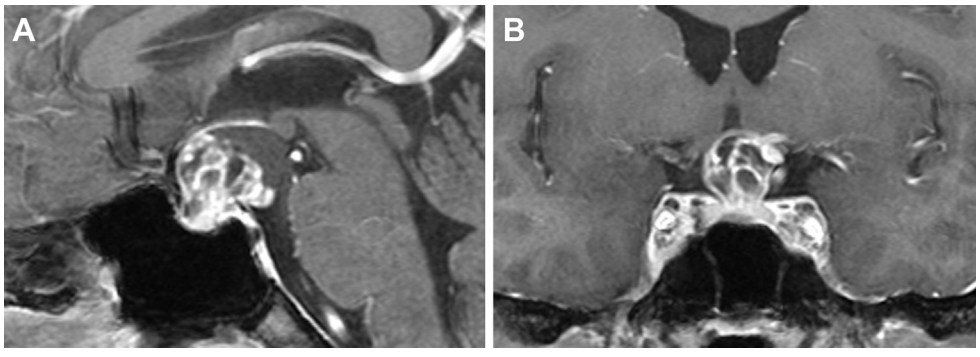

Figure 5. Case 2: coronal (**B**) and sagittal (**A**) magnetic resonance images showing a large tumor in the suprasellar region extending posterosuperiorly to the interpeduncular cistern. Both the optic chiasm and third ventricle floor were displaced upward. The pituitary stalk was not detected, suggesting the tumor originated from the stalk. The tumor was irregularly enhanced with contrast medium.

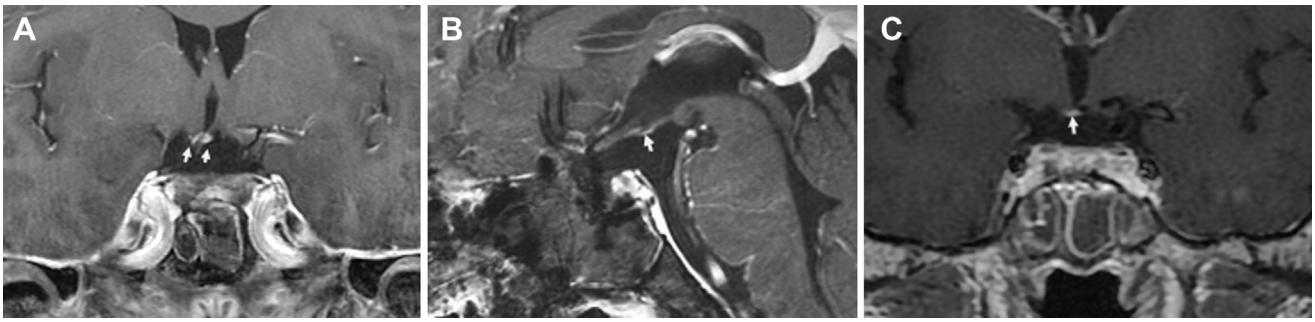

Figure 6. Case 2: postoperative magnetic resonance images showing total removal of the tumor and part of the hypothalamus was newly enhanced, apart from the sectioning point of the pituitary stalk (*arrows*) (**A**: coronal image, **B**: sagittal image). Three months after the operation, enhancement of the hypothalamus was maintained; however, the pituitary stalk had become atrophied (*arrow*) (**C**: coronal image).

CONCLUSIONS

Total removal was achieved in 91% of cases of craniopharyngioma including 96.3% at the initial surgery through extended transsphenoidal surgery with pituitary stalk sectioning. Half of the patients could discontinue ADH supplementation, which was correlated with preservation of thyroid function. The findings of hypothalamic enhancement on postoperative MR imaging may be associated with recovery from DI.

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