

# Significant improvement of intractable headache after transsphenoidal surgery in patients with pituitary adenomas; preoperative neuroradiological evaluation and intraoperative intrasellar pressure measurement

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**Clinical article**

**Significant improvement of intractable headache after transsphenoidal surgery in patients with pituitary adenomas; preoperative neuroradiological evaluation and intraoperative intrasellar pressure measurement**

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**A running head;** improvement of headache after transsphenoidal surgery

**Key words;** headache, pituitary adenoma, improvement, transsphenoidal surgery

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## **Abstract**

*Object.* Headache is the most common symptom of both primary and metastatic brain tumor, and is generally considered the primary symptom in patients with large pituitary adenomas. However, patients with small pituitary adenomas rarely complain of intractable headache, and neurosurgeons are unsure whether such small adenomas actually contribute to headache. If conventional medical treatments for headache prove ineffective, surgical removal of the adenoma can be considered as an alternative management strategy.

*Methods.* We conducted a retrospective review of 180 patients who underwent transsphenoidal surgery (TSS) for pituitary adenomas at Kanazawa University Hospital between 2006 and 2014. Patients with acute phase intratumoral hemorrhage were excluded. We identified nine patients with intractable headache as the chief complaint associated with small pituitary adenoma (diameters  $15.8 \pm 2.6$  mm, 11-20 mm), non-functioning in eight, and prolactin-secreting in one. The preoperative neuroradiological studies and headache characteristics were assessed retrospectively, and the intrasellar pressure evaluation was performed during TSS in the last seven patients.

*Results.* All nine patients had complete or substantial resolution of their formerly intractable headache after TSS. Headaches consisted of ocular pain ipsilateral to the adenoma localization within the sella in four cases and bifrontal headache in five. Magnetic resonance imaging of these patients revealed small diaphragmatic foramen, which were so narrow that only the pituitary stalk could pass. Computed tomography scans showed ossification beneath the sellar floor in the sphenoid sinus, presellar type in six cases, and choncal type in three. The adenomas included cysts in seven cases. There was no cavernous sinus invasion. Intrасellar pressure measurements averaged  $41.5 \pm 8.5$  mmHg, range 34-59, significantly higher than in control patients without headache ( $n = 12$ ), namely  $22.2 \pm 10.6$  mmHg (16-30).

*Conclusion.* In this study, the authors demonstrated the validity of TSS in the treatment of intractable headache associated with pituitary adenoma. The presence of ocular pain, especially ipsilateral to the adenoma, integrity of the diaphragm sella, and ossification in the sphenoid sinus, cyst or hemorrhage and the absence of cavernous sinus invasion were the indications for TSS for patients complaining of intractable headache and having pituitary adenomas.

## **Introduction**

The exact mechanism of headache in patients with pituitary adenoma remains unclear [1,2,3]. The widespread availability of advanced neuroradiological instruments has increased the chances of detecting patients with both pituitary adenoma and headaches. Headache is one of the major symptoms of pituitary adenoma, with a prevalence of 33-72%, although neurosurgeons occasionally cannot decide whether the pituitary adenoma causes the headache [4,5]. If the conventional medical treatment (multiple regimens, such as non-steroidal anti-inflammatory drugs, triptans, and antidepressant) proves ineffective, it would be necessary to make final decisions on whether to operate for the pituitary adenoma [6,7].

The factors contributing to the induction of headache in patients with pituitary adenoma are likely as follows; 1) compression or stretch of vessels and dural structures at the base of the brain, 2) increased sellar pressure, and 3) hormonal hypersecretion [1,3,8]. Among these factors, we focused on compression or stretch of the diaphragm sellae and the medial wall of cavernous sinus, the presence of cyst or hematoma in the adenoma, and ossification in the sphenoid sinus. In addition, intrasellar pressure (ISP) was measured intraoperatively.

## **Methods**

This study was approved by the Kanazawa University Institutional Review Board. In this retrospective clinical study, 180 patients who underwent transsphenoidal surgery (TSS) for pituitary adenomas between 2006 and 2014 at Kanazawa University Hospital were reviewed. 5 patients with acute-phase intratumoral hemorrhage were excluded due to possible confounding factors. Among 22 patients with chronic type headache (12.2%), nine suitable patients who had complained of intractable headache were found in the clinical database. Pituitary adenoma had been detected in the patients by magnetic resonance imaging (MRI). All these patients had taken a conventional medical treatment for their headache, with no sign of improvement. We compiled the following items from their clinical charts: sex, age, and headache characteristics (laterality, site, severity, quality, frequency, duration, associated symptoms, etc.). Informed consent for reviewing all their clinical data was obtained from all seven patients presented in this paper.

### *Headache evaluation*

Headache was assessed by the Headache Impact Test version-6 (HIT-6), which was

produced by the Shun-ichi Fukuhara and Glaxo Smith Kline Group of companies, and was administered by one of the authors [9,10]. This test can evaluate the impact of patients' headaches on their social activities. If the sum of the response scores for six questions was 50 or more, a considerable impact on daily living due to headache was assumed.

#### *Neuroradiological evaluation*

We utilized a 3.0-tesla MRI (GE Health care Japan Corp., Tokyo) to obtain coronal and sagittal images, before and after gadolinium administration. Neuroradiological evaluation was undertaken as follows. Tumor characteristics (maximum diameter, diameter of the diaphragmatic foramen, cavernous sinus invasion, and presence of intratumoral cyst) were evaluated by MRI signal intensity on both T1 and T2 weighted images. The integrity of dura mater at the diaphragm sellae and the medial wall of the cavernous sinus were evaluated on T2-weighted images or Fast Imaging Employing Steady State Acquisition (FIESTA) [11]. The diameters of the diaphragmatic foramen were measured on the coronal section including the pituitary stalk. The ossification of the sphenoid sinus was evaluated on the coronal and sagittal sections of the computed



tomography (CT) scan.

#### *Endocrinological evaluation*

An endocrinological study was performed preoperatively, and included determination of plasma growth hormone, insulin-like growth factor-I, prolactin, adenocorticotrophic hormone (ACTH), cortisol, thyroid-stimulating hormone, triiodothyronin, thyroxin, lutenizing hormone, and follicle stimulating hormone. After TSS, corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone, and luteinizing hormone-releasing hormone loading tests were carried out for reserve capacity evaluation of each hormone tested preoperatively.

#### *Measurement of Intrasellar Pressure*

In the last seven patients, intraoperative intrasellar pressure (ISP) was measured using intracranial pressure monitoring sensors (Codman, CA, USA). Briefly, the procedure was as follows [12,13]: an incision was made through bone and dura to admit the sensor into the adenoma. The length of these incisions was 3 mm. The depth of insertion of the sensor into the adenoma was 5 mm. The measured pressure was displayed on a monitor. Control ISPs were obtained from another 12 patients harboring

pituitary adenoma but without intractable headache. Paired Student's t-test was used for comparison between ISP before and after the removal of sellar floor, and between before and during the Valsarva maneuver. A p-value of  $<0.05$  was considered statistically significant.

## **Results**

### *Patient characteristics*

Of the nine patients reviewed, three were male and six were female, and the mean age was 47.1 (22-63) years. Eight patients had non-functioning adenomas, and one had a prolactinoma. The mean period since onset of headache was 1.7 years. The patient with prolactinoma had taken cabergoline, but became intolerant to it after three months, then consulted to our department when the headache did not resolve with painkillers.

### *Headache characteristics*

Retro-ocular pain ipsilateral to adenoma localization within the sella was found in four patients, and frontal headache with retro-ocular pains on both sides was found in five. Their headaches severity was severe in five patients and moderate in four. The pain qualities were dull in four and pressure in five. All patients had received conventional pharmacological treatment and had had no improvement. The average total HIT-6 score was 63.3 (54-72), which meant that their headaches had a great influence on their daily and social lives. However, postoperatively, eight patients said the headaches were gone, and one said his headache was almost gone. The HIT-6 scores were 36 in eight and 40 in one (Table 1).

### *Neuroradiological findings*

The mean size of the tumors present in our study was  $15.8 \pm 2.6$  mm. Seven patients had a cyst in the tumor, where the signal was almost iso-intense with CSF. The cyst signals contained hypo-intensities on T2 weighted-images, suggesting old hemorrhages. The other two adenomas present in this study were solid without a cyst. Cavernous sinus invasion was evaluated by Knops classification on the MRI coronal sections. The result was grade 2 in two case, grade 1 in three cases, and grade 0 in four cases, all of which indicated no obvious tumor invasion into the cavernous sinus. The signals of the tumors themselves were hypo-intense in three cases and iso-intense in six cases on T1-weighted images, and were hyper-intense in all nine cases in T2-weighted images.

The maximum diameters of the diaphragmatic foramen were  $3.72 \pm 1.15$  mm on average. The diameters of the foramen were so narrow that only the pituitary stalk could pass. Remarkable ossification of the sphenoid sinus was detected in all seven patients, the conchal type in three and presellar type in six, suggesting the presence of at least some extent of ossification beneath the sellar floor in all the patients (Table 2).

### *Intrasellar pressure measurement*

The average ISP in these seven patients was  $41.5 \pm 8.5$  mmHg (34-59), which is much higher than in the patients without headache (12 patients) namely  $22.2 \pm 10.6$  mmHg (16-30; n = 12, p-value < 0.01) (Table 3). ISP decreased remarkably after sellar floor removal being  $25.3 \pm 7.9$  mmHg (17-42) (p-value < 0.01). However, ISP during the Valsalva maneuver did not any change being  $39.6 \pm 7.0$  mmHg (31-53) before sellar floor removal and  $26.3 \pm 6.3$  mmHg (19-39) (statistically not significant).

### *Endocrinological findings*

The endocrinological examination described above was performed in all nine patients in this study. All patients showed hyperprolactinemia, which could be accounted for by a sectioning effect on the pituitary stalk in five patients and the presence of prolactin-producing adenoma in one (Table 1). Both cortisol and ACTH were decreased at baseline, and hyporesponse to CRH loading was observed in two patients (patients 1 and 3). The hyperprolactinemia of the five patients with non-functioning adenoma was normalized after removal of tumor by TSS, and that of the one patient with prolactinoma

was partially relieved. Meanwhile, hypocortisolemia in two patients was unchanged postoperatively.

## Discussion

Neurosurgeons occasionally have difficulty in determining whether pituitary lesions demonstrated on MRI are responsible for the headache or whether pituitary lesions together with headaches should be considered a simple co-incidence [1,7]. Although the clinical characteristics of headaches in pituitary tumor cases are extremely variable, Fleseriu et al. found that chronic daily headaches and self-reported migraines represented 75% of these cases, surpassing other types of headaches [1,5].

Headache from brain tumor is generally related to traction and displacement of intracranial pain-sensitive structures such as blood vessels, cranial nerves, and dura mater [1,8]. Inflammation involving pain-sensitive structures, meningeal irritation, meningeal involvement in spreading tumor, psychological causes, and biochemical causes have all been described as factors associated with the development of headache [6]. Pituitary tumors may provoke headache directly by a mechanical mechanism, either by eroding laterally into the cavernous sinus where they irritate the first and second divisions of the trigeminal nerve, or by involving the dural lining of the sella turcica or diaphragm of the sella, also innervated by the trigeminal nerve, or by an

increase in intracranial pressure causing dural stretch [1,4]. In our study, four patients complained of retro-ocular pains lateralized to the same side as the adenomas, suggesting local stretching of the diaphragm sellae and the medial wall of the cavernous sinus might have been present.

In order to elucidate the factors contributing to pituitary adenoma-associated headache, we focused on cystic lesion within the adenoma, erosion or invasion of the medial wall of the cavernous sinus, narrow diaphragm foramen through which only the pituitary stalk could pass, ossification of the sphenoidal sinus, and intrasellar pressure. The cavernous sinus contains pain-sensitive structures, such as the internal carotid artery, the trigeminal nerve, and its ganglion. Therefore, invasion of the cavernous sinus might be expected to cause headache [1,8]. However, Levy and Abe emphasized that large size of the pituitary tumors and cavernous sinus invasion are not essential in the development of headaches associated with pituitary adenomas [2,4]. And Levy also addressed the one of the accepted mechanisms for headache is dural stretch, because his results from big series study did not show clear association between cavernous sinus invasion and headache [14]. In our cases, the sizes of all adenomas were rather



small, less than 20 mm, and no apparent cavernous sinus invasion could be found.

If a pituitary adenoma extends superiorly or laterally, enlargement of the foramen of the diaphragm sellae or interruption of the medial wall of the cavernous sinus would occur. These two breakdowns of the dural component around the sella would suggest that increases in intracranial pressure (ICP) would be compensated (i.e., ICP would not build up). Therefore, we judge that a narrow foramen of diaphragm sellae and an intact medial wall of the cavernous sinus could induce ICP build-up and consequent dural stretching, leading to headache pain. Destrieux et al. reported that the diameter of the diaphragmatic foramen is usually more than twice the diameter of the hypophyseal stalk [15]. Thus, the foramen diameters of the defect in our nine cases were narrower than what is considered normal. In our study, removal of the sellar floor made the ICP decrease remarkably, indicating that higher ICP was relieved with the procedure. Moreover, the Valsalva maneuver did not significantly change ICP, suggesting that transmission of increased intracranial pressure was blocked by the narrowing defect of the foramen. ICP measurement in patients undergoing transsphenoidal surgery (TSS) for pituitary adenoma was pioneered by Lees et al [16,17]. They reported that their results are correlated with the radiological and endocrinological

features of the adenomas. And they proposed a hypothesis to explain the mechanism of hyperprolactinemia associated with the pituitary stalk compression syndrome.

The observation of ossification of the sphenoid sinus, whether of choncal or presellar type, in all of our nine cases was surprising. To our knowledge, there are no previous reports of a relationship between headache and ossification of the sphenoid sinus in the patients with pituitary tumors. In theory, the ossification may function as a blockade factor allowing ISP buildup in cases with pituitary adenomas. Ramakrishnan et al. reported that certain aspects of the sphenoid sinus anatomy might function to resist pituitary tumor growth into the sphenoid sinus, which may facilitate an oppositely directed suprasellar extension of the tumor [18,19]. Ossification of the sphenoid sinus of choncal or the presellar type, is accompanied by massive ossification beneath the sellar floor. Therefore, in these cases, the adenomas would tend to extend in the suprasellar direction, leading to diaphragm foramen narrowing and subsequent stretching of the diaphragm sellae, thus causing severe pain or headache.

Pituitary tumor volume has been reported to be one of the major factors to correlating with headache. Gondim et al. studied the statistical associations between

presence of headache and tumor size, optic compression, sellar destruction and cavernous sinus invasion, concluding an association between tumor extension and symptom severity [3,12]. However, in that study, the majority of the patients (81.2%) had macroadenoma and a large mean tumor size of  $24.6 \pm 15.1$ mm [8]. These results are inconsistent with the present study where the adenomas were relatively small ( $15.8 \pm 2.6$  mm). This can be reconciled if the integrity of anatomical structures surrounding the sella turcica plays a deciding role in the development headache associated with pituitary tumors.

Seven out of nine patients showed cystic changes in their adenomas, suggesting a chronic phase of intratumoral hemorrhage that was verified by the presence of an area of hypo-intensity area on the T2\* images. An important factor in the development of headache is a rapid increase in tumor size, whether by tumor growth or by intratumoral hemorrhage, which can deform the sellar wall. It is reasonable to suppose that the change of tumor size caused by the intratumoral hemorrhage would induce dural stretch around small pituitary adenomas, resulting in severe and chronic headache. Indeed, it has been reported that the ISP of the macroadenoma confined into the sella, without

destruction of the floor and with integrity of the diaphragm sellae, is higher than that of tumors with extrasellar extension [8,20]. In our series, usual endoscopic TSS for the pituitary adenomas were performed as final treatment, and the symptoms of all patients were remarkably relieved as shown by the scores of postoperative HIT-6. I believe removal of the tumor in the semi-closed intrasellar cavity like our series is the most effective treatment.

Endocrinological examination showed hyperprolactinemia in six of our patients. Five of these cases were supposed to have been caused by the sectioning effect of the pituitary stalk caused by the elevated ISP, and the remaining case was due to the constitutively prolactin-producing adenoma. However, even in the patients with prolactinoma, the intraoperative ISP was relatively high and therefore the pituitary stalk-sectioning effect of high ISP might have contributed to the hyperprolactinemia.

In conclusion, a structural barrier was found around the sellar turcica in our study group, made up of a small foramen of the diaphragm sellae superiorly, an intact medial wall of the cavernous sinus laterally, and ossification in the sphenoid sinus inferiorly. All these factors, recognized on MRI, may have contributed to confining the adenoma to

the sellar region and increasing ISP. The cystic changes, as well as this structural barrier, may be associated with intractable headache in patients with pituitary adenoma.

It is also important for decision-making to know the character of the headache, and ocular pain lateralized to the same side as the adenomas is key to recognizing a relationship between headache and adenoma. Such a confined pituitary adenoma with intractable headache is a good candidate for TSS.

### **Conflict of Interest**

All authors have no conflict of interests.

### **List of Abbreviations**

ACTH; adrenocorticotropin hormone

CRH; corticotropin-releasing hormone

CT; computed tomography

FIESTA; fast imaging employing steady state acquisition

HIT; headache impact test

ISP; intrasellar pressure

MRI; magnetic resonance imaging

PRL; prolactin

TSS; transsphenoidal surgery

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## Figure Legends

**Figure 1.** Coronal-section magnetic resonance images (MRI) with contrast agent and T1 weighted-image (WI) show the pituitary adenomas involving cysts stretching of both the diaphragma sellae and the medial wall of the cavernous sinus. (upper line left to right; case 1 to 4, lower line left to right; case 5 to 7)

**Figure 2.** Coronal-section of MRI with T2-WI or FIESTA shows that the diaphragma sellae is delineated by a line of hypo-intensity and is stretched by the adenomas, and their foramens are so narrow as to pass only the pituitary stalk. Cases are arranged as in Fig.1.

**Figure 3.** Computed tomography (CT) scan, sagittal section with bone image revealing ossification beneath the sellar floor of either presellar type or choncal type. Cases are arranged as in Fig.1.

## Tables

Table 1. Characters of headache presented by nine patients with pituitary adenomas in this study.

HIT: headache impact test

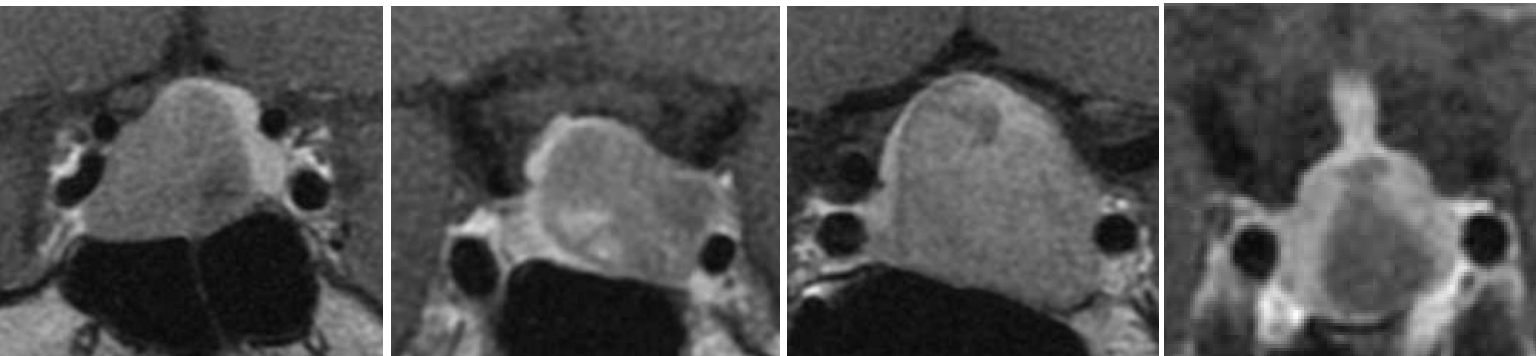
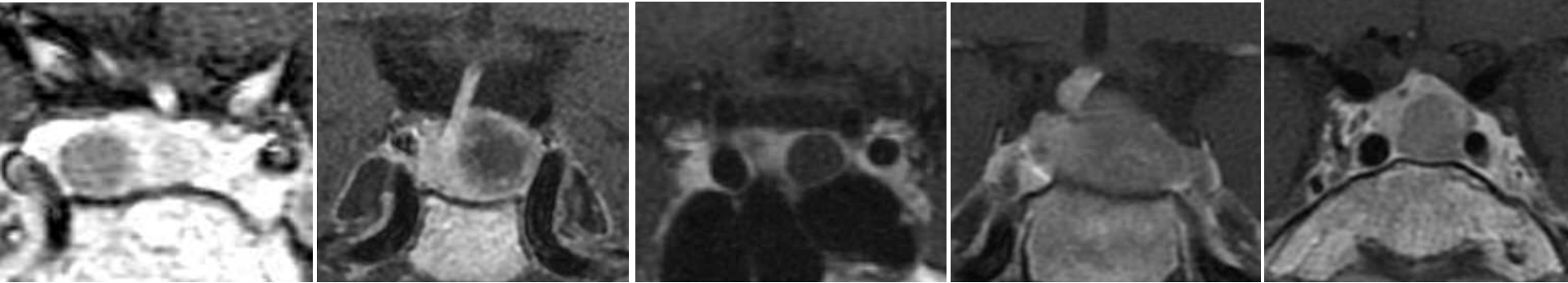
Table 2. Characters of preoperative MRI findings demonstrated by nine patients with pituitary adenomas in this study.

CS: cavernous sinus, MRI: magnetic resonance imaging, PRL: prolactin

Table 3. Results of intrasellar pressures measured by intracranial pressure monitor sensor intraoperatively.

**Figure 1**

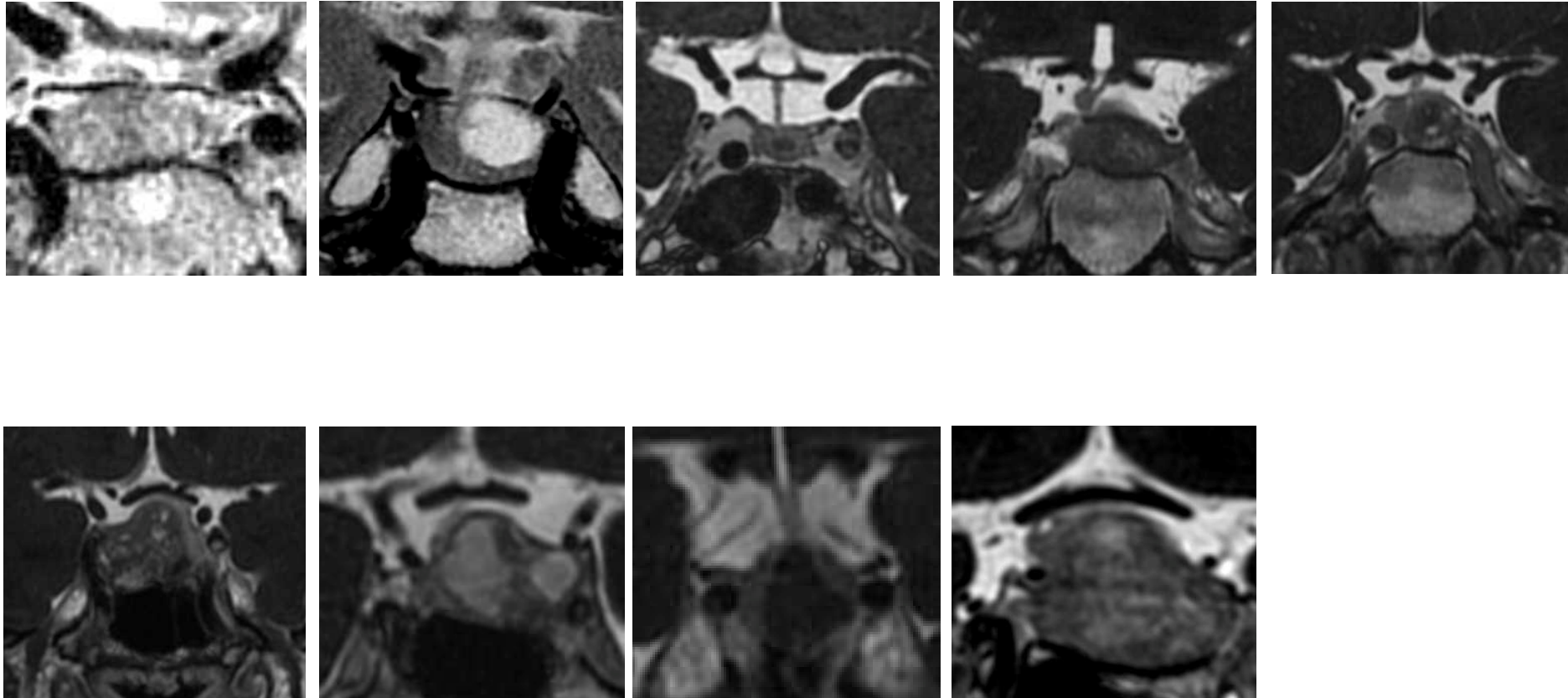
**Yasuhiko Hayashi**



1	2	3	4	5
6	7	8	9	case

**Figure 2**

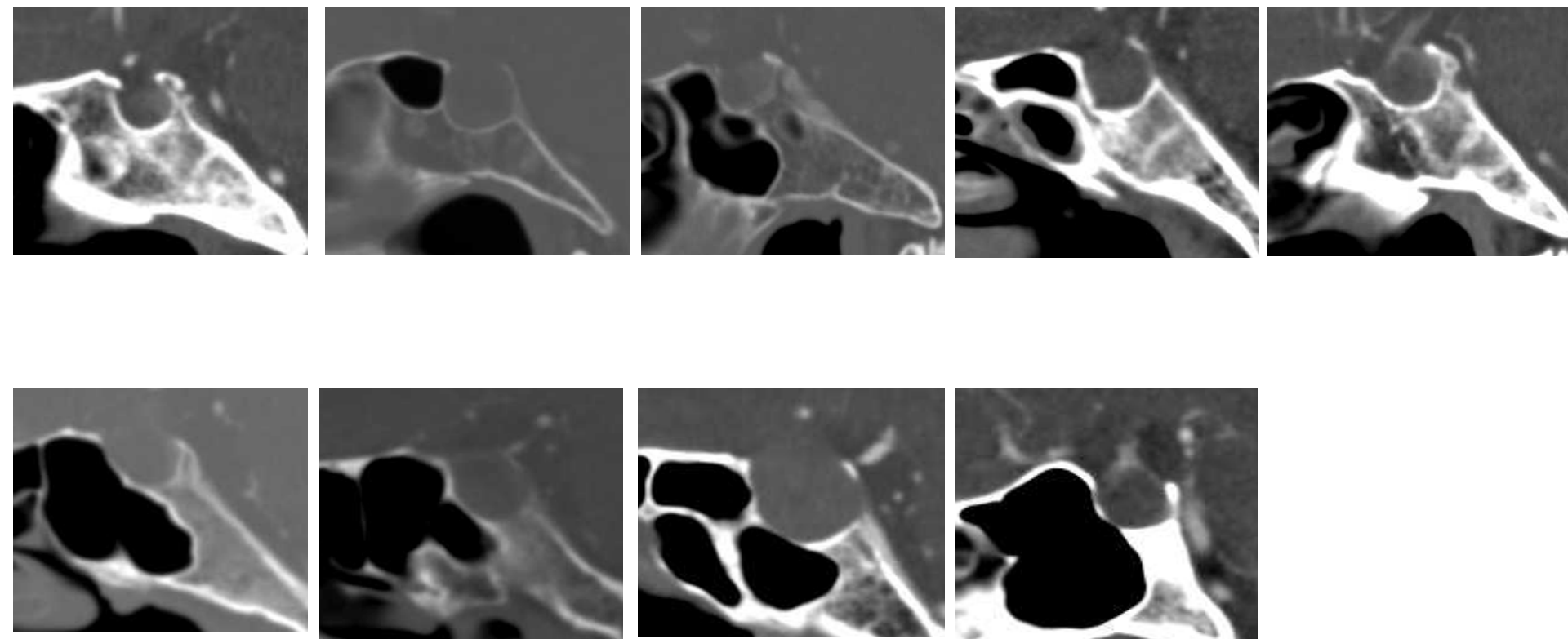
**Yasuhiko Hayashi**



1	2	3	4	5
6	7	8	9	case

**Figure 3**

**Yasuhiko Hayashi**



1	2	3	4	5
6	7	8	9	case

**Table 1**

<b>Patients</b>	<b>Age</b>	<b>Sex</b>	<b>Character of Headache</b>	<b>Quality</b>	<b>Laterality of pain</b>	<b>Suffered Period (years)</b>	<b>HIT-6</b>		<b>Awareness</b>
							<i>(preope)</i>	<i>(postope)</i>	<i>resolved</i>
1	59	F	ocular pain	pressure	+	1.5	60	36	resolved
2	63	F	ocular pain	dull	+	0.5	64	36	resolved
3	57	M	ocular pain	pressure	+	3	72	40	improved
4	58	M	ocular~frontal pain	dull	-	2.5	56	36	resolved
5	41	F	ocular~frontal pain	dull	+	1.5	68	36	resolved
6	38	F	ocular~frontal pain	pressure	-	0.8	66	36	resolved
7	44	F	ocular~frontal pain	dull	-	3	54	36	resolved
8	54	M	ocular~frontal pain	pressure	-	2	64	36	resolved
9	22	F	ocular~frontal pain	pressure	-	0.5	66	36	resolved



**Table 2**

<i>Patients</i>	<i>Adenoma</i>	<i>Size (mm)</i>	<i>MRI</i>		<i>Cyst</i>	<i>Diaphragma Foramen (mm)</i>	<i>CS invasion (Knosp)</i>	<i>Sphenoid Sinus Ossification</i>	<i>PRL(ng/mL)</i>	
			<i>T1</i>	<i>T2</i>					<i>(preope)</i>	<i>(postope)</i>
1	Non-functioning	16	hypo	hyper	+	3.3	0	conchal	63.1	13.8
2	Non-functioning	16	iso	hyper	+	3.8	0	conchal	18.6	10.4
3	Non-functioning	11	hypo	hyper	+	2.5	0	presellar	26.8	10.9
4	Non-functioning	18	hypo	hyper	-	3.6	1	presellar	32.8	17.5
5	PRL producing	14	iso	hyper	+	2.1	1	conchal	114.7	44.4
6	Non-functioning	18	iso	hyper	+	3.7	2	presellar	52.4	5.9
7	Non-functioning	17	iso	hyper	+	3.8	2	presellar	104.8	22.9
8	Non-functioning	20	iso	hyper	+	4.3	1	presellar	11.7	10.3
9	Non-functioning	13	Iso	hyper	-	6.4	0	presellar	24.1	12.1

**Table 3**

<b>Patients</b>	<b>Intrasellar pressure (mmHg)</b>	
	<i>before sellar floor removal</i>	<i>after sellar floor removal</i>
1	-	-
2	-	-
3	47 (46)	26 (25)
4	59 (52)	42 (39)
5	34 (36)	24 (27)
6	36 (37)	24 (27)
7	40 (39)	25 (24)
8	44 (45)	20 (22)
9	36 (31)	17 (19)

(during Valsalva maneuver)